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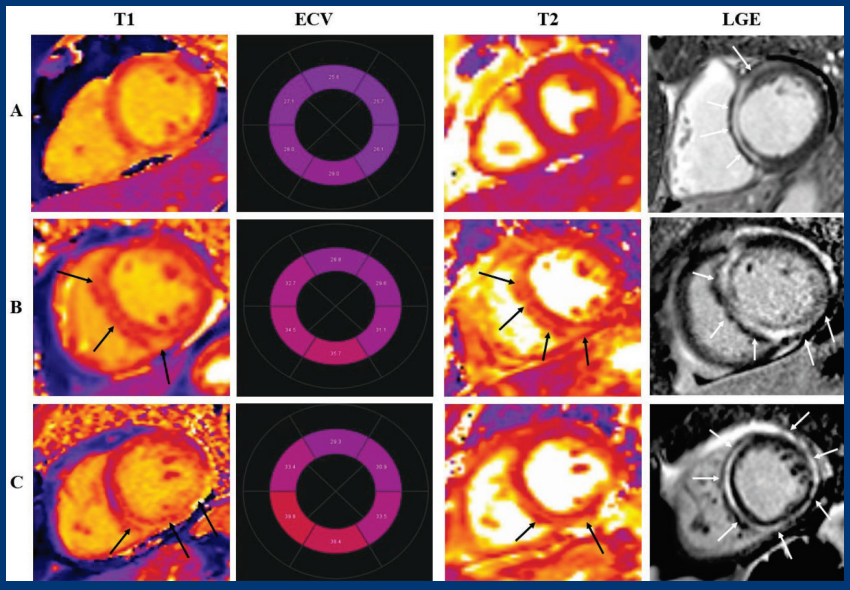

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Cardiovascular sequelae in symptomatic SARS-CoV-2 infection survivors

Grzegorz Skonieczny[1], Marta Skowrońska[2], Agnieszka Dolacińska[1], Beata Ratajczak[1], Patrycja Sulik[1], Oliwia Doroba[2], Alicja Kotula[2], Ewelina Błażejowska[2], Izabela Staniszewska[2], Olaf Domaszk[2], Piotr Pruszczyk[2]

[1]Cardiology Department and Intensive Cardiac Unit, Polyclinical Hospital, Torun, Poland
[2]Department of Internal Medicine and Cardiology, Medical University of Warsaw, Poland

Abstract

Background: *SARS-CoV-2 infection may lead to myocardial and endothelial damage. The present study sought to characterize the cardiovascular sequel in a large group of consecutive patients admitted for out-patient cardiovascular follow-up after a symptomatic COVID-19 infection.*

Methods: *The aims of this study were as follows: to evaluate the presence of post-covid cardiovascular symptoms in an unselected population of outpatients referred to a post-COVID outpatient cardiology clinic and to characterize the long-term abnormalities associated with a more severe COVID-19 infection clinical course. A total of 914 patients were included in this single-center, observational, cross-sectional study, of which 163 were hospitalized and 149 required mechanical ventilation for COVID-19 pneumonia. Patients were analyzed at follow-up according to the care setting during the initial presentation.*

Results: *The median time to follow-up was 126 days. At that time, only 3.5% of patients reported no persistent dyspnea, chest pain, or fatigue on exertion. In a follow-up echocardiographic assessment, patients who required hospitalization showed slight alterations in the pulmonary acceleration time and the tricuspid regurgitation pressure gradient, as well as reduced exercise tolerance during treadmill exercise testing when compared to patients with a benign clinical course. 24-hour Holter EKG monitoring or 24-hour blood pressure monitoring did not identify significant differences between the analyzed subgroups.*

Conclusions: *The current study reports on an association between COVID-19 severity and the presence of cardiovascular alterations at follow-up. A simple diagnostic protocol, comprising an exercise treadmill test and transthoracic echocardiography is useful in identifying patients who may benefit from regular, structured cardiovascular medical care.* (Cardiol J 2025; 32, 1: 1–8)

Keywords: myocardial damage, endothelial damage, COVID-19, long-COVID-19, PACS

Introduction

Severe cases of viral pneumonia, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may lead to myocardial injury in patients with and without previously known cardiovascular disease and is associated with higher mortality. In this regard, hypertension, diabetes, and pulmonary disease have been named as leading co-morbidities driving mortality in COVID-19 [1–4]. The direct mechanisms of myocardial injury have not been fully elucidated yet. However, as characterized in literature hereto, in the acute phase, SARS-CoV-2 displays an affinity

Address for correspondence: Agnieszka Dolacińska, Cardiology Department and Intensive Cardiac Unit, Provincial Polyclinical Hospital, ul. św. Józefa 53–59, 87–100 Toruń, Poland, tel: + 48 56 6793259, e-mail: a.langiewicz@onet.pl

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for the angiotensin converting enzyme-2 (ACE2) receptor located on the surface of myocytes which acts as the entryway for direct viral access to the cell [5]. A second possible mechanism of acute cell injury is linked to the increased expression of cytokines during COVID-19 infection leading to pericyte injury, endothelial dysfunction causing microvascular dysfunction, plaque instability generating myocardial infarction, and finally the development of myocardial fibrosis [6, 7]. The mechanisms perpetuating cardiovascular sequelae in post-acute COVID-19 patients include cell injury, downregulation of ACE2, and inflammation affecting the structural integrity of the myocardium, pericardium, and conduction system [8]. There is relevant heterogeneity reported regarding the frequency of cardiovascular complications following COVID-19, with reports most commonly identifying the development of myocarditis, arrhythmias, and heart failure [9], however, cardiac involvement seems to be correlated with COVID--19 severity [10]. Substrate-wise, evidence of myocardial fibrosis or active myocarditis was reported in cardiac magnetic resonance imaging (CMR) in up to 78% of patients and signs of inflammation in 60% of patients recovering from COVID-19, with recovering patients characterized by lower ejection fraction of the left ventricle (LVEF) and higher left ventricle (LV) volume compared with risk factor-matched controls [11]. The term "long-COVID-19" or "PACS" — post-acute COVID syndrome has been coined to describe the late multi-organ complications and accompanying persistent symptoms present after the acute phase of infection [7, 12].

The aims of this study were as follows: 1) to evaluate the presence of post-COVID cardiovascular symptoms in an unselected population of outpatients referred to a post-COVID out-patient clinic, 2) to characterize the long-term abnormalities associated with a more severe COVID-19 clinical course.

Methods

This was a single-center, observational, cross--sectional study of consecutive 914 post-COVID-19 patients evaluated between 2020–2022 at an out--patient cardiology clinic of a tertiary hospital. Patients were analyzed at follow-up according to the care setting during the initial presentation, which included either out-patient treatment (no hospitalization due to COVID-19 deemed necessary, comprising the benign clinical course subgroup), hospitalization without need for ventilation support or hospitalization requiring ventilation support (both comprising the severe clinical course subgroup). Information on the presence of persistent cardiovascular symptoms was gathered using a dedicated questionnaire. Additional studies: transthoracic echocardiography (TTE), treadmill exercise walking test (ExT), 24-hour Holter EKG monitoring, 24-hour ambulatory blood pressure monitoring (ABPM), chest imaging studies, laboratory blood panels were performed. Elements of the proposed work-up are also included in the European Society of Cardiology position paper regarding long-COVID-19 and the cardiovascular system [12].

The study was approved by the local institutional ethics committee.

Dedicated questionnaire

During the first follow-up visit to the out-patient clinic, all patients were asked to fill out a simple yes/no questionnaire regarding symptoms present during the initial COVID-19 infection and symptoms present at follow-up, which included: dyspnea, chest pain, and fatigue on exertion.

Transthoracic echocardiography

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [13]. All examinations were performed by a physician certified in echocardiography using the Affinity system (Philips).

Data on: left ventricular ejection fraction (LVEF), left atrium area (LAA), right atrium area (RAA), intraventricular septum thickness (IVS), tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation pressure gradient (TRPG), pulmonary acceleration time (AcT) were collected.

ABPM

ABPM (Oxford Oscar 2) was performed at follow-up in all patients. Data on: average systolic blood pressure (SBP avg), average diastolic blood pressure (DBP avg) were collected and analyzed.

24-hour Holter EKG monitoring

24-hour Holter EKG monitoring (Oxford 300-4L) was performed at follow-up in all patients. Data on: minimum heart rate (HR min), maximum heart rate (HR max), average heart rate (HR avg), number of supraventricular ectopic beats (SVEB), number of ventricular ectopic beats (VEB),

presence of atrial fibrillation (AF) were collected and analyzed.

Treadmill exercise walking test

A treadmill exercise walking test (GE Healthcare T2100) was performed at follow-up. Data on: metabolic equivalents (METs) were recorded and analyzed.

Imaging studies

Patients underwent chest computed tomography (CT) scans (Siemens SOMATOM Definition AS) for the diagnosis and evaluation of the severity of pulmonary lesions caused by SARS-CoV-2 during the initial presentation. Lesions were also assessed using either chest CT or X-ray during follow-up. The choice of lung imaging modality at follow-up was left to the discretion of the treating physician.

Laboratory analysis

COVID-19 was diagnosed when acute respiratory symptoms or an exacerbation of chronic respiratory symptoms were present and one of the following: SARS-CoV-2 target genes were detected using a reverse-transcriptase polymerase chain reaction (RT-PCR) assay (CovGenX) from biological material collected using nasopharyngeal swabs or with a positive immunochromatographic lateral flow test detecting the target nucleocapsid protein of SARS-CoV-2 from nasopharyngeal swabs (Abbott, IL, U.S.A.).

Data on concentrations of: D-dimer (DD), troponin I (TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine (sCrea), estimated glomerular filtration rate (eGFR) and hemoglobin (Hgb) were collected.

Plasma concentrations of troponin I were measured using a high-sensitivity automated sandwich electrochemiluminescence immunoassay (Abbott Alinity I) with the upper limit of normal values < 0.0342 μg/L.

D-dimer concentrations were quantitatively measured using an automated enzyme-linked fluorescent assay (Versen) with the upper limit of normal values 0.50 μg FEU/mL.

Data storing

A dedicated database for storing patient data was used.

Statistical analysis

Data are expressed as parameter or median followed by interquartile range. The Shapiro–Wilk test was used to identify continuous variables with a skewed distribution which were then compared using the Mann–Whitney U test. Categorical data were compared using the Chi^2 test. For all performed tests p-values of < 0.05 were considered significant. All tests were two-tailed. To explore the sequelae associated with a more severe clinical course, multivariable logistic regression models were used.

Analyses were performed using the Statistica 13 data analysis software system (TIBCO Software Inc., CA, USA) and the MedCalc software system (MedCalc Software Ltd, Ostend, Belgium).

Results

Medical records of 914 patients were analyzed: 751 (82.1%) patients received at-home treatment while 163 (17.8%) patients were treated in hospital, of which 149 (16.3% of the entire population) were treated in hospital and required mechanical ventilation for COVID-19 pneumonia. The median time from the initial presentation to the follow-up was 126 days. The flow of patients is presented in Figure 1.

Imaging studies were performed in 674 (74%) out of 914 patients, the choice of modality was left to the discretion of the treating physician. Any signs of parenchymal involvement were noted in 142 (21.1%) patients, of which all had lesions covering less than 50% of the lungs.

Patients who experienced a more complicated clinical course were characterized by a higher number of co-morbidities on follow-up (Table 1).

Symptoms-wise, the most common post-COVID-19 symptom was fatigue on exertion (872 pts, 95.4%), followed by dyspnea which was reported by 701 (77%) patients; 100 of whom subjectively identified COVID-19 infection as the leading cause of this symptom, and chest pain (440 pts, 48.1%). Out of all dyspneic patients, differences were found for BMI, number of SVEB, average SBP and DBP, measured LVEF in TTE, but not for the severity of the initial presentation. No other significant differences between analyzed factors in the aforementioned subgroups were found.

It was found that patients treated ambulatorily when compared with hospitalized patients differed on follow-up by: age, BMI, number of SVEB, average SBP, measured LVEF, LAA, RAA, IVS, TRPG, AcT in TTE, METs achieved during ExT, concentrations of DD, Hgb, and sCrea. However, the alternations in these parameters were usually not severe. However, in 9 patients (1%, one whom

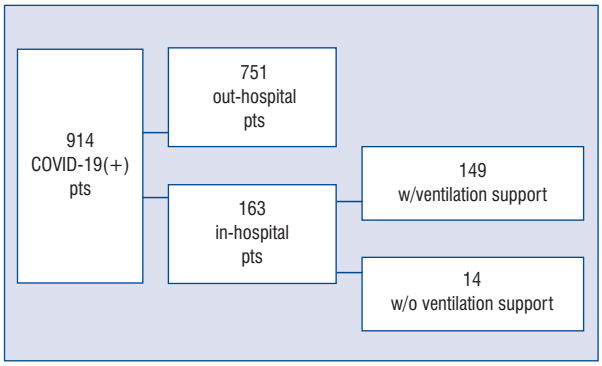

Figure 1. Flow of patients in the study

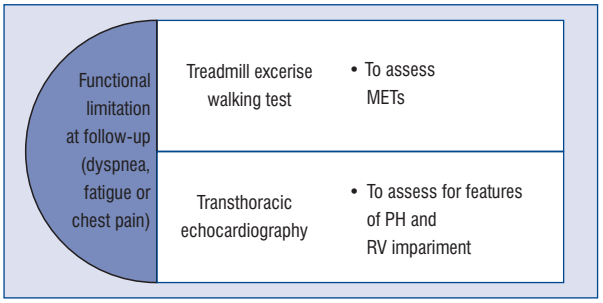

Figure 2. Proposed diagnostic algorithm for symptomatic patients with persistent dyspnea/chest pain/fatigue on exertion

Table 1. Characteristics of the study group. Data are presented as number followed by percentage. Data gathered at follow-up. Chi^2 test was used for comparison; p-values are presented in the fourth column. Statistically significant results shown in bold. A benign clinical course was defined as ambulatory treatment of SARS-CoV-2, while a severe clinical course was diagnosed in patients requiring in-hospital management

	Benign clinical course (n = 751)	Severe clinical course (n = 163)	P-value
Male/female	463/288	70/96	–
Age	54 (44–65)	**53 (43–63)**	**63 (52–70)**
BMI [kg/m^2]	27.55 (24.7–30.9)	**27.18 (24.2–30.4)**	**29.32 (26.5–32.3)**
Neoplasm (n, %)	24 (3.2%)	7 (4.3%)	0.49
Paroxysmal AF (n, %)	32 (4.3%)	11 (6.75%)	0.17
Other AF (n,%)	12 (1.6%)	4 (2.45%)	0.45
Heart failure (n,%)	58 (7.72%)	22 (13.5%)	0.02
Coronary artery disease (n, %)	32 (4.26%)	9 (5.52%)	< 0.001
Hyperlipidemia (n, %)	153 (20.4%)	50 (30.7%)	0.003
Diabetes mellitus (type 1 or type 2) (n, %)	59 (7.9%)	31 (19%)	< 0.001
COPD (n, %)	7 (0.9%)	5 (3.1%)	< 0.001
Asthma (n, %)	58 (7.7%)	7 (4.3%)	0.012
Hypertensive medication (n, %)	284 (38%)	100 (61.5%)	< 0.001
Anticoagulation/antiplatlet agent (n, %)	46 (6.1%)	27 (16.5%)	< 0.001
Statin (n, %)	124 (16.5%)	47 (29%)	< 0.001

AF — atrial fibrillation; ASA — acetylsalicylic acid; BMI — body mass index; COPD — chronic obstructive pulmonary disease; n — number

was hospitalized) significantly reduced LV ejection fractions (EF < 30%) were found at follow-up. Full results are presented in Table 2. Multiple logistic regression revealed that a severe clinical course was associated with features of pulmonary hypertension (PH, Table 3).

Finally, analyses for hospitalized patients showed that mechanically ventilated patients vs. non-mechanically ventilated hospitalized patients differed on follow-up only by total exercise capacity during the treadmill exercise walking test expressed in METs (6.5 vs. 10 METs), and Hgb levels (15 g% vs. 14 g%) (Table 4).

Discussion

The key findings emerging from our cross-sectional study are that irrespective of the clinical severity of presentation of the acute COVID-19 episode, fatigue on exertion, persistent dyspnea, and chest pain are frequently reported by patients after a median of 4 months of follow-up. In the present study, only 3.5% of the studied population had none of the aforementioned symptoms. Wang et al. reported on the presence of at least one persistent symptom in 76% of all COVID-19 survivors, with fatigue occurring most commonly [14];

Table 2. COVID-19 patients with a benign vs severe clinical course. Data gathered on follow-up. Data are presented as median followed by interquartile range. Statistically significant results shown in bold

	All, n = 914	Benign clinical course, n = 751	Severe clinical course, n = 163	P-value for benign vs. severe
SVEB (n)	16 (6–59)	15 (5–52)	23 (9–91)	0.006
HR avg [beats/min]	73 (67–79)	73 (67–79)	72 (68–79)	0.52
VEB (n)	3 (0–27)	3 (0–22)	4 (1–48)	0.09
SBP avg [mmHg]	125 (116–135)	125 (115–134)	127 (120–138)	0.016
DBP avg [mmHg]	74 (67–81)	74 (68–80)	75 (67–83)	0.25
EF [%]	65 (60–65)	65 (60–65)	60 (60–65)	0.0002
LAA [cm^2]	17.5 (15.5–20)	17 (15–19.7)	19 (16–21.5)	0.001
RAA [cm^2]	15 (13–17)	15 (13–17)	16 (14–18)	0.001
IVS [cm]	1 (0.9–1.1)	1 (0.9–1.1)	1 (1.0–1.1)	< 0.001
TRPG [mmHg]	22 (19–26)	22 (18–25)	24 (20–28)	0.001
AcT [ms]	135 (119–150)	137 (120–151)	123 (111–147)	0.001
TAPSE [cm/s]	2.4 (2.2–2.7)	2.4 (2.2–2.6)	2.4 (2.2–2.7)	0.32
METs	10 (7.0–12.2)	10 (7.1–12.8)	9.3 (7.0–10.2)	0.007
D-dimer [ng/mL]	0.36 (0.250–0.550)	0.36 (0.250–0.530)	0.42 (0.280–0.600)	0.012
Hgb [g/dL]	13.8 (13–14.8)	13.8 (12.9–14.7)	14.2 (13.3–15.2)	0.003
sCrea [mg/dL]	0.79 (0.68–0.93)	0.78 (0.67–0.92)	0.84 (0.7–0.99)	0.004
TnI [μg/L]	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.58
NT–proBNP [pg/mL]	74.1 (40.4–131.4)	74 (40.5–127.5)	75.75 (41.3–167.4)	0.43
eGFR [mL/min/1.73m^2]	93.52 (80.2–103.6)	94.7 (81.3–104.6)	89.11 (77.6–98.6)	0.42

AcT — pulmonary acceleration time; BMI — body mass index; DBP avg. — average diastolic blood pressure; EF — left ventricular ejection fraction; eGFR — estimated glomerular filtration rate; Hgb — blood hemoglobin; HR avg. — average heart rate; IVS — intraventricular septum; LAA — left atrium area; METs — metabolic equivalents; n — number; NT-proBNP — N-terminal pro–B-type natriuretic peptide; RAA — right atrium area; TAPSE — tricuspid annular plane systolic excursion; TnI — Troponin I; TRPG — tricuspid regurgitation pressure gradient; SBP avg. — average systolic blood pressure; sCrea — serum creatinine; SVEB — supraventricular ectopic beat; VEB — ventricular ectopic beat

Table 3. Cardiovascular sequelae of the severe clinical course of COVID-19 infection. Log-reg analysis. Data are presented as odds ratio followed by 95% confidence interval and p-value. Statistically significant results shown in bold

Sequelae	Median, 95% CI, p-value
AcT [ms]	1.02 (1.01–1.03); 0.002
TRPG [mmHg]	0.94 (0.90–0.98); 0.01
RAA [cm^2]	1.04 (0.93–1.15); 0.53
D-dimer [ng/mL]	1.007 (0.96–1.05); 0.19
eGFR [mL/min/1.73m^2]	1.01 (0.1–1.02); 0.11
Hgb [g/dL]	0.98 (0.94–1.006); 0.71

AcT — pulmonary acceleration time; CI — confidence interval; eGFR — estimated glomerular filtration rate; Hgb — hemoglobin; LAA — left atrium area; RAA — right atrium area; TRPG — tricuspid regurgitation pressure gradient

other reports show that even in mild infections persistent shortness of breath or dyspnea on exertion may be present in up to 20% and 56% of patients, respectively [15].

Secondly, it was found that the cardiovascular consequences of both benign and severe COVID-19 infection at later (four month), follow-up are common, but not severe and may be diagnosed with TTE and ExT. Moreover, the degree of quantifiable cardiovascular alterations differs between patients with a benign vs severe clinical course: after a median time of four months post-COVID, in TTE assessment, patients who required hospitalization had larger LAA and RAA, lower LVEF, as well as moderately higher TRPG and moderately reduced AcT values when compared to ambulatorily treated patients. The former alternations did not meet the criteria for PH, nor did they exceed the respective

Table 4. Comparison for ventilation support vs no ventilation support. Data gathered on follow-up. Data are presented as median followed by interquartile range. Statistically significant results shown in bold

	Ventilation support, n = 149	No ventilation support, n = 14	P-value
METs	6.45 (4.9–9.3)	9.7 (7.0–10.3)	0.01
Hgb [g/dL]	15.15 (14.1–16.3)	14.05 (13.05–15.1)	0.01
BMI [kg/m^2]	29.32 (26–32.2)	29.30 (26.5–32.3)	0.28
HR avg [beats/min]	74 (70–78)	29.30 (67–79)	0.63
SVEB (n)	22 (4–62)	23 (9–94)	0.84
VEB (n)	13 (1–35)	4 (1–50)	0.33
SBP [mmHg]	124 (114–130)	127 (121–139)	0.67
DBP [mmHg]	72 (67–79)	75 (67–83)	0.79
EF [%]	65 (60–65)	60 (60–65)	0.94
LAA [cm^2]	17.5 (16–26)	19 (16–21.5)	0.56
RAA [cm^2]	16 (14–18.5)	16 (14–18)	0.15
IVS [cm]	1 (0.9–1.1)	1 (1.0–1.1)	0.34
TAPSE [cm/s]	2.5 (2.0–2.7)	2.4 (2.2–2.7)	0.92
TRPG [mmHg]	24 (20–28)	24 (20–28)	0.2
AcT [ms]	121 (119–150)	123 (110–145)	0.81
D-dimer [ng/mL]	0.345 (0.240–0.435)	0.425 (0.290–0.611)	0.27
TnI [μg/L]	0.01 (0.006–0.01)	0.01 (0.01–0.01)	0.85
NT-proBNP [pg/mL]	66.15 (42.1–233.5)	76.5 (41.4–170)	0.93
eGFR [mL/min/1.73 m^2]	87.55 (77.5–108.3)	89.41 (77.6–98.6)	0.84
sCrea [mg/dL]	0.88 (0.74–0.93)	0.83 (0.7–0.99)	0.3

AcT — pulmonary acceleration time; BMI — body mass index; DBP avg. — average diastolic blood pressure; EF — left ventricular ejection fraction,; eGFR — estimated glomerular filtration rate, Hgb — blood hemoglobin; HR avg. — average heart rate; IVS — intraventricular septum; LAA — left atrium area; METs — metabolic equivalents; n — number; NT-proBNP — N-terminal pro–B-type natriuretic peptide; RAA — right atrium area; TAPSE — tricuspid annular plane systolic excursion; TnI — Troponin I; TRPG — tricuspid regurgitation pressure gradient; SBP avg. — average systolic blood pressure, sCrea — serum creatinine; SVEB — supraventricular ectopic beat; VEB — ventricular ectopic beat

reference ranges. Lastly, patients with a severer clinical course more often reported the presence of co-morbidities at follow-up.

These observations may be considered consistent with others, who report on a substantial burden of cardiovascular diseases covering both non-ischemic and ischemic entities, evident even among those patients who did not require hospitalization in a nationwide cohort of over 100,000 individuals [16]. Reports identify cardiac abnormalities, often severe, in half of all COVID-19 patients undergoing echocardiography in the acute phase [17]. The actual prevalence of PH in acute COVID-19 patients is reported at around 10% and is associated with worse in-hospital outcomes [18]. Other authors have reported on the presence of both features of PH as well as RV impairment, the latter characterized by reduced TAPSE in non-critically ill COVID-19 patients during the initial episode, with systolic LV dysfunction being less common [18].

In the current study, it was noted that only a reduction in AcT and higher TRPG values between subgroups, which may reflect the sustained lung injury, is presumably more advanced in more severe cases. No differences RV systolic function assessed with TAPSE were found. Of note, all alterations although statistically significant were in the reference range of values for the respective parameter.

Another major observation is that in this large population of post-COVID patients, exercise limitations were more prominent in patients who required mechanical ventilation due to COVID-19 pneumonia. This subpopulation of patients was also characterized by higher hemoglobin levels on follow-up, a plausible pathophysiological explanation for this may be persistent hypoxia.

The obvious barriers connected with further diagnostic testing of large populations of post-COVID patients mandates the need for more feasible diagnostic protocols. The present assessment, in an unselected consecutive follow-up of largely symptomatic post-COVID-19 patients with fatigue on excertion, studies influencing further clinical

decisions were TTE and ExT. ABPM and Holter EKG monitoring was performed, as well as basic laboratory blood analyses, and it was found that the results of these tests, although differing between the analyzed subgroups, did not modify patient management. Some authors have tested concentrations of biomarkers collected during the initial presentation as a benchmark for further follow-up: in one study increased levels of troponin T prognosticated cardiovascular complications during the index hospitalization, but not during a one-year follow-up period [19]. Current findings are similar: no statistically significant differences were found at four-month follow-up between the overall low troponin T concentrations in patients with benign vs severe clinical course [19].

Based on the present findings and on data from meta-analyses regarding the beneficial influence of structured rehabilitation on patient functional outcomes post-COVID-19, it can be proposed that these tests may be used to pinpoint candidates for rehabilitation programs and systematic echocardiographic follow-up [20].

Several study limitations should be acknowledged. Firstly, there was a lack of data on exercise capacity and LV and RV function before the COVID-19 infection, while data on co-morbidities was based on a patient survey only. Patients were analyzed according to hospitalization status and nearly all hospitalized patients received mechanical ventilation, which underlines that only the highest risk patients were admitted to the hospital. Secondly, data was lacking regarding COVID-19 vaccinations and their impact on the course of the infection. Lastly, available data limited distinguishing cause from effect in the obtained results.

Conclusions

This cohort study reports on a ubiquitous presence of persistent cardiovascular symptoms at follow-up in COVID-19 patients irrespective of the severity of clinical presentation of the acute episode. There were slight alterations found in parameters of right ventricular function and atrial sizes between patients with a benign vs severe clinical course. In patients with fatigue on exertion, a simple diagnostic protocol, comprising treadmill exercise testing and transthoracic echocardiography is useful in identifying patients who may benefit from regular, structured medical care. All the more so, particular attention should be paid to cardiovascular protection during COVID-19 infection, further, it is important to continuously acknowledge the benefits of vaccination for the prevention of commonly occurring, post-covid cardiovascular sequelae.

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Effect of COVID-19 on the prevalence of bystanders performing cardiopulmonary resuscitation: A systematic review and meta-analysis

Artur Krawczyk[1], Krzysztof Kurek[2], Gabriella Nucera[3], Michał Pruc[1, 4], Damian Świeczkowski[5], Dawid Kacprzyk[1], Ewa Skrzypek[6], Nicola Luigi Bragazzi[7], Kamil Safiejko[8], Łukasz Szarpak[2, 8, 9]

[1]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[2]Department of Clinical Research and Development, LUXMED Group, Warsaw, Poland
[3]Department of Emergency, Fatebenefratelli Hospital, ASST Fatebenefratelli and Sacco, Milan, Italy
[4]Department of Public Health, International European University, Kyiv, Ukraine
[5]Department of Toxicology, Faculty of Pharmacy, Medical University of Gdansk, Poland
[6]Department of Medical Ethics and History of Medicine, Medical University of Warsaw, Poland
[7]Department of Mathematics and Statistics, Laboratory for Industrial and Applied Mathematics (LIAM), York University, Toronto, Canada
[8]Colorectal Cancer Unit, Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[9]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, United States

Abstract

Background: *The importance of bystander cardiopulmonary resuscitation (CPR) during out-of-hospital cardiac arrests is especially important in the context of coronavirus disease 2019 (COVID-19) because it can significantly influence survival outcomes. The objective of this meta-analysis was to examine the primary outcomes of bystander CPR during the pandemic and pre-pandemic periods.*

Methods: *A search was conducted in the PubMed Central, Scopus, and EMBASE databases, as well as the Cochrane Central Register of Controlled Trials database, up to December 10, 2023. In cases where the value of I^2 was greater than or equal to 50% or the Q-test indicated that the p-value was less than or equal to 0.05, the studies were considered to be heterogeneous. Sensitivity assessment was performed using the leave-one-out methodology. The study protocol was registered in PROSPERO with the ID number CRD42023494912.*

Results: *Twenty-five articles were included in this meta-analysis. Pooled analysis showed that bystander CPR frequency during the COVID-19 pandemic was 38.8%, compared to 44.8% for the pre-pandemic period (odds ratio: 1.04; 95% confidence interval: 0.93–1.16; $p = 0.48$).*

Conclusions: *The article's conclusions indicate that the COVID-19 pandemic influenced a reduction in bystander CPR compared to the pre-pandemic period, but this difference was not statistically significant. Further research is recommended to understand attitudes, including the fears of witnesses, before performing CPR on patients with suspected or confirmed infectious diseases. The study highlights the importance of bystander intervention in emergency situations and the impact of a pandemic on public health response behaviors.* (Cardiol J 2025; 32, 1: 9–18)

Keywords: COVID-19, bystander cardiopulmonary resuscitation (CPR), out-of-hospital cardiac arrest (OHCA), pandemic impact, meta-analysis, public health

Address for correspondence: Ewa Skrzypek, PhD, MD, Department of Medical Ethics and History of Medicine, Medical University of Warsaw, ul. Zwirki i Wigury 61, 02–091 Warszawa, Poland, tel: +48604075561, e-mail: ewa.skrzypek@wum.edu.pl

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Introduction

Identifying that an individual is experiencing cardiac arrest, requesting support, and initiating bystander cardiopulmonary resuscitation (CPR) greatly enhances the likelihood of survival after a cardiac arrest that occurs outside of a medical facility [1, 2]. Currently, there is significant discussion over the impact of coronavirus disease 2019 (COVID-19) on non-traumatic out-of-hospital cardiac arrest (OHCA), particularly in relation to the outcomes that occur when the cardiac arrest happens outside of a hospital setting. This debate is taking place within the context of the COVID-19 pandemic. This period is often referred to as the COVID-19 era in scientific literature, and comparisons are being made to times before the pandemic. Based on Fan et al. [3], specific disparities were observed in the outcomes at the University Medical Center. These disparities included a decrease in the survival rate upon admission from 44.6% to 39.4%, a decrease in the survival rate upon discharge from 17.5% to 14.9%, and a deterioration in the neurological condition of the patients. However, hospitals with a lower level of reference did not exhibit comparable tendencies [3]. The structure of medical procedures provided during the intervention of Emergency Medical Services (EMS) has also changed, including a reduction in intubation attempts, a decrease in epinephrine administration, and a greater likelihood of completing resuscitation without return of spontaneous circulation (ROSC) at the scene [4]. The above observations were confirmed in a recently published meta-analysis, mainly in the context of pre-hospital death, survival to hospital admission (SHA), and survival to hospital discharge (SHD). Furthermore, there was a notable rise in the occurrence of OHCAs during the first wave of the COVID-19 pandemic, along with a decrease in the frequency of bystander CPR in areas with a high COVID-19 incidence [5].

However, further research of this subject is required. An in-depth analysis of the disparities between the waves of the pandemic should be conducted. One study separated the duration of the pandemic, from February 21, 2020 to December 31, 2020, into two periods. Both periods were analyzed and showed a comparable rise in the number of OHCAs [6]. However, what about the later time and the following surges in illness prevalence? Furthermore, particularly during the first phase of the COVID-19 pandemic, a particular constraint that might impact the results after OHCA was the scarcity of healthcare personnel and other resources within the healthcare system [7]. Healthcare personnel were largely engaged in the provision of care for COVID-19 patients and were reassigned from other departments [8–10]. An important issue that could influence outcomes after OHCA was also reduced motivation to perform CPR, especially in the case of bystander CPR [11]. Medical professionals' representatives have also said that the primary reason discouraging them from doing CPR was the fear of acquiring COVID-19. Additionally, the fear of contacting COVID-19 contributed to the reluctance of as many as 34% of medical professionals to conduct CPR [12].

Considering the aforementioned factors, the objective of this meta-analysis was to examine the primary outcome of bystander CPR during the pandemic and pre-pandemic periods. Additionally, the secondary outcomes included bystander witness parameters such as the frequency of bystander witnessing, activation of public access defibrillators, the occurrence of shockable heart rhythms, and the influence of these factors on survival rates to hospital admission, survival rates to hospital discharge, and survival with good neurological outcomes.

Methods

Literature search

This meta-analysis was performed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13]. This study was reported in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42023494912). The protocol was developed a priori and accepted by all authors, and no protocol changes were made during the study. Given the nature of this investigation, ethics committee approval was not required.

Four databases (PubMed Central, Scopus, and EMBASE, as well as the Cochrane Central Register of Controlled Trials) were systematically searched up to December 10, 2023. Furthermore, Google Scholar was searched to identify additional studies through forward searches until December 12, 2023. We manually searched the reference lists of the included studies to identify additional eligible studies. The phrases we used for the literature search were as follows: "cardiac arrest" OR "out-of-hospital cardiac arrest" OR "OHCA" OR "heart arrest" OR "cardiopulmonary resuscitation" OR "CPR" OR "sudden cardiac death" AND "bystander" AND "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "COVID-19" OR "nCOV" OR "novel coronavirus".

Eligibility criteria

The inclusion criteria were as follows: studies on patients with OHCA with no gender and age restrictions, comparing bystander CPR occurrence in the pre-pandemic and pandemic periods, and English language.

The following exclusion criteria were applied: review articles, articles concerning the pediatric population, letters to editors, editorials, studies with non-original data, and studies without a comparator group.

Two authors (A.K. and M.P.) independently evaluated the studies found through the database search by using the aforementioned criteria in conjunction with the abstract and title. To resolve the conflicts, a third reviewer was consulted (L.S.). Two authors (A.K. and M.P.) independently evaluated the studies that made the title/abstract screening on the basis of the same criteria in the full texts. In cases of disagreement, a third reviewer (L.S.) was consulted to resolve the issues.

Data extraction

Two of the authors (A.K. and M.P.) independently extracted data. Disagreements were resolved through discussion with all authors and consensus. A standardized form was developed to extract the following data from eligible studies: (i) authors, country, and year of publication; (ii) study sample characteristics; (iii) resuscitation characteristics (i.e., cardiac arrest bystander witnessed, home location of OHCA, medical etiology of OHCA, implementation of public access defibrillation, and shockable rhythm occurrence); (iv) bystander CPR ratio; and (v) additional OHCA outcomes, e.g., SHA, SHD, and SHD with good neurological outcome, defined as grade 1 or 2 in Cerebral Performance Category (CPC) scale [14].

Quality assessment

Two authors (A.K. and G.N.) independently performed quality assessment in accordance with the Newcastle Ottawa Scale (NOS) [15]. Within this scale, every study is assessed based on 8 criteria that are divided into 3 categories: the selection of study groups, the comparability of the groups, and the determination of the conclusion. Each item was assessed on a scale of 1 point, except for comparability, which had a potential score of 2 points. The overall score ranged from 0 to 9, with higher ratings denoting superior quality. The potential scores achievable with this instrument ranged from 0 to 9. Research with a total score of 7 or more was deemed to be of good quality [16].

Statistical analysis

The statistical analyses were conducted using Review Manager (version 5.4, Nordic Cochrane Center, Cochrane Collaboration) and Stata (version 18, Software for Statistics and Data Science, StataCorp, College Station, TX, USA). The analyses were conducted using a two-tailed approach, with statistical significance defined as a p-value less than 0.05. For dichotomous data, we used odds ratios (OR) as the measure of effect along with 95% confidence intervals (CIs). For continuous data, we employed standardized mean differences (MD) with a 95% CI. The study provided the continuous results as the median, range, and interquartile range (IQR). For studies that did not provide the average value plus or minus the standard deviation (SD): 1. If a range or 95% CI was provided, the SD was computed using this information. 2. If the median with range or IQR was provided, these values were utilized to assess the skewness of the data. If the data did not have any bias, the mean and SD were computed [17]. Heterogeneity was assessed statistically using the Q test and I^2 statistics. If the value of I^2 was less than 50% and the Q-test indicated that the p-value was greater than 0.05, the studies were deemed to be in good agreement. In this case, a fixed-effects model was used for the combined analysis. Conversely, if the value of I^2 was greater than or equal to 50% or the Q-test indicated that the p-value was less than or equal to 0.05, the studies were considered to be heterogeneous. In such instances, a random-effects model was employed for the combined analysis [18]. We employed Egger's test and funnel plots to examine potential bias, and we assessed publication bias using funnel plot tests for asymmetry, but only if a single meta-analysis included more than 10 trials. In addition, a sensitivity assessment was performed using the leave-one-out methodology, in which 1 study was excluded at a time, and the overall impact size was estimated to identify possibly influential situations.

Results

The process of inclusion and exclusion, detailed in the PRISMA flow diagram, is presented in Figure 1. The search identified a total of 2453 records. After removing 1611 articles by automation tools, a further 760 articles were excluded after screening their title and abstract. Fifty-seven reports were considered irrelevant and excluded after the full texts had been reviewed. Finally, 25 studies were enrolled for meta-analysis [8, 19–42].

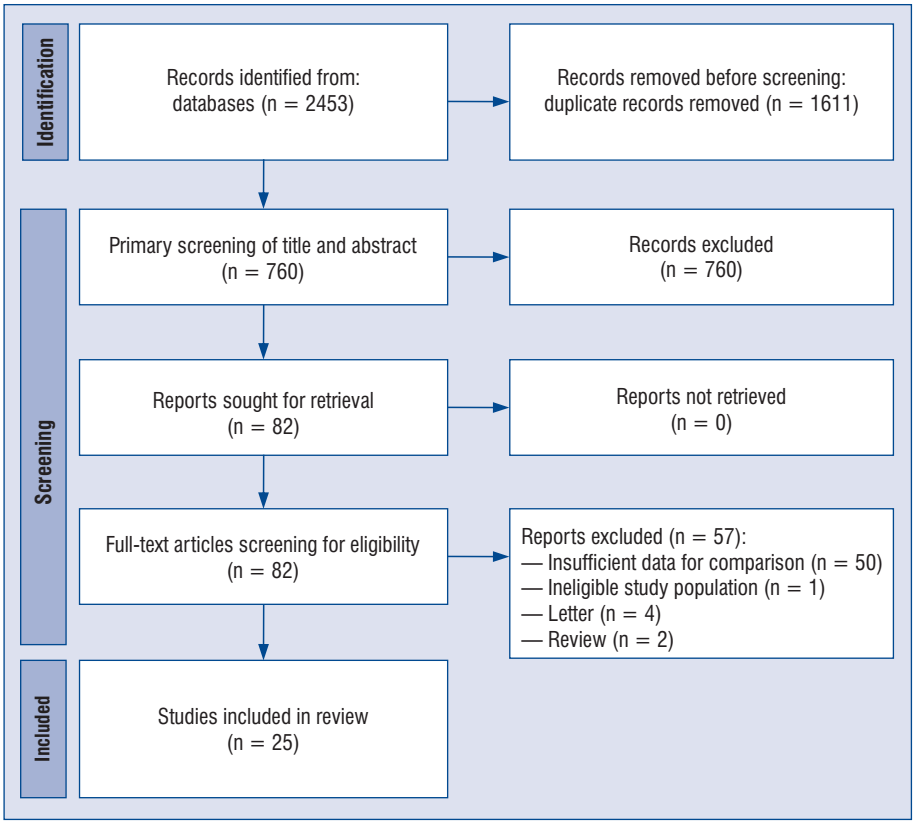

Figure 1. Flow diagram of the search strategy and study selection

Basic characteristics of included trials

Twenty-five articles were included in the analysis, with available data on 253,156 OHCAs. The participant baseline characteristics of the included studies are shown in Table 1. All the selected studies were published between 2020 and 2023. Of those 25 studies, 6 were performed in the USA, 2 in Australia, 2 in China, 2 in Italy, 2 in South Korea, 2 in Taiwan, 2 in Thailand, and one in each of the following countries: France, Germany, Japan, Spain, Sweden, Switzerland, and the United Kingdom (Fig. 2). The NOS scores of the 8 included studies were ≥ 7 (Table 1).

