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ORIGINAL ARTICLE

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Coronary slow flow is not an adverse prognostic factor in MINOCA patients in the 5-year follow-up

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ABSTRACT

Introduction: The research aimed to compare the characteristics and outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA) patients with coronary slow flow (CSF) vs. normal coronary flow (no CSF) in a 5-year follow-up.

Material and methods: Between 2010–2015 were identified 111 patients as having final MINOCA diagnosis and available calculated corrected TIMI frame count (cTFC). CSF was defined as cTFC greater than 27 frames per second in any of the three coronary arteries. The primary endpoint was the 5-year major adverse cardiovascular events rate, defined as cardiac death, myocardial infarction, or hospitalization due to angina.

Results: The mean cTFC was 28.9 ± 6.1 frames per second (median: 28, IQR 24–33; min-max: 19–58). 62 (55.9%) patients had normal coronary flow, and 49 (44.1%) had CSF. Patients did not differ in sex (females no CSF *vs.* CSF: 58% *vs.* 61%, p = 0.7) or age (63 ± 15 years *vs.* 63 ± 13 years, p = 0.8). Patients with CSF characterized higher rates of chronic kidney disease (0 *vs.* 8.2%, p = 0.035). No statistically significant difference was observed for any of the analysed points. MACE rates for no CSF *vs.* CSF were 9.6% *vs.* 14.3% (HR 0.80, 95% CI 0.28–2.96, p = 0.7), respectively.

Conclusions: CSF was not associated with a higher risk of adverse events among MINOCA patients at five years.

Key words: ischaemia with non-obstructive coronary arteries, INOCA, microcirculation dysfunction, acetylcholine, coronary flow reserve

Introduction

A substantial number of patients presenting with symptoms of myocardial infarction (MI) show non-obstructive coronary arteries. This syndrome has amazed clinicians globally, and the term myocardial infarction with non-obstructive coronary arteries (MINOCA) was introduced [1]. Initially, MINOCA was perceived as a benign syndrome with favourable outcomes; however, now it is well understood that MINOCA patients characterize worse prognosis, definitely worse than patients with really normal coronary arteries [2–4]. Consequently, a full understanding of MINOCA underlying mechanisms is desired to initiate an individualized therapy that could also improve the quality of life.

The coronary slow flow (CSF) phenomenon is described as a delay in the propagation of the contrast medium within coronary arteries during coronary angiography [5]. CSF is often quantified by thrombolysis in myocardial infarction (TIMI) flow grade 2 or corrected TIMI frame count (cTFC) during coronary angiography [6]. CSF may impact one or more epicardial arteries and is associated with impaired myocardial perfusion. In several research studies, CSF was related to unfavourable long-term outcomes, repeated cardiovascular events (acute coronary syndrome, cardiac arrhythmias), including even cardiac death [7–10].

Blood rheological properties and CSF are proposed as potential MINOCA mechanisms [11]. In some research papers, it was suggested that CSF might be diagnosed in MINOCA patients during coronary angiography [12], but the potential clinical significance of CSF in the MINOCA patients population has not been widely analysed [13]. The authors identified only one study showing the impact of CSF on MINOCA patients' outcomes, but only in a 2-year follow-up [14].

The present study aimed to compare the characteristics and outcomes between MINOCA patients with CSF and normal coronary flow in a 5-year follow-up.

Material and methods

Study Design and Participants

The data were obtained retrospectively from the hospital database. First were analysed all patients who underwent coronary angiography due to MI. Then, patients with coronary angiography with non-obstructive coronary arteries (lesions < 50% of diameter stenosis) with MINOCA final diagnosis were identified. The final analysis included patients in whom angiography recording was available, and cTFC could be calculated. This study compared various baseline demographic and clinical characteristics, laboratory data, and clinical outcomes at a 5-year follow-up between MINOCA patients with normal coronary flow (no CSF) and with CSF.

Data Collection

The authors retrieved demographic, clinical, periprocedural, and laboratory data from the hospital database. The following comorbidities were considered: arterial hypertension, dyslipidaemia, diabetes mellitus, peripheral artery disease, atrial fibrillation, chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2), prior coronary artery bypass grafting, prior percutaneous coronary intervention (PCI), prior MI, and clinical data associated with MI: type, disease advancement, treatment strategy, and periprocedural complications. Additionally, the authors gathered information on echocardiographic parameters (left ventricular ejection fraction) and laboratory findings assessed at admission. Also, information on medications at discharge was gathered.