Primary outcome analysis

Twenty-five studies reported bystanders performing CPR during the pandemic and pre-pandemic periods. Pooled analysis showed that bystander CPR frequency during the COVID-19 pandemic was 38.8%, compared to 44.8% for the pre-pandemic period (OR: 1.04; 95% CI: 0.93–1.16; p = 0.48; Fig. 3). The results from the sensitivity analysis did not alter the direction.

Secondary outcomes analysis

Twenty-one studies reported bystander witnessed parameters among pandemic and pre-pandemic periods. In the pandemic period, the frequency of bystander witnessing was 49.9%, while in the pre-pandemic period it was 55.3% (OR: 0.94; 95% CI: 0.88–1.00; p = 0.04; **Suppl. Fig. S1**). Public access defibrillators activation in the COVID-19 pandemic and pre-pandemic periods also varied and amounted to 5.2% compared to 5.7%, respectively (OR: 0.66; 95% CI: 0.55–0.80; p < 0.001). Pooled analysis showed that shockable rhythm during the pandemic period occurred in 9.5% compared to 11.7% in the pre-pandemic period (OR: 0.90; 95% CI: 0.84–0.96; p = 0.002). Pooled analysis showed that in the COVID-19 pandemic period, the time to EMS arrival was statistically significantly longer compared to the pre-pandemic period (MD: 1.43; 95% CI: 1.00–1.86; p < 0.001; **Suppl. Fig. S2**).

Survival to hospital admission was statistically significantly lower for the pandemic period compared to the pre-pandemic period and was,

Table 1. Baseline characteristics of the study populations among included trials

Study	Country	Study design	Study group	No. of patients	Age, years	Male, n (%)	Home location of OHCA, n (%)	Medical etiology of OHCA, n (%)	NOS score
Baldi et al., 2020	Italy	Multicenter longitudinal prospective registry	Pre-pandemic	520	79 (65–86)	300 (57.7)	420 (81.0)	456 (89.0)	9
			Pandemic	694	77 (67–85)	430 (62.0)	623 (90.0)	613 (93.0)	
Baldi et al., 2021	Switzerland	Population-based, observational study	Pre-pandemic	933	71 (58–82)	636 (68.2)	596 (66.6)	761 (81.6)	8
			Pandemic	911	70 (56–80)	623 (68.4)	633 (71.4)	774 (85.0)	
Ball et al., 2020	Australia	Retrospective cohort study	Pre-pandemic	1218	67 (52–78)	845 (69.4)	929 (77.9)	965 (79.2)	8
			Pandemic	380	69 (54–80)	250 (65.8)	269 (72.3)	342 (90.0)	
Biskupski et al., 2022	USA	Single-center retrospective study	Pre-pandemic	28	65	17 (60.7)	15 (53.6)	5 (18.0)	7
			Pandemic	86	59	52 (60.5)	52 (60.5)	10 (12.0)	
Breglia et al., 2022	Italy	Retrospective observational study	Pre-pandemic	64	71.3 ± 17.3	46 (71.9)	NS	5 (7.8)	8
			Pandemic	50	71.1 ± 14.3	35 (70.0)	NS	20 (40.0)	
Chavez et al., 2022	USA	Secondary analysis of Texas CARES	Pre-pandemic	3619	63 (51–74)	2307 (63.8)	2926 (80.9)	NS	8
			Pandemic	4418	63 (51–74)	2781 (63.0)	3831 (86.7)	NS	
Chugh et al., 2022	USA	Prospective, population--based study	Pre-pandemic	1315	71.3 ± 15.8	857 (65.2)	NS	1315 (100)	8
			Pandemic	907	69.5 ± 17.0	586 (64.6)	NS	907 (100)	
Fothergill et al., 2021	UK	Retrospective, observational study	Pre-pandemic	1724	68 ± 20	1069 (62.0)	1474 (85.5)	522 (76.4)	9
			Pandemic	3122	71 ± 19	1839 (59.0)	2899 (92.9)	757 (66.7)	
Hosomi et al., 2022	Japan	Secondary analysis of the All-Japan Utstein Registry	Pre-pandemic	32,024	83 (75–89)	18,116 (56.6)	NS	19,806 (61.8)	8
			Pandemic	31,894	83 (76–89)	18,195 (57.0)	NS	20,131 (63.1)	
Kim et al., 2023	South Korea	Cross-sectional, retrospective, observational study	Pre-pandemic	25,355	67.6 ± 17.0	16,373 (64.6)	18,631 (73.5)	19,661 (77.5)	8
			Pandemic	26,566	68.0 ± 16.9	17,056 (64.2)	20,103 (75.7)	21,033 (79.2)	
Lai et al., 2020	USA	Population-based, cross-sectional study	Pre-pandemic	1336	68 ± 19	752 (57.1)	NS	NS	8
			Pandemic	3989	72 ± 18	2183 (55.8)	NS	NS	
Leung et al., 2023	China	Retrospective cohort study	Pre-pandemic	1502	76.8 ± 4.2	844 (56.2)	769 (51.2)	NS	9
			Pandemic	2185	77.7 ± 4.2	1293 (59.2)	1330 (60.9)	NS	
Li et al., 2023	China	Retrospective study	Pre-pandemic	19,027	82.0 ± 3.3	10,225 (53.7)	15,514 (81.5)	18,267 (96.0)	9
			Pandemic	30,962	83.3 ± 3.2	16,384 (52.9)	24,212 (78.2)	29,968 (96.8)	
Lim et al., 2021	South Korea	Retrospective observational study	Pre-pandemic	891	70.07 ± 15.06	577 (64.8)	592 (66.4)	NS	9
			Pandemic	1063	71.05 ± 14.98	647 (60.9)	761 (71.6)	NS	

→

Table 1 (cont.). Baseline characteristics of the study populations among included trials

Study	Country	Study design	Study group	No. of patients	Age, years	Male, n (%)	Home location of OHCA, n (%)	Medical etiology of OHCA, n (%)	NOS score
Liu et al., 2023	USA	Retrospective cohort study	Pre-pandemic	2837	64 (52–75)	1859 (65.5)	1875 (65.5)	1686 (59.4)	9
			Pandemic	3142	63 (51–75)	2005 (63.8)	2339 (74.4)	1754 (55.8)	
Liu et al., 2023b	Taiwan	Retrospective study	Pre-pandemic	567	76 (64–85)	313 (55.4)	427 (75.3)	NS	8
			Pandemic	497	78 (65–85)	292 (59.0)	384 (77.7)	NS	
Marijon et al., 2020	France	Population-based, observational study	Pre-pandemic	30,198	68.7 ± 17.9	18,668 (61.8)	22,822 (75.6)	NS	8
			Pandemic	519	69.7 ± 17.0	334 (64.4)	460 (90.2)	NS	
Ortiz et al., 2020	Spain	Secondary analysis of Spanish OHCA Registry	Pre-pandemic	1723	65.6 ± 16.9	1210 (70.2)	1042 (60.8)	NS	8
			Pandemic	1446	64.4 ± 16.5	1027 (71.0)	988 (68.3)	NS	
Phattharapornjaroen et al., 2022	Thailand	Retrospective cohort study	Pre-pandemic	76	70.0 ± 17.5	46 (60.5)	38 (50.0)	25 (32.9)	8
			Pandemic	60	65.4 ± 19.4	33 (55.0)	34 (56.7)	18 (30.0)	
Ristau et al., 2022	Germany	Epidemiological study	Pre-pandemic	5016	69.7 ± 16.9	3270 (65.2)	3145 (62.8)	3663 (73.0)	8
			Pandemic	5308	69.7 ± 16.6	3503 (65.9)	3519 (66.5)	3878 (73.1)	
Riyapan et al., 2022	Thailand	Multicentered, retrospective, observational study	Pre-pandemic	341	62.7 ± 18.5	210 (61.6)	239 (70.1)	165 (61.1)	9
			Pandemic	350	63.4 ± 19.4	208 (59.4)	259 (74.0)	155 (52.7)	
Sultanian et al., 2021	Sweden	Observational registry-based study	Pre-pandemic	930	70.8 ± 16.6	604 (64.9)	710 (76.3)	785 (90.8)	9
			Pandemic	1016	69.6 ± 17.8	697 (67.4)	784 (77.2)	640 (80.2)	
Talikowska et al., 2021	Australia	Retrospective cohort study	Pre-pandemic	501	60 (46–74)	345 (68.9)	370 (73.9)	389 (77.6)	8
			Pandemic	145	61 (46–74)	101 (69.7)	117 (80.7)	105 (72.4)	
Uy-Evanado et al., 2020	USA	Retrospective cohort study	Pre-pandemic	231	69.1 ± 17.4	137 (59.3)	145 (62.8)	NS	8
			Pandemic	278	64.9 ± 18.3	174 (62.6)	210 (75.5)	NS	
Yu et al., 2021	Taiwan	Retrospective cohort study	Pre-pandemic	570	70.9 ±16.5	353 (61.9)	453 (79.5)	NS	8
			Pandemic	622	70.4 ± 16.2	394 (63.3)	514 (82.6)	NS	

CARES — Cardiac Arrest Registry to Enhance Survival; NOS — Newcastle Ottawa Scale; NS — not specified; OHCA — out-of-hospital cardiac arrest

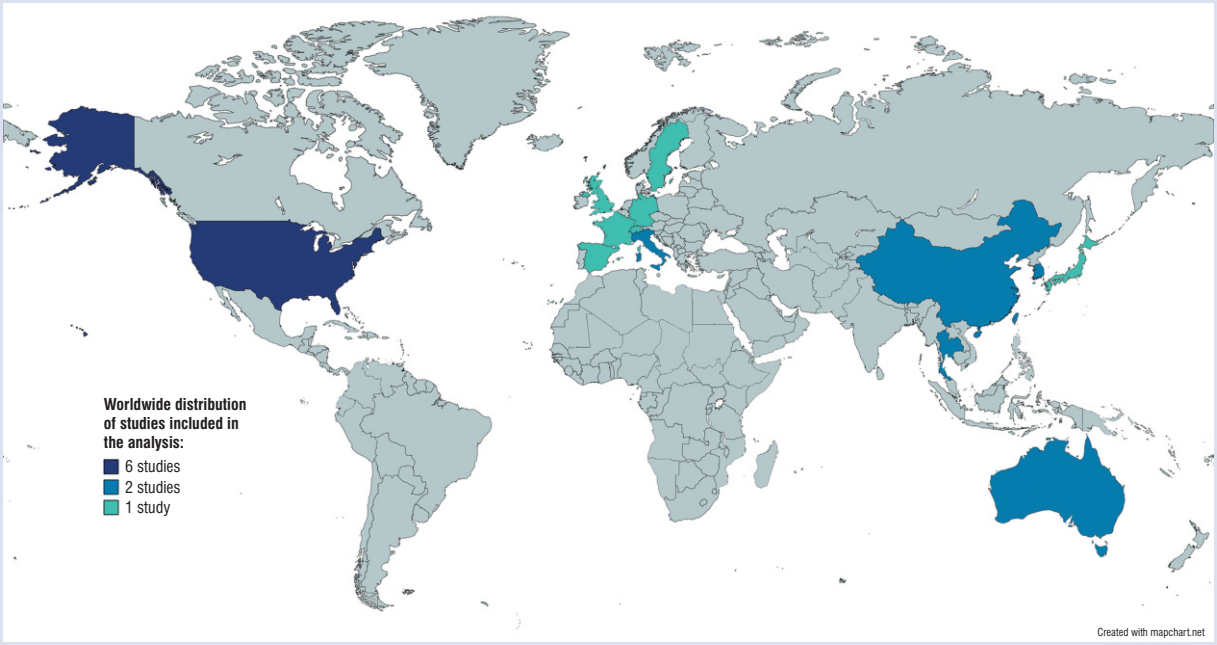

Figure 2. Global distribution of included trials

Study of subgroup	Pandemic period Events	Total	Pre-pandemic period Events	Total	Weight	Odds ratio M–H, Random, 95% CI
Baldi 2021	282	911	309	933	4.4%	0.91 [0.74, 1.10]
Baldi 2020	140	694	162	520	3.9%	0.56 [0.43, 0.73]
Ball 2021	299	380	889	1218	3.8%	1.37 [1.04, 1.80]
Biskupski 2022	16	86	10	28	1.0%	0.41 [0.16, 1.06]
Breglia 2022	37	50	28	44	1.1%	1.63 [0.67, 3.93]
Chavez 2022	1863	4418	1670	3619	4.9%	0.85 [0.78, 0.93]
Chugh 2022	467	907	742	1315	4.5%	0.82 [0.69, 0.97]
Fothergill 2021	718	1135	359	683	4.4%	1.55 [1.28, 1.88]
Hosomi 2022	16118	31894	15704	32024	5.1%	1.06 [1.03, 1.10]
Kim 2023	16145	26566	15103	25355	5.1%	1.05 [1.02, 1.09]
Lai 2020	1359	3989	441	1336	4.8%	1.05 [0.92, 1.20]
Leung 2023	701	2185	392	1502	4.7%	1.34 [1.15, 1.55]
Li 2023	722	30962	396	19027	4.8%	1.12 [0.99, 1.27]
Lim 2021	636	1063	541	891	4.5%	0.96 [0.80, 1.16]
Liu 2023	2040	3142	1180	2837	4.9%	2.60 [2.34, 2.89]
Liu 2023 (B)	299	497	300	567	4.0%	1.34 [1.05, 1.72]
Marijon 2020	239	500	10945	17972	4.5%	0.59 [0.49, 0.70]
Ortiz 2020	538	1446	788	1723	4.7%	0.70 [0.61, 0.81]
Phattharapornjaroen 2022	28	60	26	76	1.6%	1.68 [0.84, 3.37]
Ristau 2022	2112	5308	1938	5016	5.0%	1.05 [0.97, 1.14]
Riyapan 2022	119	350	133	341	3.6%	0.81 [0.59, 1.10]
Sultanian 2021	577	1016	533	930	4.5%	0.98 [0.82, 1.17]
Talikowska 2021	108	145	368	501	2.8%	1.05 [0.69, 1.61]
Uy-Evanado 2020	141	278	142	231	3.3%	0.65 [0.45, 0.92]
Yu 2021	409	622	301	570	4.1%	1.72 [1.36, 2.17]
Total (95% CI)		**118604**		**119259**	**100.0%**	**1.04 [0.93, 1.16]**
Total events	46113		53400			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 482.08$, df = 24 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: Z = 0.71 (P = 0.48)

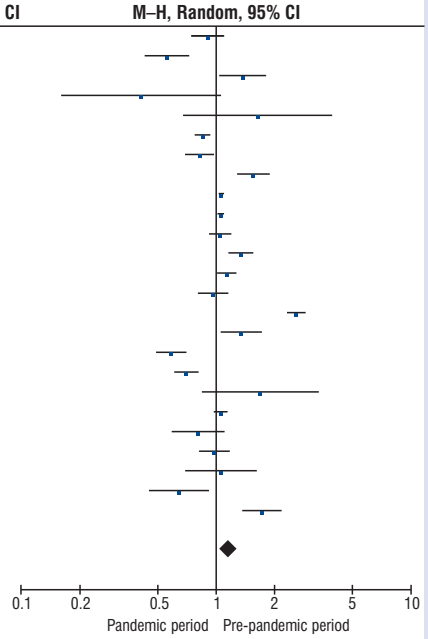

Figure 3. Forest plot of bystander cardiopulmonary resuscitation (CPR) among COVID-19 pandemic vs. pre-pandemic periods. The center of each square represents the odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

respectively, 9.9% vs. 16.5% (OR: 0.68; 95% CI: 0.59–0.78; p < 0.001). COVID-19 also influenced survival to hospital discharge as well as SHD with good neurological outcomes, which were statistically significantly worse: 7.0% vs. 10.4% (OR: 0.56; 95% CI: 0.48–0.66; p < 0.001) and 6.1% vs. 8.7%

(OR: 0.64; 95% CI: 0.54–0.77; $p < 0.001$), respectively (**Suppl. Fig. S3**).

Discussion

Our meta-analysis revealed that the incidence of bystander CPR during the COVID-19 pandemic was 38.8%, in contrast to 44.8% during the pre-pandemic era. Contrary to the prevailing view, this outcome did not exhibit statistical significance. Following the first surge of the COVID-19 pandemic, several investigations documented alterations in the occurrence of cardiac arrest and a decrease in the administration of CPR by those present at the scene [35]. Nevertheless, the findings from the following investigations remain inconclusive. Prior to the conclusion of 2020, during a span of less than 8 months after the implementation of lockdown measures, a comprehensive investigation on the relationship between COVID-19 and OHCA revealed a decrease in the rates of CPR performed by bystanders [43]. However, a meta-analysis performed in 2021 found no noticeable difference in the frequencies of bystander CPR [44]. Presently, after a duration exceeding 2 years, it is evident that these changes have yet to transpire in a substantial manner. However, we have a comprehensive understanding of the remaining factors associated with bystanders of the occurrence, which have already had a noteworthy influence. The rate of bystander witnessing significantly decreased during the pandemic in comparison to the period before the pandemic (49.9% vs. 55.3%); similarly in the case of public access defibrillator activation (5.2% vs. 5.7%), shockable rhythm (9.5% vs. 11.7%), time from EMS activation to arrival on scene, SHA (9.9% vs. 16.5%), SHD (7.0% vs. 10.4%), as well as SHD with a good neurological outcome (6.1% vs. 8.7%). COVID-19 may have altered several variables of OHCA incidence and therapy. As a result of increased remote employment and decreased availability of public transportation, the site of arrests shifted. Prior to the implementation of the lockdown measures, around 70% of instances of cardiac arrests took place inside residential dwellings [45]. Post-lockdown, many studies indicate a rise in the frequency of arrests transpiring inside residences, accompanied by a decline in the occurrence of cardiac arrests in public settings [35, 46]. Significantly, the provision of bystander CPR and the placement of AED pads had a notable drop during the COVID-19 pandemic. Possible factors contributing to this phenomenon included a reduction in the ratio of OHCA incidents transpiring in public settings and OHCA incidents being noticed by bystanders due to individuals opting to remain at home and refraining from nonessential excursions. Moreover, the need to engage in close physical contact with patients, such as when applying AED pads and doing rescue breathing, may present a challenge for witnesses. Nevertheless, experiencing a cardiac arrest at home is more likely to be witnessed by a bystander who has a personal connection to the patient. It is possible that there has previously been exposure to a potential virus in a shared living area, which implies that the fear of becoming infected with the virus may have less impact on the decision to begin CPR. EMS staff take into account whether a bystander has previously started CPR while determining if they should commence CPR. Consequently, the probability of EMS initiating resuscitation is reduced, and these factors again significantly influenced SHA and SHD.

Limitations of the study

This study has both strengths and limitations. First, the study design of the included trials in this meta-analysis, which is predominantly observational, may not establish causality between observed phenomena. Another limitation of the study is the varying numbers of patients in each study. In addition, the unique circumstances of the COVID-19 pandemic may affect the outcomes and might not be applicable to non-pandemic conditions. Uncontrolled external variables, such as changes in healthcare policies or public behavior during the pandemic, could influence the outcomes. Among the strengths of the study are its design as a meta-analysis, the timeliness of the topic, and the fact that it is the most up-to-date systematic review and meta-analysis.

Conclusions

This meta-analysis showed that the COVID-19 pandemic influenced the reduction of bystander CPR compared to the pre-pandemic period; however, the difference did not show statistical significance. Further research is needed to determine attitudes, including the fears of witnesses, to an event before undertaking CPR on a patient with a sub-pandemic or confirmed infectious disease.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author (E.S.).

Ethics statement: Given the nature of this investigation, the Ethics Committee was not relevant.

Author contributions: Conceptualization, A.K. and L.S.; methodology, A.K., K.K., and L.S.; software, N.L.B.; validation, A.K., K.K., and L.S.; formal analysis, A.K., N.L.B.; investigation, A.K., K.K., M.P., E.S., and L.S.; resources, A.K., K.K., L.S., and G.N.; data curation, A.K., N.L.B, and L.S; writing — original draft preparation, A.K., K.K., D.S., and L.S.; writing — review and editing, all authors; visualization, A.K.; supervision, K.K. and L.S.; project administration, A.K. All authors have read and agreed to the published version of the manuscript.

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Differences in coronary microcirculation measurements during regadenoson vs. adenosine — induced hyperemia

Rafał Januszek[1, 2], Wojciech Siłka[3], Natalia Bukała[3], Michał Chyrchel[1, 4], Wojciech Wańha[5], Andrzej Surdacki[1, 4], Stanisław Bartuś[1, 4]

[1]Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[2]Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[3]Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[4]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

ABSTRACT

Background: *Little is known about the similarity of microcirculation assessment outcomes performed with regadenoson and adenosine. The aim of the current study was to compare coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) assessment using adenosine and regadenoson, and to evaluate predictors regarding the size of differences.*

Methods: *44 patients were enrolled and diagnosed between 2021 and 2023. Fractional flow reserve (FFR), CFR and IMR were measured twice in the circumflex (Cx) (n = 8) or left anterior descending (LAD) (n = 36) artery: once with continuous infusion of adenosine (Adenocor 140 μg/kg/min) and 10 minutes later with regadenoson (Rapiscan 400 μg i.v.).*

Results: *Averaged results were quantified with adenosine and regadenoson for FFR (0.81 [0.75 ÷ 0.89] vs. 0.80 [0.73 ÷ 0.88]), CFR (3.84 [1.67 ÷ 4.08] vs. 3.97 [1.78 ÷ 4.32]) and IMR (20.01 [11 ÷ 24.5] vs. 20.25 [10.75 ÷ 23]), respectively. None of the differences were statistically significant. Among the significant (p < 0.05) predictors of greater ΔCFR, the following can be noted: prior percutaneous transluminal angioplasty/carotid artery stenting (β = 2.35), oral anticoagulant usage (β = 0.89), and prior stroke/transient ischaemic attack (TIA) (β = 1.09), with the latter being also confirmed for greater ΔIMR (β = 8.89). Moreover, patients with New York Heart Association (NYHA) class II/III, as compared to those with NYHA class I, were more likely to have greater ΔIMR (β = 11.89).*

Conclusions: *Regadenoson may be a feasible alternative to adenosine in coronary microcirculation assessment, as it produces similar outcomes. Selected factors were found to be predictors of greater differences in IMR, CFR and FFR values according to the agent used for coronary hyperemia.* (Cardiol J 2025; 32, 1: 19–25)

Keywords: adenosine, coronary flow reserve, fractional flow reserve, index of microcirculation resistance, regadenoson

Introduction

Assessment of coronary microvascular circulation, i.e. coronary flow reserve (CFR) and index of microcirculatory resistance (IMR), are among the most effective indicators for assessing myocardial blood supply and functional abnormalities of the coronary arteries in patients without obstructive coronary artery disease and symptomatic angina or heart failure. In multiple, heretofore published

Address for correspondence: Rafał Januszek, MD, PhD, Department of Cardiology and Cardiovascular Interventions, University Hospital in Krakow, ul. Kopernika 17, 31–501 Krakow, Poland, tel: +48 12 424 71 70, fax: +48 12 424 71 80, e-mail: jaanraf@interia.pl

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studies, the usefulness has been presented of microcirculation testing, as its outcomes are associated with patients' prognosis as well as concomitant diseases and major adverse cardiac event (MACE) occurrence in selected patient subgroups [1–7]. Moreover, such assessment could potentially provide further insight into patients' underlying disease, which regular coronary angiography often omits [8].

It is crucial for measurements to be performed correctly, i.e. under conditions of maximum passive hyperemia. To do so, adenosine infusion is considered as the gold standard. However, it may initiate side effects, such as shortness of breath, bronchospasm, flushing, chest pain and transient atrioventricular conduction block [9]. Hence, in certain subgroups of patients, such as in those with a contraindication to using adenosine, i.e. with reactive airway diseases, it is convenient to introduce regadenoson instead. It works as a more selective agent and can be administrated as a simple bolus via peripheral line. Therefore, it provokes a smaller number of side effects [9]. Importantly, regadenoson was proved to be equivalent to adenosine for FFR assessment [10, 11]. However, there are concerns regarding its feasibility in the CFR and IMR assessments. Studies reported that regadenoson-induced hyperemia is stable, similar to adenosine time-wise, and produces fewer side effects in patients with stable coronary artery disease (CAD) [9, 12]. However, there is a lack of solid data on measurement similarity with adenosine, and overall, the data regarding regadenoson usage during an invasive microcirculatory assessment remains insufficient.

The current study was aimed at identifying whether adenosine and regadenoson used for hyperaemia deliver similar results, and as well other factors, which can influence the difference in FFR, CFR and IMR measurements — using adenosine or regadenoson.

Methods

Population

Coronary microcirculation measurements were analyzed in 44 patients admitted to the invasive cardiology department from 2021 to 2023 with a suspicion of CAD. Patients with indications for physiologically-guided assessment of coronary lesions (with a stenosis of 40 to 80% on visual examination) were eligible for the study. All participants provided their written informed consent. The bioethics committee of the documented university approved the study design (No. 1072.6120.27.2022). The study was conducted in line with the 1964 Declaration of Helsinki.

Physiological examination of coronary arteries with use of adenosine and regadenoson

The examination of the coronary microcirculation was performed during a single angiographic procedure. The FFR, IMR and CRF were measured twice on the same artery. Angiography was performed in the 8 circumflex coronary arteries (Cx) and in the 36 left anterior descending coronary arteries (LAD).

To achieve maximal hyperemia, continuous infusion of adenosine via a peripheral vein was administrated at the dosage of 140 μg/kg/min. Measurements were taken using the dedicated Abbott PressureWire™ X pressure guidewire (Abbott Vascular, Santa Clara, CA). FFR was calculated as the lowest average distal pressure (Pd)/aortic pressure (Pa) from 3 consecutive heartbeats during maximal hyperemia. CFR was calculated as the ratio of mean transit time (Tmn) at rest/hyperemic Tmn, whereas IMR was calculated from the Pd × Tmn equation determined during hyperemia. After the cessation of adenosine, i.e., 10 minutes, a regadenoson test was performed. To achieve maximal hyperemia in this case, 400 μg of regadenoson (Rapiscan 1 amp. 400 mcg, GE Healthcare AS, Nycoveien 1, Norway) was administrated through the peripheral line as a 4-mL bolus (10-second-long infusion) followed by a 10-mL NaCl flush.

Statistical analysis

The analysis of quantitative variables was carried out by calculating the mean, standard deviation, median and quartiles. Analysis of qualitative variables was performed by calculating the number and percentage of occurrences for each value. Univariate analyses of the effect of each potential variable predictor on ΔFFR, ΔCFR and ΔIMR (quantitative variables) were performed using linear regression. The results were presented as regression model parameter values. The normality of variable distribution was checked using the Shapiro–Wilk test. Comparisons regarding the values of quantitative variables in two repeated measures was performed using the Wilcoxon paired t-test. A non-parametric test was used because the differences in the studied parameters were not normally distributed. The analysis assumed a significance level of 0.05. Thus, all p-values

below 0.05 were interpreted as indicating significant relationships. Analysis was performed using the R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/).

Results

General characteristics

The study included 44 patients (37 males) undergoing coronary angiography, and their general characteristics are shown in Tables 1 and 2. The mean age of the population was 66.82 (± 8.02) years. The majority of patients clinically presented with Canadian Cardiovascular Society (CCS) 1 (54.5%), whereas half of study group had New York Heart Classification (NYHA) class II or above (50%). In terms of cardiovascular risk factors, most patients displayed arterial hypertension (86.4%) and hyperlipidemia (79.6%). Furthermore, prior percutaneous coronary intervention (PCI) (63.6%) and myocardial infarction (MI) in (56.8%) were frequent in the studied population. There were also 16 (36.4%) patients with a history of nicotine dependence in their medical records. Almost one-third of the patients (29.6%) presented symptoms of heart failure and diabetes mellitus. Furthermore, more than half of the patients had evinced hypokinesia during routine echocardiography, while mean left ventricle ejection fraction (LVEF) totalled 46.8 ± 15.2% (Table 3).

Biochemical indices

As is shown in Table 4, there were no abnormalities found in the investigated biochemical indices among the study group.

Pharmacotherapy

By analyzing medical records, almost all patients received acetyl-salicylic acid (ASA; 88.6%) and statins (84.1%) at baseline. As the vast majority of the patients were struggling with arterial hypertension, most of them had taken at least 2 blood-pressure-lowering drugs such as beta-blockers (75.0%), angiotensin-converting enzyme inhibitors (ACEIs; 61.4%), diuretics (31.8%) and calcium channel blockers (CCBs; 25.0%). What is worth mentioning, almost half of the study group had taken proton-pump inhibitors (PPIs; 47.7%). Selected patients received $P2Y_{12}$ inhibitors (18.2%), oral anticoagulants (OACs; 15.9%) and clopidogrel (15.9%). More details are shown in Table 5.

Table 1. Baseline characteristic of patients

Selected indices	Overall group n = 44
Age [years]	66.82 (± 8.02)
Male sex, (n) %	37 (84.09%)
Body mass index [kg/m^2]	27.72 (24.9–30.17)
Hospitalisation time [days]	3 (2.0–5.25)
SBP [mmHg]	139.39 (± 22.2)
DBP [mmHg]	83.55 (± 11.48)
Heart rate	71.27 (± 13.53)
NYHA class	
I	17 (38.64%)
II	9 (20.45%)
II/III	4 (9.09%)
III	9 (20.45%)
CCS class	
I	24 (54.54%)
II	9 (20.45%)
II/III	2 (4.55%)
III	3 (6.82%)
III/IV	1 (2.27%)

All data are expressed as absolute numbers (percentages), means (± SD) or medians (Q1–Q3). CCS — C anadian Cardiovascular Society; DBP — diastolic blood pressure; NYHA — New York Heart Association; SBP — systolic blood pressure

Table 2. Clinical characteristic of patients

Selected indices	Overall group n = 44
CAD	41 (93.18%)
Arterial hypertension	38 (86.36%)
Hyperlipidaemia	35 (79.55%)
Overweight	30 (68.18%)
Prior PCI	28 (63.64%)
Prior MI	25 (56.82%)
Smoking	16 (36.36%)
Diabetes myelitis	13 (29.55%)
Heart failure	13 (29.55%)
Atrial fibrillation	8 (18.18%)
Stroke/TIA	5 (11.36%)
Prior PTA/CAS	4 (9.09%)
Kidney failure	4 (9.09%)
Hypothyroidisms	4 (9.09%)

All data are expressed as absolute numbers (percentages).
CAD — coronary artery disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; PTA/CAS — percutaneous transluminal angioplasty/carotid artery stenting; TIA — transient ischemic attack

Table 3. Echocardiography parameters

Selected indices	Overall group n = 44
LVEF [%]	46.77 (± 15.15)
Akinesia	14 (31.82%)
Hypokinesia	23 (52.27%)

All data are expressed as absolute numbers (percentages) and mean (± SD). LVEF — left ventricle ejection fraction

Table 4. Biochemical indices

Selected indices	Overall group n = 44
Total cholesterol [mmol/L]	3.75 (3.2–4.45)
LDL [mmol/L]	1.9 (1.4–2.55)
HDL [mmol/L]	1.1 (1–1.32)
TG [mmol/L]	1.3 (0.98–2.26)
Creatinine [μmol/L]	94.2 (76.33–110.5)
MDRD eGFR [mL/min/1.73m^2]	68.5 (61–89.25)
TSH [μIU/mL]	1.39 (0.98–2.14)
WBC [10^3/μL]	8.27 (± 2.23)
RBC [10^6/μL]	4.6 (± 0.48)
HGB [g/dL]	14.21 (± 1.4)
HCT [%]	41.75 (38.75–43.42)
PLT [10^3/μL]	219 (193.5–256.25)

All data are expressed as absolute numbers (percentages), means (± SD) or medians (Q1–Q3). eGFR — estimated glomerular filtration rate; HCT — hematocrit; HDL — high-density lipoprotein; HGB — hemoglobin; LDL — low-density lipoprotein; MDRD, RBC — red blood cells; PLT — platelets; TG — triglycerides; TSH — thyroid stimulating hormone; WBC — white blood cells

Table 5. Pharmacotherapy

Selected indices	Overall group n = 44
ASA	39 (88.64%)
Statin	37 (84.09%)
Beta-blocker	33 (75%)
ACEI	27 (61.36%)
PPI	21 (47.73%)
Diuretic	14 (31.82%)
CCB	11 (25%)
P2Y$_{12}$ inhibitor	8 (18.18%)
OACs	7 (15.91%)
Clopidogrel	7 (15.91%)
Insulin	6 (13.64%)
Levothyroxine	2 (4.55%)

All data are expressed as absolute numbers (percentages). ACEI — angiotensin-converting enzyme inhibitors; ASA — acetylsalicylic acid; CCB —calcium channel blockers; OAC — oral anticoagulants; PPI — proton-pump inhibitors

Comparison between regadenoson and adenosine in FFR, CFR and IMR values

Measurements were conducted in the LAD (n = 36) and Cx arteries (n = 8). The median FFR was high in both cases, when using adenosine and regadenoson (0.81 [0.75 ÷ 0.89] and 0.80 [0.73 ÷ 0.88], respectively). No significant differences were noted between FFR, CFR and IMR values in the compared study groups (Fig. 1). The difference between measurements with adenosine and regadenoson proceeded on the same artery were: ΔFFR = 0.02 (0.01 ÷ 0.04), ΔCFR = 0.6 (0.29 ÷ 1.55) and ΔIMR = 3.5 (1.38 ÷ 7.1) (Tab. 6).

Factors related to change between coronary circulation measurements when using adenosine vs. regadenoson — linear regression models

It was revealed that CAD presence and ASA usage were significant predictors of smaller absolute ΔFFR between compared microcirculation methods (β = –0.06, p = 0.006 and β = –0.03, p = 0.046, respectively; Fig. 2). On the other hand, prior percutaneous transluminal angioplasty/ /carotid artery stenting (PTA/CAS) was proved to be a significant predictor of increased ΔFFR (β = 0.046, p = 0.01; Fig. 2).

When considering ΔCFR, the following predictors of its change could be observed: CAD (β = –2.15, p < 0.001), prior PTA/CAS (β = 2.35, p < 0.001), history of stroke/transient ischemic attack (TIA) (β = 1.09, p = 0.03), ASA and OACs usage (β = –1.31, p = 0.009 and β = 0.89, p = 0.04, respectively). Furthermore, on average, for every increase in left ventricle ejection fraction by 1%, the ΔCFR decreased by 0.02 (β = –0.02, p = 0.049, Fig. 2).

Similar to previous results, the use of ASA was related to reduced ΔIMR (β = –8.66, p = 0.03), whereas a history of stroke/TIA predicted an increment in ΔIMR (β = 8.9, p = 0.03). Moreover, as compared to NYHA I class, the presence of II/III class was also related to increased absolute ΔIMR (β = 11.89, p = 0.02; Fig. 2).

Discussion

Contrary to the assessment of FFR, there is limited data regarding regadenoson usage in microcirculation coronary circulation assessments. The present analysis is one of the first to provide insight into this issue. The main findings of the current study are as follows:

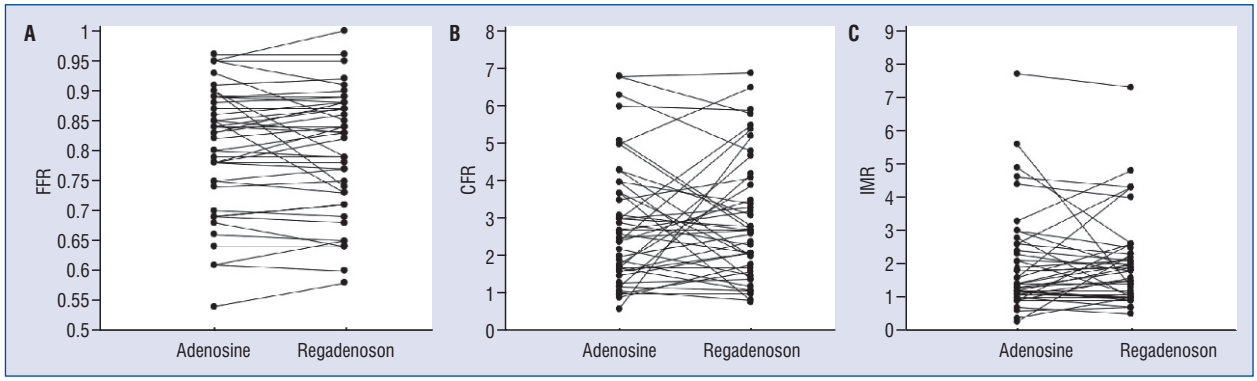

Figure 1. Coronary functional assessment with use of regadenoson and adenosine. Panels **A**, **B**, and **C** show results of measurements (fractional flow reserve [FFR], coronary flow reserve [CFR], and index of microcirculatory resistance [IMR], respectively) in each patient (n = 44) performed with adenosine and regadenoson subsequently. Differences between averaged values obtained using adenosine and regadenoson did not reach statistical significance (p = 0.459 for panel **A**, p = 0.964 for panel **B** and p = 0.745 for panel **C**)

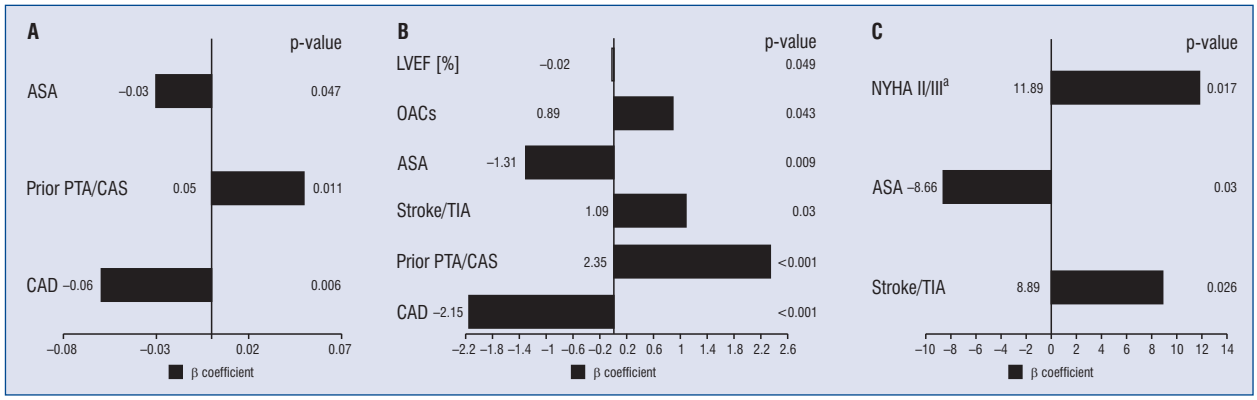

Figure 2. Predictors of change size in coronary circulation measurement values assessed using adenosine vs. regadenoson — linear regression models. **A.** Beta coefficients regarding predictors of ΔFFR; **B.** Beta coefficients regarding predictors of ΔCFR; **C.** Beta coefficients regarding predictors of ΔIMR. [a]As compared to NYHA class I. ASA — acetylsalicylic acid; CAD — coronary artery disease; CAS — carotid artery stenting; CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of microcirculatory resistance; LVED — left ventricle ejection disease; NYHA — New York Heart Association; OAC — oral anticoagulants; PTA — peripheral transluminal angioplasty; TIA — transient ischemic attack

Table 6. Quantitative differences in outcomes of coronary functional assessment with use of regadenoson vs. adenosine

Parameter	Overall group (n = 44)
ΔFFR	0.02 (0.01–0.04)
ΔCFR	0.6 (0.29–1.55)
ΔIMR	3.5 (1.38–7.1)

All data are expressed as median (Q1–Q3). CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of microcirculatory resistance

1. There were no significant differences in the average FFR, CFR or IMR values in assessments with regadenoson as compared to adenosine;
2. Heightened differences in the microcirculatory measures were predicted by the following: history of stroke/TIAs, prior PTA/CAS, OACs usage, more advanced NYHA class;
3. Treatment with ASA and a diagnosis of CAD at baseline as well as LVEF values were predictors of decreased differences in microcirculatory assessments obtained with regadenoson and adenosine.

In general, regadenoson is a selective agonist of A_{2a} receptors, which along with its reversibility, is associated with a lower risk of adverse effects among patients. This also included those with comorbidities, and overall, contraindications to regular adenosine usage [13]. Moreover, in other studies, it has been

reported that maximal hyperemia can be achieved faster with regadenoson, underscoring further the favorable outcomes of its usage [14]. This, sequentially, in light of the facts that its infusion preparation and administration are simpler than Adenosine infusion, reduces time spent in catheterization laboratory as well [9, 15]. Despite the aforementioned advantages, regadenoson poses several limitations. Firstly, its implementation may produce higher costs [16]. Moreover, the necessity for reliable microcirculatory assessment stability of hyperaemia induced by this agent is still a subject of debate. This is due to the fact that regadenoson was reported to have a varying duration of hyperemic effect, which considering guidelines recommending its single-dose administration, produce uncertainty whether the operator was provided enough time to perform a reliable assessment [17]. Therefore, in patients characterised with complex lesions necessitating multiple coronary flow measurements and additional pullback recordings, adenosine remained superior.

Regarding FFR, the present study confirms a lack of significant differences between the adenosine and regadenoson approach. The reliability of the latter in FFR measurements has been reported in a number of other studies [9–12, 17–20]. For instance, in a study conducted by Nair et al., the authors revealed excellent correlations between regadenoson and adenosine in lesion assessment ($r = 0.99$, $p < 0.001$) [10].

Given the results of the current study, it can be concluded that regadenoson is a valid tool in invasive coronary flow and IMR testing among patients with high FFR (averaged on the whole population). However, as several predictors of larger disparities between two hyperemia-inducing agents were indentified, the reproducibility of our results in other clinical situations are called to question. Since we did not explore the characteristics of these changes regarding the value in measurements between adenosine *vs*. regadenoson testing, the discussion at this point should be extrapolated carefully. It was observed, for example, that a history of stroke/TIA, prior PTA/CAS and higher NYHA class were significant predictors of increased discrepancies between investigated hyperemia-inducing agents. It may be the case that the epicardial and microcirculatory flows among patients characterized by a more serious "clinical burden" were more prone to changes, given the fact that the procedure was prolonged. Overall, to decisively confirm regadenoson feasibility, more focus needs to be placed on specific patient cohorts as well as and specific lesion characteristics, which the present study lacked.

Despite the fact that the means of measurements for IMR and CFR do not significantly differ statistically, insight into the pairs shows that some of the measurements differed dramatically depending on the use of regadenoson or adenosine for the induction of passive hyperemia. There are certainly a number of factors beyond those found to be significant in the statistical analysis, and from present observations, these certainly include hemodynamic conditions that change throughout the study. It should be noted that the regadenoson and adenosine assays were performed at least 10 minutes apart. During this time, some patients' blood pressure changed, some calmed down during the examination, while some began to get nervous, e.g. due to back pain or to other parts of the skeletal system. Another factor that affects the hemodynamic of circulation is the temperature in the laboratory, which in many patients, causes a feeling of cold and the consequences associated with it. Another problem is keeping the guidewire in the same place in both chambers. While waiting for the next measurement, the guidewire often migrates with consecutive heartbeats, and it becomes necessary to correct the guidewire position before subsequent measurements.

To sum up, it is often not possible to create the same hemodynamic conditions for both measurements, which could certainly have influenced the obtained results. This occurs despite the determinations being made by experienced operators.

Limitations

There are some limitations of the present study, including the relatively small group of studied patients, although sufficient statistical power was achieved to draw the discussed conclusions. Furthermore, focus was not put onto differentiating whether the change in differences between adenosine and regadenoson testing was due to the former or latter agent while considering a predicting factor. Nevertheless, the envisaged hope is that there will be a further continuation of the study and enlargement of the study group.

Conclusions

From the preliminary findings, it can be suggested that regadenoson is a feasible alternative to adenosine in microcirculation assessment, as it produces similar outcomes. Selected factors were found to be predictors of greater differences in

IMR, CFR and FFR values according to the agent used for coronary hyperemia.

Data availability statement: Data are available on special request.

Ethics statement: The study was approved by the local bioethics committee and was conducted in line with the 1964 Declaration of Helsinki.

Author contributions: R.J. — conducting the study, gathering data, preparing manuscript, organising statistician, supervising, S.B., R.J — projecting the study, W.S., N.B. — preparing and gathering data, writing draft of the manuscript, A.S., W.W. — editing manuscript, supervising.

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Conflict of interest: None declared.

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The impact of shock therapy on depression development and remote prognosis in cardiac resynchronization therapy recipients

Tomasz Podolecki[1, 2], Robert Pudlo[3], Michał Mazurek[2], Monika Kozieł-Siołkowska[2], Joanna Boidol[2], Oskar Kowalski[2], Radosław Lenarczyk[1, 2], Zbigniew Kalarus[1, 2]

[1]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Silesian Center for Heart Diseases in Zabrze, Poland
[3]Department of Psychiatry, Medical University of Silesia, Tarnowskie Gory, Poland

Abstract

Background: *The aim of this study was to assess the incidence and clinical significance of depression in patients with cardiac resynchronization therapy with an implantable cardioverter-defibrillator (CRT-D). The study was also to evaluate the impact of shock therapy on depression development and long-term prognosis.*

Methods: *The prospective study encompassed 396 consecutive heart failure (HF) patients implanted with CRT-D. All patients completed the Beck Depression Inventory (BDI-II) and underwent a psychiatric examination at baseline. 221 patients free of depressive symptoms at baseline were included into the final analysis. The assessment of psychiatric status was routinely repeated every 6 months as well as after the shock delivery. The primary outcome was a composite endpoint of death or hospitalization for HF.*

Results: *During long-term observation (median 37.1 months) 52 (23.5%) patients suffered from an implantable cardioverter-defibrillator (ICD) shock, whereas 48 (21.8%) subjects developed depression. The incidence of new-onset depression was significantly higher in patients after shock delivery (Shock Group), CRT non-responders and subjects with atrial fibrillation. The risk for a composite endpoint was higher in the Shock Group than subjects without an ICD intervention: 57.7% vs. 25.4% and in patients with new-onset depression compared to the population free of this disorder: 62.5% vs. 24.9% (all $p < 0.001$). New-onset depression (HR 1.7) and an ICD shock (HR 2.1) were strong independent predictors of poor prognosis.*

Conclusions: *Depression is a common mental disorder in CRT-D recipients, that adversely affects long-term prognosis. Subjects suffering from ICD shocks and those with HF progression are at higher risk of experiencing depressive symptoms.* (Cardiol J 2025; 32, 1: 26–34)

Keywords: depression, chronic heart failure, resynchronization therapy, implantable cardioverter-defibrillator, shock therapy

Address for correspondence: Tomasz Podolecki, MD, PhD, Silesian Centre for Heart Diseases in Zabrze, ul. M. Curie-Skłodowskiej 9, 41–800 Zabrze; tel: +48 32 47 93 353, e-mail: tomekpod@interia.pl

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Introduction

Chronic heart failure (HF) is associated with a significantly increased prevalence of depression, anxiety and other mood disorders [1–4]. It is estimated that around 30–40% of HF patients are burdened with a concomitant depressive syndrome, and the severity of HF symptoms is associated with higher probability of development of mood disorders [2, 5]. According to previous studies, depression may deteriorate HF symptoms leading to even a 3-fold increase in mortality [6–9]. However, there are very poor data concerning the incidence of new-onset depression in patients with severe HF who were implanted with a cardiac resynchronization therapy defibrillator (CRT-D).

The beneficial effect of an implantable cardioverter-defibrillator (ICD) therapy on reducing the risk of sudden cardiac death (SCD) in patients with HF and significantly reduced left ventricular ejection fraction (LVEF) is incontrovertible [10, 11]. However, ICD shocks have also been reported to be associated with the increased mortality [12, 13]. Additionally, ICD interventions may potentiate psychological distress, impair daily activities and lead to reduced quality of life [14, 15]. Whereas, there are poor and conflicting data on the impact of ICD shocks on the development or deterioration of pre-existing depression [16, 17].

Therefore, the primary aim of this study was to assess the incidence and clinical significance of depression that developed in CRT-D recipients. The secondary aim was to evaluate the impact of ICD shocks on depression development and long-term prognosis.

Methods

A single-center, prospective, non-randomized study was conducted at the Department of Cardiology, Congenital Heart Diseases and Electrotherapy of the Silesian Center of Heart Diseases (Zabrze, Poland). From January 2012 to December 2018 every HF patient admitted for the first-time CRT-D implantation was screened for potential participation in the study.

The inclusion criteria were as follows:

1. A first-time CRT-D implantation according to the guidelines of the European Society of Cardiology [18, 19];
2. Age range of 18-80 years;
3. Signed informed consent.

The exclusion criteria encompassed:

1. Simultaneous participation in other clinical studies;
2. A prior stroke or head injury with severe neurological deficit;
3. Epilepsy;
4. Parkinson's disease;
5. Dementia, amnesic syndrome, delusional disorders or hallucinations;
6. Alcohol or drug abuse;
7. Already diagnosed (pre-existing) recurrent depressive or bipolar disorders;
8. Schizophrenia;
9. Inability to undertake follow-up (FU) visits.

Out of 396 consecutive CRT-D patients recruited into the study as many as 233 subjects free of depression symptoms were eligible for further analysis. Among them 12 patients did not complete any FU visits (2 died before the first visit whereas 10 subjects were lost to FU), hence, 221 patients were included into the final analysis. Patients who experienced *de novo* depressive symptoms during long-term observation comprised the Depression Group, while the rest of the patients constituted the Depression-free Group. Moreover, the whole population was divided on account of an ICD shock — subjects who suffered from shock therapy were included into the Shock Group, whereas the others represented the Control Group.

Prior to CRT-D implantation, all patients had undergone a two-stage psychiatric evaluation. In addition to a psychiatric examination by one of two experienced psychiatrists (study co-investigators), every patient had to complete two self-report questionnaires: the Beck Depression Inventory (BDI) and the EQ-5D scale. The EQ-5D scale is a standardized measure of health status, consisting of the descriptive system and visual analogue scale. The EQ-5D descriptive system assesses five domains: self-care, mobility, usual activities, pain/discomfort and anxiety/depression. There are 3 statements concerning every domain and a patient is to indicate the most appropriate one in each of the 5 domains. Whereas the EQ-5D visual scale records a patient's self-rated health on an analogue scale (range from 0 — the worst imaginable health state, to 100 — the best imaginable health state). The BDI includes 21 questions concerning a patient's mental state during the previous week — a patient is to indicate one of four answers (range from 0 to 3) for each question.

Additionally, all patients underwent clinical assessment, including physical examination, 12-lead electrocardiogram (ECG) and transthoracic echocardiography (TTE) at enrollment.

Depression was diagnosed according to the criteria of the Diagnostics and Statistical Manual of Mental Disorders (DSM-IV) [20].

Routine follow-up visits were performed at 3 (± 1 week), 6 (± 2 weeks) and 12 months (± 2 weeks) after the procedure, and every 6 months (± 2 weeks) thereafter. The median follow-up was 37.1 months (range: 3.2–79.4 months). Every follow-up visit consisted of a history taken with NYHA (New York Heart Association) class re-assessment, physical examination and device check-up — data concerning CRT-D functioning, including pacing thresholds, occurrence of ventricular/supraventricular tachycardia, antitachycardia pacing or appropriate/inappropriate shocks were obtained during a device interrogation. Psychiatric evaluation including questionnaire completion was repeated during every follow-up visit. Additionally, a standard transthoracic echocardiogram (TTE) was repeated at 12-month follow-up visit.

The primary endpoint was a major adverse cardiac event (MACE), defined as a composite of hospitalization for decompensated HF and all-cause mortality. Data on potential MACEs were collected during scheduled visits, *via* telephone calls from patients or their relatives, from hospital records and death certificates, as well as from records obtained from the insurer — the National Health Fund. The secondary endpoint was defined as the development of depression in patients with no history of depressive symptoms before the study enrollment.

Patients were considered to be CRT responders if a decrease of at least 1 NYHA class (clinical response) was observed or an increase in left ventricular ejection fraction (LVEF) of more than 5% (echocardiographic response) was documented 12 months after a CRT-D implantation.

Categorical variables were expressed as number and percentage, whereas continuous parameters as mean ± standard deviation (SD). The comparative analysis between groups was performed with the Student t-test for continuous parameters, and the Chi-square or Fisher exact test, as appropriate, were used for dichotomous variables. The independent MACE predictors were identified with the multivariate Cox-regression model and expressed as hazard ratio (HR) with 95% confidence interval (CI). All parameters which differed significantly between patients who developed MACE and those free of MACE were considered covariates in the multivariate analysis. Cumulative proportions of patients free of MACE were plotted as Kaplan–Meier survival curves and compared with log-rank tests between different categories. P value < 0.05 was considered statistically significant. The software package Statistica (version 13.1, StatSoft Inc., Tulsa, OK, USA) was used for statistical analysis.

The Medical Ethics Committee of the Silesian Medical University approved the study protocol. The study was conducted according to the ethical guidelines of the Declaration of Helsinki.

Device settings

Pacing and antiarrhythmic settings of CRT devices were programmed identically in all patients. Pacemakers were set into DDD mode (except for patients with permanent atrial fibrillation [AF]) with a lower pacing rate of 50 beats per minute (bpm). Two detection zones were programmed for ventricular arrhythmias: ventricular tachycardia zone (VT > 170 bpm) and ventricular fibrillation zone (VF > 214 bpm). Pre-discharge settings were maintained throughout the whole follow-up period and no routine reprogramming was allowed unless clear indications occurred (for example: low CRT pacing or inappropriate ICD therapies due to AF).

Results

During long-term observation 52 (23.5%) patients had at least one high-energy ICD intervention. The incidence of AF was the only parameter that differed significantly between subjects from the Shock Group and those free of shock therapy: 59.6% vs. 41.4%, respectively ($p < 0.05$). Among 221 patients free of depression symptoms at baseline 48 (21.8%) developed depressive symptoms during long-term follow-up. The rate of new-onset depression was significantly higher in patients with AF, poorer CRT response and those with an increase of at least 1 NYHA class (all $p < 0.05$). Moreover, the risk of depression was increased 5-fold in subjects after an ICD shock compared to the population free of high-energy intervention ($p < 0.001$). The baseline characteristics of these groups were summarized in Tables 1 and 2.

According to the multivariate analysis only an ICD shock (HR 3.4) and increase in NYHA class by at least one class (HR 1.9) were independent predictors of depression development.

Patients who experienced MACE during long-term observation had significantly lower LVEF, higher NYHA class and were more often burdened with AF in comparison with patients free of MACE (all $p < 0.05$). Moreover, an ICD

Table 1. The baseline characteristics of the Shock Group and Control Group

Parameter	Shock Group (n = 52)	Control Group (n = 169)	P-value
Male, n [%]	40 (76.9)	133 (78.7)	NS
Age [years]	65.6 ± 10.6	64.2 ± 12.9	NS
Ischaemic CHF, n [%]	36 (69.2)	119 (70.4)	NS
NYHA class	2.66 ± 0.45	2.56 ± 0.53	NS
Diabetes mellitus, n [%]	23 (44.2)	71 (42.0)	NS
Arterial hypertension, n [%]	28 (53.9)	100 (59.2)	NS
AF total, n [%]	31 (59.6)	70 (41.4)	< 0.05
COPD, n [%]	7 (13.5)	19 (11.2)	NS
Hypothyroidism, n [%]	8 (15.4)	24 (14.2)	NS
QRS duration [ms]	157.3 ± 14.3	160.9 ± 13.9	NS
LVEF [%]	26.4 ± 7.8	27.3 ± 8.9	NS
LVEF < 20%, n [%]	13 (25.0)	31 (18.3)	NS
Moderate MR, n [%]	19 (36.5)	57 (33.7)	NS
Severe MR, n [%]	8 (15.4)	20 (11.8)	NS
CRT pacing, n [%]	95.11 ± 6.47	96.25 ± 5.62	NS
CRT responders, n [%]	38 (73.1)	142 (84.0)	NS
Beta-blocker, n [%]	49 (94.2)	164 (97.0)	NS
ACE-I/ARB, n [%]	46 (88.5)	154 (91.1)	NS
Loop diuretics, n [%]	47 (90.4)	152 (89.9)	NS

ACE-I/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF — atrial fibrillation; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronization therapy; LVEF — left ventricle ejection fraction; MR — mitral regurgitation; NYHA — New York Heart Association

Table 2. The baseline characteristics of the Depression Group and Depression-free Group

Parameter	Depression Group (n = 48)	Depression-free Group (n = 173)	P-value
Male, n [%]	38 (79.2)	135 (78.0)	NS
Age [years]	65.6 ± 10.1	64.3 ± 12.4	NS
Ischemic CHF, n [%]	33 (68.8)	122 (70.5)	NS
NYHA class at baseline	2.64 ± 0.51	2.57 ± 0.44	NS
Change in NYHA class:			
improved by at least 1 class, n [%]	20 (41.7)	114 (65.9)	< 0.05
worsened by at least 1 class, n [%]	12 (25.0)	14 (8.1)	< 0.05
Diabetes mellitus, n [%]	22 (45.8)	72 (41.6)	NS
Arterial hypertension, n [%]	26 (54.2)	102 (59.0)	NS
AF total, n [%]	30 (62.5)	78 (45.1)	< 0.05
ICD shock, n [%]	30 (62.5)	22 (12.7)	< 0.001
COPD, n [%]	5 (10.4)	21 (12.1)	NS
Hypothyroidism, n [%]	9 (18.8)	23 (13.3)	NS
QRS duration [ms]	160.1 ± 11.4	157.6 ± 13.5	NS
LVEF [%]	26.7 ± 9.0	27.2 ± 8.6	NS
LVEF < 20%, n [%]	9 (18.8)	35 (20.2)	NS
Moderate MR, n [%]	18 (37.5)	58 (33.7)	NS
Severe MR, n [%]	5 (10.4)	23 (13.3)	NS
CRT pacing [%]	92.8 ± 8.1	96.9 ± 7.4	< 0.05
CRT responders, n [%]	31 (64.6)	149 (86.1)	< 0.05
Beta-blocker, n [%]	46 (95.8)	167 (96.5)	NS
ACE-I/ARB, n [%]	43 (89.6)	157 (90.8)	NS
Loop diuretics, n [%]	44 (91.7)	155 (89.6)	NS

ACE-I/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF — atrial fibrillation; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator; LVEF – left ventricle ejection fraction; MR — mitral regurgitation; NYHA — New York Heart Association

Table 3. The baseline characteristics of patients who experienced MACE and those free of MACE

Parameter	MACE Group (n = 73)	MACE-free Group (n = 148)	P-value
Male, n [%]	59 (80.8)	114 (77.0)	NS
Age [years]	65.9 ± 8.9	63.9 ± 11.7	NS
Ischemic CHF, n [%]	53 (72.6)	102 (68.9)	NS
NYHA class	2.77 ± 0.39	2.49 ± 0.48	< 0.001
Diabetes mellitus, n [%]	35 (47.9)	59 (39.8)	NS
Arterial hypertension, n [%]	43 (58.9)	85 (57.4)	NS
AF total, n [%]	44 (60.3)	57 (38.5)	< 0.05
ICD shock, n [%]	30 (41.1)	22 (14.9)	< 0.001
COPD, n [%]	9 (11.8)	17 (11.5)	NS
Hipothyroidism, n [%]	12 (12.3)	20 (13.5)	NS
Depression *de novo*, n [%]	30 (41.1)	18 (12.2)	< 0.001
QRS duration [ms]	160.4 ± 11.5	159.7 ± 12.8	NS
LVEF [%]	25.1 ± 9.2	28.1 ± 8.7	< 0.05
LVEF < 20%, n [%]	22 (30.1)	22 (14.9)	< 0.05
Moderate MR, n [%]	28 (38.4)	48 (32.4)	NS
Severe MR, n [%]	15 (20.6)	13 (8.8)	< 0.05
CRT pacing [%]	93.36 ± 9.69	96.5 ± 7.38	< 0.05
CRT responders, n [%]	51 (69.9)	129 (87.2)	< 0.05
Beta-blocker, n [%]	71 (97.3)	142 (96.0)	NS
ACE-I/ARB, n [%]	65 (89.0)	135 (91.2)	NS
Loop diuretics, n [%]	67 (91.8)	132 (89.2)	NS

ACE-I/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF – atrial fibrillation; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronization therapy; LVEF — left ventricle ejection fraction; MR — mitral regurgitation; NYHA — New York Heart Association

Table 4. Twelve-month and long-term prognosis in the Depression Group and Depression-free Group

Parameter	Depression Group (n = 48)	Depression-free Group (n = 173)	P-value
12-month follow-up			
Mortality, n [%]	3 (6.3)	8 (4.6)	NS
DHF, n [%]	7 (14.6)	13 (7.5)	NS
MACE, n [%]	9 (18.8)	18 (10.4)	NS
Long-term follow-up			
Mortality, n [%]	10 (20.8)	19 (11.0)	0.074
DHF, n [%]	24 (50.0)	31 (17.9)	< 0.001
MACE, n [%]	30 (62.5)	43 (24.9)	< 0.001

DHF — hospitalization for decompensated heart failure; MACE — major adverse cardiac event

shock and new-onset depression were associated with significantly higher risk of MACE (both $p < 0.001$). Additionally, poorer prognosis was more likely in CRT non-responders and patients with severe mitral regurgitation (MR) (all $p < 0.05$). The baseline characteristics of these groups are shown in Table 3.

The risk for a composite endpoint was significantly higher in the Shock Group than in the Control Group: 57.7% vs. 25.4% ($p < 0.001$), as well as in patients with new-onset depression compared to the population free of this disorder: 62.5% vs. 24.9% ($p < 0.001$). However, the incidence of MACE was the highest in patients from the Shock Group with concomitant depression, as it was nearly a 3-fold increase in comparison with subjects from the Control Group: 70.0% vs. 25.4% ($p < 0.001$), and over a 3-fold increase when compared to patients free of an ICD shock and depression: 70.0% vs. 22.5%, respectively ($p < 0.001$). The data on clinical outcomes were presented in Tables 4 and 5 as well as in Figure 1.

Table 5. Twelve-month and long-term prognosis in the Shock Group and Control Croup

Parameter	Shock Group (n = 52)	Control Group (n = 169)	P-value
12-month follow-up			
Mortality, n [%]	4 (7.7)	7 (4.1)	NS
DHF, n [%]	7 (13.5)	13 (7.7)	NS
MACE, n [%]	10 (19.2)	17 (10.1)	0.077
Long-term follow-up			
Mortality, n [%]	10 (19.2)	19 (11.2)	NS
DHF, n [%]	23 (44.2)	32 (18.9)	< 0.001
MACE, n [%]	30 (57.7)	43 (25.4)	< 0.001

DHF — hospitalization for decompensated heart failure; MACE — major adverse cardiac event

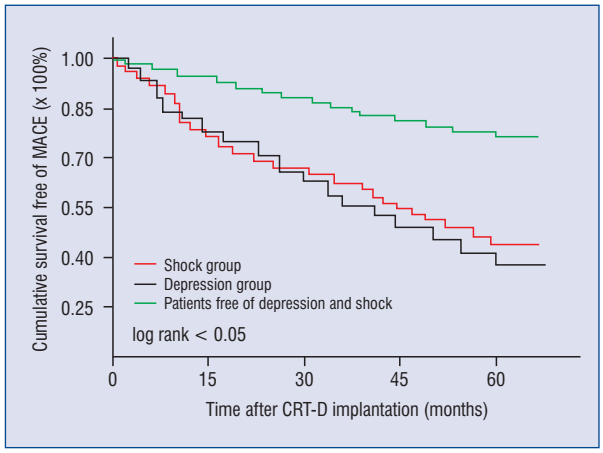

Figure 1. Kaplan–Meier curves of cumulative survival without MACE (Major Adverse Cardiac Events)

Table 6. The independent predictors of major adverse cardiac events — Cox-regression model

Parameter	Hazard ratio ± 95% CI	P-value
Depression	1.72 (1.37–2.07)	< 0.05
NYHA class	1.44 (0.83–2.06)	NS
Atrial fibrillation	1.28 (1.05–1.51)	< 0.05
Severe MR	1.79 (1.18–2.40)	< 0.05
LVEF	0.98 (0.95–1.01)	NS
CRT pacing	0.99 (0.97–1.01)	NS
ICD shock	2.11 (1.63–2.59)	< 0.001
CRT non-response	1.49 (0.78–2.21)	NS

CI — confidence interval; CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator; LVEF — left ventricle ejection fraction; MR — mitral regurgitation; NYHA — New York Heart Association

The multivariate analysis demonstrated that an ICD shock (HR = 2.1), severe MR (HR = 1.8), new-onset depression (HR = 1.7) and AF (HR = 1.3) were the independent predictors for a composite endpoint in the analyzed population. The results of multivariate analysis are presented in Table 6.

Discussion

The main findings of the present study can be summarized as follows. Firstly, it was shown that depression is a common clinical problem amongst HF patients receiving CRT-D. Secondly, patients experiencing an ICD shock therapy are at the highest risk of depression development. Thirdly, both depression and shock therapy portend significantly worse prognosis in CRT recipients.

It was demonstrated that over 20% of CRT-D recipients suffer from new-onset depression after a device implantation. According to available research the current study is the first to assess the prevalence of new-onset depression in a CRT-D population. The vast majority of published studies reported the incidence of depression in HF population at the moment of an ICD/CRT-D implantation or irrespectively of the presence of a high-energy device, whereas findings herein strictly concern patients with no history of depression before a CRT-D implantation [2, 3, 5, 21]. Moreover, it is of great importance, that the diagnosed depression was in a two-step protocol — first, a self-reported patient questionnaire was to be completed and secondly the diagnosis was further verified clinically by a psychiatrist, whereas the majority of previous studies used a self-reported survey as the only diagnostic tool for depression diagnosis [15, 21]. Owing to this, the present results seem to be more precise, as the prevalence of depression might be stacked when it is assessed only on the basis of self-reported tests [5]. According to previous data depression affects between 20% and 65% HF patients [2, 3, 5, 21]. The present results are mainly consistent with these reports, however they are closer to the upper threshold, as apart from 163 (41.2%) already depressed patients not included into the study, newly diagnosed depressive

syndrome was indicated in 48 (12.1% of the whole population) patients after a device implantation. The high risk of depression development in patients with severe HF should not be surprising, as symptomatic HF was reported to be the single most important clinical correlate of depression and anxiety [22]. Moreover, higher NYHA class is associated with worse psychological functioning and impaired quality of life (QoL) [4, 21]. Additionally, ICD\CRT-D recipients may have some concerns about the risk of receiving an unexpected shock therapy or device-related social and professional restrictions, that might increase psychological distress [14, 22].

There are conflicting data on the impact of ICD shocks on depression development. Luyster et al. reported that a high-energy ICD therapy, apart from poor social support and worse physical functioning, were associated with significantly higher risk of depression [23]. The consistent results were provided by Johansen et al. as they demonstrated a strong impact of ICD shocks on depression and anxiety development. They also found symptomatic HF to be the most powerful predictor of psychological distress in ICD recipients [22]. Moreover, Jacq et al. observed that the risk of depressive symptoms correlated significantly with the number of shocks [24]. On the contrary, no association between ICD shocks and depressive symptoms was observed in a prospective study including 308 ICD recipients [25]. In addition, Pedersen et al., demonstrated that symptomatic HF and type D personality, but not high-energy ICD therapy, predicted persistent depression after an ICD implantation [16].

The current study found that exposure to shocks has a negative impact on psychological state, resulting in over a 3-fold increased risk of new-onset depression. It seems reasonable and intuitive that patients who have experienced an ICD shock are more anxious and prone to be depressed than those who had no shock. An ICD therapy is sudden, painful and unpredictable; therefore, it might be expected to contribute to mental health disorders. The anticipation of receiving another shock can further increase psychological distress and promote depressive symptoms. Besides, concerns about shock delivery might also lead to limitations in daily functioning and social withdrawal both resulting in higher risk of depression occurrence [4, 14].

The present study demonstrated that both depression and ICD shock are strong independent predictors of worse prognosis in CRT-D recipients. Although ICDs and CRT-Ds improve long-term survival in severe HF patients, shocks have been found to significantly increase long-term mortality [13, 26–28]. According to the vast majority of the studies both appropriate and inappropriate interventions portend poor prognosis, however, those for ventricular arrhythmias are associated with more deleterious effects [13, 26–28]. It is still questionable, whether shocks are only a marker of the severity of HF or whether they potentiate the risk because of direct myocardial stunning [26]. Powell et al. reported no adverse impact of inappropriate shocks for sinus tachycardia or non-arrhythmic reasons (oversensing, noise, artifacts) on outcomes [13]. Moreover, antitachycardia pacing was demonstrated to be associated with over a 2-fold increased risk of death [29]. These findings might support the hypothesis, that an ICD shock is rather a marker of a more advanced disease.

The association between depression and unfavorable remote prognosis in HF populations has been already widely reported. In contrast to earlier studies, the prevalence and impact of depression was assessed in a homogenous population of first--time CRT-D recipients, nevertheless the present findings were generally consistent with previous results [8, 16, 30]. Depressed patients are less likely to comply with medical treatment, furthermore the adherence to therapy is proportional to the severity of depression [5, 16]. Moreover, depression leads to social withdrawal contributing to limitations in daily activities. Therefore, patients with depressive symptoms less often participate in cardiac rehabilitation and show worse compliance with secondary prevention lifestyle interventions [5, 16]. Besides, patients who suffer from depression might have a tendency to avoid medical visits and might be less willing to look for help if any medical complications arise [5, 16].

There are some findings to date, indicating that remission from depression may exert a beneficial effect on prognosis in HF population [31, 32]. It might be expected, that better compliance to complex medical treatment, sleep disorders reduction and increased physical activity might be the main factors that influence positively the remote outcomes in this population. Hence, it seems crucial to assess psychological co-morbidities in every HF patient, not only with indications for a high-energy device implantation. However, it should be emphasized that repeated re-assessments of mental status are required, especially in case of HF deterioration or after an ICD shock [19]. Once the depression is diagnosed, a patient should receive psychological support and medical therapy ought to

be administered under strict and constant psychiatric supervision [19]. Management of depression is complex and burdened with a high rate of failure, therefore, further studies are needed to establish the most effective treatment regimen of depression in severe HF patients.

Limitations of the study

The present study has several limitations. Firstly, the results were derived from a single-center, non-randomized, prospective, observational study, with all the shortcomings associated with such data. Secondly, although patients with new-onset depression were offered antidepressive treatment, only slightly over 50% of them agreed to take antidepressants. Hence, the Depression Group was not homogenous, as it consisted of patients with treated as well as untreated depression. However, because of a small number of participants this population could not be divided into patients taking antidepressants and those who declined psychiatric treatment.

Conclusions

Depression is a common mental disorder in CRT-D recipients, affecting over 20% of patients after a device implantation. Subjects suffering from ICD shocks, as well as those with HF progression are at significantly higher risk of experiencing depressive symptoms. Apart from repeated depression screening, every effort should be made to avoid factors contributing to depression, as it adversely affects long-term outcomes in the HF population.

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Silent cerebral ischemic lesions in ablation-naïve patients with non-valvular atrial fibrillation: Does the pulmonary vein anatomy matter?

Andrzej Głowniak[1], Anna Drelich-Zbroja[2], Adam Tarkowski[1], Paweł Marzęda[3, 4], Katarzyna Wojewoda[1, 4], Katarzyna Wysokińska[1, 4], Anna Wysocka[5], Monika Miazga[2], Anna Jaroszyńska[6], Krzysztof Kaczmarek[7], Andrzej Jaroszyński[6], Michał Orczykowski[8]

[1]Department of Cardiology, Medical University of Lublin, Lublin, Poland
[2]Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Lublin, Poland
[3]Department of Occupational Medicine, Medical University of Lublin, Lublin, Poland
[4]Doctoral School, Medical University of Lublin, Lublin, Poland
[5]Department of Internal Medicine and Internal Nursing, Faculty of Health Sciences, Medical University of Lublin, Lublin, Poland
[6]Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[7]Department of Electrocardiology, Medical University of Lodz, Lodz, Poland
[8]Department of Cardiac Arrhythmias, S. Wyszynski Institute of Cardiology, Warsaw, Poland

Abstract

Background: *Silent cerebral ischemic lesions (SCILs) detected by magnetic resonance imaging (MRI) can precede symptomatic stroke, the risk of which is increased five-fold in atrial fibrillation (AF) patients. In our study, we aimed to evaluate the initial incidence of SCILs in the population of patients referred for ablation due to symptomatic AF and to identify possible risk factors.*

Methods: *A total of 110 patients, with a mean age (SD) of 59.9 (9.4) years, referred for ablation, were included in the study. In all patients, MRI was performed before the procedure to evaluate the incidence of SCILs in the ablation-naïve patients.*

Results: *MRI revealed preexisting SCIL in 81/110 patients (73.6%). Notably, SCILs were found in all patients with CHA_2DS_2-VASc score ≥ 4. In univariable analysis, age ($p < 0.001$), CHA_2DS_2-VASc score ($p = 0.001$), hypertension ($p = 0.01$), and anticoagulation duration ($p = 0.023$) were identified as significant risk factors for SCILs, while the presence of anatomical variants of left-sided common pulmonary veins trunk (LCPV) had negative prognostic value ($p = 0.026$). Multivariable logistic regression analysis identified age ($p < 0.001$) as the risk factor of preexisting SCILs, whereas the presence of LCPV trunk was associated with significantly lower ($p = 0.005$) SCILs incidence.*

Conclusions: *Silent cerebral ischemic lesions detected in MRI are frequent in the population of patients with non-valvular AF. The incidence of SCILs is higher in patients with long history of arrhythmia and higher CHA_2DS_2-VASc score. The relationship between the anatomy of pulmonary veins and the incidence of SCILs needs further investigation.* (Cardiol J 2025; 32, 1: 35–42)

Keywords: atrial fibrillation, silent cerebral infarcts, silent stroke

Address for correspondence: Andrzej Głowniak, MD, PhD, Department of Cardiology, Medical University of Lublin, ul. Jaczewskiego 8, 20–954 Lublin, Poland, tel./fax: +48 724 45 92, e-mail: andrzej.glowniak@umlub.pl

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Introduction

Atrial fibrillation (AF) is associated with an up to five-fold higher risk of symptomatic stroke [1, 2], mainly due to the loss of mechanical function of the atria. Symptomatic stroke can be considered as a visible tip of the iceberg, with much more frequent silent cerebral ischemic lesions (SCILs), detected by magnetic resonance imaging (MRI), hidden below the water [3]. The clinical significance of this phenomenon is being discussed; however, there are data linking silent cerebral lesions with dementia and gradual cognitive decline [4–7]. The clear association between atrial fibrillation and cognitive dysfunction lead to the expert consensus on best practice for the prevention of cognitive decline in the AF population [8]. The known risk factors for thromboembolic complications in the AF population include age, sex, prior stroke, and existing comorbidities: congestive heart failure, diabetes, and vascular disease, integrated in the CHA_2DS_2-VASc score calculation [9]. This score, however, is designed to estimate the risk of symptomatic stroke in patients with atrial fibrillation. Less is known regarding the risk factors for asymptomatic cerebral lesions. Several parameters, including body mass index (BMI), CHA_2DS_2-VASc score, AF duration and type, and concomitant vascular disease [10–14], have been postulated so far. However, in a recently published retrospective analysis of 3 prospective studies, Herm et al. identified age as the only significant risk factor of MRI-detected asymptomatic cerebral ischemic lesions [15]. Conversely, with meticulous long-term monitoring, asymptomatic atrial fibrillation can be detected in up to 49% of patients suffering from cryptogenic stroke [16–18]. Moreover, the chance of detection of silent AF increases with the duration of ECG monitoring [19, 20].

Because silent cerebral lesions can precede symptomatic ischemic stroke [21], the identification of potential risk factors for SCILs is of great importance. In our study, we aimed to evaluate the initial incidence of SCILs detected in preprocedural MRI in the population of patients with symptomatic atrial fibrillation referred for pulmonary vein isolation procedure and identify their potential risk factors.

Methods

Study population

A total of 110 consecutive patients (82 males) with a mean [standard deviation (SD)] age of 59.9 (9.4) years, with documented episodes of symptomatic AF, referred for catheter ablation in our center, were included in the study. None of the patients had a history of stroke or transient ischemic attack (TIA), and all patients were neurologically asymptomatic on admission. All patients received oral anticoagulants — vitamin K antagonists or novel oral anticoagulants (NOACs) — for at least 4 weeks prior to hospital admission.

Exclusion criteria involved previous AF ablation, history of stroke/TIA, enlarged (> 50 mm) left atrium (LA), presence of intracardiac thrombus, valvular heart disease, left ventricular (LV) ejection fraction ≤ 40%, severe heart failure (NYHA class IV), thyroid dysfunction, pregnancy, and contraindication to magnetic resonance imaging. Patient characteristics, including the factors potentially related to thromboembolic risk, are presented in Table 1. The study protocol was approved by the institutional review board (approval number KE-0254/292/2012), and written informed consent was signed by all patients.

Magnetic resonance imaging

In all participants, diffusion-weighted MRI (DW-MRI) was performed before the ablation procedure to evaluate the incidence of SCILs in the ablation-naïve patients. DW-MRI (1.5 Tesla Siemens Avanto) was performed using the standard sequences: T1, T2, FLAIR, SWI/DWI, and 3D FLAIR as described before [22–24]. All MRI scans were analyzed by a certified radiologist, who was blinded to the clinical status of the patients.

Statistical analysis

The statistical analysis was carried out with Tibco Statistica 13.3 (StatSoft, Palo Alto, CA, USA). Normal distribution of continuous variables was tested using the Shapiro-Wilk test. Depending on the distribution, the values of the parameters were presented as arithmetic means and their SD or median and interquartile range (IQR). Student's t test was used for independent variables and the Mann-Whitney U-test as an intergroup comparison component. The distributions of discrete variables in groups were compared with Pearson's chi-square test or Fisher's exact test. Additionally, logistic regression models were fitted to identify risk factors associated with the incidence of SCI. A backward elimination models was built, and nonsignificant variables were removed sequentially until only those significant at $p < 0.05$ remained. From these models, adjusted odds ratios (OR) and 95% confidence intervals were derived; corresponding p values were from Wald's test. Goodness

of fit was checked using Hosmer-Lemeshow's test. The error was set at 5% and significance at a p value < 0.05.

Results

Overall incidence and predictive factors of silent cerebral ischemic lesions

The mean age (SD) of patients enrolled in the study was 59.9 (9.4) years, and the majority were males (82; 74.6%). More than 90% of the population suffered from paroxysmal atrial fibrillation (101; 91.8%), and the arrhythmia was diagnosed approximately 3 years before (median [IQR] 36.0 [24.0–48.0] months). The most prevalent comorbidity was arterial hypertension (83; 74.1%), which was followed by diabetes (23; 20.5%). The overall thromboembolic risk of the studied group assessed with the CHA_2DS_2-VASc score was moderate to median (IQR) 1.0 (1.0–3.0). Detailed characteristics, including the factors potentially related to thromboembolic risk, are presented in Table 1.