Corrected TIMI frame count calculation

Two experienced interventional cardiologists blinded to the clinical outcomes evaluated coronary flow. Coronary flow was assessed using cTFC [6]. The first frame was the one where the contrast agent fulfilled the complete width of the artery ostium, touching both borders of the lumen, and the forward motion of the contrast agent was observed. The final frame was when the contrast agent reached the prespecified endpoint of each vessel. The endpoints were as follows: left anterior descending coronary artery - the distal bifurcation (i.e., "moustache," "whale tail," or "hay fork") of the left anterior descending coronary artery (LAD), left circumflex coronary artery - the most distal bifurcation of the longest marginal branch, and right coronary artery — the first branch of the posterolateral artery. The TIMI frame count for the LAD was divided by 1.7 to receive the cTFC in the LAD. The authors defined CSF as greater than 27 frames per second in any of the three coronary arteries, as described previously [14, 15].

Study endpoints

The primary study endpoint was to compare the 5-year rate of major cardiovascular adverse events (MACE) defined as joined rates of cardiac death, MI, and recurrent hospitalization due to angina. The secondary endpoints included all-cause death, cardiac death, MI, PCI, and recurrent hospitalization due to angina rates at five years.

Statistical methods

Descriptive statistics were presented: mean, standard deviation, minimum, 25% centile, median, 75% centile, and maximum for continuous variables; count and per cent for categorical variables. Pearson's Chi-squared test or Fisher's exact test was performed to compare categorical variables between two groups (e.g., no CSF vs. CSF patients). Fisher's exact test was used when at least one of the subgroups had count = 0. Wilcoxon rank sum test was performed to compare continuous variables between two groups (e.g., no CSF vs. CSF patients). P-value < 0.05 was statistically significant. Kaplan-Meier estimators with 95% CI were calculated to compare 5-year survival curves for various endpoints between groups (e.g., no CSF vs. CSF patients). If a given endpoint occurred for a particular patient more than once in a 5-year follow-up period, then survival time was assumed as the time to the first occurrence of this endpoint. Notably, in the case of MACE (a composite endpoint), survival time was assumed as the time to the first occurrence of either cardiac death, myocardial infarction, or angina pectoris hospitalization. Statistical analyses were performed using R software version 4.2.1 (2022-06-23 ucrt) —"Funny-Looking Kid" Copyright (C) 2022 The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit).

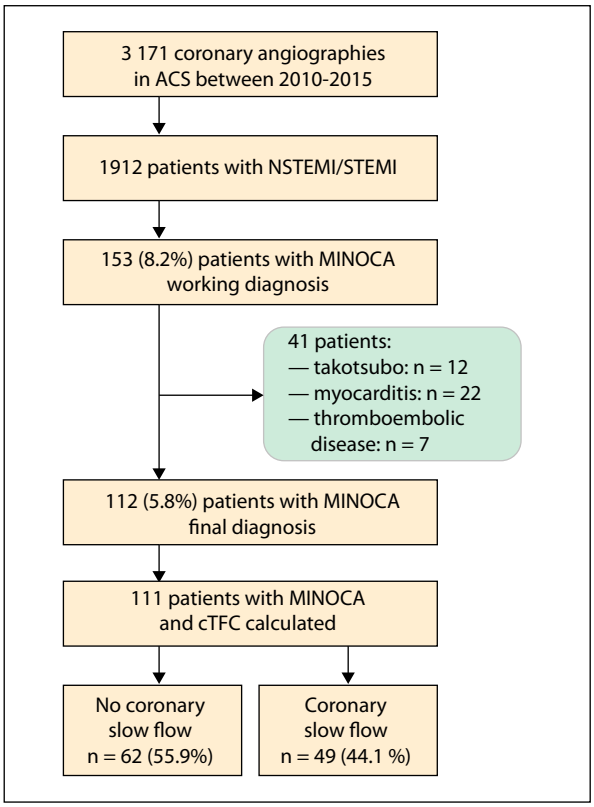

Figure 1. Study flowchart. ACS — acute coronary syndrome; cTFC — corrected TIMI frame count; MINOCA — myocardial infarction with non-obstructive coronary arteries; NSTEMI — non-ST-elevation myocardial infarction; STEMI — ST-elevation myocardial infarction