Comparison of clinical parameters between the study groups

MRI revealed preexisting SCILs (Fig. 1) in 81 out of 110 (73.6%) patients included in the study. The patients were divided into 2 groups depending on the MRI findings:

— SCIL (+) group — including 81 patients with MRI-detected silent cerebral ischemic lesions, of mean (SD) age 63.0 (7.6) years, 22 females (27.2%);

— SCIL (−) group — including 29 patients without MRI-detected silent cerebral ischemic lesions, of mean (SD) age 51.4 (8.6) years, 6 females (20.7%).

The demographic data, comorbidities, essential echocardiographic and laboratory parameters, together with anatomical variants of pulmonary venous drainage, of patients with and without detected cerebral lesions are presented in Table 2. In univariable analysis, CHA_2DS_2-VASc score ($p < 0.001$) together with its co-factors: age ($p < 0.001$) and hypertension ($p = 0.013$), as well as the time from AF diagnosis ($p = 0.030$), were identified as significant predictors for SCILs. Remarkably, SCILs were found in all patients with CHA_2DS_2-VASc score ≥ 4 (Fig. 2). Conversely, the presence of the anatomical variant of left-sided common pulmonary veins trunk (LCPV) had negative prognostic value ($p = 0.031$) for MRI-detected cerebral ischemic lesions.

Multivariable logistic regression analysis

The logistic regression model based on the variables that were different between the SCIL (+) and SCIL (−) groups identified age ($p < 0.001$) as the only significant risk factor of preexisting SCILs, whereas the presence of the anatomical variant of LCPV trunk was associated with significantly lower ($p = 0.005$) incidence of silent ischemic brain lesions (Tab. 3).

Discussion

Overall incidence of SCILs in the AF population

In our study, we have demonstrated a relatively high incidence of silent ischemic brain lesions in the group of patients with non-valvular atrial fibrillation and moderate risk of thromboembolic events, as assessed with the CHA_2DS_2-VASc score. Previously reported incidence rates of pre-ablation occurrence of silent cerebral lesions in AF patients varies from 14.5% reported by Miki et al. [12] up to 92% in the persistent AF subgroup, published by Gaita et al. [10]. Our finding of 73.6% incidence of SCILs is very similar to the recently published data by Wieczorek et al. [14], who reported a 74.3% incidence rate of silent brain lesions in a similar but less populated group of 74 patients referred for AF ablation.

The identified risk factors for SCILs

In multivariable logistic regression analysis, we have identified age as the only risk factor for SCILs in the studied group of patients with symptomatic recurrences of atrial fibrillation, which is not an unusual finding. Age has been reported as a strong risk factor for MRI-detected silent cerebral ischemic lesions in the general population [25, 26]. Longitudinal studies suggest an annual incidence of SCILs of between 2% and 4% [27]. This is an obvious consequence of the aging process itself, as well as the age-dependent increased rate of comorbidities known to be risk factors for thromboembolic events: arterial hypertension, diabetes, and heart failure [9–12]. This is even truer considering the population of AF patients. In the reports published so far [3, 4, 10–14], age was the only common risk factor for the presence of silent cerebral lesions in the AF population, which was additionally confirmed with our observation. We have also observed a strong correlation between the incidence of SCILs and the CHA_2DS_2-VASc score, which is in fact a combination of known

Table 1. Characteristics of the patients*

Parameter	All patients (n = 110)	SCIL (+) (n = 81)	SCIL (–) (n = 29)	P-value
	Mean (SD)/Median (IQR)			
Age [years]	59.9 (9.4)	63.0 (7.6)	51.4 (8.6)	< 0.001
Male, n [%]	82 (74.6)	59 (72.8)	23 (79.3)	0.62
BMI [kg/m^2]	27.4 (3.6)	27.3 (3.8)	27.7 (2.9)	0.96
CHA_2DS_2-VASc score	1.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	0.0006
LA diameter [mm]	42.7 (3.3)	42.9 (3.4)	42.1 (3.1)	0.17
LVEF [%]	61.2 (4.9)	61.2 (5.0)	62.8 (4.5)	0.15
CHF, n [%]	3 (3.3)	3 (3.7)	0 (0)	0.56
Hypertension, n [%]	83 (74.1)	65 (80.3)	16 (55.2)	0.010
Diabetes, n [%]	23 (20.5)	20 (24.7)	3 (10.3)	0.12
Vascular disease, n [%]	12 (10.7)	10 (12.4)	2 (6.9)	0.51
LCPV trunk, n [%]	18 (16)	8 (9.9)	8 (27.6)	0.031
RMPV, n [%]	20 (17.9)	11 (13.6)	9 (31.0)	0.0498
Persistent AF, n [%]	9 (8)	7 (8.6)	2 (6.9)	1.0
Anticoagulation duration [months]	32.0 (21.5)	34.8 (17.6)	24.2 (28.6)	0.001
Time from diagnosis [months]	36.0 (24.0–48.0)	36.0 (26.0–48.0)	28.0 (20.0–44.0)	0.030
CRP [mg/L]	0.99 (0.38–2.82)	1.0 (0.4–2.8)	0.9 (0.3–2.9)	0.47
BNP [pg/mL]	49.1 (25.5–91.3)	51.2 (30.1–92.0)	42.1 (21.4–78.0)	0.21
Urea [mg/dL]	40.1 (9.7)	40.5 (10.31)	38.9 (7.54)	0.47
Creatinine [mg/dL]	0.9 (0.2)	0.9 (0.22)	0.9 (0.21)	0.75
eGFR [mL/min]	81.7 (14.3)	80.3 (14.44)	85.8 (13.43)	0.075
RBC [×10^12/L]	4.8 (0.4)	4.7 (0.45)	4.9 (0.38)	0.12
WBC [×10^9/L]	7.1 (1.7)	7.3 (1.77)	6.7 (1.54)	0.13
HCT [%]	43.3 (3.5)	43.2 (3.53)	43.8 (3.41)	0.36
HGB [g/dL]	14.4 (1.1)	14.3 (1.1)	14.7 (1.16)	0.15
PLT [×10^9/L]	224.1 (61.0)	224.6 (60.40)	222 (63.53)	0.90
MPV [fL]	8.8 (1.6)	8.8 (1.54)	8.7 (1.74)	0.70
PCT [%]	0.2 (0.1)	0.2 (0.06)	0.2 (0.06)	0.73

*Data presented as mean (SD) or median (IQR). AF — atrial fibrillation; BNP — brain natriuretic peptide; BMI — body mass index; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; HCT — hematocrit; HGB — hemoglobin; LA — left atrium; LV — left ventricle; LCPV — left common pulmonary vein; MPV — mean platelet volume; PLT — platelets; PCT — plateletcrit; RBC — red blood cells; RMPV — right middle pulmonary vein; WBC — white blood cells

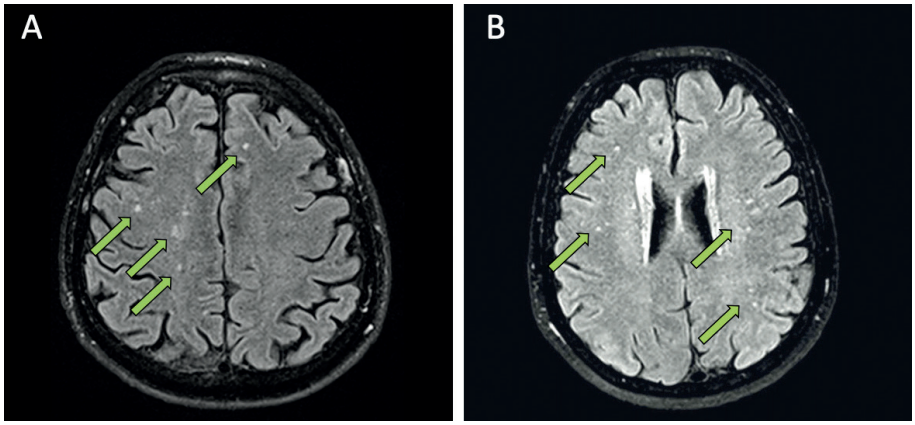

Figure 1. MRI-detected (FLAIR sequence) disseminated hyperintense cerebral lesions localized in frontal and parietal lobe white matter in two ablation-naïve patients with non-valvular atrial fibrillation (**A** and **B**)

Table 2. Uni- and multivariable analysis of silent cerebral ischemic lesion incidence in ablation-naïve AF patients

Parameter	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age [years]	1.2 (1.1–1.3)	< 0.001	1.2 (1.13–1.34)	< 0.0001
Male, n [%]	0.7 (0.3–1.9)	0.49		
BMI [kg/m^2]	0.96 (0.8–1.1)	0.56		
CHA_2DS_2-vasc score	2.2 (1.3–3.4)	0.0013		
LA diameter [mm]	1.1 (0.95–1.2)	0.28		
LV ejection fraction	0.9 (0.85–1.0)	0.15		
CHF, n [%]	–	1.0		
Hypertension, n [%]	3.3 (1.3–8.2)	0.01		
Diabetes, n [%]	2.8 (0.8–10.4)	0.11		
Vascular disease, n [%]	1.9 (0.4–9.2)	0.43		
LCPV trunk, n [%]	0.29 (0.1–0.9)	0.026	0.11 (0.025–0.52)	0.005
RMPV, n [%]	0.35 (0.13–0.96)	0.05		
Persistent AF, n [%]	1.3 (0.25–6.5)	0.77		
Anticoagulation duration [months]	1.03 (1.0–1.05)	0.023		
Time from diagnosis [months]	1.01 (0.99–1.04)	0.26		
CRP [mg/L]	1.0 (0.9–1.1)	0.68		
BNP [pg/mL]	1.0 (0.99–1.0)	0.33		
Urea [mg/dL]	1.02 (1.0–1.1)	0.47		
Creatinine [mg/dL]	1.4 (0.2–10.8)	0.74		
EGFR [ml/min]	0.97 (0.9–1.0)	0.078		
RBC [×10 ^ 12/L]	0.45 (0.2–1.3)	0.13		
WBC [×10 ^ 9/L]	1.2 (0.9–1.6)	0.13		
HCT [%]	0.9 (0.8–1.1)	0.36		
HGB [g/dL]	0.7 (0.5–1.1)	0.15		
PLT [×10 ^ 9/L]	1.0 (1.0–1.0)	0.9		
MPV [fL]	1.1 (0.8–1.4)	0.70		
PCT [%]	3.78 (0.002–6050.8)	0.72		

AF — atrial fibrillation; BMI — body mass index; BNP — brain natriuretic peptide; CI — confidence interval; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; HCT — hematocrit; HGB — hemoglobin; LA — left atrium; LV — left ventricle; LCPV — left common pulmonary vein; MPV — mean platelet volume; OR — odds ratio; PLT — platelets; PCT — plateletcrit; RBC — red blood cells; RMPV — right middle pulmonary vein; WBC — white blood cells

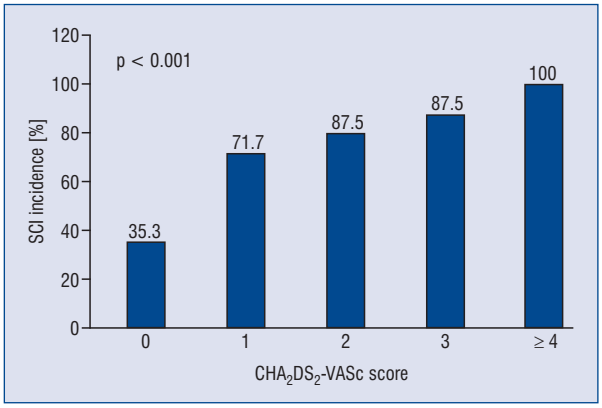

Figure 2. Incidence of silent cerebral ischemic lesions

stroke risk factors, which is consistent with the recently published data [28]. Interestingly, incorporation of pre-existing silent cerebral lesions into the CHA_2DS_2-VASc score calculation may alter the risk-benefit ratio of anticoagulation [29], and new multi-factor risk scales are being proposed [30]. Moreover, in the studied population a trend towards association of decreased eGFR and increased BNP with SCILs was observed. This is consistent with the data published by Kim et al. [31], who reported kidney dysfunction as an independent risk factor for the presence and number of SCILs in generally healthy adults, and by Matusik et al. [32], who demonstrated the prothrombotic and antifibrinolytic

alterations in AF patients with stage 4 chronic kidney disease irrespective of clinical stroke risk factors, as well as with the increased NT-proBNP level [33].

Can specific pulmonary vein anatomy be a predictor for SCILs in the AF population?

In our group, multivariable logistic regression analysis identified the presence of an anatomical variant of common trunk of left-sided pulmonary veins as a negative predictor for MRI-detected brain lesions. The typical configuration of pulmonary veins is characterized by 2 pulmonary veins with separate ostia on each side of the left atrium, and it can be found in approximately 70% of the general population. The common ostium of both left-sided veins (left common trunk) is the most frequent (about 30%) anatomical variant of PV anatomy, and the second is the presence of one or more additional (usually right-sided) pulmonary veins [34]. There are no reports linking pulmonary vein anatomy and risk of thromboembolic events, except for pulmonary arteriovenous malformation, but in such cases the phenomenon of paradoxical embolism is the obvious cause of stroke [35]. Nevertheless, because the atrial fibrillation itself is a well-known risk factor for thromboembolic events, we can hypothesize that the gap in the link between PV anatomy and MRI-detected silent brain lesions can be filled with the anatomy-dependent arrhythmia burden. Indeed, there are several published reports on the association between the PV anatomy and susceptibility to atrial arrhythmias. The weak point of this theorem is the fact that in most papers a positive correlation between anatomical variants of pulmonary venous drainage and AF incidence is reported [36–39]. Interestingly, the anatomical variation usually linked with AF susceptibility is the presence of additional/ /multiple right-sided veins [36], which is not always true for the presence of common ostia, and some authors use the general term of "atypical anatomy" to analyze its potential role as the risk factor for AF occurrence. In a recently published paper [39], the authors reported a positive correlation between the anomalies of pulmonary veins (in general) and AF occurrence. However, when only the presence of common ostia (both left- and right-sided) was considered, the opposite trend was demonstrated: a common ostium was identified less frequently in the AF group compared to the control group (11% vs. 15%) [39]. Perhaps the "anatomical anomaly" itself should not be considered as an AF risk factor, but simply the total number of pulmonary veins instead. The fewer pulmonary veins (and thus less complicated atrial anatomy), the fewer triggers (and possibly also less substrate) to initiate and sustain atrial fibrillation. This hypothesis finds extra support in the reports demonstrating positive correlation between left atrial diverticula (also referred to as additional appendages) and AF occurrence [40–42]. Obviously, this is only one possible explanation of our findings, and the potential "protective" effect of the anatomical variant of PV common trunk against thromboembolic events clearly needs further investigation.

Limitations of the study

There are several limitations of our study. Firstly, it is a single-center analysis, performed on a relatively low number of patients, which may constrain our capacity to draw substantial conclusions. Secondly, the duration of oral anticoagulation may differ between the analyzed patients, depending on their additional thromboembolic risk factors, reflected in the CHA_2DS_2-VASc score, which could have an impact on the incidence of MRI-detected silent brain lesions but in the opposite way to our findings, considering that high CHA_2DS_2-VASc values are a strong indication of permanent oral anticoagulation. Thirdly, our study was conducted on a group of patients referred for AF ablation and consequently did not include patients in a rate-control strategy with persistent long-lasting AF nor with extremely enlarged atria, because these groups would probably not benefit from the ablation procedure. Therefore, caution is needed when converting our findings to the general AF population.

Conclusions

In the present study, we were able to demonstrate that MRI-detected silent cerebral ischemic lesions are frequent in the population of patients with symptomatic non-valvular atrial fibrillation, naïve to invasive cardiac intervention. The incidence of SCILs is higher in patients with a long history of arrhythmia and with higher CHA_2DS_2-VASc score. The relationship between the anatomy of pulmonary veins and the incidence of SCILs needs further investigation.

Data availability statement: The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement: The study conforms to the guiding principles of the Declaration of Helsinki,

the study protocol was approved by institutional review board (approval number KE-0254/292/2012), and all patients gave informed consent before the procedures.

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Author contributions: AG and MO conceptualized the article. PM, KWoj, KWys, and AnnJ were responsible for data curation. AG and MJ established the methodology and performed the analysis. AG, AT, and AW administered and supervised the project. AG, MJ, AndJ, KK, and MO were responsible for validation. AG and MJ visualized the results. AG, AT, KK, and MO wrote the original draft. MJ, PM, KWoj, KWys, AW, AnnJ, and AndJ reviewed and edited the paper. All authors have read and agreed to the final version of the manuscript.

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Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment — preliminary study

Paweł Siwołowski, Piotr Gajewski, Mateusz Sokolski, Robert Zymliński, Mateusz Guzik, Joanna Szachniewicz, Piotr Ponikowski

Department of Cardiology, Institute of Heart Diseases, University Hospital, Wroclaw, Poland

Abstract

Background: *The aim of the study was to analyze the potential relationship between the diuretic response, the clinical profile and the concentrations of selected biochemical markers and to identify a group of patients who will benefit from a new form of therapy combining standard diuretic therapy with the use of a RenalGuard® system.*

Methods: *This is a retrospective study of 19 patients (mean age 67 ± 10 years, 95% men) hospitalized due to acute decompensated heart failure (ADHF, NYHA class III–IV, BP 125 ± 14/73 ± 16 mmHg, eGFR 58 ± 24) with persistent overhydration despite standard therapy. A targeted comparative analysis of selected clinical and biochemical parameters was performed to determine the parameters associated with a better diuretic response [good diuretic responders (GDR) group].*

Results: *The good diuretic responders group had significantly lower levels of creatinine (1.23 ± 0.4 vs. 1.69 ± 0.35, p = 0.025) magnesium 0.70 ± 0.14 vs. 0.83 ± 0.09, p = 0.030) and blood urea nitrogen (BUN, 28 ± 11 vs. 39 ± 10, p = 0.045). Additionally, in GDR group a statistically significant greater ability to dilute urine in the 12th and 24th hour of therapy was found.*

Conclusions: *The results of the study indicate the potential use of the RenalGuard® system in combination with standard intravenous diuretic therapy for controlled dehydration in the treatment of a selected group of patients with ADHF. It is advisable to identify the detailed mechanisms of GDR and characterize this group of patients more precisely.* (Cardiol J 2025; 32, 1: 43–52)

Keywords: acute heart failure, decongestion, diuretic response, spot urine analysis, biomarkers

Introduction

Despite a robust body of knowledge on heart failure pathogenesis and treatment, exacerbation of heart failure symptoms remains one of the main causes of hospitalization in hospital wards in patients over 65 years of age and is still related to high mortality and frequency of rehospitalizations [1]. In-hospital mortality among patients hospitalized due to acute heart failure (AHF) ranges from 4 to 10%, and the incidence of death and re-hospitalization exceeds 45% in a one-year follow-up. The most common form of clinical manifestation in patients with acute heart failure (50–70% of cases)

Address for correspondence: Paweł Siwołowski, Department of Cardiology, Institute of Heart Diseases, University Hospital, ul. Borowska 213, 50–556 Wrocław, Poland, tel: + 48 608378555, e-mail: patiks@yahoo.com

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is the so-called acute decompensated heart failure (ADHF). Initial clinical evaluation of patients with decompensated heart failure allows for easy identification of four different hemodynamic profiles, including the largest group of patients with symptoms of overhydration, without reduced peripheral perfusion, i.e., the so-called "wet-warm" profile [2].

Regardless of the cause of decompensation, one of the basic goals in treating patients with acute decompensated heart failure and symptoms of fluid overload is the rapid and safe elimination of overhydration using, among others, loop diuretics. It is known that excessive increase in the volume of the extravascular space is, alongside hyponatremia and increased blood urea nitrogen (BUN), one of the most important factors of poor prognosis in patients with decompensated heart failure. The associated chronic activation of many neurohormonal factors (mainly the renin-angiotensin-aldosterone system or vasopressin), in the group of patients treated for chronic heart failure, causes a gradual decrease in the effectiveness of standard pharmacological treatment, and as a consequence leading to partial or complete resistance to diuretic treatment and progressive overhydration.

The first-line treatment option for exacerbation of chronic heart failure symptoms in patients with symptoms of congestion and overhydration remains loop diuretics, often in combination with vasodilators [1, 3–5]. The main goal of diuretic therapy is to remove excess fluid from the body. First, excess fluid is removed from the intravascular space and then a volume of fluid is moved from the extravascular space to the vessels of the vascular bed at a rate known as plasma refill rate (PRR). From a clinical point of view, the key element for the safety and effectiveness of diuretic therapy is the ability to achieve a stable, fully controlled rate of excess fluid movement from the extravascular space to the vascular bed. If the rate of excess fluid removal from the intravascular space is too fast in relation to the plasma refill rate, excessive emptying of the intravascular space may occur, resulting in a decrease in cardiac output and decreased renal perfusion, which leads to the activation of a number of renal and extrarenal mechanisms of sodium and water retention in the body and, consequently, to the development of diuretic resistance [6, 7]. There are also no clear guidelines on the optimal dosing of diuretics, monitoring their efficacy and safety in terms of the risk of excessive diuretic effect (excessive dehydration), kidney damage and worsening of long-term prognosis. This is an extremely relevant clinical problem because deterioration of renal function during hospitalization due to exacerbation of heart failure symptoms is very common and has a significant impact on prognosis. As does chronic kidney disease coexisting with heart failure, which is an independent factor of poor prognosis in patients with acute heart failure [8]. Moreover, it should be considered that the use of furosemide in treatment of patients hospitalized in intensive care units is associated with a significant risk of acute kidney damage [9]. There is therefore still a need to develop new, safe and effective methods for eliminating overhydration and monitoring diuretic therapy in patients with acute heart failure.

Aim of the study

The aim of the study was to assess the use of a loop diuretic (furosemide) in combination with the method of controlled dehydration using the RenalGuard® system in patients with ADHF and concomitant chronic kidney disease, hospitalized due to ADHF, and to attempt to identify a group of patients who will derive significantly greater benefit from this form of therapy, based on the analysis of the potential relationship between the diuretic response and the clinical profile of these patients and the concentrations of selected biochemical markers.

Methods

The analysis was performed based on a prospective, single-center study conducted in patients hospitalized in the 4th Military Clinical Hospital in Wroclaw due to ADHF.

The study involved a non-randomized, retrospective analysis of the therapy of 19 patients hospitalized due to ADHF [NYHA class III–IV, BP 125 ± 14/73 ± 16 mmHg, estimated glomerular filtration rate (eGFR) 58 ± 24] with persistent symptoms of overhydration despite standard therapy based on the use of an intravenous loop diuretic. The study was conducted with the approval of the local Bioethics Committee of the Lower Silesian Chamber of Physicians and the Bioethics Committee at the Medical University of Wroclaw (opinion No. KB — 210/2019) and in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All patients gave their written informed consent to participate in the study before being included in the study.

The most important inclusion criteria for the study included:

1. Primary diagnosis of acute heart failure as the cause of hospitalization.

2. Clinical signs of overhydration (despite standard treatment of acute heart failure with intravenous furosemide), which included: persistent dyspnea at rest or with minimal physical effort at screening and recruitment, basal crackles, peripheral edema ≥ +1 (on a scale 0–3 +) on physical examination and radiological evidence of pulmonary congestion on plane chest X-ray.
3. Elevated natriuretic peptide levels: B-type natriuretic peptide (BNP) ≥ 500 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 2000 pg/mL; in patients ≥ 75 years of age or with current atrial fibrillation (at the time of inclusion), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL.
4. Systolic blood pressure ≥ 100 mmHg at the start and end of the screening test.
5. Previous chronic kidney disease defined as an eGFR between presentation and enrollment to the study ≥ 25 and < 90 mL/min/1.73 m^2, calculated using the MDRD (modification of diet in renal disease) equation.

The exclusion criteria included mainly:

1. Total urine output < 200 mL or average urine rate < 50 mL/hour in the Diuretic Challenge.
2. Patient is managed on, or there is a plan to manage on, renal replacement therapy (RRT) such as ultrafiltration, hemofiltration or dialysis.
3. Dyspnea due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), which may interfere with the ability to interpret the primary cause of dyspnea.
4. Patients with blood pressure > 180 mmHg at the time of enrollment or persistent heart rate > 130 bpm.
5. Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis.

The intravenous administration of a loop diuretic recommended by the current European Society of Cardiology (ESC) guidelines in the treatment of patients with acute heart failure was combined with the use of the RenalGuard® system, which operates by administering 0.9% saline solution by intravenous infusion in an amount proportional to the continuously measured volume of urine obtained per hour. The loop diuretic (furosemide) was administered in an individual dose for each patient, determined by the treating physician, necessary to ensure a time-planned negative fluid balance value.

Patients treated with intravenous furosemide during the first 24 hours of hospitalization, underwent a therapy combining intravenous furosemide with the use of the RenalGuard® system and the fluid loss limit (FLL) determined by the treating physician for the next 24 hours. The RenalGuard® system infusion catheter was connected to the patient via a peripheral venous access, and a urine reservoir placed on the device scale was connected to a standard Foley catheter placed in the patient's bladder for continuous monitoring of urine output. At the beginning of therapy, all patients received 40 mg of furosemide as an intravenous bolus. In the first hour of therapy, hydration was continued in a 1:1 ratio to the obtained diuretic effect (matched fluid balance phase), and then the desired fluid balance was set (desired fluid balance phase) at − 100 mL/h. (Fig. 1) Subsequent doses of furosemide and the drug administration regimen (intravenous bolus or continuous intravenous infusion) were determined based on the assessment of the patient's clinical condition in order to achieve the assumed negative fluid balance. The study lasted up to 24 hours or until the assumed fluid loss was achieved, indicating the achievement of euvolemia, as assessed by the study doctor. In all patients, the symptoms of heart failure and diuretic effect were assessed, blood and urine were collected for laboratory assessment of selected biochemical parameters and biomarkers such as creatinine, eGFR, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), endothelin-1 (ET-1), kidney injury molecule-1 (KIM-1) at specific time intervals during therapy, at discharge and during 30-day follow-up, as well as the relationship between the diuretic response and the sodium ions and creatinine levels in urine.

Statistical analysis

Normally distributed continuous variables were described by means ± standard deviation, non-normally distributed variables were described by medians with (upper and lower quartiles), categorical variables were given as counts and percentages. The normality of the distribution was tested using the Shapiro–Wilk test. The statistical significance of differences between time points was assessed using the paired samples t-test or the Wilcoxon test. Differences between the good and poor diuretic response groups were assessed using the unpaired t test or the Mann–Whitney test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATISTICA 13 software (StatSoft Poland, Krakow, Poland).

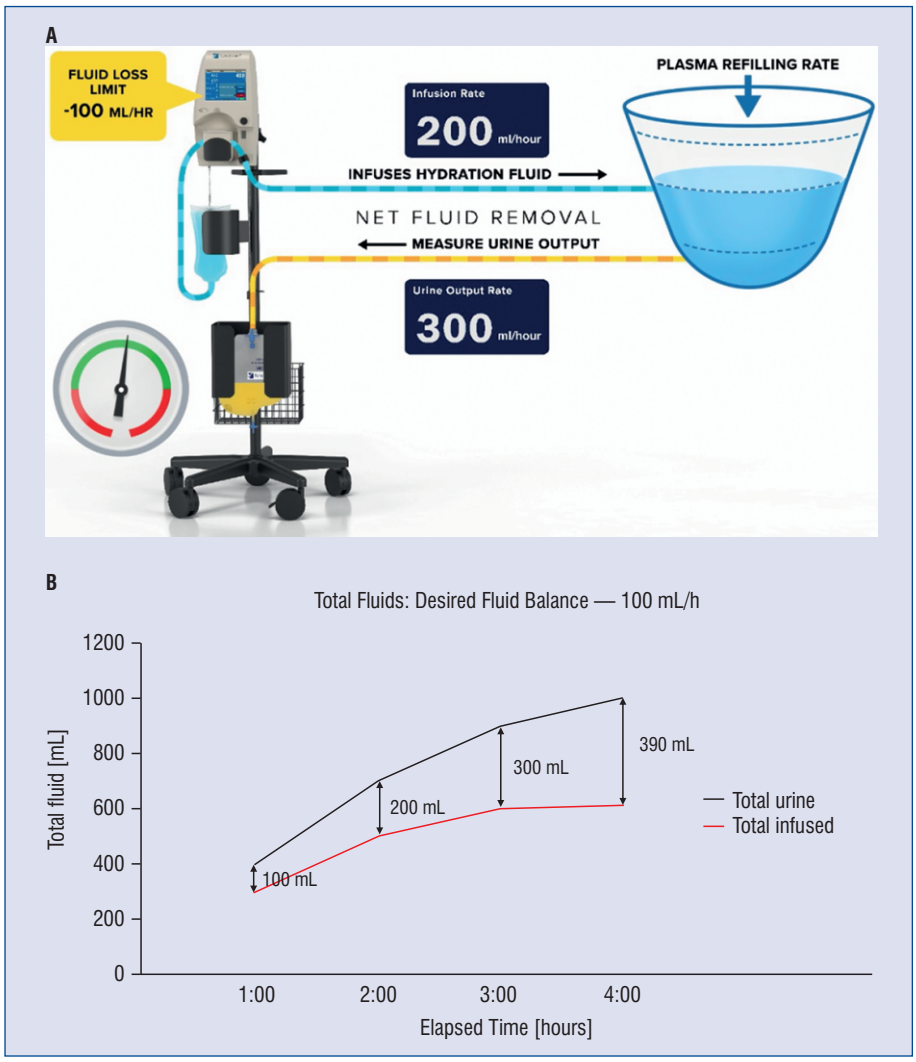

Figure 1 A, B. Diagram of the RenalGuard® system

Results

The clinical characteristics of the study population are summarized in Table 1. The vast majority of the study group were men (95%), the mean age was 67 ± 10 years. Immediately before enrollment to the study, 16 patients (84%) presented with symptoms of heart failure in NYHA class IV, the remaining patients were in NYHA class III. The mean systolic blood pressure on admission was 125 ± 14 mmHg, NTproBNP level was 4492 (2662 –6806) pg/mL, and hospitalization time 14 ± 9 days.

Diuretic effect

The mean duration of the RenalGuard® therapy in the analyzed group of patients was 25 ± 1 hours. The diuretic response during therapy expressed in milliliters (mL) was assessed per 40 mg of furosemide, obtaining a median for the entire study population of 933 mL/40 mg (Table 2).

Based on the median obtained in this way, the study population was divided into two groups:

1. Those patients who achieved a better diuretic effect and clinical response during the therapy were called "good diuretic responders" (GDR).
2. Those patients who achieved a worse diuretic effect and had less benefit from the therapy were called "worse diuretic responders" (WDR) (Table 3).

Biochemical parameters

In the next stage, a targeted comparative analysis of selected clinical and biochemical parameters was performed for the first time in both groups to determine in detail the parameters associated with a better diuretic response and the greatest clinical benefit after the applied therapy. In the GDR group,

Table 1. Clinical characteristics of the population

Variable		Good diuretic response	Worse diuretic response	P-value
Patients, n	19	10	9	
Age, years	67 ± 10	66 ± 13	69 ± 7	0.806
Male sex, n [%]	18 (95)	9 (90)	9 (100)	0.48
NYHA class I/II/III/IV before inclusion	0/0/3/16	0/0/1/9	0/0/2/7	0.465
Left ventricular ejection fraction [%]	34 ± 15	32 ± 13	37 ± 17	0.743
Acute heart failure *de novo* [%]	8 (42)	3 (30)	5 (55)	0.259
Ischaemic aetiology of heart failure [%]	8 (42)	6 (60)	2 (22)	0.958
Days in hospital before inclusion	2 ± 1			
LOS (days)	14 ± 9.4	12.6 ± 9.3	15.7 ± 9.9	0.391
Signs and symptoms				
Patient's self-reported weight gain [kg]	8.6 ± 5.8			
Congestion at admission < 1/3 / 1/3–2/3 / > 2/3 [%]	2 (11)/16 (84)/1 (5)			
Peripheral oedema + / ++ / +++ [%]	8 (42)/3 (16)/8 (42)			
JVP < 6/6–12/> 12 [cm]	1 (5)/14 (74)/4 (21)			
Heart rate at baseline [bpm]	76 ± 15	74 ± 15	78 ± 16	0.713
Systolic blood pressure at admission [mmHg]	125 ± 14	125 ± 11	125 ± 18	0.967
Central venous oxygen saturation [%]	49 ± 12			
Treatment before admission				
Furosemide dose before hospitalisation [mg]	80 [40–160]			
Baseline laboratory parameters				
Haemoglobin [g/dL]	12.9 ± 1.3	13.1 ± 1.56	12.6 ± 1.08	0.513
White blood count [10^9/L]	6.7 ± 1.6	6.8 ± 1.33	6.7 ± 2.01	1.000
PLT [10^9/L]	164 ± 54	170 ± 54	159 ± 57	0.838
AST [IU/L]	32 ± 15	34 ± 16	30 ± 14	0.595
ALT [IU/L]	29 ± 21	33 ± 24	25 ± 17	0.743
Bilirubin [mg/dL]	1.6 ± 0.6	1.5 ± 0.5	1.7 ± 0.7	0.513
Albumin [mg/dL]	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.3	0.462
Sodium [mmol/L]	138 ± 4	138 ± 3.7	137 ± 4.3	0.870
Potassium [mmol/L]	4.1 ± 0.5	4.1 ± 0.5	4.0 ± 0.4	0.653
Serum osmolality [mmol/L]	277 ± 9			
Creatinine [mg/dL]	1.45 ± 0.4	1.23 ± 0.4	1.69 ± 0.35	0.025
eGFR baseline [mL/min/1.73 m^2]	57 ± 23	68 ± 25	47 ± 14	0.079
BUN [mg/dL]	33 ± 12	28 ± 11	39 ± 10	0.045
NTproBNP [pg/mL]	4492 (2662–5806)	3684 (2635–5624)	5389 (4695–6448)	0.066
Urine sodium [mmol/L]	70 ± 45	73 ± 43	66 ± 49	0.563
Urine chloride [mmol/L]	88 ± 32	103 ± 32	72 ± 24	0.120
Urine creatinine [mg/dL]	98 ± 54	120 ± 55	73 ± 43	0.230

ALT — alanine aminotransferase; AST — Aspartate Aminotransferase; bpm — beats per minute; BUN — blood urea nitrogen; eGFR — estimated glomerular filtration rate; JVP — jugular venous pressure; LOS — length of stay; NT-proBNP — N-terminal pro B-type natriuretic peptide); PLT — platelets

Table 2. Diuretic response during therapy (per 40 mg of furosemide)

	Nvalid	Mean	Median	Lower quartile	Upper quartile	SD
Diuretic response mL/40 mg	19	1043,860	933,3333	700,0000	1400,000	508,3625

SD — standard deviation

Table 3. Two groups based on the median for the entire population: 933 mL/40 mg

	Good diuretic response 1	Nvalid	Mean	Median	Lower quartile	Upper quartile	SD
Good diuretic response mL/40 mg	1,00	9	1448,148	1400,000	1066,667	1900,000	426,2599
Worse diuretic response mL/40 mg	0,00	10	680,0000	725,0000	600,0000	800,0000	211,6659

SD — standard deviation

Table 4. Biochemical parameters — comparison

Variable	Good diuretic response GDR	Worse diuretic response WDR	P-value
Creatinine [mg/dL]	1.23 ± 0.4	1.69 ± 0.35	0.025
BUN [mg/dL]	28 ± 11	39 ± 10	0.045
Magnesium [mg/dL]	0.70 ± 0.14	0.83 ± 0.09	0.030
Cystatin C [mg/dL]	1.36 ± 0.5	1.85 ± 0.6	0.112
NGAL [ng/mL]	21.38 ± 17.16	19.61 ± 21.81	0.755
ET-1 [pg/mL]	13.97 ± 9.77	71.02 ± 169.25	0.134
KIM-1 [pg/mL]	140.67 ± 25.45	1177.25 ± 2716.97	0.404

BUN — blood urea nitrogen; ET-1 — endothelin-1; KIM-1 — kidney injury molecule-1; NGAL — neutrophil gelatinase-associated lipocalin

significantly lower levels of creatinine, magnesium and BUN were found (Table 4).

Moreover, the analysis of electrolyte levels in spot urine samples collected at specific time intervals of therapy revealed no significant differences of sodium and chloride ions concentrations at the beginning, in the 1st, 6th, and 12th hour and after the end of therapy (Fig. 2).

The relationships between the diuretic response and the concentrations of sodium ions and creatinine in urine used as markers of the kidney's ability to dilute urine (uCreat in baseline to uCreat in subsequent timepoints) and the relationships between natriuresis and urine dilution (water excretion) defined as uNa/uCreat were also analyzed in the studied patient population. In the GDR group, a statistically significant greater ability to dilute urine was found in the 12th and 24th hour of therapy, with no differences in uNa/uCreat concentration values (Fig. 3).

It is also worth noting the significantly lower total dose of the loop diuretic used to achieve the expected diuretic effect. In the assessment of clinical symptoms, patients from the GDR group were characterized by less severe symptoms of overhydration, such as jugular venous pressure (JVP), pulmonary congestion or peripheral edema (Fig. 4).

Discussion

Overhydration, with or without signs of hypoperfusion, is a major cause of hospitalization in patients with ADHF, regardless of the geographic region [10]. From a historical point of view, the first alternative method of dehydration to loop diuretics in patients with ADHF and signs of overhydration was continuous venovenous ultrafiltration [11, 12]. The randomized UNLOAD trial, which evaluated the clinical effect of ultrafiltration versus standard diuretic therapy in the treatment of acute heart failure, demonstrated greater net weight loss and fluid loss within 48 hours and a lower rate of rehospitalization due to heart failure symptoms

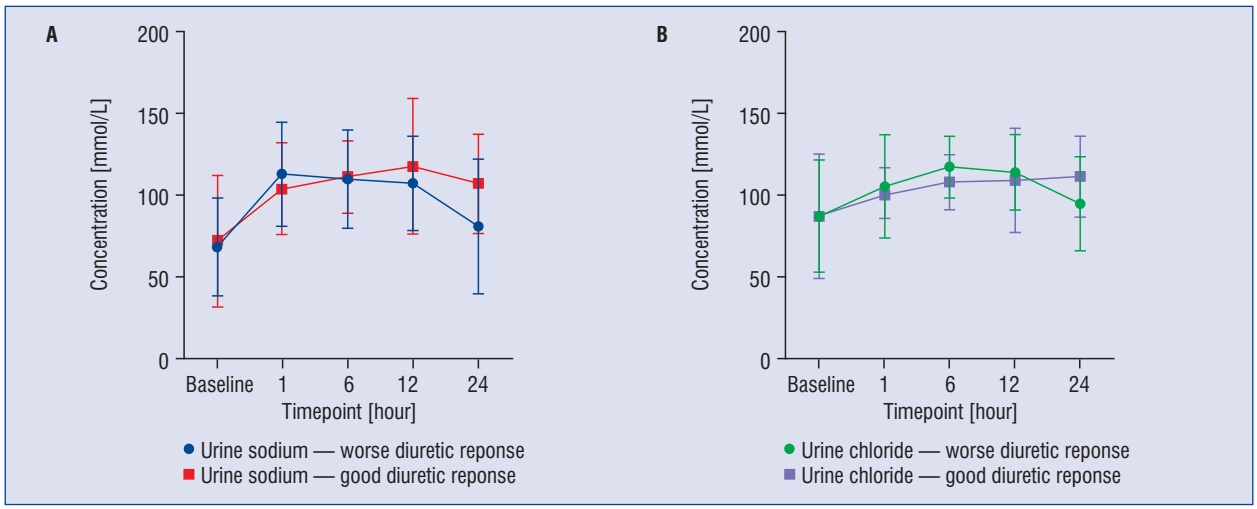

Figure 2 A, B. Sodium and chloride urine concentration

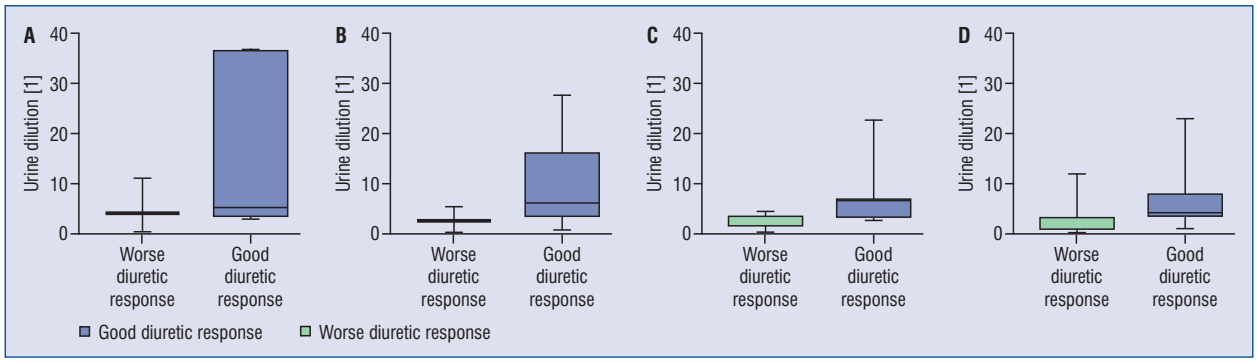

Figure 3. Urine dilution 1 h (**A**); Urine dilution 6 h (**B**); urine dilution 12 h (**C**); urine dilution 24 h (**D**)

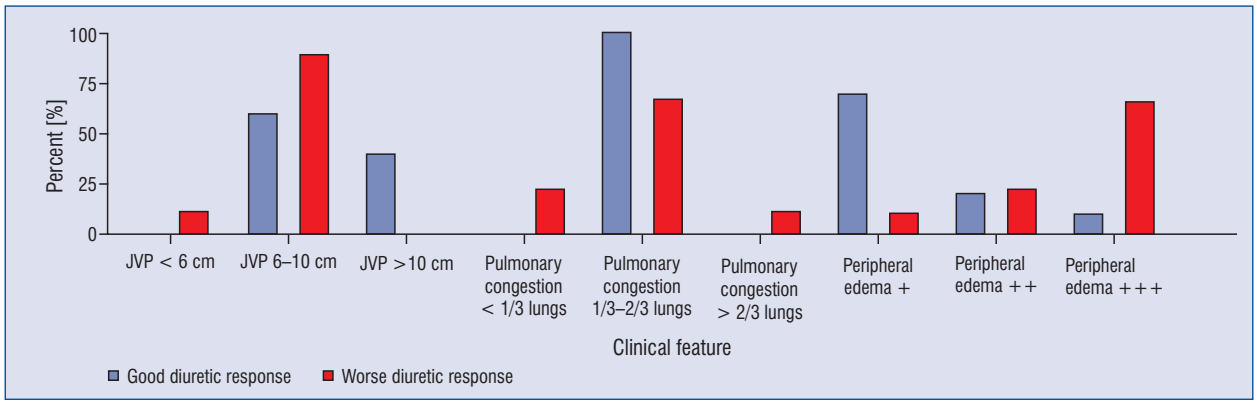

Figure 4. Clinical feature

at 90-day follow-up [13]. In contrast to previous clinical trials, a study published in 2012 highlighted for the first time a significant limitation of the use of this method, namely the risk of exacerbation of chronic kidney disease in a group of patients treated with ultrafiltration who had a significant increase in urea nitrogen and creatinine levels [14]. In the study by Vazir et al. [15], the saturation of central venous blood was analyzed during ultrafiltration and an increase in venous oxygen tension and

a decrease in creatinine concentration were observed in the first phase of dehydration. After obtaining 2 liters of removed fluid volume, a decrease in CvO2 and deterioration of renal function were noted. The authors of the study suggest that the deterioration of renal function may be related to transient changes in cardiac output occurring during ultrafiltration. The above observation may be of significant importance in the context of the safety of controlled dehydration using the RenalGuard® system, because in the study group there was no significant variability of CvO2 during the therapy; 49 ± 12% at baseline, 57 ± 8% after 6 hours and 54 ± 14% after 24 hours ($p = 0.1$).

To date, a number of clinical trials have been conducted using the RenalGuard® system, proving its efficacy in preventing post-contrast nephropathy, including in the group of patients with chronic kidney disease undergoing urgent or planned percutaneous coronary revascularization procedures [16–19]. Based on a previously conducted analysis of the safety and efficacy of the RenalGuard® system in treating patients with ADHF, the procedure was well tolerated and none of the patients had any infections or other complications related to the procedure, either during or after the treatment phase. All patients noted significant improvement in heart failure symptoms. The primary efficacy endpoint in preventing excessive fluid loss — actual fluid loss not exceeding the target fluid loss after completion of RenalGuard® therapy — was met in all 19 (100%) patients. During the 30-day follow-up, no deaths or serious adverse events were reported in the study population. Maintaining venous volume expansion and renal perfusion pressure may have additional nephroprotective effects [20].

The authors of a consensus statement by the Heart Failure Association of the European Society of Cardiology published in 2021 drew attention to the need to profile patients with heart failure in the context of making therapeutic decisions depending on the coexistence of factors such as heart rate (below 60 bpm or above 70 bpm, atrial fibrillation, symptomatic hypotension, eGFR below 30 or above 30 mL/min, hyperkalemia and clinical symptoms of overhydration [21]. Currently, many authors also emphasize the role of sodium and chloride ions in the pathophysiology of water and electrolyte metabolism disorders in the course of acute heart failure and the assessment of their concentrations in spot urine samples as predictors of response to diuretic therapy and independent factors allowing the identification of high-risk patients in the course of ADHF episodes [22–25]. Researchers are also focusing on explaining the interrelationship between urinary sodium and creatinine concentrations and the response to standard diuretic therapy, which is measured by the ability to dilute urine [26, 27]. In the analyzed population, a significantly greater ability to dilute urine was found in the group of patients who were characterized by a better diuretic response (GDR).

It is interesting to note that higher urinary sodium concentrations were observed between groups at subsequent time points, in the group with a better overall diuretic response, but no significant differences were found when the correlation between natriuresis and urine dilution (sodium concentration corrected for urine creatinine concentration) was taken into account, which is consistent with the fact that natriuresis is a strong factor determining the diuretic response. Patients with a better diuretic response showed a greater ability to dilute urine at later time points (> 12 hours) despite the same natriuresis. Despite differences in diuretic response, no significant differences were found in the serum concentrations of renal damage markers such as Cystatin or Kim-1. However, a trend towards higher endothelin concentrations was observed at subsequent time points in patients with better response to treatment, which may support increased activation of this system as a compensatory mechanism in response to increased urine production by the kidneys (fluid loss).

Conclusions

The results of the study indicate the potential use of the RenalGuard® system in the treatment of a selected group of patients with ADHF and symptoms of overhydration, in combination with standard intravenous diuretic therapy for controlled dehydration. Based on the analysis of selected biochemical parameters, a correlation was demonstrated between the concentrations of creatinine, urea nitrogen (BUN), magnesium in serum and the diuretic response of patients undergoing therapy with the RenalGuard® system. Some differences in sodium and chloride ions concentrations in urine samples collected at specific time intervals were also observed, but they were statistically insignificant. Limitations of the study resulting from the small size of the study population, single-center cohort and retrospective analysis prevented precise determination of the clinical profile of the group of patients with ADHF who could be expected to have a good diuretic response without an increased risk

of glomerular filtration deterioration secondary to concomitant chronic kidney disease.

Further work to determine the precise hemodynamic and biochemical profile of a larger population of patients with the optimal effect after this form of therapy may improve the future efficacy and safety of renal replacement therapies, currently widely used in cardiac intensive care units in patients treated for ADHF.

Data availability statement: All patients gave their written informed consent to participate in the study before being included in the study.

Ethics statement: The study was conducted with the approval of the local Bioethics Committee of the Lower Silesian Chamber of Physicians and the Bioethics Committee at the Medical University of Wroclaw (opinion No. KB — 210/2019) and in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Conflict of interest: None declared.

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A real-life clinical application of cardiac magnetic resonance imaging in patients with acute myocarditis — one-center observational retrospective study

Bartosz Gruchlik[1, 2], Agnieszka Nowotarska[1, 2], Sylwia Ścibisz-Brenkus[1, 2], Martyna Nowak[1, 2], Wiktor Werenkowicz[1, 2], Małgorzata Niemiec[1, 2], Andrzej Swinarew[3, 4], Barbara Mika[3], Wojciech Wróbel[1, 2], Maciej Haberka[5], Bartłomiej Stasiów[6], Katarzyna Mizia-Stec[1, 2]

[1]First Department of Cardiology, Medical University of Silesia, Katowice, Poland
[2]Member of the European Reference Network on Heart Diseases — ERN GUARD-HEART
[3]Faculty of Science and Technology, University of Silesia in Katowice, Chorzow, Poland
[4]Institute of Sport Science, The Jerzy Kukuczka Academy of Physical Education, Katowice, Poland
[5]Second Department of Cardiology, Medical University of Silesia, Katowice, Poland
[6]The Unit of Diagnostic Imaging, Medical University of Silesia, Katowice, Poland

Abstract

Background: *The diagnosis of acute myocarditis is complex, with cardiac magnetic resonance (CMR) being a recommended diagnostic method. This study aimed to evaluate the real-life use of CMR in the diagnosis of acute myocarditis and to correlate CMR results with the degree of myocardial damage.*

Methods: *This is a retrospective, observational tertiary single-center study of 90 consecutive patients (F/M: 18/72, mean age: 39 ± 14 years) hospitalized between 2015–2022 with a clinical diagnosis of acute myocarditis. The study population was divided into two groups: patients who underwent CMR+ and those who did not undergo CMR — In the CMR+ group, various sequences, including T1/T2-weighted imaging, late gadolinium enhancement (LGE), and mapping techniques, were used to assess myocardial inflammation and damage.*

Results: *CMR was performed in 39 patients (43.3%, F/M: 10/29, mean age: 41 ± 16 years). In this group, myocardial edema (increased T2 signal intensity) was detected in 29 patients, and LGE (signal intensity 2 standard deviations cabove normal on T1 images) was found in 39 patients. Diagnosis based on Lake Louise Criteria was possible in 29 cases. Edema negatively correlated with TnT levels ($r = –0.412$, $p < 0.05$) and positively with the number of LGE segments ($r = 0.372$, $p < 0.05$). Significant correlations were found between LVEF and LGE mass ($r = –0.360$, $p < 0.05$), and maximal TnT levels ($r = –0.38$, $p < 0.05$). CMR+ patients had lower myocardial damage markers and CRP concentrations compared to CMR– patients.*

Conclusions: *CMR is underused in diagnosing acute myocarditis. Myocardial damage markers correlate with CMR-detected edema and volumetric measures, but not LGE extent. More research is needed to enhance risk assessment and treatment.* (Cardiol J 2025; 32, 1: 53–61)

Keywords: acute myocarditis, cardiac magnetic resonance, late gadolinium enhancement, region of interest mass, Lake Louise Criteria

Address for correspondence: Prof. Katarzyna Mizia-Stec, MD, PhD, First Department of Cardiology, Medical University of Silesia, ul. Ziołowa 45/47, 40–635 Katowice, Poland; tel: 32 359 88 90, 32 359 87 29, e-mail: kmiziastec@gmail.com

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Introduction

Acute myocarditis is an inflammatory disease characterized by myocardial edema, necrosis, and inflammatory cell infiltration. Despite a high mortality rate of up to 50%, its classification, diagnosis, and treatment are still being developed [1]. Clinical presentation and diagnostic/therapeutic processes vary widely between centers.

The gold standard for diagnosis is myocardial biopsy, but its reliability is limited due to difficulty in sampling the diseased area. Its invasive nature and potential complications further restrict its use, reserving the procedure for high-risk patients (e.g., those with cardiogenic shock or suspected eosinophilic or giant-cell myocarditis) and not recommended for low-risk cases [2].

While the cause and clinical manifestations of myocarditis are often unclear, myocarditis can be clearly visualized with cardiovascular magnetic resonance imaging (CMR). CMR is a non-invasive imaging modality that allows for the assessment of both volumetric values and myocardial changes. Using CMR both dimensions and function of the heart chambers assessment and the various tissue characterization techniques are available. Tissue characterization in CMR involves different imaging sequences to assess the composition and condition of the myocardium. T1-weighted imaging, with the assessment of late gadolinium enhancement (LGE), allows visualization of permanent damage to the myocardium due to the replacement of myocardial cells by fibrous tissue. T2-weighted imaging shows myocardial edema, reflecting reversible myocardial damage and potentially present even in the absence of LGE. Extracellular volume fraction (ECV) calculation, though not the focus of this study, is another marker of myocardial tissue remodeling and provides a physiologically intuitive unit of measurement [2–5].

The Lake Louise Criteria (LLC) are a set of diagnostic criteria established to standardize the diagnosis of myocarditis using CMR. The updated LLC established LGE and T2 weighted imaging techniques and demonstrated the growing importance of quantitative mapping in diagnosing myocarditis [2, 5].

According to the updated LLC, CMR findings are consistent with myocarditis if at least two of the following criteria are met: a regional or global increase in myocardial signal intensity on T2-weighted images consistent with edema; an early increase in global gadolinium myocardial gain factor between myocardium and skeletal muscles in T1-weighted images; or at least one focus of non-ischemic regional redistribution on inverse resting gadolinium-enhanced T1-weighted images [6, 7].

Although the LLC, first published in 2009 and updated in 2018, are the recommended criteria for the definitive diagnosis of clinically suspected acute myocarditis, they are not always applied in practice [8]. There are several reasons for this. Firstly, the use of LLC is most relevant in the acute phase of the disease, and applying it in different stages of myocarditis might result in divergent or even misinterpreted evaluations. Secondly, CMR findings can vary depending on the experience and protocols of the CMR laboratory, leading to inconsistencies in interpretation. Furthermore, logistical challenges such as the availability of CMR technology and trained personnel can also limit the routine application of LLC. In most cases, a history of viral infection and laboratory tests for myocardial damage should be interpreted together with imaging results from methods such as echocardiography and CMR. However, using retrospective data, we aim to summarize the tertiary center experience in CMR use. This will contribute data on improving the myocarditis diagnostic process, especially since, despite recent advances in imaging techniques, the diagnosis, monitoring, and prognostication of patients in this clinical setting remain challenging.

The study aimed to evaluate real-life CMR use in the diagnosis of acute myocarditis and refer CMR results to the degree of myocardial damage.

Methods

Patient population

This study was approved by the research ethics board. It is a retrospective and observational study of 90 consecutive patients (F/M: 18/72, mean age: 38.7 ± 14.2 years) hospitalized in the 1st Department of Cardiology in a tertiary cardiovascular centre between 2015 and 2022 with a clinical diagnosis of acute myocarditis. The clinical diagnosis of acute myocarditis was based on case history, markers of inflammation (hsCRP) and myocardial injury (troponin, CK-MB levels), imaging non-invasive methods (echocardiography and CMR), and coronary angiography ruling out coronary artery disease. In this study, ECG findings of patients were not described, as they did not play a significant role in the present investigation.

Patients with contraindications for CMR (acute heart failure, cardiogenic shock, respiratory insufficiency, eGFR < 30 mL/kg/1.73 m^2, claustrophobia), patients with previous myocarditis and comorbidities

significantly influencing heart function (coronary artery disease, valve heart disease, congenital heart disease, cardiomyopathies), patients with LGE suggestive of myocardial ischemia/infarction (subendocardial or transmural) were excluded from the analysis.

Clinical characteristics included: demographic data, BMI (body mass index), duration of hospitalization, co-morbidities (RTI — respiratory tract infection; systemic hypertension), heart rate, blood tests (maximal levels of CRP, troponin T, CK-MB, D-dimer, GFR, fasting glucose), echocardiographic parameters (LVEF — left ventricle ejection fraction; LVESD — LV end-systolic volume; LVEDV — LV end-diastolic volume; LA area — left atrial area; RA area — right atrial area).

Taking into consideration CMR use, the study population was divided into two groups: those who underwent CMR (CMR+) and those who did not (CMR–). Comparisons of the clinical characteristics of the study groups as well as the analysis of the CMR results were done. The CMR results were analysed regarding the following aspects: number of LV LGE occupied segments, markers of myocardial damage (maximal levels of CRP, troponin T, CK-MB, LVEF in TTE and CMR, RVEF in CMR), and pharmacotherapy implemented during hospitalization and administered at the moment of CMR imaging (including: angiotensin-converting-enzyme inhibitors/ACEI, angiotensin receptor neprilysin inhibitor/ARNI, mineralocorticoid receptor antagonist/MRA, loop diuretics and beta-blockers).

Patients with mildly expressed symptoms of myocarditis in the current study refer to those presenting with minimal symptoms, such as exercise limitation classified as NYHA I/II, non-specific chest pains, and no resting dyspnea or edema.

CMR protocol and imaging analysis

CMR imaging was obtained during the first 10 days of hospitalization. The CMR images were acquired on 1.5-T systems (Optima MR450w, GE Healthcare) with a dedicated phased-array cardiac coil or body matrix coil using an electrocardiography-gated breath-hold protocol. Cine-CMR sequences included steady-state free precession (SSFP) imaging, while T2-weighted imaging sequences used a triple inversion recovery technique. Diagnosis of myocarditis was based on cine-CMR, T2-weighted imaging, and T1-weighted late gadolinium enhancement imaging.

Data on myocardial edema and LGE were analyzed by a specialist with many years of experience in cardiac magnetic resonance imaging. Due to differences in protocols over the evaluated period, pulmonary congestion was not consistently revealed in all exams and thus was not included in the analysis.

In the present study, the number and percentage of occupied left ventricular (LV) LGE segments were counted using the Cardiac VX program in a short-axis projection. American Heart Association (AHA) 16-segment model for segmentation was used.

For image analysis, T2-weighted imaging was used to detect myocardial edema by measuring the signal intensity, which is considered elevated if it is more than two standard deviations (2SD) above that of normal myocardium. LGE imaging was performed to detect areas of fibrosis, with LGE defined as regions with signal intensity greater than 2SD above that of normal myocardium.

To specifically determine the amount of LGE, the region of interest (ROI) mass (exact weight of LGE in the heart muscle) and ROI % (ratio of ROI mass to LV mass) were calculated. For the program to count the number of occupied segments in a given examination, the endocardium was marked, then the border of the epicardium, thus separating the myocardium. Also marked were the intersection point between the LV and right ventricle (RV), the so-called threshold, and proceeded in the same way in each segment.

The enhancement pattern in LGE was also assessed, with particular attention to non-ischemic patterns such as mid-wall, epicardial, or patchy enhancement, which are characteristic of myocarditis. The ROI was selected by manually outlining the area of hyperenhancement on LGE images, ensuring it was above the 2SD threshold relative to normal myocardium.

These detailed methods allowed quantification of the extent of myocardial damage and to correlate it with clinical and laboratory findings, providing a comprehensive assessment of myocarditis in the patient population.

Statistical analysis

The study population was first dichotomized into 2 groups of patients who underwent CMR and those who did not. Clinical characteristics and outcomes were compared between groups. Continuous variables were presented as mean ± standard deviation or median ± inter quartile (IQ) and categorical as absolute values and percentages. Normality was verified using the Shapiro–Wilk test. The comparisons of groups were based

on students' two-sample t-tests or nonparametric Mann–Whitney U tests, as appropriate. The differences in proportions between groups were analysed using the $\chi 2$ test. A p-value ≤ 0.05 was considered statistically significant for all tests. To analyse the correlation, the Pearson's and/or Spearman's rank correlation coefficients were used. All other analyses were performed using MedCalc® version 20.015 software.

Results

Clinical characteristic: CMR(+) vs. CMR(–) groups

Baseline characteristics of groups of patients with CMR vs. those without CMR done during the diagnostic process were summarized in Table 1. Patients who underwent CMR (CMR+) were more likely to have hypertension, lower heart rates, and lower levels of markers of myocardial injury and inflammation (TnT, CK-MB, CRP) compared to those who did not undergo CMR (CMR–). They also had different cardiac structural parameters, with higher LVEDV and larger LA areas. The differences in medication use were not statistically significant between the groups (Fig. 1).

CMR results — general data

In the CMR(+) group, the oedema was revealed in 29 (74%) and LGE in 39 (100%) patients. It allowed for the diagnosis of acute myocarditis based on LLC in 29 (74%) cases.

Several LV segments with LGE were also analysed — the mean number of LGE-occupied LV segments was 11.6 ± 2.3 (range: 6–16). The average value of ROI mass was 10.2 ± 13.4 g, and ROI % was 9.19 ± 0.6%.

The volumetric CMR parameters of the whole CMR (+) group were as follows: the LVEF was 51.8% ± 11.8. The LV mass value was estimated to be 128 ± 45.7 g/m^2. Mean LV ESV and LV EDV were respectively: 83.8 ± 53.2 and 162 ± 54.3 mL; the mean stroke volume (SV) was 78.7 ± 19mL. The right ventricle volumetric parameters were as follows: right ventricular EF (RVEF): 57.5% ± 6.3, RV end-systolic volume (RVESV): 53 ± 16.6 mL, RV end-diastolic volume (RVEDV): 120.2 ± ± 32.4 mL.

CMR results- number of LGE-occupied segments and clinical characteristics

Patients were divided into two subgroups according to LGE-occupied segments. The number of LV segments with LGE ranged from 6–10 in 12 (30.8%) and 11–16 in 27 (69.2%) patients. There were no differences regarding clinical characteristics between the subgroups, particularly in the biochemical markers of myocardial damage.

A comparison of the subgroups is presented in Table 2.

Table 1. Characteristics of the study group

Group characteristics	CMR (+)* n = 39	CMR(–)* n = 51	P-value
Sex [F/M], n [%]	10 (25.6%)/ /29 (24.6%)	8 (15.7%)/ /43 (84.3%)	NS
Age [years]	40.8 ± 16.2	37.1 ± 14.3	NS
BMI [kg/m^2]	24.4 ± 4.2	24.3 ± 5.5	NS
Duration of hospitalization [days]	6.3 ± 3	5 ± 1.6	NS
Comorbidities			
RTIs, n [%]	11 (28%)	29 (56%)	0.05 < p < 0.10
Hypertension, n [%]	33 (84.6%)	18 (35%)	0.001
Heart rate [bpm]	68.51 ± 12.4	78.5 ± 16.9	< 0.005
Blood tests			
TnT [μg/mL]	0.36 ± 0.7	0.70 ± 1.2	< 0.01
CK-MB [IU/L]	20.41 ± 11.6	43.84 ± 24.6	< 0.005
CRP [mg/L]	16.48 ± 27.8	58.76 ± 72.1	< 0.001
Glucose level [mg/dL]	96.33 ± 19.1	107.18 ± 26.1	0.05 < p < 0.10
eGFR [mL/ /min/1,73m^2]	112.93 ± 38	120 ± 39	NS
Standard TTE parameters			
LVEF [%]	49.15 ± 0.5	53.18 ± 0.5	NS
LVESV [mL]	89.24 ± 53.0	93.92 ± 34.7	< 0.005
LVEDV [mL]	138.59 ± 55.2	114.51 ± 34.7	< 0.01
LA area [cm^2]	19.6 ± 4.3	17.3 ± 3.3	< 0.05
RA area [cm^2]	14.9 ± 2.7	15.4 ± 3.1	NS
Medicines			
ACEI, n [%]	29 (74%)	23 (46%)	NS
ARNI, n [%]	8 (20%)	3 (6%)	NS
MRA, n [%]	23 (59%)	15 (29%)	NS

*CMR(+) patients diagnosed with myocarditis who had CMR done during their hospitalization. CMR(–) patients diagnosed with myocarditis who did not have CMR done during their hospitalization; ACEI — angiotensin-converting-enzyme inhibitors, ARNI — angiotensin receptor neprilysin inhibitor, CK-MB — creatine kinase-MB, CMR — cardiac magnetic resonance, CRP — C-reactive protein, GFR — glomerular filtration rate, LA area — left atrium area, LESV — left ventricular end-systolic volume, LVEDV — left ventricular end-diastolic volume, LVEF — left ventricular ejection fraction, MRA — mineralocorticoid receptor antagonist, RA area — right atrium area, RTIs — respiratory tract infections, TnT — troponin T

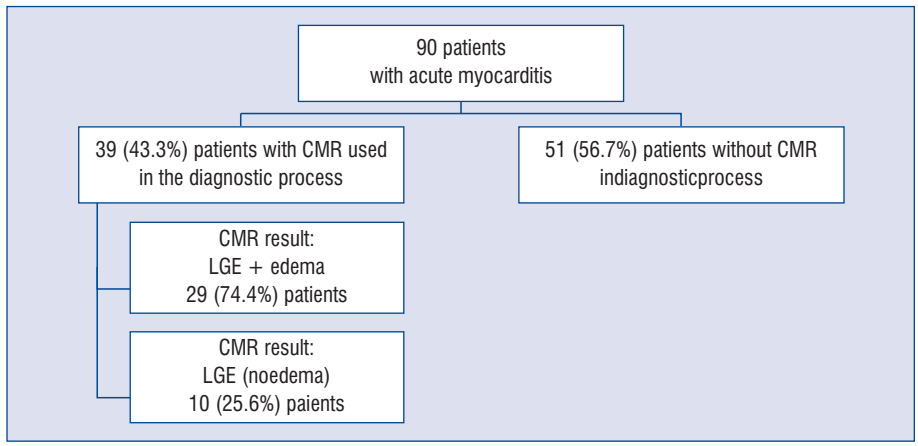

Figure 1. CMR in the diagnostic process of patients with acute myocarditis; CMR — cardiac magnetic resonance; LGE — late gadolinium enhancement

Table 2. Comparison of the subgroups of patients based on the number of LGE occupied LV segments in CMR

Variable	6–10 LGE occupied segments, n = 12	11–16 LGE occupied segments, n = 27	P-value
Sex (F/M)	3 (25%)/9 (75%)	7 (25.9%)/20 (74.1%)	NS
Age [years]	39.5 ± 13.3	41.3 ± 17.6	NS
BMI [kg/m^2]	23.2 ± 2.3	24.9 ± 4.7	NS
Duration of hospitalization [days]	5.3 ± 1.9	6.7 ± 3.4	NS
Comorbidoties			
RTIs, n [%]	2 (17%)	9 (33%)	NS
Hypertension, n [%]	10 (83%)	23 (85%)	NS
Heart Rate [bpm]	69.7 ± 11.2	68 ± 13	NS
Blood tests			
TnT [μg/mL]	0.56 ± 1.0	0.26 ± 0.4	NS
CK-MB [IU/L]	22.75 ± 16	19.37 ± 9	NS
CRP [mg/L]	0.33 ± 20.2	0.52 ± 30.9	NS
eGFR [ml/min/1,73m^2]	124.13 ± 36.8	108 ± 38.3	NS
Standard TTE parameters			
LVEF [%]	47.1 ± 11.7	53.6 ± 6.9	NS
LVESV [mL]	94.4 ± 59.7	61.4 ± 14.8	< 0.005
LVEDV [mL]	159.62 ± 62.9	134.5 ± 18.8	< 0.01
LA area [cm^2]	21.43 ± 5.0	16.13 ± 2.4	NS
RA area [cm^2]	15.84 ± 4.8	12.92 ± 1.4	NS
CMR			
ROI MASS [g]	6.44 ± 5.8	12.24 ± 15.5	NS
ROI [%]	6.97 ± 5.5	10.79 ± 10.4	NS
Edema, n [%]	7 (58%)	22 (82%)	NS
Medicines			
ACEI, n [%]	8 (68%)	22 (80%)	NS
ARNI, n [%]	0 (0%)	5 (19%)	NS
MRA, n (%)	7 (58%)	16 (59%)	NS
Loop diuretic, n [%]	3 (22%)	0 (0%)	NS
Beta-blocker, n [%]	7 (58%)	22 (81%)	NS

ACEI — angiotensin-converting-enzyme inhibitors, ARNI — angiotensin receptor neprilysin inhibitor, CK-MB — creatine kinase-MB, CMR — cardiac magnetic resonance, CRP — C-reactive protein, GFR — glomerular filtration rate, LA area — left atrium area, LESV — left ventricular end-systolic volume, LVEDV — left ventricular end-diastolic volume, LVEF — left ventricular ejection fraction, MRA — mineralocorticoid receptor antagonist, RA area — right atrium area, RTIs — respiratory tract infections, TnT — troponin T

Table 3. Data dependency between different variables

CMR variables:	CMR: LGE — ROI MASS	P-value	CMR: edema	P-value	CMR: LVEF	P-value
Blood tests						
TnT	r = 0.05	NS	**r = –0.41** r_s = –0.23	< 0.05	**r = –0.33** **r_s = –0.38**	0.05
CK-MB	r = –0.04	NS	r = –0.27	NS	r = 0.19	NS
CRP	r = 0.04	NS	r = 0.04	NS	r = –0.07	NS
Left ventricle ejection fraction						
LVEF (TTE)	**r = –0.57** **r_s = –0.47**	< 0.05	r = –0.19	NS		
LVEF (CMR)	**r = –0.36** **r_s = –0.40**	< 0.05	r = –0.13	NS		
Medicines						
ACEI	r = –0.06	NS	r = –0.21	NS	r = 0.28	NS
ARNI	r = 0.14	NS	r = 0.23	NS	**r = –0.45** r_s = **–0.45**	< 0.05
MRA	r = 0.28	NS	r = 0.23	NS	**r: –0.33** **r_s: –0.33**	< 0.05
Loop diuretics	r = 0.38	< 0.05	r = 0.09	NS	**r = –0.66** **r_s = –0.55**	< 0.05
Beta-blockers	r = 0.13	NS	r = –0.08	NS	r = –0.23	NS

ACEI — angiotensin-converting-enzyme inhibitors, ARNI — angiotensin receptor neprilysin inhibitor, CK-MB — creatine kinase-MB, CMR — cardiac magnetic resonance, CRP — C-reactive protein, LVEF — left ventricular ejection fraction, MRA — mineralocorticoid receptor antagonist, p — probability value, r — Pearson correlation coefficient, rs — Spearman's rank correlation coefficient, TnT — troponin T, TTE — transthoracic echocardiogram

CMR results and markers of myocardial damage

Relationships between the following CMR results: LVEF, ROI mass, and oedema in regards to the markers of myocardial damage and inflammation were analysed.

LVEF correlated negatively with maximal TnT levels ($r = –0.38$, $p < 0.05$). The presence of oedema correlated negatively with TnT levels ($r = –0.41$, $p < 0.05$) and positively with the number of LGE-occupied segments ($r = 0.37$, $p < 0.05$).

There was a significant correlation between LGE ROI mass and LVEF in CMR ($r = –0.36$, $p < 0.05$) as well as in TTE ($r = –0.57$, $rs = –0.47$, $p < 0.05$). The correlation between ROI mass and the number of LGE-occupied segments ($r = 0.50$, $rs = 0.45$, $p < 0.05$) was found.

No statistical significance was found concerning correlations between the CK-MB, CRP and CMR parameters (p = NS) (Table 3).

CMR results and pharmacotherapy

Relationships between the following CMR results: LVEF, ROI mass, and oedema concerning pharmacotherapy were analysed.

There were negative correlations between LVEF in CMR and administration of ARNI ($r = –0.45$, $p < 0.05$), MRA ($r = –0.33$, $p < 0.05$) and loop diuretics ($r = –0.66$, $p < 0.05$); and positive correlation between ROI MASS and loop diuretics intake ($r = = 0.38$, $p < 0.05$; but $rs = 0.22$, $p > 0.05$) (Table 3).

Discussion

Diagnosis of acute myocarditis is complex and requires different diagnostic tools. Both case history of viral infection and laboratory imaging tests are critical for the management [9–11].

In the study, the focus was on the evaluation of CMR application in the diagnosis of acute myocarditis. The present findings revealed that real-life CMR use in this setting was limited to patients with less pronounced clinical symptoms and laboratory tests. Also correlated were the CMR results with the extent of myocardial damage.

The current study compared subjects with and without CMR use. Patients' CMR(+) were characterized by less specific symptoms that ambiguously confirmed the diagnosis. Moreover, in these patients, the results of laboratory tests were less overt, and in some cases, also inconclusive — lower levels of troponin, CK-MB and CRP. It was suspected that in these patients CMR was necessary to confirm myocarditis.

The gold standard for the diagnosis of acute myocarditis is myocardial biopsy [13]. However, due to its low availability, high cost, and invasiveness, CMR is a more accessible and safer method. CMR is useful in the clinical decision-making process to take appropriate steps in stratifying patients' health risk. According to the updated LLC, CMR is the primary method for detecting signs of acute myocarditis and other markers of myocardial damage associated with myocarditis [14]. Optimal CMR imaging should include visualization of LGE, oedema and congestion.

According to available research, a lack of data on congestion constitutes a limitation of this study. Due to the marked sequence in CMR, LGE and oedema were determined in the documented laboratory. In the group of patients with CMR, 100% had LGE and 74% had oedema which allowed for diagnosis based on LLC in 29 cases (74%). In all patients a non-ischemic pattern of LGE was found.

According to the present study, the laboratory test results such as troponin, CK-MB and CRP levels did not correlate with LGE presence and the number of LV segments involved. This finding is consistent with some publications [14–16]. It should be underlined, that LGE is present both in the acute phase of myocarditis and can be a result of previous processes that may explain the current results. On the other hand, CMR was performed in patients with mildly abnormal laboratory tests — in such groups a confirmation of relationships is more difficult. In addition, the lack of a direct correlation between the presence of LGE and the level of laboratory markers of inflammation may indicate the ability of CMR to reveal features of myocardial inflammation, which, for some reason, cannot be reflected in routine blood tests. These reasons include the temporal dissociation between blood marker levels and imaging findings, the focal nature of myocardial damage that might not significantly affect systemic blood markers, and the possibility of subclinical inflammation that does not alter routine blood test results.

The data on LGE are of different clinical value. The prognostic potential of LGE in the population of patients with suspected myocarditis has already been demonstrated in many studies [17–20]. LGE is a better predictor of cardiac death and all-cause mortality compared to other functional CMR measures, including LVEF [21].

CMR volumetric parameters of the entire CMR(+) group showed a mean LVEF of 51.8%, which indicated, in some patients, a mild impairment of cardiac function. The group of patients with myocarditis was characterized by increased LV mass, estimated at a mean value of 128 g, and increased LV ESV and LV EDV which corresponds with the process of myocardial remodelling. The SV was within the normal range (range: 60–100 mL). The right ventricular ejection fraction was 57.5%. RVESV and RVEDV were also elevated, which may suggest right ventricular involvement in myocarditis.

The study also examined the relationship between CMR volumetric results and laboratory markers of inflammation and myocardial damage. LVEF showed a negative correlation with maximal levels of TnT. This points to the fact that impaired heart function was associated with higher troponin T levels, reflecting greater myocardial damage.

Oedema also correlated negatively with TnT levels which is in concordance with the fact that oedema represents ongoing myocardial damage [5]. In addition, oedema was positively correlated with the number of segments occupied by LGE. It indicates a relationship between oedema and the degree of myocardial involvement.

The timing of the laboratory tests and CMR was carefully coordinated. Blood tests, including measurements of TnT, CK-MB, and CRP levels, were conducted at the initial presentation of the patients and were repeated at 24-hour intervals for up to 72 hours to monitor changes over time. CMR was performed within 48–72 hours after the initial presentation to capture the acute phase of myocardial inflammation and damage. This approach allowed for a comprehensive assessment of the dynamic changes in both laboratory markers and imaging findings.

In the present study, the relationship between CMR results and pharmacotherapy was also determined. LVEF in CMR showed a negative correlation with the use of MRA, ARNI and loop diuretics. Interestingly, ROI mass showed a positive correlation with the intake of loop diuretics. This may suggest that patients with a more advanced inflammatory process and LV involvement require more intensified medical management. According to the literature data, CMR LVEF is a better predictor of treatment intensification than LGE [22]. Intensified therapy in the present study typically involved combination therapy, higher dosages of medications, and longer treatment periods.

Echocardiography (TTE) plays a crucial role in the initial assessment of patients with suspected myocarditis. It is often the first imaging modality used and can provide valuable information on ventricular function, wall motion abnormalities, and

the presence of pericardial effusion. TTE findings can influence the clinical decision-making process by prompting further investigation with more advanced imaging techniques like CMR.

The current study as a retrospective one-centre analysis has some limitations. There were limited number of patients analysed. However, several exclusion criteria were used and the group examined was well selected. Thanks to it the final results reflect the clinical importance of the problem of acute myocarditis and real-life low frequency of CMR use. It can be suspected that in some cases with acute heart failure, the CMR was not done because of the critical state of the patients. Due to differences in the protocols over the evaluated period, the congestion was not revealed in all exams and thus, it was not included in the analysis.

Conclusions

The present study reveals that although CMR is a valuable tool in diagnosing acute myocarditis, its use in real-world clinical practice is often limited to patients with milder symptoms. It was found that in patients with acute myocarditis, markers of myocardial damage are associated with oedema observed in CMR and CMR volumetric parameters, but they do not correlate with the presence or extent of LGE.

It should be noted, however, that this study had a relatively small number of patients, which may limit the robustness of the conclusions. Other limitations include the lack of long-term follow-up and the potential for selection bias. Further research is needed to address these limitations, validate these findings, and expand our understanding of the role of CMR in myocarditis. Larger studies with more diverse patient populations and extended follow-up periods will help improve risk assessment, guide therapeutic decisions, and ultimately enhance clinical management for patients with myocarditis.

Author contributions: Bartosz Gruchlik: analysis of CMR results, co-author of the work concept, coordination of each stage of work creation; Agnieszka Nowatorska: responsible for preparing the introduction; Sylwia Ścibisz-Brenkus: responsible for the preparation of the methodology section; Martyna Nowak: responsible for the development of the research results; Wiktor Werenkowicz: responsible for the development of the research results; Małgorzata Niemiec: responsible for developing the discussion; Andrzej Swinarew: help in analyzing the results of the study; Barbara Mika: help in analyzing the results of the study; Wojciech Wróbel: analysis of CMR results; Maciej Haberka: analysis of CMR results; Bartłomiej Stasiów: help in analyzing the results of the study; Katarzyna Mizia-Stec: author of the concept of work, coordinating each of the stages of work.

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Shaping cardiac diagnostics: The role of myocardial tissue mapping in unraveling ring-like fibrosis

Katarzyna E. Gil[1], Vien T. Truong[2], Saurabh Rajpal[1], Karolina M. Zareba[1, 3]

[1]Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, United States
[2]Christ Hospital Health Network, Cincinnati, United States
[3]Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University, Columbus, United States

Abstract

Background: *Patients with non-ischemic cardiomyopathy exhibit a range of myocardial fibrosis (MF) patterns on cardiovascular magnetic resonance (CMR) late gadolinium enhancement (LGE) imaging. Data suggests that ring-like MF is associated with worse prognosis. In the present study it was sought to analyze the prevalence of parametric mapping abnormalities in ring-like MF and their prognostic value for arrhythmic events.*

Methods: *Patients undergoing clinical CMR at 1.5T/3T were evaluated for ring-like MF defined as midwall/subepicardial fibrosis involving ≥ 3 contiguous left ventricular segments. CMR protocol included cine imaging, T1 and T2 mapping, and LGE. Mean native T1, ECV, and T2 values and a number of mid short axis segments with elevated values were calculated. LGE extent was assessed segmentally. Arrhythmic outcomes were defined as appropriate device shock, premature ventricular contractions ≥ 10%, non-sustained/sustained ventricular tachycardia, or ventricular fibrillation.*

Results: *In total 49 patients (53 ± 17 years, 26.5% female) were analyzed. Many patients had elevated global/segmental mapping values: 45%/76% in native T1, 57%/57% in T2, and 57%/78% in ECV. During median follow-up of 12 months, arrhythmic events occurred in 65% of patients. There was no association between native T1/T2 elevation or number of LGE segments and arrhythmic outcomes. There was a significant association between ECV and arrhythmic outcomes, both septal ECV ($p = 0.036$) and any segmental ECV elevation ($p = 0.03$).*

Conclusions: *T1 and T2 myocardial tissue abnormalities are common in patients with ring-like MF. ECV elevation was associated with arrhythmic events in this cohort. Further studies are needed to establish the diagnostic and prognostic value of parametric mapping in patients with ring-like MF.*
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Keywords: cardiovascular magnetic resonance imaging, parametric mapping, ring like fibrosis, ventricular arrhythmia

Address for correspondence: Katarzyna Elżbieta Gil, MD, PhD, 452 W 10th Ave Columbus, 43210 OH, tel: 614-907-5600, fax: 614-292-4550, e-mail: katarzyna.gil@osumc.edu

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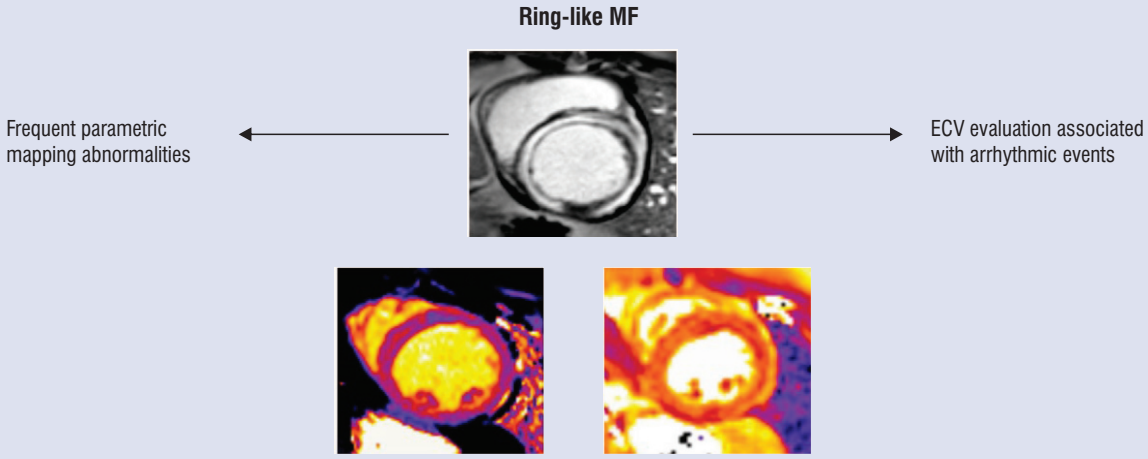
Graphical Abstract



MF — myocardial fibrosis, ECV — extracellular volume fraction

Introduction

Patients with non-ischemic cardiomyopathy (NICM) exhibit a range of myocardial fibrosis (MF) patterns, which can be evaluated using cardiovascular magnetic resonance (CMR) through late gadolinium enhancement (LGE) imaging. The presence of left ventricular (LV) nonischemic MF is associated with adverse prognosis [1, 2]. There is an increasing amount of data showing that a ring-like MF pattern, defined as dense midwall to subepicardial MF involving at least 3 contiguous LV segments, is associated with approximately 3-fold increase in risk of malignant ventricular arrhythmia (VA) in comparison to other MF patterns [1]. The ring-like MF pattern has been described in left dominant arrhythmogenic cardiomyopathies (ALVC), but the true prevalence and etiology remain unclear [1–5]. It is possible that ring-like MF is a common arrhythmogenic marker for a heterogeneous group of etiologies including both genetic and chronic inflammatory cardiomyopathies (CMP) [5, 6].

Recently established ALVC diagnostic criteria require both CMR and genetic testing for establishing a diagnosis [4, 7, 8]. ALVC with ring-like MF is seen in patients with desmosomal and other genetic variants [4]. Diagnosis may be complicated by relatively normal LV ejection fraction with frequent VA or by episodic myocardial injury that may clinically resemble myocarditis or sarcoidosis [1–4, 9, 10]. This "hot phase" might occur in desmoplakin (DSP) CMP, a distinct form of ALVC [9, 10]. Other known ALVCs subtypes, including filamin C or phospholamban CMPs, are not known to be associated with intermittent myocardial inflammation injury [7, 9]. It is likely that patients with ring-like MF and negative genetic testing represent either a distinct genetic CMP caused by an unknown gene variant, or a chronic inflammatory CMP [4, 7]. Endomyocardial biopsy may be considered in such cases to exclude myocarditis or sarcoidosis, although the predominantly subepicardial septal LGE location limits its utility [4].

Risk stratification in ring-like MF is challenging [1]. Myocardial tissue mapping is often used for NICM risk stratification, but limited data exists in patients with ring-like MF. Extracellular volume (ECV) fraction elevation, a marker of microscopic interstitial fibrosis calculated based on T1 mapping, has been associated with adverse outcomes in various cohorts including CMPs [11–16]. The degree of T2 elevation, consistent with myocardial edema and inflammation, is a reliable predictor of major adverse cardiac events and heart failure hospitalization in patients with myocarditis [17, 18]. T2 elevation in hypertrophic cardiomyopathy can be used as a marker for arrhythmogenicity, and in dilated cardiomyopathy identifies patients with low probability of reverse remodeling [17, 19].

Analysis of parametric mapping in conjunction with the MF pattern could help with understanding the pathophysiology, as well as to improve diagnosis, phenotyping and prognosis assessment in patients with ring-like MF. A more refined risk stratification, that includes parametric mapping

abnormalities, could potentially identify a subset of patients at high risk of VA who may benefit the most from implantable cardioverter-defibrillator (ICD) [2]. In the case of confirmed inflammatory CMPs, the window of opportunity for potential inflammatory modulation may be at an early disease stage, preceding the development of LV systolic dysfunction [9].

Aim

The goal of this study was to analyze the prevalence of parametric mapping abnormalities in ring-like MF and their predictive value regarding arrhythmic events.

Methods

Patients

This is a retrospective study assessing myocardial tissue mapping in patients with ring-like MF. The study was approved by The Ohio State University's Institutional Review Board who waived informed consent. Consecutive patients undergoing clinical CMR on 1.5T (Magnetom Sola and Avanto, Siemens Medical Solutions; Erlangen, Germany) and 3T scanners (Vida, Siemens Medical Solutions; Erlangen, Germany) between May 2020 and May 2023 were evaluated for the presence of ring-like fibrosis by querying imaging reports for the search terms "ring-like" and "circumferential", and each study's images were subsequently reviewed for inclusion criteria. Inclusion criteria were age ≥ 18 years old, and the presence of ring-like MF on LGE imaging. Ring-like MF was defined as dense midwall or subepicardial fibrosis involving at least 3 contiguous LV segments (Fig. 1). The electronic medical record was reviewed for demographic and clinical data, and cardiac testing (electrocardiography, telemetry, Holter/event monitor, implantable loop recorder/ICD/cardiac resynchronization therapy defibrillator (CRT-D) device interrogation, electrophysiology study, genetic testing, stress testing, echocardiography, coronary computed tomography angiography, single photon emission computed tomography, left heart catheterization).

The exclusion criteria, known to be associated with LGE and parametric abnormalities, were as follows: amyloidosis, hypertrophic cardiomyopathy, hypertensive heart disease, hemochromatosis, ischemic CMP, congenital heart disease, or neuromuscular disorders. Additionally, precautions were taken to exclude cardiac sarcoidosis based on the following criteria: high-grade atrioventricular block, endomyocardial biopsy positive for non-necrotic granulomas, or confirmed extracardiac sarcoidosis [20]. Patients with implanted pacemakers and defibrillators at the time of CMR were excluded. To ensure comprehensive outcome data, only patients who were followed within The Ohio State University health system were included.

CMR image & acquisition

Patients with NICM and ring like MF on LGE undergoing clinical CMR at 1.5 and 3 T were retrospectively analyzed. CMR images were acquired using standardized protocols including cine imaging, pre- and post-contrast T1 mapping, T2 mapping, and LGE imaging [21].

LV volumes and left ventricular ejection fraction (LVEF) were measured from short-axis stacks of cine frames that covered the LV. Parametric mapping was analyzed using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). Native and post-contrast myocardial T1 values (Modified Look-Locker Inversion Recovery) were measured on mid short axis (SAX) maps both in the septum and within the 6 segments according to American Heart Association (AHA) classification [22]. The endocardial and epicardial borders of the pre- and post-contrast T1 maps were traced within the myocardium to avoid any blood pool contamination (regions of interest were drawn automatically after excluding 10% of the endo- and epicardium). ECV was calculated for the septum and each of the 6 myocardial segments using the standard formula [23]. Foci of nonischemic LGE were not excluded from ECV measures since such practice would bias ECV measures, and spatial variation of MF was not wanted as it could confound its quantification [24]. Hematocrit (within 30 days, typically on same day as CMR scan) was utilized for ECV calculation.

T2 values (T2-prepared balanced steady state free precession pulse sequence with the use of adiabatic T2 preparation pulse during systole) were measured on the mid SAX map in 6 AHA segments [17]. The endocardial and epicardial borders of the T2 maps were traced within the myocardium to avoid any blood pool contamination (regions of interest were drawn automatically after excluding 10% of the endo- and epicardium). Mapping values were defined as elevated when > 2 standard deviations from field strength specific local normative values were obtained according to guidelines [25]. CMR reference values for the myocardium were based on institutionally established normative control data (**Suppl. Tab. 1**). Mean T1,

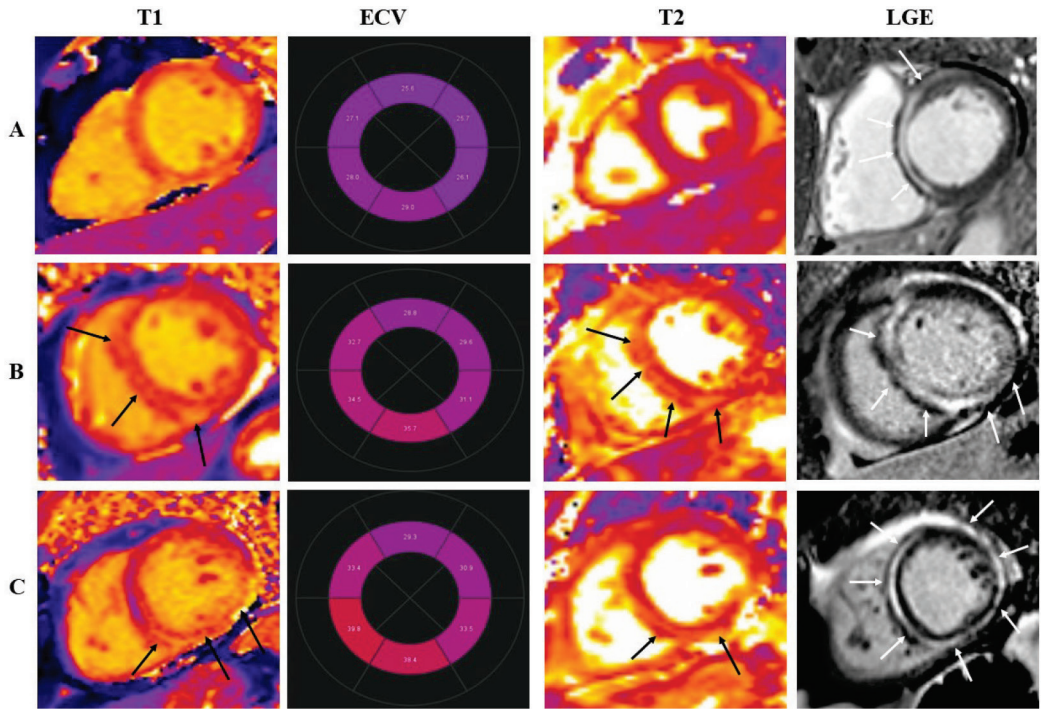


Figure 1 A–C. Myocardial tissue mapping and late gadolinium enhancement imaging (LGE) in patients with ring-like fibrosis. **A:** Continuous midmyocardial LGE in the anterior and septal walls (arrows). Normal native T1, ECV and T2 values. **B:** Extensive midmyocardial to near transmural LGE in the anterior, septal and inferior walls with corresponding elevation of the native T1 and T2 values in the septal and inferior walls (arrows). ECV is elevated in the septal, inferior, and inferolateral walls. **C:** Extensive midmyocardial to subepicardial circumferential LGE with elevation of the native T1 and T2 values in the inferoseptal and inferior walls (arrows). There is corresponding ECV elevation in the septal, inferior and inferolateral walls.

ECV, and T2 values as well as the number of segments with elevated values were calculated.

LGE imaging was obtained using phase sensitive inversion recovery motion corrected sequences. The presence, pattern, and extent of LGE was assessed by two level 3 CMR readers blinded to outcome data. LGE patterns were as follows: subendocardial, midwall, subepicardial and transmural. LGE extent was reported both using the AHA classification and the full-width half maximum technique as a percentage of the LV quantified with semi-automated planimetry (manually corrected, mean ± 6SD) [22, 26]. The number and location of segments with contiguous LGE on the same SAX slice was assessed.

Follow-up & outcomes

Patient follow-up was performed by review of the electronic medical record. Follow-up duration was calculated from the date of CMR. Given the small sample size, short duration of the follow-up, and low number of deaths during the analyzed period (2 patients died during the follow-up), only arrhythmic outcomes were evaluated. All patients were monitored for arrhythmia. Assessment was based on analysis of telemetry, Holter, event monitor, implantable loop recorder and ICD/CRT-D device interrogation. The arrhythmic event was defined as premature ventricular contraction burden above 10%, non-sustained ventricular tachycardia, sustained ventricular tachycardia, cardiac arrest secondary to ventricular tachycardia or ventricular fibrillation, or appropriate ICD/CRT-D shock [27].

Statistical analysis

Categorical data are presented as frequency (percentage) and comparison between groups was performed using the chi-square test or the Fisher exact test. The distribution of continuous variables was assessed by examining skewness, kurtosis, histograms, and QQ plots. Continuous variables are presented as mean ± standard deviation (SD) for normal distributions or median (interquartile range) for non-normal distributions. To analyze differences in continuous variables between the two groups, the Student t-test was used

for variables with a normal distribution, while the Wilcoxon rank-sum test was employed for those without a normal distribution. The relationships between continuous variables were assessed using Pearson's correlation coefficient (r) for normally distributed variables and Spearman's rank correlation coefficient for non-normally distributed ones. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) and R software, version 3.5.3 (The R Foundation, Vienna, Austria).

Results

Baseline characteristics

Of 7250 patients undergoing CMR between May 2020 and May 2023, a total of 49 (0.7%) were included in the analysis. No other patients scanned within that study period demonstrated ring-like MF based on the study definition. The mean age of the cohort was 53 ± 17 years with 73.5% of patients being male (Tab. 1). In total, 34 patients were scanned using 1.5 T scanners and 15 patients/30.6% using 3T scanner. The left ventricle was enlarged in 24 (50%) patients by sex specific indexed LV volumes [28]. Mean LVEF was 37 ± 14% with 73% of patients demonstrating LVEF below 50%. Right ventricular (RV) dysfunction was common with mean RVEF of 46 ± 13%, and 51% of patients presenting with RVEF below 50%. The electrophysiology study was performed in 11 patients (22.4%) and positive in 7 patients/64% of cases for inducible arrhythmias. Genetic testing was positive in all 8 patients (16.3%) who underwent assessment and included the following gene variants: filamin C (2 patients), desmoplakin (1 patient), desmoglein (1 patient), phosphopantothenoylcysteine synthetase (1 patient), acid alpha-glucosidase (1 patient), fukutin-related protein (1 patient), and variants of unknown significance (1 patient). Endomyocardial biopsy was negative for inflammation in all 4 patients (8.2%) referred for the procedure.

Myocardial fibrosis characteristics and parametric mapping

Ring-like MF most often involved septal/inferior/lateral walls (67%) with a median of 4.5 (3–6) LV segments on the basal or mid SAX slices (Tab. 1). Mean LGE burden was 25.6 ± 9.9%. Parametric mapping quality was good with all available maps being analyzed, and hematocrit was obtained in all patients. A significant portion of patients had elevated global values on tissue mapping: 45% in native T1, 57% in T2, and 57% in ECV. Segmental analysis revealed elevation in any of the mid short axis AHA segments in 76% for T1, 78% for ECV, and 57% patients for T2 values. Native T1 and T2 values were most often elevated in AHA segments 8–10. There was no association between global or segmental T1, T2 or ECV elevation and decrease in biventricular systolic function (Suppl. Tab. 2).

Association of tissue indices and arrhythmic outcomes

Follow-up was available in all patients. Over a median follow-up of 12 (6.3–25) months, arrhythmic events occurred in 65% of patients (Tab. 1). There was no association between native T1 or T2 elevation and arrhythmic outcomes (Tab. 2). There was a significant association between ECV and arrhythmic outcomes, both septal ECV ($p = 0.036$) as well as any segmental ECV elevation ($p = 0.03$; Tab. 2). There was a trend towards more frequent arrhythmic events in patients with a higher number of AHA segments involved ($p = 0.06$). There was no association between the number of all LGE segments and arrhythmic outcomes (Tab. 2). A trend towards higher LGE burden in patients with arrhythmic events did not reach statistical significance ($p = 0.13$).

Discussion

The prevalence of parametric mapping abnormalities and its utility in assessing prognosis in ring-like MF was investigated. It was demonstrated that T1 and T2 myocardial tissue abnormalities are common in patients with ring-like MF. It was noted that septal and segmental ECV elevation was associated with arrhythmic events in patients with ring-like MF over a 12-month follow-up. Native T1 and T2 mapping abnormalities, although highly prevalent, were not found to be associated with arrhythmic events in the present cohort. This study supports recent data that LGE in patients with ring-like MF is most often localized to the inferior and lateral walls.

Parametric mapping abnormalities appear to be more frequent in patients with ring-like MF than reportedly in other types of NICM. ECV is elevated in approximately 33–41%, and T2 in approximately 27% of patients with heart failure of nonischemic etiology [15, 29, 30]. ECV is routinely assessed in NICM using the same method as in the present study, without exclusion of nonischemic LGE. This is supported by a lack of established methodology and risk of bias of ECV measurement due to spatial

Table 1. Baseline clinical and imaging characteristics of patients with ring-like myocardial fibrosis

Characteristic	Whole cohort (n = 49)
Age, mean (SD), y	52.8 ± 16.9
Male, n [%]	36 (73.5)
BSA, mean (SD), [m^2]	2.07 ± 0.27
BMI, mean (SD), [kg/m^2]	30.2 ± 6.2
Hypertension, n [%]	28 (57.1)
Diabetes, n [%]	13 (26.5)
Chronic kidney disease, n [%]	10 (20.4)
Hyperlipidemia, n [%]	22 (44.9)
Coronary artery disease, n [%]	14 (28.6)
Atrial fibrillation, n [%]	13 (26.5)
Cerebral vascular accident, n [%]	3 (6.1)
Chronic obstructive pulmonary disease, n [%]	5 (10.2)
Obesity, n [%]	11 (22.4)
Obstructive sleep apnea, n [%]	8 (16.3)
Substance use, n [%]	7 (14.3)
Family history of cardiomyopathy, n [%]	12 (24.5)
Pharmacotherapy, n [%]	
Beta blocker	43 (87.8)
Calcium channel blocker	4 (8.2)
Angiotensin converting enzyme inhibitor	7 (14.3)
Angiotensin receptor blocker	13 (26.5)
Angiotensin receptor/neprilysin inhibitor	18 (36.7)
Mineralocorticoid receptor antagonist	26 (53.1)
Diuretics	18 (36.7)
Sodium-glucose cotransporter-2 inhibitor	18 (36.7)
Nitrate	5 (10.2)
Vasodilator	4 (8.2)
Anticoagulant	9 (18.4)
Antiplatelet	19 (38.8)
Statin	24 (49)
Antiarrhythmic drug	10 (20.4)
Steroid	6 (12.2)
CMR parameters, mean (SD)	
LVEDVI, [mL/m^2]	105.0 (89.0–137.0)
LV enlargement by LVEDVI, n [%]	24 (50)
LVESVI, [$mL/m^{2)}$	66.0 (45.0–107.0)
LVEF, [%]	37.3 ± 13.8
LVEF < 50%, n [%]	36 (73.5)
RVEDVI, [mL/m^2]	85 (69.0–100.0)
RV enlargement by RVEDVI, n [%]	5 (10.2)
RVESVI, [mL/m^2]	41.0 (33.0–61.0)
RVEF, [%]	46.0 ± 12.6
RVEF < 50%, n [%]	25 (51)
Myocardial tissue characterization	
T1 mapping, n [%]	
Global native T1 elevation	22 (44.9)

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Table 1 (cont.). Baseline clinical and imaging characteristics of patients with ring-like myocardial fibrosis

Characteristic	Whole cohort (n = 49)
Septal native T1 elevation	25 (51.0)
Native T1 elevation in mid-short axis AHA segments (7–12)	37 (75.5)
Median mid-short axis AHA segments (7–12) with T1 elevation, median (IQR)	3 (1–4)
ECV, n [%]	
Global ECV elevation	28 (57.1)
Septal ECV elevation	30 (61.2)
ECV elevation in mid-short axis AHA segments (ECV)	38 (77.6)
Median mid-short axis AHA segments (7–12) with ECV elevation, median (IQR)	4 (1–6)
T2 mapping, n [%]*	
Global myocardial T2 elevation, n [%]	19 (43.2)
T2 elevation in mid-short axis AHA segments (7–12), n [%]	25 (56.8)
Median Mid-short axis AHA segments (7–12) with T2 elevation, median (IQR)	1 (0–4)
LGE, No. of segments (%)	
Transmural pattern, n [%]^	3 (6.1)
Subepicardial pattern, n [%]	34 (69.4)
Midmyocardial pattern, n [%]	47 (95.9)
LGE extent (FWMH, %), mean ± SD	25.6 ± 9.9
Ring-like pattern location, No. of contiguous LGE segments (%)	
Anterior and septal walls involved	1 (3.3)
Septal, inferior and lateral walls involved	20 (66.7)
Anterior, septal and inferior walls involved	2 (6.7)
Anterior, septal, inferior and lateral walls involved	7 (23.3)
All 6 segments involved in 1 SAX (base or mid) slice	19 (38.8)
Number of segments with continuous LGE, median (IQR)	4.5 (3–6)
Arrhythmia prevention/monitoring, n [%]	
D-ICD	16 (32.7)
Subcutaneous ICD	6 (12.2)
CRT-D	3 (6.1)
Implantable loop recorder	5 (10.2)
Holter	22 (44.9)
Arrhythmic events, n [%]	
Total arrhythmic events	32 (65.3)
Premature ventricular contraction burden > 10%	6 (12.2)
Non-sustained ventricular tachycardia	30 (61.2)
Sustained ventricular tachycardia	7 (14.3)
Cardiac arrest secondary to ventricular tachycardia/ventricular fibrillation	6 (12.2)
Appropriate ICD/CRT-D shock	3 (6.1)
Electrophysiology study¥, positive, n [%]	7 (63.6)

*A total of 44 patients underwent T2 mapping
¥A total of 11 patients underwent EP study
^All 3 patients with transmural LGE had no evidence of coronary artery disease on cardiac catheterization. The transmural LGE segments were contiguous with subepicardial and midmyocardial segments.
Biventricular enlargement defined per sex specific guidelines for LVEDVI and RVEDVI [42].
The arrhythmic event was defined as premature ventricular contraction burden above 10%, non-sustained ventricular tachycardia, sustained ventricular tachycardia, cardiac arrest secondary to ventricular tachycardia or ventricular fibrillation, or appropriate ICD/CRT-D shock.
SD — standard deviation; BSA — body surface area; BMI — body mass index; CMR — cardiovascular magnetic resonance imaging; LVEDVI — left ventricular end-diastolic volume index; LV — left ventricular; LVESVI — left ventricular end-systolic volume index; LVEF — left ventricular ejection fraction; RVEDVI — right ventricular end-diastolic volume index; RV — right ventricular; RVESVI — right ventricular end-systolic volume index, RVEF — right ventricular ejection fraction, AHA — American Heart Association, IQR — Interquartile range, ECV — extracellular volume fraction; LGE — late gadolinium enhancement imaging; FWHM — full-width half-maximum technique; ICD — implantable cardioverter--defibrillator; CRT-D — cardiac resynchronization therapy with defibrillator

Table 2. Arrhythmic events in patients with ring like myocardial fibrosis and myocardial tissue mapping abnormalities

Myocardial tissue characterization	Arrhythmic event (+) (n = 32)	Arrhythmic event (–) (n = 17)	P-value
Native T1 mapping			
Global T1 elevation	14 (43.8%)	8 (47.1%)	0.83
Septal T1 elevation	16 (50.0%)	9 (52.9%)	0.85
Any segmental T1 elevation	25 (78.1)	12 (70.6)	0.73
Number of AHA mid short segments (7–12) with T1 elevation	3 (1–5)	1 (0–3.75)	0.24
ECV			
Global ECV elevation	20 (62.5%)	8 (47.1%)	0.30
Septal ECV elevation	23 (71.9%)	7 (41.2%)	0.036
Any segmental ECV elevation	28 (87.5)	10 (58.8)	0.03
Number of AHA mid short segments (7–12) with ECV elevation	5 (2–6)	2 (0–5.5)	0.06
T2 mapping			
Global T2 elevation	12 (41.4%)	7 (46.7%)	0.74
Any segmental T2 elevation	15 (51.7%)	10 (66.7%)	0.34
Number of AHA mid short segments (7–12) with T2 elevation	0 (0–3.75)	1 (0–4.0)	0.65
LGE			
Number of AHA segments with nonischemic LGE	12.5 ± 3.1	10.8 ± 3.5	0.08
Nonischemic LGE burden (%), mean ± SD	27.3 ± 10.4	22.8 ± 8.7	0.13

The arrhythmic event was defined as premature ventricular contraction burden above 10%, non-sustained ventricular tachycardia, sustained ventricular tachycardia, cardiac arrest secondary to ventricular tachycardia or ventricular fibrillation, or appropriate ICD/CRT-D shock. ECV — extracellular volume fraction; AHA — American Heart Association; LGE — late gadolinium enhancement

variation of MF. Extracellular matrix expansion has a continuous spectrum between diffuse and focal, and ECV allows quantification of its extent [31, 32]. The link between arrhythmogenic CMP and inflammation is well known, although better studied in arrhythmogenic RV than LV CMP [33]. The current finding of frequent myocardial inflammation in patients with ring-like MF agrees with autopsy results in DSP CMPs, which demonstrate extensive inflammation and myocardial necrosis, associated with fibrous and fatty tissue repair [34]. Limited autopsy data from patients with filamin C CMP also confirms the presence of inflammation accompanied by fibrosis [35]. It is probable that symptoms and signs during the "hot phase" in DSP CMP could be a manifestation of myocyte necrosis [34]. Parametric mapping may be crucial in identifying patients with DSP CMP requiring immunosuppressive therapy to prevent LV fibrosis and dysfunction at an early stage [33, 36]. Currently there is no consensus regarding treatment in the acute phase of disease [36]. The role and extent of inflammation is unclear in other causes of ring-like MF, but it presumably reflects an active phase of the disease and precedes LV dysfunction [33].

The present data suggests that parametric mapping may play a role in prognosis assessment in patients with ring-like MF. Evaluation of ECV appears beneficial in this patient population and a more tailored arrhythmia treatment approach may be indicated in cases of ECV elevation. If confirmed in large multicenter studies, parametric mapping could be added as a potential risk factor to sudden cardiac death scores recommended in CMPs without LVEF < 35% [7]. Currently only high-risk gene variants, LGE presence, and history of unexplained syncope are taken into consideration [7, 37]. In a recent large study, only ECV, in addition to LGE and LVEF, has been shown to be a strong and independent predictor of ventricular arrhythmia and sudden death in NICM [38]. In that population, elevated ECV further discriminated the risk of arrhythmic events among LGE positive patients [38]. The lack of association between native T1 and T2 mapping abnormalities and arrhythmic outcomes in the current analysis may relate to the small cohort and short follow-up.

The predominance of inferior and lateral wall LGE in the cohort is consistent with recently published data [4, 7]. The etiology of this phenomenon remains unclear. Interestingly, significant LV dysfunction was present in a majority of the presented patient population. That is in contradiction to the recently published data on ALVC suggesting that regional LV involvement without reduction of global systolic function is more common due to sparing of the subendocardial layer of the myocardium [4, 7, 8, 37]. Given the known correlation between LGE extent and LVEF, the relatively high number of segments with LGE and high LGE burden may suggest that ALVC in the current study was more advanced [37]. Presumably, ring-like MF may not be limited to ALVC patients and may be an indicator of CMPs with fibrofatty replacement of heterogeneous etiologies. Interpretation of the present results is limited by the lack of routine genetic testing in all study patients, although in a recent study conducted by Bietebeck M. et al. [5] an underlying genetic cause was found only in 61% of patients with ring-like fibrosis [4–6]. Genetic testing results were similar to the present patient population and included the following gene variants: filamin C (35%), desmosomal as well as nondesmosomal arrhythmogenic CMP genes (43%), lamin A/C (LMNA) (13%), and variants of unknown significance (9%). Of note, in a large multicenter cohort of patients with dilated and non-dilated left ventricular CMPs, septal LGE — and not the pathogenic/like pathogenic variant in arrhythmogenic genes — was a powerful independent predictor of major arrhythmic events [39]. That further emphasizes the importance of CMR in risk stratification of patients with NICM.

The lack of association between LGE burden and prognosis may be partially attributed to the high LGE burden observed across the entire study population. Notably, the presence and pattern of LGE, rather than its extent, have demonstrated prognostic significance in NICM [[38, 40, 41]. LGE is a good predictor of monomorphic ventricular tachycardia, but not polymorphic ventricular tachycardia or ventricular fibrillation in that patient population [38]. Hypertrophic cardiomyopathy is the only cardiomyopathy in which the quantitative extent of LGE has a prognostic role [40].

Limitations

Given the retrospective nature of the study, small sample size and short follow-up, this single center study may be underpowered to detect differences in the incidence of arrhythmic events among patients with native mapping elevations. Therefore, the present findings should be validated in larger, multicenter cohorts with longer follow-up. Genetic testing and endomyocardial biopsy were not routinely performed in all patients; however, patients with other inflammatory etiologies such as sarcoidosis were excluded to the extent possible upon review of all available clinical data.

Conclusions

T1 and T2 myocardial tissue abnormalities are common in patients with ring-like MF. ECV elevation was associated with arrhythmic events in this cohort. Further studies are needed to establish the diagnostic and prognostic value of parametric mapping in patients with ring-like MF.

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Evaluating the effect of the antiPCSK9 vaccine on systemic inflammation and oxidative stress in an experimental mouse model

Amir Abbas Momtazi-Borojeni[1, 2], Maciej Banach[3–6], Amirhossein Sahebkar[7–9]

[1]Healthy Ageing Research Centre, Neyshabur University of Medical Sciences, Neyshabur, Iran
[2]Department of Medical Biotechnology, School of Medicine, Neyshabur University of Medical Sciences, Neyshabur, Iran
[3]Faculty of Medicine, John Paul II Catholic University of Lublin, Lublin, Poland.
[4]Ciccarone Center for the Prevention of Cardiovascular Disease, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA
[5]Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[6]Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Poland
[7]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[8]Center for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[9]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Iran

Abstract

Background: *To investigate whether the antiPCSK9 vaccine can affect the CRP and oxidative stress (OS) during acute systemic inflammation.*

Methods: *Male albino mice were randomly divided into three groups: non-treated mice (the sham group), treated with a nonspecific stimulator of the immune response — Freund's complete adjuvant (CFA; the CFA group), and vaccinated mice treated with CFA (the vaccine group). The vaccine group was subcutaneously immunized with the antiPCSK9 formulation, 4 × in bi-weekly intervals. To induce inflammation, all mice were subjected to the CFA challenge after the vaccination plan. The hsCRP level and OS status were evaluated by a mouse CRP assay kit and the pro-oxidant antioxidant balance (PAB) assay, respectively.*

Results: *The vaccine induced a high-titer IgG antiPCSK9 antibody, which was accompanied with a significant PCSK9 reduction (–24.7% and –28.5% compared with the sham and CFA group, respectively), and the inhibition of PCSK9/LDLR interaction (–27.8% and –29.4%, respectively). hsCRP was significantly increased in the vaccine and CFA groups by 225% and 274%, respectively, when compared with the sham group; however, it was non-significantly decreased (–18%; $p = 0.520$) in the vaccine group in comparison with the CFA group. The PAB values indicated that OS was significantly increased in the CFA group (by 72.7%) and the vaccine group (by 76%) when compared to the sham group; however, there was no significant difference in the PAB values between the vaccine and CFA groups.*

Conclusions: *The antiPCSK9 vaccine failed to significantly reduce the serum hs-CRP and OS induced in the CFA-challenged albino mice.* (Cardiol J 2025; 32, 1: 73–82)

Keywords: C-reactive protein, inflammation, oxidative stress, PCSK9 vaccine

Address for correspondence: Prof. Amirhossein Sahebkar, PharmD, PhD, FESC, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948954, Iran, e-mail: amir_saheb2000@yahoo.com

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Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a well-known regulator of cholesterol homeostasis, which acts via the binding to the hepatocyte low-density lipoprotein (LDL) receptor (LDLR) that will be consequently targeted to the lysosomal degradation [1–4]. Immediately after the discovery of PCSK9 protein and its function, growing evidence from genetic association studies showed PCSK9 inhibition as a potential lipid-lowering target [1–5]. Currently there are several types of PCSK9 inhibitors such as the FDA-approved PCSK9 monoclonal antibodies (mAbs) alirocumab and evolocumab [6–9] and small interference RNA against mRNA PCSK9 [10]. Additionally, there are under-investigation oral PCSK9 inhibitors (e.g., macrocyclic peptide MK-0616) [11–14]. Finally, there are antiPCSK9 vaccines [15–21], which have emerged as effective therapeutics for ameliorating hypercholesterolemia and atherosclerosis in preclinical studies.

Besides the role in cholesterol metabolism, there is also experimental and clinical evidence showing that PCSK9 can act as a pro-inflammatory mediator, however, there are contradictory reports regarding the effect of PCSK9 inhibitors on inflammation [22]. Inflammation contributes to the initiation and progression of atherosclerosis up to plaque rupture and erosion, causing atherosclerotic cardiovascular disease (ASCVD) [23].

High-sensitivity C-reactive protein (hs-CRP) is an acute-phase mediator mainly produced by the hepatocytes, which is considered as a sensitive but non-specific biomarker of systemic inflammation [24]. Hs-CRP has been known as a risk marker/risk enhancer and potential risk factor for atherosclerosis [25] as well as a strong cardiovascular risk predictor [26], however the casual association between hs-CRP and CVD events has not been confirmed [27]. Mechanistically, hs-CRP can elevate the LDL uptake by macrophages and consequently accelerate foam cell formation, which has a direct role in the initiation of atherosclerotic plaque formation [28]. Several epidemiological studies have indicated a positive and strong association between plasma levels of PCSK9, hs-CRP, and acute-phase inflammation in patients with coronary artery disease (CAD) [29–31]. Nevertheless, despite the aforementioned association between PCSK9 and hs-CRP, there is evidence indicating no association between the treatment with mAbs-based PCSK9 inhibitors and changes in hs-CRP levels in CVD patients [32–36].

Other important inflammation modulators are reactive oxygen species (ROS) and related enzymes responded to oxidative stress, such as myeloperoxidase (MPO), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase. Oxidative stress is observed when there is an imbalance between the ROS generation and elimination, due to the impaired antioxidant defence system and/or the exacerbated activity of pro-oxidant enzymes [37]. It has been found that there is a link between PCSK9 production and oxidative stress [38–41], mediated predominantly by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent ROS generation [42, 43]. There are reports that demonstrated the up-regulatory effect of ROS on the PCSK9 expression and *vice versa* in vascular cells, leading to destructive inflammatory responses within atherosclerotic plaques [42–44]. Notably, the PCSK9 inhibition, by either the gene manipulation or anti-PCSK9 monoclonal antibodies, has been found to significantly attenuate ROS-mediated oxidative damage in the *in vitro* cellular model [45, 46] and various animal models [47, 48].

To the best of our knowledge, the antiPCSK9 vaccines on the hs-CRP level and the oxidative stress in an experimental inflammation model is understudied. During the recent few years, we have developed an antiPCSK9 vaccine [21] that could effectively induce the safe and long-lasting generation of the functional antiPCSK9 antibodies, which was accompanied with significant therapeutic [49, 50] and preventive [51, 52] effects against hypercholesterolemia and atherosclerosis in mouse and primate models. In the present study, we aimed to find whether the PCSK9 inhibition using the antiPCSK9 vaccine can affect the hs-CRP level and the oxidative stress during systemic inflammation.

Methods

The vaccine preparation

An immunogenic peptide construct containing PCSK9 and tetanus epitopes was designed using AFFITOME® technology [21, 53]. The peptide sequence (Table 1) with a purity grade of > 95% was synthesized and high-performance liquid chromatography (HPLC)-purified by ChinaPeptides Co., Ltd. (Shanghai, China). The peptide was adsorbed to 0.4% Alum adjuvant (Sigma-Aldrich) at the 1:1 (v:v) ratio and used for *in vivo* studies on mice.

Table 1. Sequences of the immunogenic peptides used in the current study

Peptide name	Sequence	Immunogenicity
PCSK9	S-I-P-W-N-L-E-R-I-T-P-V-R	B cell epitope
Tetanus	A-Q-Y-I-K-A-N-S-K-F-I-G-I-T-E-L	T cell epitope
PCSK9 peptide vaccine	SIPWNLERITPVRkkAQYIKANSKFIGITEL	

*A 2 lysine-spacer sequence (kk) as the target sequence of cathepsin protease involved antigen processing

Animals

8–10 weeks old albino mice (28 ± 3 g) were purchased from the laboratory animal research centre of Razi Vaccine and Serum Research Institute, Mashhad, Iran. All animal handling procedures were carried out in strict accordance with the Animal Welfare guidelines approved by the Institutional Ethics Committee and Research Advisory Committee of the Mashhad University of Medical Sciences, Iran (code: IR.MUMS.PHARMACY.REC.1400.010). The animals were housed in an air-conditioned room at a constant temperature of 22 ± 2°C with 12:12 h light/dark cycle and fed a standard rodent diet and water ad libitum. At the end of the study, all animals were euthanized by intravenous injection (30 mg/kg) of thiopental sodium.

Vaccination plan

Thirty male albino mice were randomly divided into three groups, including non-treated mice (the sham group), the mice treated with the Freund's complete adjuvant (CFA; the CFA group), and the vaccinated mice treated with CFA (the vaccine group). The vaccine group was subcutaneously immunized with the antiPCSK9 formulation (15 μg/mouse), four times in bi-weekly intervals, while the sham and CFA groups received the phosphate buffer by a similar route. After the vaccination plan, all mice were subjected to the CFA challenge to evaluate the effect of the antiPCSK9 vaccine on inflammation and oxidative stress status.

Developing CFA-challenged mice

To develop an animal model with acute inflammation and oxidative stress, the method of Fehrenbacher et al. [54] with some changes was used. In brief, CFA emulsion (0.5 mg/ mL) was prepared via mixing 0.5 mL of CFA (1 mg/mL of *Mycobacterium tuberculosis*, heat-killed and dried; Sigma-Aldrich, St. Louis, MO, USA) in 0.5 mL of sterile 0.9% saline buffer. The CFA group and the vaccine group were treated with 50 μL of freshly prepared homogeneous CFA emulsion (0.5 mg/mL) by subcutaneous injection into the left hind paw, while the sham group received 50 μL of the saline buffer by a similar route. According to our previous evaluation of CRP's kinetic [55], the serum hs-CRP reaches the highest level in CFA-challenged albino mice after 16-24 h; thus, a point in time was selected to evaluate the effect of the antiPCSK9 vaccine on inflammation and oxidative stress status. Mice were anesthetized and blood was withdrawn by cardiac drainage into a dry tube. Serum was separated by centrifugation at 1800 g for 10 min and kept at −20°C prior to analysis.

Evaluating the serum hs-CRP level and oxidative stress

To find the effect of the antiPCSK9 vaccine on acute inflammation, serum concentrations of hs-CRP were measured using a mouse CRP ELISA kit (Abcam; ab157712). To determine oxidative stress status, the pro-oxidant antioxidant balance (PAB) in the serum samples was assayed according to the previously described method [56]. In brief, a mix of 10 μL of each serum sample or standard solution and 200 μL of fresh working solution [containing TMB/ /DMSO solution, 0.05 M acetate buffer (pH 4.5), 100 mM chloramine T fresh solution, and 25 U of peroxidase enzyme solution] was loaded into a 96-well plate and incubated in a dark place for 12 minutes at 37°C. Then, 100 μL of 2 N HCL was added to each well and the OD was measured at 450 nm, with a reference wavelength of 620 nm or 570 nm. A standard curve was prepared using standard solutions with different proportions (0–100%) of hydrogen peroxide (250 μM) and uric acid (3 mM in 10 mM NaOH). Finally, the samples' PAB values were measured according to the prepared standard curve. The values of the PAB assay were expressed in an arbitrary HK (Hamidi-Koliakos) unit based on the percentage of hydrogen peroxide detected in the standard solution.

Evaluating the vaccine efficacy

To determine the efficacy of the antiPCSK9 vaccine in mice, plasma antiPCSK9 antibody titer, plasma PCSK9 concentration, and antibody inhibited PCSK9/LDLR interaction were measured as described in the following subsections.

Measuring plasma antiPCSK9 antibodies

The ELISA method was employed to evaluate the titer of plasma antiPCSK9 antibodies in vaccinated mice. In brief, 100 μL of serially diluted plasma samples (1:400 × 1:4) were loaded and incubated for 1h at 37°C in a 96-well Nunc-MaxiSorp plate coated with PCSK9 peptide. To detect attached antiPCSK9 antibodies, HRP-conjugated anti-mouse IgG (H + L) (Sigma Aldrich; dilution 1:1000) was added and incubated for 1 h at 37°C followed by the addition of the substrate TMB (3,3',5,5'-tetramethylbenzidine, Sigma-Aldrich) for 10 min at room temperature (RT). The optical density (OD) at 450 nm was measured with a microwell plate reader (Sunrise, Tecan, Switzerland) and the titers were defined as the dilution factor referring to 50% of the maximal optical density ($OD_{max}/2$). The results were presented as the mean titers ± SD of all animals per group.

Measuring plasma PCSK9 concentration

The concentration of plasma PCSK9 protein in vaccinated mice was measured by a PCSK9 ELISA kit (CircuLexTM, Cy-8078, MBL, Woburn, MA) in accordance with the manufacturer's manual. In brief, 100 μL of the diluted plasma samples (1:100) was incubated on a 96-well microplate for 1 h at RT. An HRP-conjugated anti-PCSK9 antibody was incubated for 1 h followed by adding the substrate reagent and stop solution, all at RT. The microwell plate reader was used to detect the OD at 450 nm. Eventually, a standard curve provided by the supplier was defined to measure the plasma concentration of PCSK9.

Evaluating the effect of plasma antiPCSK9 antibodies on the PCSK9-LDLR interaction

The potential of vaccine-induced antibodies to inhibit the interaction of PCSK9/LDLR was assayed by using a PCSK9-LDLR *in vitro* binding assay kit (CircuLex™, Cy-8150, MBL, Woburn, MA) in accordance with the manufacturer's manual. In brief, 100 μL of vehicle control or the plasma samples of vaccinated mice were loaded in a 96-well microplate pre-coated with the recombinant EGF-A domain of LDLR containing the binding site for PCSK9. Thereafter, the reaction was immediately initiated by adding a "His-tagged PCSK9 wiled type" solution incubated for 2 h followed by adding a biotinylated anti-His-tag monoclonal antibody for 1 h at RT. Subsequently, HRP-conjugated streptavidin was incubated for 1 h at RT followed by adding the substrate reagent and stop solution. The OD at 450 nm was measured with the microwell plate reader. Notably, the higher ELISA OD indicates a higher amount of PCSK9-LDLR interaction, while in the presence of plasma containing antiPCSK9 antibodies the interaction is inhibited and consequently a reduced ELISA OD will be detected.

Statistical analysis

One-way ANOVA and Tukey-Kramer post-hoc multiple comparison tests were carried out to measure the significance of the difference among groups, (Graph Pad Prism Software, version 9.0, San Diego, CA). Data were reported as mean ± SD. Data with $p < 0.05$ were regarded to be statistically significant.

Results

The antiPCSK9 vaccine induced the functional antibodies in albino mice

Upon three boosters, the antiPCSK9 vaccine was found to significantly promote a high-titer IgG antibody against the PCSK9 peptide in albino mice — the antiPCSK9 antibody titer (ODmax/2) was 12,925 ± 929 in the vaccinated mice, two weeks after the last immunization (Fig. 1A). The plasma concentration of free PCSK9 was found to be significantly ($p \leq 0.001$) reduced by –24.7% and –28.5% in the vaccine group when compared to the sham and CFA group, respectively (Fig. 1B). Moreover, to determine whether the vaccine-induced antiPCSK9 antibodies can inhibit PCSK9 function, CircuLex PCSK9-LDLR *in vitro* binding assay kit was employed. In the presence of the vaccinated mice's plasma samples, *in vitro* binding of murine PCSK9 and LDLR in the vaccinated group was significantly ($p < 0.05$) reduced by –27.8% and –29.4% when compared to the plasma samples of the sham group and the CFA group, respectively (Fig. 1C).

The antiPCSK9 vaccine and acute inflammation in CFA-challenged mice

It was shown that the antiPCSK9 vaccine could not significantly affect the increased level of serum hs-CRP in the CFA-challenged albino mice — the serum levels of hs-CRP in the vaccine, CFA, and sham groups were 14.65 ± 4.66 mg/L,

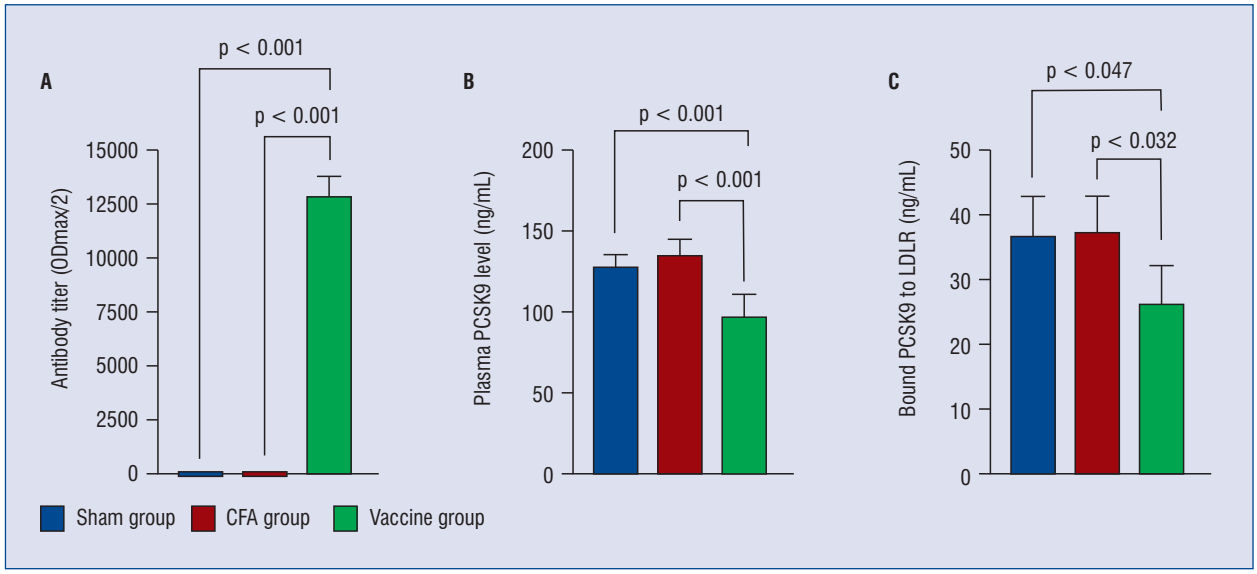

Figure 1. The efficacy of the antiPCSK9 vaccine in albino mice, two weeks after the last immunization. The sham group involved non-treated mice, the CFA group involved the CFA-treated mice, and the vaccine group involved mice who after vaccination were treated with the CFA. **A** — The antiPCSK9 antibody titer (ODmax/2) in the vaccinated and non-vaccinated albino mice. **B** — The plasma concentrations of the free PCSK9 in the vaccine, CFA, and sham groups were 97.4 ± 13.8 ng/mL, 136.2 ± 9.8 ng/mL, and 129.4 ± 7.8 ng/mL, respectively. **C** — *In vitro* PCSK9/LDLR binding assay. The levels of bound PCSK9 to LDLR in assays using the plasma samples of the vaccine, CFA, and sham groups, were 26.4 ± 5.4 ng/mL, 37.4 ± 5.6 ng/mL, and 36.6 ± 6.4 ng/mL, respectively. Data are expressed as mean ± SD (10 mice per group). Pooling of samples was performed to obtain sufficient sample volume for assay, when needed. Statistical differences at a p-value less than 0.05 were considered to be significant

17.84 ± 5.37 mg/L, 6.5 ± 2.02 mg/L, respectively (Fig. 2). The statistical analysis indicated that the level of hs-CRP was significantly increased in the vaccine and CFA groups by 225% ($p = 0.037$) and 274% ($p = 0.004$), respectively when compared with the sham group. It was non-significantly decreased in the vaccine group in comparison with the CFA group (by 18%, $p = 0.520$).

The antiPCSK9 vaccine and the oxidative stress in CFA-challenged mice

To determine the effect of the antiPCSK9 vaccine on oxidative stress, the balance between the plasma pro-oxidant load and antioxidant capacity was evaluated using the PAB assay. It was shown that the antiPCSK9 vaccine could not significantly affect the serum pro-oxidant/antioxidant status in CFA-challenged albino mice. The PAB values in the vaccine, CFA, and sham groups were 54.22 ± 10.93 HK, 53.19 ± 9.8 HK, and 30.8 ± 6.7 HK, respectively (Fig. 3). The PAB value (oxidative stress) was significantly increased in the CFA group (by 72.7%, $p < 0.001$) and the vaccine group (by 76%, $p < 0.001$) when compared with the sham group with no significant difference between the vaccine and CFA groups.

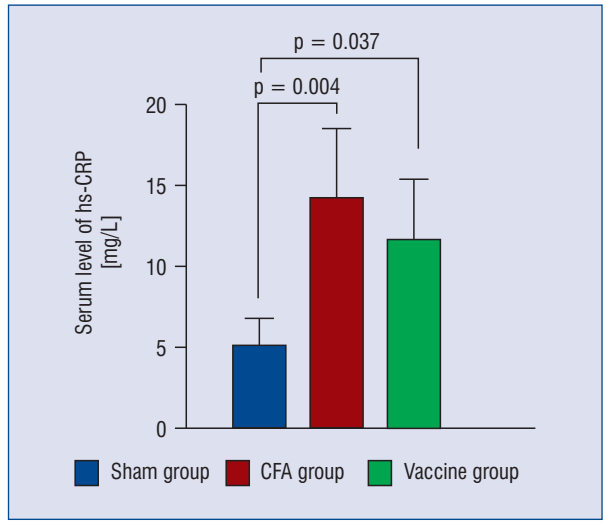

Figure 2. The effect of the antiPCSK9 vaccine on the serum level of hs-CRP in albino mice. The sham group involved non-treated mice, the CFA group involved the CFA-treated mice, and the vaccine group involved mice who after vaccination were treated with the CFA. Pooling of samples was performed to obtain sufficient sample volume for assay, when needed. Data are expressed as mean ± SD (10 mice per group). Statistical differences at a p-value less than 0.05 were considered to be significant

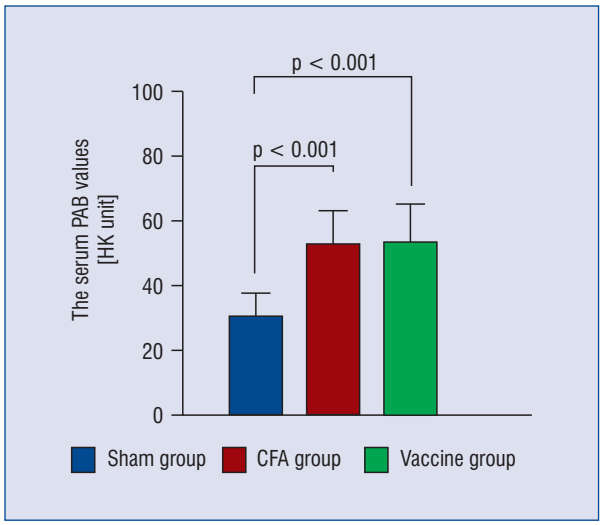

Figure 3. The effect of the antiPCSK9 vaccine on the serum PAB (pro-oxidant antioxidant balance) in albino mice. The PAB values were expressed in an arbitrary HK (Hamidi-Koliakos) unit. The sham group involved non-treated mice, the CFA group involved the CFA-treated mice, and the vaccine group involved mice who after vaccination were treated with the CFA. Pooling of samples was performed to obtain sufficient sample volume for assay, when needed. Data are presented as mean ± SD (10 mice per group). Statistical differences at a p-value less than 0.05 were considered to be significant

Discussion

The present study indicated that, despite inducing the production of the functional antiPCSK9 antibodies, the antiPCSK9 vaccine failed, despite numerical reduction, to significantly reduce the serum hs-CRP in the CFA-challenged albino mice. It was also observed that there was a lack of any reducing effect on the oxidative stress in this model. The production of the functional antiPCSK9 antibodies bounding blood circulating PCSK9 protein and consequently reducing the plasma level of PCSK9 and its interaction with the live LDLR has also been detected in previous studies, supporting the efficacy of this antiPCSK9 vaccine [21, 49–52].

Of note, there has been a paucity of studies evaluating the association of an antiPCSK9 vaccine and the serum hs-CRP levels in the inflammatory condition. A recent study [57] indicated that the present antiPCSK9 vaccine did not change the serum level of hs-CRP in healthy rhesus macaque monkeys. There have also been several clinical trials that investigated the effect of mAb-based PCSK9 inhibitors on inflammatory markers, especially on the hs-CRP levels, in patients with CVD, supporting the present results [31–36]. Data of the EQUATOR study, a randomized, multicenter, double-blind, and placebo-controlled phase II trial, demonstrated that 6 months of treatment with the antiPCSK9 mAb RG7652 did not change levels of the serum hs-CRP and pro-inflammatory cytokines IL-6 and TNF-α in patients at high risk for or with established CAD [31]. Similarly, a study in patients with stable CAD after premature myocardial infarction and very high lipoprotein(a) levels showed that plasma levels of hs-CRP were not altered after 6 months of treatment with the PCSK9 inhibitors alirocumab or evolocumab [32]. Consistently, no association between baseline levels of hs-CRP and efficacy of evolocumab in reducing adverse cardiovascular outcomes was also found in the FOURIER trial [33]. On the other hand, the larger efficacy of PCSK9 inhibitors in the reduction of CVD events was observed in the very high-risk patients with high baseline levels of hs-CRP [34, 58, 59]. These findings can be further supported by two independent meta-analyses of randomized controlled trials that failed to find a significant effect of antiPCSK9 mAbs on serum/plasma levels of hs-CRP [34, 35]. Therefore, the aforementioned findings imply that hs-CRP is not a response mediator to PCSK9 inhibitors, contrary to other lipid lowering drugs, especially statins, and more recently bempedoic acid (*via* AMP-activated kinase pathway activation) [60, 61].

Moreover, oxidative stress is an important inflammation modulator, and the current results indicated that the antiPCSK9 vaccine does not change the CFA-induced oxidative stress in albino mice. Similarly, a clinical trial showed that the administration of evolocumab had no impact on the activity of key antioxidant enzymes including catalase, SOD, and GSH-Px in erythrocytes of patients with CAD [62]. However, there are several reports showing the protective effect of PCSK9 inhibition against oxidative stress, by reducing the pro-oxidant load. An *in vitro* study showed that evolocumab could significantly reduce the concentration of malondialdehyde (MDA) and the ROS-mediated oxidative damage in human umbilical vein endothelial cells [45]. Another PCSK9 inhibitor, alirocumab, was found to decrease oxidative stress reactions in a rat model of alcoholic liver disease by reducing lipid peroxidation, the MPO activity, and frequency of infiltrating MPO-generating cells in the liver [48]. These findings suggest that although inhibition of the circulating PCSK9 does not affect the blood antioxidant capacity, it can reduce the pro-oxidant load through oxidative stress conditions. Of note,

since the present result was based on the PAB assay that shows the general changes of both pro-oxidants and antioxidants simultaneously in the serum/plasma samples, the lack of the effect of the antiPCSK9 vaccine on the PAB values may be due to a high load of the blood pro-oxidants in the CFA-challenged albino mice [63–71].

There are some limitations deserving acknowledgment. Firstly, despite the fact that a widely used inflammation model was used in this study, every experimental model of inflammation has limitations, and the results of this study may not be applicable to other types of inflammation, especially chronic inflammation such as that found in atherosclerosis. Secondly, there are many differences in the inflammation process between humans and rodents that should be considered when interpreting the results. Another noteworthy point is that in this study, the PCSK9 peptide vaccine was used in pure form without any delivery system, while the previous reports of the current group have mainly focused on the nanoliposomal form of the vaccine. Therefore, the comparison of liposomal and non-liposomal forms of peptide vaccine in terms of the effect on inflammatory and oxidative indicators can be investigated in future studies. Finally, according to the observed decrease in serum CRP levels in the vaccine group, conducting additional studies in this regard is suggested.

Conclusions

The results of the present study indicate that the antiPCSK9 vaccine, despite its significant efficacy in inhibiting PCSK9 function, could not protect against the CFA-induced acute systemic inflammation and oxidative stress in mice.

Acknowledgment: The study is reported in accordance with the ARRIVE guidelines (PLoS Bio 8(6), e1000412,2010).

Conflict of interests: M.B.: speakers bureau: Amgen, Daichii Sankyo, KRKA, Polpharma, Novartis, Sanofi-Aventis, Teva, Zentiva; consultant to Adamed, Amgen, Daichii Sankyo, Esperion, NewAmsterdam, Novartis, Sanofi-Aventis; Grants from Amgen, Daichii Sankyo, Mylan/Viatris, Novartis, and Sanofi; all other authors have no conflict of interest.

Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding authors on reasonable request.

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REVIEW ARTICLE

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Maintenance therapy with a P2Y12 receptor inhibitor after cangrelor in patients with acute coronary syndrome. The ELECTRA-SIRIO 2 investigators' viewpoint

Jacek Kubica[1], Piotr Adamski[1], Robert Gajda[2], Aldona Kubica[3], Małgorzata Ostrowska[1*], Gavino Casu[4], Diana A. Gorog[5, 6], Paul A. Gurbel[7], Tomasz Hajdukiewicz[8], Miłosz Jaguszewski[9], Young-Hoon Jeong[10, 11], Agata Kosobucka-Ozdoba[3], Zuzana Motovska[12], Piotr Niezgoda[1], Maciej Piasecki[1], Przemysław Podhajski[1], Paolo Raggi[13], Uzeyir Rahimov[14], Jolanta M. Siller-Matula[15, 16], Grzegorz Skonieczny[17], Łukasz Szarpak[18, 19], Paweł Szymański[20], Udaya Tantry[7], Eliano P. Navarese[4]

[1]Department of Cardiology and Internal Medicine, *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Gajda-Med District Hospital in Pultusk, Poland
[3]Department of Cardiac Rehabilitation and Health Promotion, *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland
[4]Department of Clinical and Interventional Cardiology, Sassari University Hospital, Italy
[5]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom
[6]Centre for Health Services Research, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom
[7]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, USA
[8]Department of Cardiology, Provincial Hospital, Elblag, Poland
[9]Department of Cardiology, Medical University of Gdansk, Poland
[10]CAU Thrombosis and Biomarker Center, Heart and Brain Hospital, Chung-Ang University Gwangmyeong Hospital, Korea
[11]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[12]Cardiocenter, Third Faculty of Medicine, Charles University, University Hospital Kralovske Vinohrady, Prague, Czech Republic
[13]Division of Cardiology and Department of Medicine, University of Alberta, Edmonton, Canada
[14]Department of Cardiology, Baku Medical Plaza Hospitals, Azerbaijan
[15]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland
[16]Department of Cardiology, Medical University of Vienna, Austria
[17]Chair of the Cardiology Clinic Ward and Acute Cardiac Care Unit, L. Rydygier Provincial Integrated Hospital, Torun, Poland
[18]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine Houston, TX, USA
[19]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[20]Department of Cardiology, Interventional Cardiology, and Electrophysiology with Cardiac Intensive Care Unit, Tertiary Care Hospital in Grudziadz, Poland

Address for correspondence: Małgorzata Ostrowska, MD, PhD, Department of Cardiology and Internal Medicine, *Collegium Medicum*, Nicolaus Copernicus University, ul. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel: +48 52 5854023, fax: +48 52 5854024, e-mail: m.ostrowska@cm.umk.pl

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Abstract

According to the ESC guidelines, cangrelor may be considered in P2Y12-inhibitor-naïve acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). The aim of this review is to summarize available evidence on the optimal maintenance therapy with P2Y12 receptor inhibitor after cangrelor. Transitioning from cangrelor to a thienopyridine, but not ticagrelor, can be associated with a drug-drug interaction (DDI); therefore, a ticagrelor loading dose (LD) can be given any time before, during, or at the end of a cangrelor infusion, while a LD of clopidogrel or prasugrel should be administered at the time the infusion of cangrelor ends or within 30 minutes before the end of infusion in the case of a LD of prasugrel. Administration of any oral antiplatelet agent at the end of a cangrelor infusion will also result in a transient period of increased platelet reactivity. The inter-individual variability of this period is difficult to predict because it depends on many factors related to the patient and the treatment. In addition, experimental studies indicate that cangrelor may exert a cardioprotective effect beyond the blockade of platelet aggregation. Considering the available data, the potential use of cangrelor in ACS patients goes well beyond the current indications. Furthermore, we believe that it might be prudent to avoid use of thienopyridines during and soon after a cangrelor infusion until conclusive data on the effect of the DDI on the clinical outcome are available. On the other hand, ticagrelor seems to be an optimal oral agent for continuation of P2Y12 inhibition in patients receiving cangrelor infusion. (Cardiol J 2025; 32, 1: 83–89)

Keywords: antiplatelet therapy, cangrelor, ticagrelor, P2Y12 receptor inhibition

Introduction

The optimal treatment of patients with acute coronary syndrome (ACS) should be focused on myocardial salvage by prompt restoration of myocardial perfusion, cardioprotection preventing reperfusion injury, and prevention of infarct-related artery re-occlusion due to a thrombotic event [1, 2]. The potent oral P2Y12 receptor inhibitors, prasugrel and ticagrelor, provide significant reduction of thrombotic events in ACS patients when compared with clopidogrel, and are therefore recommended as the first-line therapy in this subset of patients [1–7]. However, even prasugrel and ticagrelor may fail to achieve adequate platelet inhibition in ACS patients undergoing immediate invasive treatment. The onset of action of oral P2Y12 receptor inhibitors is substantially delayed in patients diagnosed with ST-segment elevation myocardial infarction (STEMI) [8, 9], especially in those who are critically ill [10–12], including patients undergoing targeted temperature management [13–17], or if morphine is used [18–22]. All such cases result in inadequate platelet inhibition during primary percutaneous coronary intervention (PCI), when the antiplatelet effect is most desired. In contrast to commonly used oral P2Y12 receptor inhibitors with delayed onset and offset of action, the favorable properties of intravenous P2Y12 receptor inhibitor cangrelor make it a desirable agent in the setting of high-risk ACS. Cangrelor is a potent, quickly reversible, direct-acting P2Y12 receptor antagonist with a linear and dose-dependent pharmacokinetic profile with predictable plasma levels, reaching optimal platelet inhibition within minutes after the start of infusion. It is rapidly metabolized through dephosphorylation by an endonucleotidase located on the surface of vascular endothelial cells, with an elimination half-life of 2.9 to 5.5 minutes [23–26]. Platelet function recovers within 60–90 minutes after termination of cangrelor infusion [27–29]. These unique properties of rapid onset and offset of antiplatelet effect make cangrelor an attractive therapeutic option complementary to available oral antiaggregatory agents. The aim of this review is to discuss available evidence on the optimal maintenance therapy with P2Y12 receptor inhibitor after cangrelor in patients with ACS.

The current place of cangrelor in the treatment of ACS patients

According to the ESC guidelines cangrelor may be considered in P2Y12 inhibitor-naïve patients undergoing PCI in STEMI and non-ST-elevation ACS (class IIb recommendation) or in those who are considered unable to absorb oral agents [1, 2]. Cangrelor should be administered in a bolus of 30 mcg/kg i.v. followed by 4 mcg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer) [2].

The European Medicines Agency approved the use of cangrelor in patients undergoing PCI who did not receive another P2Y12 receptor inhibitor

before the procedure and in subjects in whom oral P2Y12 inhibitor therapy is not feasible or desirable [31].

In the latest ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization, cangrelor is recommended for patients undergoing PCI, who are naïve to oral P2Y12 receptor inhibitors, to reduce periprocedural ischemic events (class 2B recommendation with level of evidence B-R) [32].

The Food and Drug Administration approved cangrelor in the United States as an adjunct to PCI to reduce the risk of stent thrombosis, periprocedural myocardial infarction, and repeated revascularization in patients not pre-treated with an oral P2Y12 inhibitor and without indication to receive glycoprotein IIb/IIIa inhibitors [33].

The timing of administration of oral P2Y12 inhibitors in patients receiving an infusion of cangrelor at the time of PCI should be drug specific (Central Illustration). According to the ESC guidelines in the transition from cangrelor to a thienopyridine, the thienopyridine should be administered immediately after discontinuation of cangrelor with a loading dose (LD) (clopidogrel 600 mg or prasugrel 60 mg); to avoid a potential drug-drug interaction (DDI), prasugrel may also be administered 30 min before the cangrelor infusion is stopped. Ticagrelor (LD 180 mg) should be administered at the time of PCI to minimize the potential gap in platelet inhibition during the transition phase [2].

The potential of cangrelor in the treatment of ACS patients

The results of the ATLANTIC trial provided good evidence for the clinical benefits associated with early inhibition of P2Y12 platelet receptors [35]. The study conducted in 1862 patients with STEMI failed to show superiority of early, pre-hospital administration of ticagrelor LD versus later administration in the catheterization laboratory, with regard to the co-primary end points defined as the proportion of patients who did not have 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients who did not meet the criteria for thrombolysis in myocardial infarction (TIMI) flow grade 3 in the infarct-related artery at angiography before PCI. The lack of benefit of the tested strategy of earlier ticagrelor administration was suggested to have resulted from a relatively small time difference of 31 minutes between the prehospital vs. in-hospital administration. Moreover, as many as 50% of the study participants received morphine, which may have further influenced the outcome of the study. In fact, a subgroup analysis revealed superiority of the tested strategy, as far as the primary endpoint was concerned, only in patients who had not received morphine [35]. Additionally, administration of morphine has been reported in the past to be associated with delayed onset of action of ticagrelor [36] and increased use of glycoprotein IIb/IIIa inhibitors [37].

P2Y12 receptor inhibition with cangrelor has the potential to produce even better results because it has an earlier, more potent effect, overcoming the impact of delayed and decreased absorption seen with oral P2Y12 inhibitors in patients with STEMI, in cardiogenic shock, in those receiving morphine or undergoing mild therapeutic hypothermia [8, 9, 11, 13, 14, 17, 18, 38, 39]. Sufficient platelet inhibition may also be uncertain in patients with nausea or vomiting, or in those who are unable to swallow or promptly absorb orally administered P2Y12 receptor inhibitors, i.e., patients who are sedated and/or intubated. In contrast, cangrelor produces rapid, effective, and predictable platelet inhibition in these subgroups of patients [25, 26, 29].

In addition, experimental studies indicate that cangrelor may exert a cardioprotective effect beyond the blockade of platelet aggregation [40, 41]. This effect appears to be related to the same signal transduction pathway involved in pre- and post-conditioning. Administration of cangrelor shortly before reperfusion in rabbits reduced infarct size by approximately 50% [40]. Cangrelor-related myocardial salvage was dose dependent and correlated with the degree of inhibition of platelet aggregation. Cardioprotection was absent when cangrelor was used in crystalloid-perfused isolated hearts, indicating the involvement of an undefined whole-blood component in this process. This myocardium saving effect against reperfusion injury may be a class effect and hence common for all P2Y12 inhibitors. However, with cangrelor the protective effect develops within a short time — typically required in the target population of patients with myocardial infarction and occluded infarct-related artery [41, 42]. To date, these experimental findings have never been tested in a clinical trial.

Interactions of cangrelor with oral inhibitors of P2Y12 receptor

Cangrelor rapidly disappears from the plasma after termination of infusion due to its very short half-life. Furthermore, because of its reversible

binding, the drug dissociates from the P2Y12 receptors, making them available for binding with clopidogrel active metabolite [26, 29]. To continue P2Y12 inhibition after a PCI, it is necessary to transition to an oral agent in the immediate post--procedure period. However, transitioning from cangrelor to a thienopyridine (clopidogrel and prasugrel), but not ticagrelor, can be associated with a DDI [43–51].

Steinhubl et al. [46] showed that cangrelor and clopidogrel administered alone in healthy volunteers produce the expected level of platelet inhibition. The anticipated effect of clopidogrel treatment did not occur when cangrelor was initiated simultaneously. Such an effect was not found when clopidogrel was started upon completion of the cangrelor infusion. However, a transient recovery of platelet reactivity was observed as the inhibitory effect of cangrelor disappeared, followed by further inhibition as the clopidogrel was metabolized to its active form [46]. The *in vitro* experiments reported by Dovlatova et al. provided a mechanistic explanation for these findings and showed the possibility of a parallel scenario arising when prasugrel is used in the place of clopidogrel [47]. They confirmed the interaction between cangrelor and both thienopyridines, limiting the antiplatelet effect of clopidogrel and prasugrel to a degree dependent on the concentration of cangrelor. Presumably, occupation of the platelet P2Y12 receptors by cangrelor prevents the covalent binding of the clopidogrel or prasugrel metabolite. Therefore, due to the relatively short half-life of the active metabolites of clopidogrel and prasugrel, administration of thienopyridines at high concentrations of cangrelor precludes irreversible blocking of P2Y12 receptors, and the full effect of oral therapy may not be achieved until the subsequent administration of the second dose of the drug [47–50]. On the other hand, administration of any oral antiplatelet agent at the end of cangrelor infusion will also result in a transient period of increased platelet reactivity. The inter-individual variability of this period is very difficult to predict because it depends on many factors related to the patient and treatment.

In contrast to thienopyridines, a lack of interaction between cangrelor and ticagrelor reported in several studies [44, 53, 54] is to be expected because the mechanism of action of these reversible P2Y12 receptor inhibitors is similar. Therefore, the LD of ticagrelor should be administered at the initiation of cangrelor infusion or even before. As a result, when the cangrelor infusion is stopped and the drug is rapidly cleared from the circulation, ticagrelor can bind to the P2Y12 receptors. During the transition period, the platelet reactivity should reflect current plasma concentrations of both these agents [53].

These findings may be clinically relevant, but much more data are required to validate our limited knowledge of the transition from intravenous to oral inhibitor of P2Y12 receptor [45–47, 51–55].

Summary

Considering the available data, the potential use of cangrelor in ACS patients goes far beyond the current indications. Furthermore, we believe that it might be prudent to avoid use of thienopyridines during and soon after a cangrelor infusion until conclusive data on the effect of the DDI on clinical outcome are available. On the other hand, ticagrelor seems to be an optimal oral agent for continuation of P2Y12 inhibition in patients receiving a cangrelor infusion.

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ZM — reports research grants from Idorsia; PR — reports lecture fees/honoraria from Amgen, Novo Nordisk, and Novartis outside the submitted work; EPN — reports research grants from Abbott, Amgen, and lecture fees/honoraria from Amgen, AstraZeneca, Bayer, Pfizer, and Sanofi-Regeneron, outside the submitted work; AK-O, TH, RG, PN, MP, PP, UR, JMS-M, GS, ŁS, PS, UT — none.

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Rationale and design of the MICE study: Exploration of the temporal relation between electrical and mechanical events during myocardial ischemia

Niya Mileva[1, 2*], Teodora Yaneva-Sirakova[3*], Irina Hristova[4], Despina Georgieva[4], Greta Koleva[4], Dimitra Psalla[5], Ranko Georgiev[6], Dobrin Vassilev[1, 4]

[1]Medica Cor Hospital, Ruse, Bulgaria
[2]Medical Faculty, Medical University of Sofia, Sofia, Bulgaria
[3]Medical Institute of the Ministry of Interior, Cardiology Clinic, Sofia, Bulgaria
[4]Department of Health Care, University of Ruse "Angel Kanchev", Ruse, Bulgaria
[5]Laboratory of Pathology, School of Veterinary Medicine, Aristotle University of Thessaloniki, Greece
[6]Central Veterinary Clinic, Sofia, Bulgaria

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Background

The contemporary treatment of coronary artery disease (CAD) is based on our understanding of the myocardial ischemic process and the hypothesis of "ischemic cascade" [1]. This concept was developed more than 30 years [1]. The term "cascade" indicates that the requirements from the previous step should be met for every consecutive stage to occur (**Suppl. Fig. 1**). Thus, it postulates that at the time of acute ischemia, there is a reduction of blood flow (supply-demand mismatch), then left ventricular diastolic, followed by systolic dysfunction, electrocardiogram (ECG) abnormalities, and lastly-angina. A drop in oxygen supply reduces adenosine triphosphate production and results in lactic acidosis, which causes electrical dysfunction. This process is directly followed by cellular mechanical dysfunction [2]. It can be conferred that on a cellular level, biomechanical and electrical changes coincide. However, human circulation has collateral flow and other metabolic reserves on the tissue level [3, 4]. Thus, the exact metabolic consequences of oxygen supply-demand mismatch in the given heart remain unknown [3]. The speed of electrical and mechanical changes in the myocardium depends on many factors: the amount of affected myocardium, collateralization, myofilament isoforms, energy stores, etc. [4–9]. These factors were studied separately.

Based on current knowledge, there are a constellation of ischemia-induced processes at a cellular level and a cascade at the tissue level, which sounds highly improbable [10]. It is hypothesized herein, that ischemic changes (electrical and mechanical) in myocardial function are not uniform and depend on the extent of flow reduction and the location of the ischemic zone. For the reevaluation of the ischemic processes both on a cellular and tissue level, a simultaneous recording is needed of the mechanical and electrical activity at the same location in the heart.

According to available research, no experimental or clinical study has explored myocardial biochemical, mechanical, and electrical events simultaneously, at a single location, during ischemia until the

Address for correspondence: Niya Mileva, MD, Medical University Sofia, Georgi Sofiiski 1, 1431 Sofia, Bulgaria, tel: +35 9897983936, e-mail: nmileva91@gmail.com
*These authors contributed equally to this manuscript

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present study. Preliminary observations during the percutaneous coronary intervention (PCI) in humans suggest that the movement of the PCI wire positioned in a coronary artery during ischemia should follow the general left ventricle (LV) wall mechanics at that time [11]. In addition, animal-based experiments using a porcine model with simultaneous contrast-enhanced transesophageal (TOE) assessment of myocardial kinetics was performed. The results of these experiments showed excellent correlation between TOE and PCI wire assessment [12]. It has been demonstrated that the ECG signal acquired intracoronary should be at least as accurate as the conventional surface ECG, and it will provide precise simultaneous information from the same region of interest [11, 13]. The sequence of events is important, as the current understanding of diagnosis of myocardial ischemia is based on sequence of events during ischemic cascade. It is given a clear superiority in recommendations of imaging modalities over ECG stress testing [9]. The lower sensitivity and specificity of ECG stress test is explained based on ischemic cascade, while it is possible that the reason is the influence of different chest geometric factors [14]. This is mere speculation, but if the ischemic cascade existed, the prognostic implications of different ischemia provocative tests should be different, as mechanical contraction failure should signify a higher decrease in flow, i.e. higher grade stenoses, anatomic and/or functionally. According to available research, there is no publication supporting such a relationship.

Therefore, the objective of the current study is to explore the temporal relationship between electrical and mechanical events during early myocardial ischemia using a single PCI wire, which could be easily applied in clinical practice for patients undergoing invasive coronary angiography and PCI.

Methods

Study design

MICE is an investigator-initiated prospective, observational, single-center diagnostic performance study of 323 patients. Patients eligible for the study are those with chronic coronary syndrome that were referred for invasive coronary angiography and a significant stenosis. All patients will undergo conventional coronary angiography with a simultaneous recording of intracoronary ECG and left ventricular wall motion at rest, followed by exact measurements in a condition of induced acute ischemia. Detailed inclusion and exclusion criteria are described in Table 1.

The study protocol has been approved by the local Ethics Committee. All study subjects will be managed in accordance with the Declaration of Helsinki and provided with written informed consent prior to undergoing any study-specific procedures. This study is registered as www.clinicaltrials.gov number NCT04061525. The study leadership is composed of a principal investigator, a co-principal investigator and steering committee. Clinical events will be adjudicated by an independent clinical events committee.

Primary and secondary endpoints

Primary endpoint of the study is the feasibility of the method using a single PCI-wire for the evaluation of the sequence of occurrence of electrical and mechanical myocardial events during acute ischemia induction, assessed as percentage of successful simultaneous recordings of mechanical and electrical changes after ischemia induction by inflation of a coronary balloon into the target lesion.

The secondary endpoints include: 1) Proportion of patients in which mechanical events occurred as a first manifestation of ischemia; 2) Proportion of patients in which electrical events occurred as a first manifestation of ischemia; 3) Periprocedural myonecrosis evaluated by the extent of post-PCI troponin and Creatin phosphokinase MB fraction elevation 4) All-cause death at 12-month follow-up; 5) Cardiovascular death at 12-month follow-up; 6) Non-fatal myocardial infarction at 12-month follow-up; 7) New onset angina or heart failure symptoms at 12-month follow-up; 8) Target lesion revascularization at 12-month follow-up.

Patient selection

Patients eligible for the study will be those with chronic coronary syndrome that were referred for invasive coronary angiography and a significant, ≥ 50% diameter stenosis artery scheduled for intervention. Patients with acute coronary syndrome and hemodynamically unstable patients will be excluded from the protocol. Furthermore, patients with left bundle branch block, pacemaker stimulation, permanent atrial fibrillation, LV ejection fraction less than 40%, previous myocardial infarction in the area of interest, or Q-wave on surface ECG at the same zone. Also, patients with left main coronary artery stenosis, total coronary occlusion, previous coronary artery bypass grafting (CABG), primary cardiomyopathy, will be excluded.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age ≥ 18 years	1. Age < 18- or > 90-years old
2. Willing and able to provide written informed consent	2. Acute coronary syndromes
3. Patients with chronic coronary syndrome	3. Hemodynamic instability
4. Indication for invasive coronary angiography	4. Left main coronary artery stenosis
5. Significant ≥ 50% diameter stenosis	5. Total coronary occlusion
	6. Previous CABG
	7. Left ventricular dysfunction EF < 40%
	8. Previous myocardial infarction in the area of interest
	9. Myocardial scar (Q-wave on superficial ECG) in the area of interest
	10. Left or right bundle branch block
	11. Atrial fibrillation/flutter
	12. Pacemaker stimulation
	13. Severe renal dysfunction, defined as an eGFR < 30 mL/min/1.73m^2
	14. Cardiomyopathy (dilated, hypertrophic, amyloidosis, arrhythmogenic right ventricular dysplasia)
	15. Left bundle branch block or baseline ST segment depression >1 mm
	16. Unable to provide written IC

CABG — coronary artery bypass grafting; ECG — electrocardiogram; EF — ejection fraction; eGFR — estimated glomerular filtration rate; IC — informed consent

Study procedures

Examination at rest

1. Invasive coronary angiography will be performed following standard protocol, after intracoronary nitroglycerin injection (100–200 μg). Then the projection providing the best visualization of the movements of the target coronary artery will be chosen.
2. After placement of a pressure measuring device (pressure wire or coronary pressure microcatheter) at least 10 mm below the distal edge of the coronary stenosis, nonhyperemic indexes will be recorded. A fractional flow reserve measurement will be performed using intracoronary papaverine injection (20 mg for left coronary artery and 15 mg for right coronary artery). After achievement of steady-state FFR is measured and then a pull-back for assessment of pressure step-ups will be performed.
3. A non-polymeric coronary guidewire 0.014" PCI wire is introduced in the target artery with a radiopaque part at least 10 mm distal from the coronary ostium and in a coronary artery segment with maximal movement amplitude of a coronary artery segment of interest. The radiopaque distal part of PCI wire should be located in mid to distal segment of the target artery with the highest amplitude of vessel contraction. The proximal outer end of the PCI wire is connected to a unipolar ECG electrode. Then the movement of the radiopaque part of the coronary wire and the icECG will be recorded for a baseline record of 5 cardiac cycles. Furthermore, the patient will be asked to report the severity of chest pain experiencing grading it from 1 being the lowest to 10 being the most severe pain during the remaining part of the procedure.

Ischemia induction

4. PCI balloon with a length of 6 to 10 mm and a diameter of 70–100% of the distal reference diameter of target vessel will be positioned on the PCI wire. The balloon will be inflated up to maximal configuration and will be kept dilated for a duration of 60 seconds. Every 10 seconds, a recording of the fluoroscopy

(without contrast injection) for 3–5 consecutive cycles are performed. The icECG recording is obtained during the time of balloon inflation and the patient is asked to report the severity of chest pain if/when it appears. After 60 seconds the balloon will be deflated and removed from the artery. During the next 60 seconds the recording continues — wire movements on fluoroscopy are made after each 10 seconds interval. The whole procedure is digitally recorded by a high-resolution camera capturing both icECG and the angiographic screen. The time of both monitors are synchronized for analysis of event timing.

Final evaluation

5. Final angiography and icECG will be recorded two minutes after the balloon dilatation. The patient is asked to report the severity of chest pain that is being experienced. Further treatment strategy (stent implantation, drug-eluting balloon inflation etc.) and medical therapy will be at the discretion of the treating physicians. Adherence to the ESC guideline recommendation is encouraged.

Intracoronary ECG analysis

Intracoronary ECG is acquired by attaching an alligator clip to 0.014-inch PCI wire (Runthrough, Terumo Japan; Sion Blue, Asahi, Japan, BMW Universal II, Abbott Vascular, USA) positioned in the distal third of a major coronary artery. The clamp is connected to a precordial ECG V1 — lead. In case of coronary stenosis at a bifurcation site, a second wire is allowed with recording function from the side branch with the same parameters as from the wire in the main vessel. A second wire is attached to the ECG V2 — lead.

The recorded intracoronary and surface ECG leads, with simultaneously recorded aortic blood pressure curves will be printed and analyzed consecutively. The speed of the ECG recording is 50 mm/s and ECG amplitude was calibrated as 10 mm/mV. Measurement of the ST-segment shift is based on the determination of the isoelectric line and the Junction-(J)-point. The isoelectric line represents the reference line for the measurement and is set at the TP-interval as recommended [13]. The J-point is defined as the transition of the QRS-complex to the ST-segment, 80 ms after the end of QRS-complex. Using these two markers the calculation of the ST-segment shift is performed as the difference in mV between the isoelectric line and the ST-amplitude at the J-point. The ST-segment elevation is equal to or more than 0.1 mV was accepted as a sign of ischemia.

Analysis of PCI-wire kinetics

Motion of the PCI wire will be recorded by fluoroscopy storing mode (at 7.5 frames per second) throughout the cardiac cycle, both at rest and during the ischemia induction. Various parameters described in detail in the supplementary material will be measured and compared between the rest and acute ischemia phases (**Suppl. Fig. 1, 2**). To ensure simultaneous recording of the events, the two monitors for angiography and hemodynamics were placed close to each other. A dedicated camera obtaining the full range of both monitors recorded the whole study. The recording was used for analysis and synchronization of the exact timing of each mechanical and electrical event. The timing of each mechanical event was matched with the records from the icECG. A detailed description is illustrated in (**Suppl. Fig. 2**).

Statistical analysis

The MICE study is designed to assess: 1) the feasibility of the method for simultaneous evaluation of the consequence of electrical and mechanical myocardial changes during early myocardial ischemia using a single PCI wire. For the feasibility analysis, the rate of procedures with successful simultaneous recording of myocardial electrical and mechanical events during rest and ischemia induction will be calculated. The sample size was calculated based on previous data from COSIBRIA study [11], that 70% of patients have dynamic ST-segment elevation during coronary bifurcation PCI. If the same percentage is assumed in the current study, then 322.68 patients will be needed to detect differences in mechano-electrical coupling with 80% power and 95% level of confidence. Thus 323 patients will be needed. All analyses will be performed using Statistical Package for Social Sciences, version 25.0 (SPSS, PC version, Chicago, IL, USA) and R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient enrollment started in July 2022, and until July 2023, 69 patients and 82 vessels were included. Mean age was 67 ± 5, 74% were males, and 25% were diabetics. The target vessels assessed was LAD/diagonal in 56 of the cases (69%), LCX/OM in 20 cases (24%), and RCA in six cases

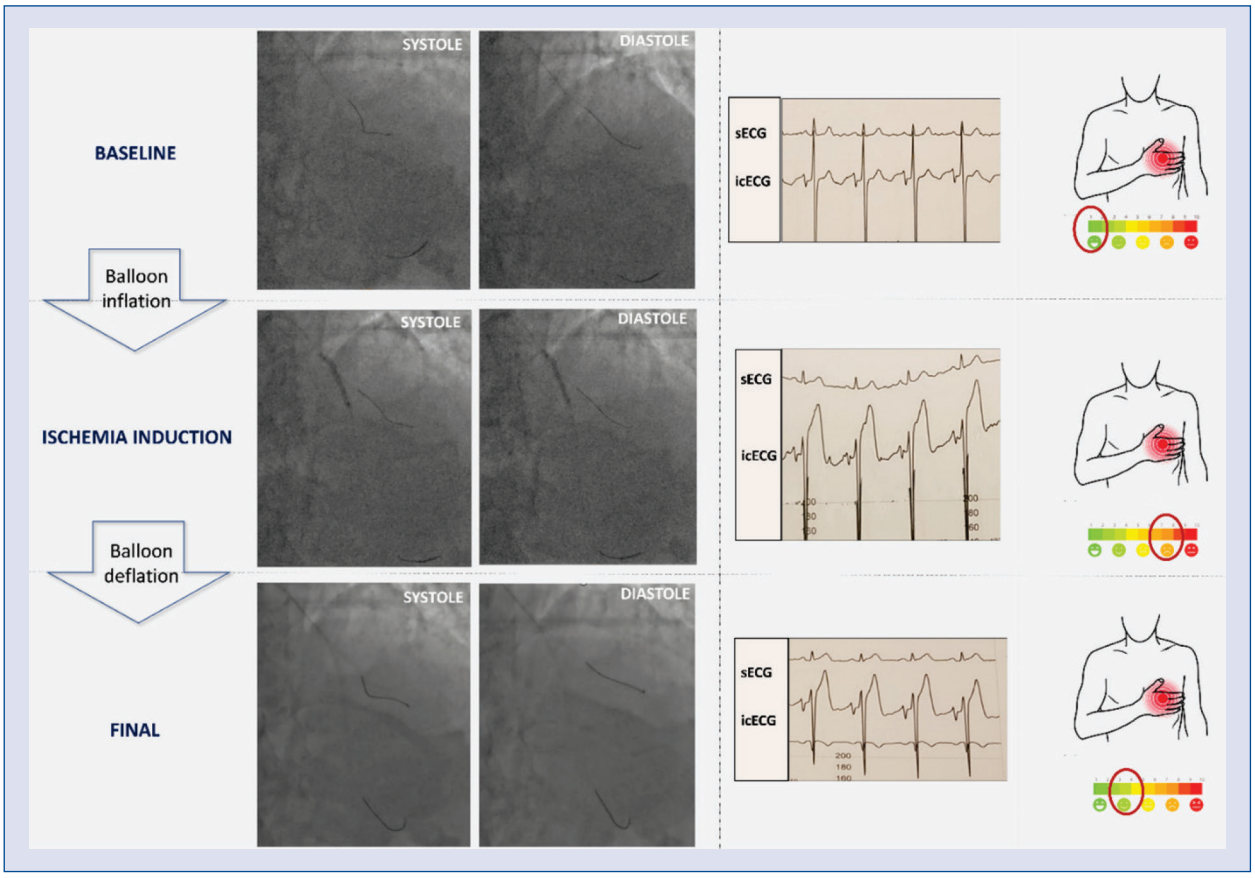

Figure 1. Case example; illustration of the mechanical and electrical events upon ischemia stimulation with balloon inflation; iECG — intracoronary electrocardiogram; sECG — surface electrocardiogram

(7%). Simultaneous recording of the mechanical and electrical changes after temporary ischemia induction was feasible and successful in 100% of the cases. In 55% (n = 45) of the vessels, the electrical changes with ST-elevation on intracoronary ECG were registered as the first manifestation of ischemia. In 36% (n = 30) the first ischemia manifestation was the reduction in the left ventricular contraction. In 9% (n = 7) of the cases electrical and mechanical changes were registered simultaneously and neither of the two events could be recorded as the first to occur. The case example is illustrated in Figure 1. Completion of enrollment is expected in September 2024.

Discussion

The diagnosis and treatment of myocardial ischemia caused by coronary artery disease still represent a significant problem. One of the reasons is that the current understanding of the ischemic process still relies on theconcept of "ischemic cascade". This perception is implemented in clinical practice guidelines about patients with the CAD treatment strategy. According to the current recommendations, patients with ECG changes, especially those with accompanying chest pain, have the highest priority for invasive diagnostics and treatment [15–17]. However, previous data demonstrating the ischemic cascade theory reveals inconsistent results among investigators [18–20]. In some studies, a decreased flow was assumed to cause ischemia based on observations of relatively unchanged systolic blood pressure-heart rate product as a surrogate for oxygen consumption [6, 18]. Other studies accept flow disturbances as a surrogate of ischemia, which is questionable, considering a sizeable biological variation between people [7].

It is generally accepted that myocardial contraction ceases within seconds/minutes of interrupted or decreased coronary blood flow [1, 6, 21–23]. With the decrease in coronary blood flow, first, the function of the subendocardium is impaired, and with further reduction, the whole cardiac wall contraction stops. It should be noted

that observations about the sequence of events are not concordant. Some studies report a simultaneous decrease in the extent of muscle contraction of the whole myocardial wall, probably because of the tethering effect between neighbor myofibrils. According to available research, there is no description of how the contraction and local pattern of left ventricular wall contraction interacts with the regional pattern of movement of coronary arteries. The research in that area was concentrated only on the assessment of global LV function and its relationship with atherosclerosis development [24–28].

The hypothesis herein, is that part of the inconsistency about the importance of ischemia as a clinical decision trigger is due to methods for its verification, which is a result of erroneous acceptance of the "ischemic cascade" dogma. For example, in the ISCHEMIA study, a couple of different tests were used to demonstrate ischemia — nuclear perfusion via SPECT or PET (showing metabolic changes during ischemia), echocardiography, cardiac magnetic resonance (perfusion and mechanical consequences) and exercise ECG test [29]. The problem is that each of these tests demonstrates a different stage of the "ischemic cascade", and as such, the result of each test is incomparable to each other.

According to available research, this is the first study to explore myocardial mechanical and electrical events simultaneously during ischemia in a man. The element of simultaneity in evaluating ischemic processes is critical to understanding which events have higher predictive value. Interventions demonstrating reduction of infarct size, based on epicardial ECG recording, later, failed to do so in clinical trials. Therefore, intracoronary ECG registration may provide much more accurate information in combination with a recording of mechanical events simultaneously. It is essential to examine which event occurs first and which factors are associated with discrepancies if/when they exist.

Intracoronary ECG was first developed to detect potential epicardial changes in an animal study [30]. It was demonstrated as a very sensitive tool for early ischemia detection [31–34]. It could also be used to assess the viability of myocardium during PCI and evaluate the adequacy of coronary collateral circulation [13, 35–37]. The present study demonstrated that icECG ST-segment elevation in side branches after coronary bifurcation stenting is equally sensitive and more specific for ongoing ischemia detection than FFR [38]. Furthermore, it was demonstrated that some changes in icECG after bifurcation stenting are associated with long-term mortality, and others have shown an increased rate of major adverse cardiovascular events [39–41]. Moreover, the experimental data has described a good sensitivity and specificity of epicardial electrodes for detecting ischemia, even in the subendocardial region [42].

All processes that develop during acute ischemia are deeply interconnected. Therefore, only the simultaneous registration of the mechanical and electrical changes could provide the exact diagnosis of acute ischemia. Thus, a method for concurrent registration of electrical and mechanical events using a single PCI wire was proposed. This method could be easily applied in everyday clinical practice allowing for a better understanding of the intricate process of myocardial ischemia. This, in its favor, may result in saving patients' lives and result in a reduction in medical costs. A further study is to prove the concept in a porcine model.

Limitations

The present study has several possible limitations. First, its observational nature. Second, the sample size is relatively small; nevertheless, the study is powered to assess the feasibility of the method using a single PCI wire for simultaneous evaluation of the events during early ischemia. It will provide a base for further studies, with bigger sample sizes to better understand the temporal relationship between ischemic mechanical and electrical changes in the myocardium. Furthermore, echocardiographic assessment during the protocol would provide additional information regarding left ventricular diastolic and systolic function.

Conclusions

This prospective, single-center study will determine the feasibility of a method for simultaneous registration for electrical and mechanical myocardial changes during acute ischemia using a single PCI wire in humans. This could allow for a better understanding of the ischemic process and benefit future diagnosis and therapy of patients with CAD.

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Multivessel disease treated with a double-kiss culotte and chronic total occlusion with support of quantative flow ratio, intravascular ultrasound and shockwave intravascular lithotripsy

Mateusz Barycki[1*], Piotr Rola[1, 3*], Adrian Włodarczak[2, 3], Szymon Włodarczak[2], Yoshinobu Onuma[4], Patrick W. Serruys[4, 5], Maciej Lesiak[6]

[1]Department of Cardiology, Provincial Specialized Hospital in Legnica, Legnica, Poland
[2]Department of Cardiology, Copper Health Centre (MCZ), Lubin, Poland
[3]Faculty of Medicine, Wroclaw University of Science and Technology, Wroclaw, Poland
[4]Department of Cardiology National University of Ireland, Galway (NUIG), Ireland
[5]CORRIB Research Centre for Advanced Imaging and Core laboratory, NHLI Imperial College London, United Kingdom
[6]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

A 72-year-old man with a history of hypertension, hypercholesterolemia, and type 2 diabetes was admitted to the cardiology unit for unstable coronary angina. Coronary angiography revealed advanced multivessel coronary disease with stenoses in the left anterior descending (LAD) artery, proximal circumflex (Cx) artery, obtuse marginal (OM) branches, and a total chronic occlusion (CTO) in the right coronary artery (RCA) (Fig. 1A) (SYNTAX Score: 39 points). Left ventricular ejection fraction was 55%.

The patient was scheduled for evaluation by the Heart Team. However, the patient refused surgical treatment. Percutaneous coronary intervention (PCI) planning involved quantitative flow ratio (QFR) assessment from an independent core laboratory (LAD QFR-0.78; Cx/OM1 QFR-0.79, OM2 QFR--0.90; OM3 QFR-0.74; distal Cx QFR-0.79) (Fig. 1B).

During the procedure, a no-flow phenomenon occurred after wiring the Cx and OM1 branch (Fig. 1C). Treatment decisions relied on the QFR and intravascular ultrasound (IVUS) assessment. The distal Cx was stented with two overlapping drug-eluting stents (DES): 2.25 × 16 mm and 2.5 × 20 mm. The Cx/OM1 bifurcation was managed using the double-kiss culotte technique with two DES: 2.5 × 20 mm and 3.0 × 12 mm. IVUS revealed severe stent under-expansion distally to the bifurcation (Fig. 1D, E). Additional interventions, including a non-compliant balloon and shockwave intravascular lithotripsy with a 3.0 × 12 mm catheter (80 impulses), were performed to achieve full stent expansion (Fig. 1F).

The LAD was treated with three overlapping DES: 2.25 × 8 mm, 2.5 × 38 mm, and 2.75 × 38 mm under IVUS guidance. Staged CTO-RCA-PCI, performed after ischemia was demonstrated in a stress ECHO, involved an antegrade wire escalation technique and the implantation of two DES: 2.5 × 32 mm (Fig. 1G).

Conflicts of interest: None to declare.

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Address for correspondence: Mateusz Barycki MD, Department of Cardiology, Provincial Specialized Hospital Legnica, ul. Iwaszkiewicza 5, 59–220, Legnica, Poland, tel: +48 609 560 059, e-mail: mateuszbarycki@gmail.com
*These authors contributed equally to this work.

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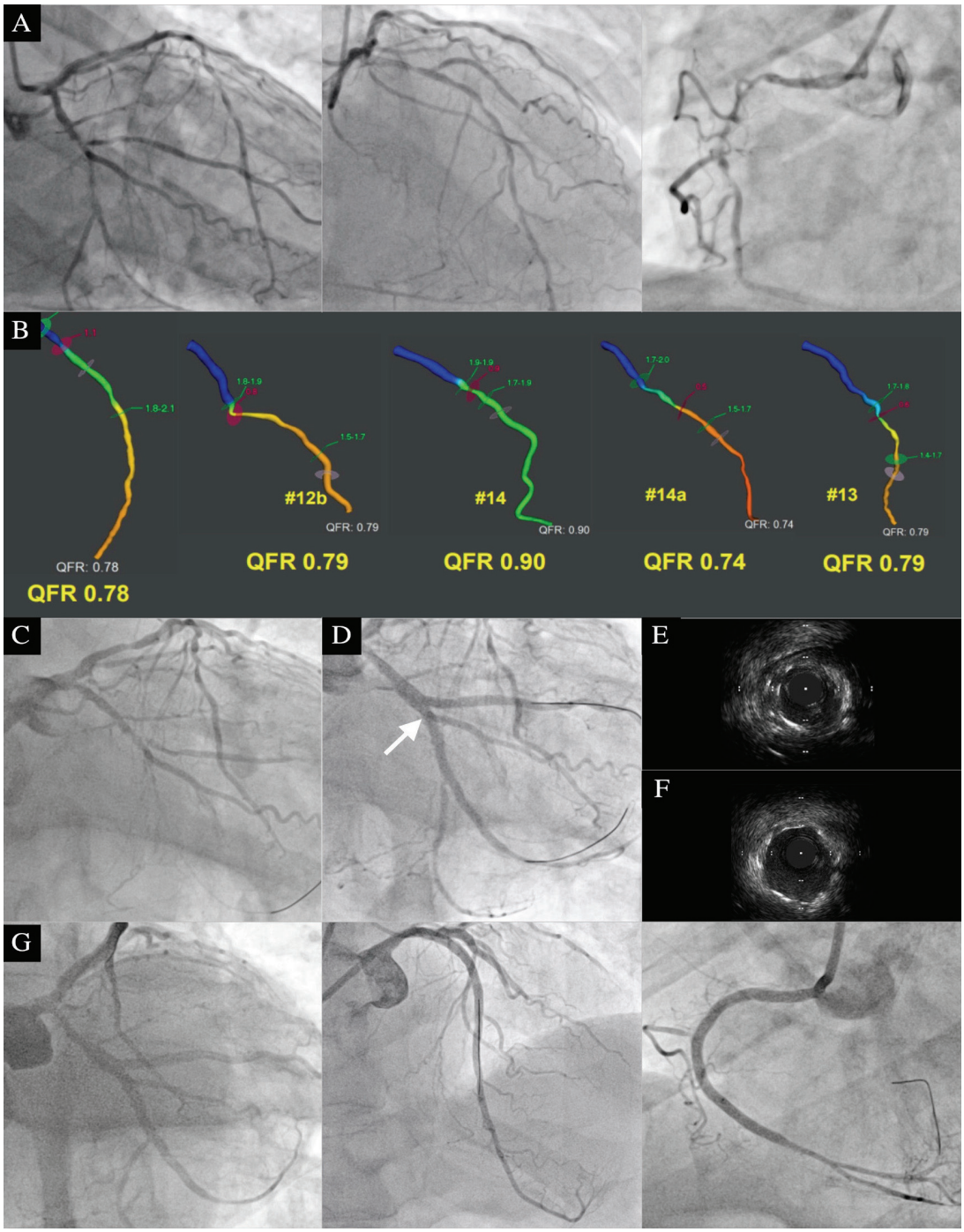

Figure 1. A. Initial coronary angiography of the left and right coronary arteries showing multivessel coronary disease; **B.** External core lab quantitative flow ratio assessment; **C.** No-flow phenomenon observed after wiring the Cx and OM1 branch; **D.** Although good angiographic results were achieved with the double-kiss culotte technique for Cx/OM1 bifurcation stenting, subsequent control IVUS revealed severe stent under-expansion (white arrow) with a minimum stent area (MSA) of 3.34 mm ^ 2 (**E**); Following treatment with Shockwave Intravascular Lithotripsy (S-IVL) (80 pulses), control IVUS showed a MSA of 5.67 mm ^ 2 (**F**); **G.** Final coronary angiograms after LAD and Cx/OM1 PCI and staged CTO-RCA PCI

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Air embolism resulting from atrioesophageal fistula following thoracoscopic atrial fibrillation ablation

Fangxiao Gong, Sen Ye

Emergency and Critical Care Center, Intensive Care Unit, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, China

A 72-year-old man with a 3-year history of atrial fibrillation (AF) underwent thoracoscopic bipolar radiofrequency ablation under cardiopulmonary bypass, including pulmonary vein isolation with connecting roof and inferior lines and a connection between the left atrial appendage and the left superior pulmonary vein. He had a history of hypertension and no digestive diseases. On day 2 post-ablation, he developed fever (38.3°C), hypoxemia (PaO_2/FiO_2 211 mmHg), and pneumonia, requiring intubation for mechanical ventilation on day 4 in the ICU. On day 20, he developed Klebsiella pneumoniae bacteremia and fell into a coma on day 23.

Head CT revealed multiple low-density lesions and pneumocephalus in both cerebral hemispheres (Fig. 1A). Thoracic CT showed air had extravasated outside the esophagus and entered into the pericardium near the left atrium (LA) (Fig. 1B). An esophageal endoscopy revealed a deep ulcer in the esophagus (Fig. 1C). The diagnosis was atrioesophageal fistula (AEF). Unfortunately, he succumbed to brain herniation and shock.

AEF is a rare and life-threatening complication following AF ablation, with an incidence of < 0.1% to 0.25%. However, the incidence data mainly comes from catheter ablation, whereas this patient developed AEF due to thoracoscopic ablation, which is a rare occurrence. CT scans are the preferred diagnostic tool, showing air extravasation near the LA or surrounding the esophagus. Untreated AEF has an almost 100% mortality rate, with early surgical repair being the primary treatment. Due to severe cerebral edema, deep coma, and poor prognosis, the family chose conservative management over surgery.

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Address for correspondence: Fangxiao Gong, Emergency and Critical Care Center, Intensive Care Unit, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Road, Hangzhou 310014, China, tel: +86-571-85894222, e-mail: gfx195@163.com

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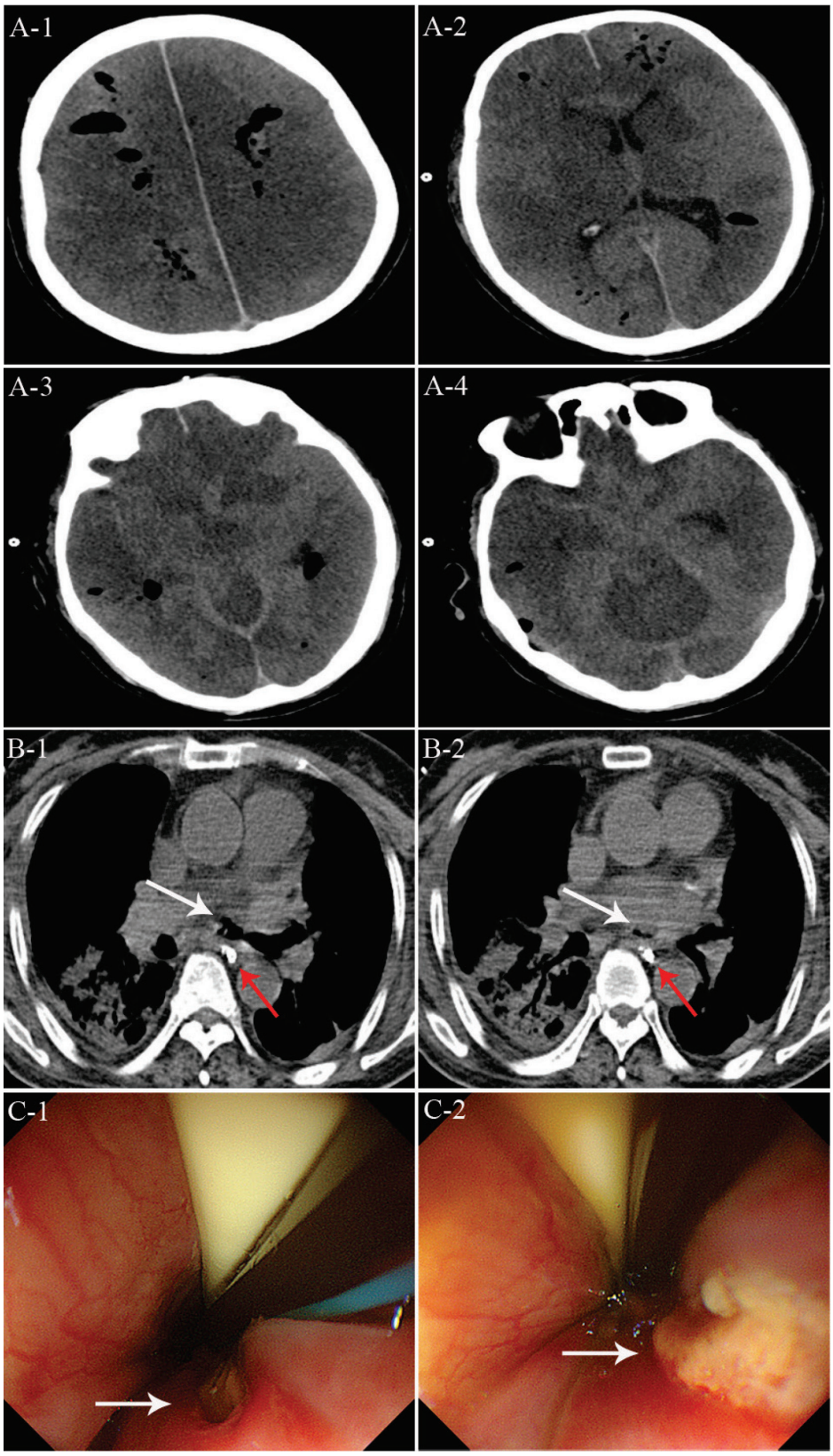

Figure 1. A. The head CT revealed multiple embolic infarcts and air embolism in both cerebral hemispheres. Brain swelling was also revealed by the CT scan. The accumulation of air gradually decreased from the cranial apex to its base (A1–A4); **B.** Chest CT showed air spilling out of the esophagus (B1) andinto the pericardium near the LA (B2) (indicated by white arrows). Red arrows indicated the location of the esophagus, where the nasointestinal tube had been inserted; **C.** A deep ulcer with a diameter of 0.8 cm was detected in the esophagus by endoscopy (indicated by white arrows), situated approximately 30 cm from the incisor

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Complete intramyocardial course of dominant left anterior descending coronary artery and its branches: "Myocardial bridging of the whole ventricular coronary tree"

Paolo Ciliberti[1], Davide Curione[2], Luca Borro[3], Teresa Santangelo[2], Alessio Perazzolo[4], Aurelio Secinaro[2, 3]

[1]Cardiology Unit, Bambino Gesù Children's Hospital IRCSS, Rome, Italy
[2]Advanced Cardiothoracic Imaging Unit, Bambino Gesù Children's Hospital IRCSS, Rome, Italy
[3]Multimodality Imaging Research Unit, Bambino Gesù Children's Hospital IRCSS, Rome, Italy
[4]Department of Radiological and Hematological Sciences, Università Cattolica del Sacro Cuore, Rome, Italy

An 18-year-old boy underwent cardiac magnetic resonance (CMR) imaging because of left ventricle excessive trabeculation (Fig. 1A). CMR showed an abnormal myocardial signal, hyperintense in the SSFP (Fig. 1B) and late enhancement sequences, at the level of the mid-basal interventricular septum close to the left coronary territory. A CT scan was performed, which showed a complete intramyocardial course of the left anterior descending artery (LAD) (see **Supplementary Video**). The coronary arteries arose normally. The entire coronary tree was mainly constituted by the LAD and its branches. Both the right coronary artery (RCA) and the left circumflex artery (LCX) were diminutive, terminating at the level of the atrioventricular grooves and giving rise to secondary intramyocardial branches. After the bifurcation of the left main stem, a "dominant" LAD deepened into the myocardium throughout its course, as shown in the 3D reconstruction with myocardium in transparency (Fig. 1C, D). LAD gave rise to a large intramyocardial diagonal branch, then it continued within the interventricular septum as a large septal/perforating vessel, encircling the left ventricular cavity (Fig. 1E). The cinematic rendering view of the heart (Fig. 1F) shows the smooth epicardial surface with no superficial coronary vessels.

Complete intramyocardial course of an entire coronary is exceptionally rare. Furthermore, in this patient the RCA and LCX were limited to the atrioventricular grooves, where they coursed within the epicardial fat, and there was no significant myocardial mass. Therefore, all the coronary vessels supplying ventricular mass were intramyocardial, representing a sort of "myocardial bridging of the whole ventricular coronary tree".

Conflicts of interest: None declared.

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Supplementary material: Suppl. Video

Address for correspondence: Paolo Ciliberti, MD, PhD, Cardiology Consultant, Cardiology Unit, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00165, Rome, Italy; tel: (+39) 0668591-2796, e-mail: paolo.ciliberti@opbg.net

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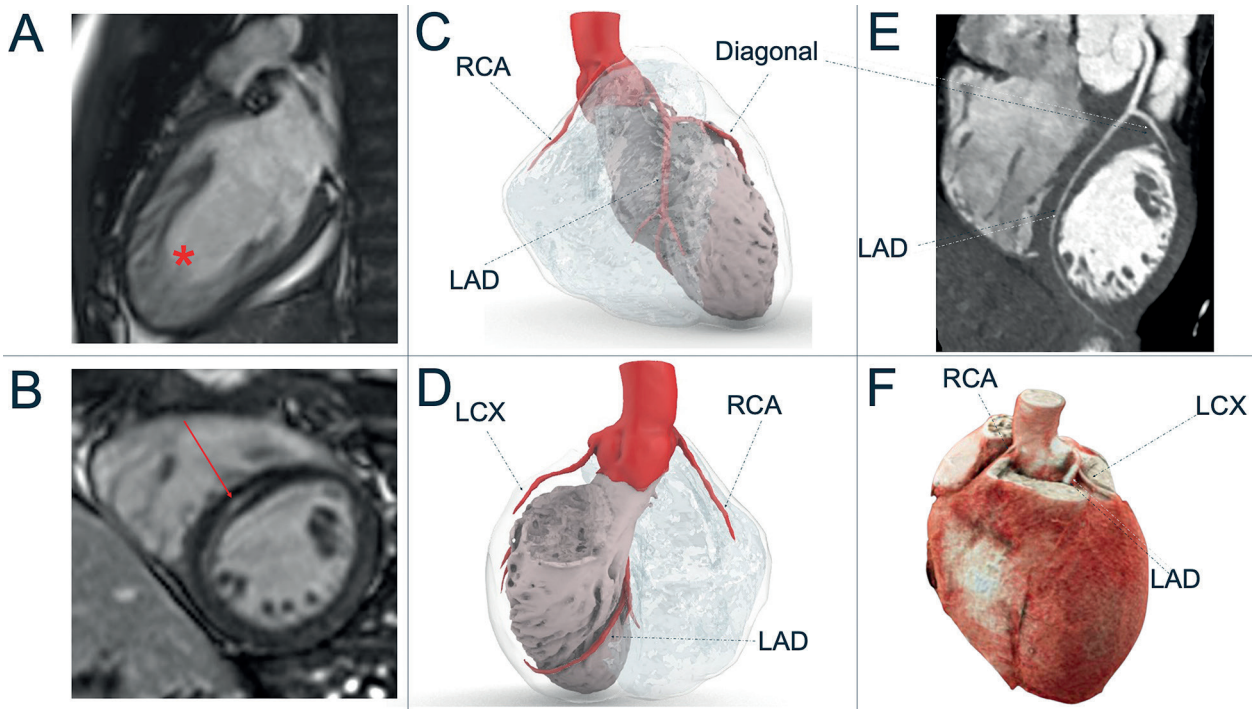

Figure 1. A, B. CMR imaging revealing excessive LV trabeculation (panel A) and abnormal intra-myocardial signal (panel B, arrow); **C, D.** CT 3D reconstruction showing complete intramyocardial (myocardium in transparency) course of the left anterior descending artery (LAD) and its branches; **E.** Curved multiplanar reformatting CT scan imaging, showing the complete LAD intramyocardial course; **F.** CT cinematic rendering displaying the smooth epicardial surface with absence of epicardial major coronary vessels

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IVUS-guided cap puncture of a stumpless chronic total occlusion with sliptream technique

Mohsen Mohandes, Cristina Moreno, Luis Mauricio Torres, Humberto Coimbra, José Luis Ferreiro

Interventional Cardiology Unit, Cardiology Division, Joan XXIII University Hospital, Pere Virgili Health Research Institute (IISPV), Tarragona, Spain

A 65-year-old woman suffering from exertional angina, underwent coronary angiography. A stumpless chronic total occlusion (CTO) was identified in the proximal left anterior descending (LAD) coronary artery, receiving epicardial collaterals from the right coronary artery (RCA). Percutaneous coronary intervention (PCI) was scheduled and an intravascular ultrasound (IVUS) catheter (OptiCross™, Boston Scientific Corp., Natick, MA, USA) was placed in a side branch adjacent to the CTO proximal cap, in order to identify it and guide the puncture. A dual lumen microcatheter (MC) (ASAHI SASUKE, Asahi Intecc, Tokyo, Japan) was inserted on the same IVUS mounted guidewire (GW) through rapid exchange (RX) lumen of MC, and a CTO GW (ASAHI Gaia Second, Asahi Intecc) was introduced through the over-the-wire (OTW) lumen. The Gaia second wire successfully penetrated the CTO entry, identified between 7 and 10 o'clock in IVUS image. The procedure was completed retrogradely using epicardial collaterals with successful result after implanting 3 drug eluting stents (DES) (Fig. 1).

This technique called Slipstream was firstly described by Kinoshita Y et al. and involves a combination of IVUS and a dual-lumen MC placed on the same GW through RX lumen and can facilitate the penetration of GW from subintimal space into true lumen. In our case, this technique was used to identify the CTO entry. This technique can offer more backup support and better proximal cap visualization during the CTO GW manipulation through the OTW lumen, compared to conventional IVUS guidance where the IVUS catheter and a single lumen MC are placed separately on two GWs.

Conflict of interest: None declared.

Consent statement: The patient signed informed consent.

Address for correspondence: Mohsen Mohandes, MD, PhD. Interventional Cardiology Unit, Cardiology Division, Joan XXIII University Hospital, Pere Virgili Health Research Institute (IISPV); Dr. Mallafré Guasch, Tarragona, Spain, 43005, tel/fax: 0034-977295817, e-mail: mohandesmohsen@hotmail.com

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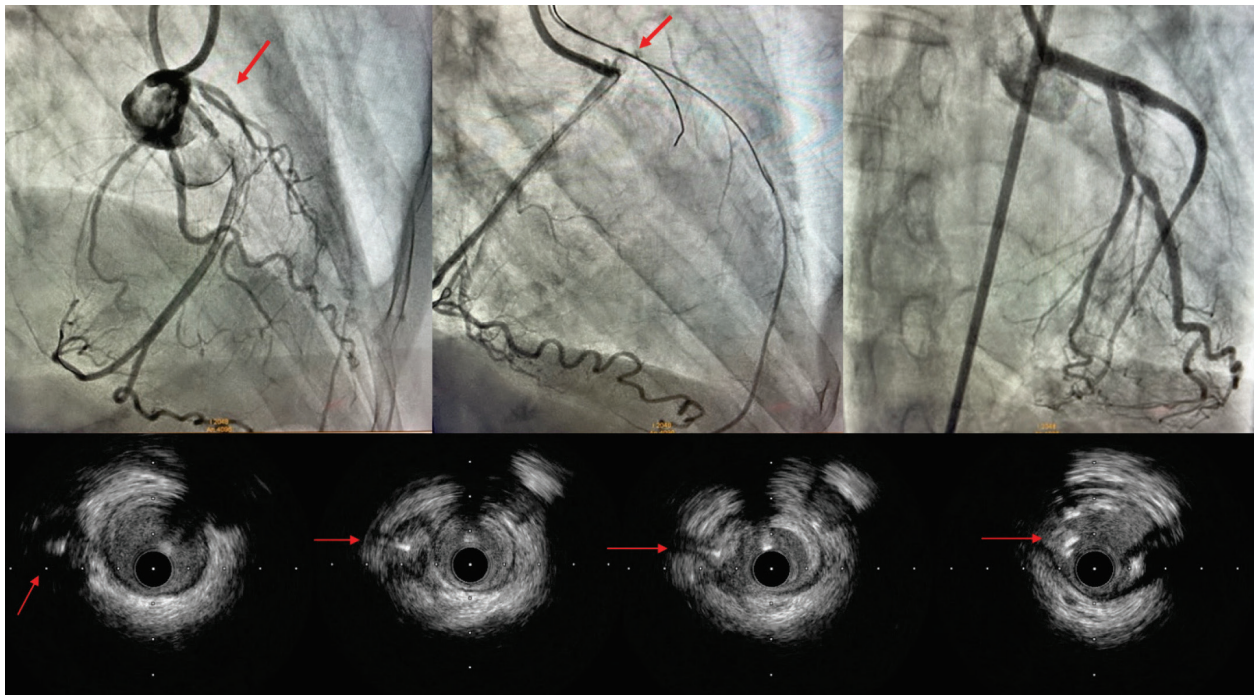

Figure 1. Bilateral injection shows a stump-less and long chronic total occlusion segment of LAD mid segment, with entry point presumably close to a septal branch (up left). IVUS catheter was placed into the septal branch after deeply advancing a floppy wire within this side branch. Afterward, a double lumen MC (ASAHI SASUKE, Asahi Intecc, Tokyo, Japan) was inserted on the same IVUS mounted guidewire through RX lumen of the microcatheter (up mid). IVUS examination revealed the CTO stump between 7 and 10 o'clock during the manipulation of a dedicated CTO GW through OTW lumen of the MC. Pulling back the IVUS catheter confirmed the correct puncture of CTO entry (sequence of IVUS images; lower). Successful final result after implanting three DESs (upper right). CTO — chronic total occlusion; DES — drug eluting stent; IVUS — intravascular ultrasound, LAD — left anterior descending coronary artery; MC — microcatheter; OTW — over-the-wire; RX — rapid exchange