Results

Baseline characteristics

Between 2010–2015 were identified 3171 coronary angiography procedures performed due to acute coronary syndrome, from which 153 had working MINOCA diagnosis, and the final diagnosis of MINOCA was ascribed to 112 (5.8%) patients. cTFC was available in 111 patients, and among them, 62 (55.9%) had normal coronary flow, and 49 (44.1%) — had coronary slow flow (Fig. 1). The mean cTFC was 28.9 ± 6.1 frames per second (median: 28, IQR 24–33; min–max: 19– 8). Baseline characteristics are presented in Table 1. Patients did not differ in terms of sex (females no CSF vs. CSF: 58% vs. 61%, p = 0.7) or age (63 ± 15 years vs. 63 ± 13 years, p = 0.8). However, patients with CSF characterized higher rates of chronic kidney disease (0 vs. 8.2%, p = 0.035). Table 2 presents laboratory findings at admission. There were no significant differences between the groups. Only no CSF patients had lower levels of troponin T, mainly within the range of 0–500 ng/mL (69%), whereas CSF patients had troponin

Table 1. Baseline characteristics

Parameter	No CSF N = 62	CSF N = 49	P-value
Females	36 (58%)	30 (61%)	0.7
Age [years]	63 ± 15	63 ± 13	0.8
Body mass index [kg/m^2]	28.4 ± 6.5	27.2 ± 4.9	0.7
Myocardial infarction type at presentation			
NSTEMI	52 (84%)	41 (84%)	0.8
STEMI	10 (16%)	8 (16%)	
Arterial hypertension	31 (50%)	27 (55%)	0.6
Diabetes type 2	8 (13%)	6 (12%)	> 0.9
Dyslipidaemia	18 (29%)	10 (20%)	0.3
Prior myocardial infarction	0	0	–
Prior PCI	0	0	–
Prior CABG	0	0	–
Chronic kidney disease	0	4 (8.2%)	0.035
Atrial fibrillation	16 (26%)	9 (18%)	0.4
Peripheral artery disease	1 (1.6%)	–	> 0.9
Smoking	6 (9.7%)	7 (14%)	0.5
LVEF [%]	58 ± 10	59 ± 11	0.3
Coronary lesions			
No lesions	32 (52%)	18 (37%)	
< 30%	21 (34%)	20 (41%)	0.2
30–50%	9 (14%)	11 (22%)	

CABG — coronary artery bypass grafting, LVEF — left ventricular ejection fraction, NSTEMI — non-ST-elevation myocardial infarction, PCI — percutaneous coronary intervention, STEMI — ST-elevation myocardial infarction

Table 2. Laboratory findings at admission

Parameter	No CSF N = 62	CSF N = 49	P-value
RDW [%]	13.54 ± 1.05	13.64 ± 1.19	> 0.9
MPV [fL]	8.32 ± 1.13	8.44 ± 1.10	0.5
MCV [fL]	91.2 ± 5.7	90.2 ± 6.1	0.3
NT-proBNP [pg/mL]	2351 ± 1563	5016 ± 6863	0.6
C-reactive protein	1.8 ± 3.3	5.9 ± 14.1	0.4
LDL [mmol/L]	2.54 ± 1.14	2.64 ± 0.88	0.5
Creatine [μmol/L]	84 ± 22	88 ± 41	0.6
Maximal troponin T [ng/mL]			
0–500	43 (69%)	23 (47%)	< 0.045
501–2500	16 (26%)	23 (47%)	
2501–10000	3 (4.8%)	3 (6.1%)	
10000+	0 (0%)	0 (0%)	

MCV — mean corpuscular volume; MPV — mean platelet volume; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RDW — red cell distribution width

T levels mainly within the range of 0–500 ng/ml (47%) and 2501–10000 ng/mL (47%), $p < 0.045$.

Management at discharge

All included patients were discharged. Table 3 presents medications prescribed at discharge. All patients received similar treatment. However, in CSF patients was observed a trend for a higher prevalence of prescribing Ca-blockers (18% vs. 33%, $p = 0.060$).

Outcomes at five years

Survival rates at five years are presented in Table 4, and Kaplan-Meier curves for MACE are shown in Figure 2. No statistically significant difference for any analysed points was observed. MACE rates for no CSF vs. CSF were 9.6% vs. 14.3% (HR 0.80, 95% CI 0.28–2.96, $p = 0.7$), respectively.

Table 3. Medications at discharge

Parameter	No CSF N = 62	CSF N = 49	P-value
ASA	59 (95%)	46 (96%)	> 0.9
Clopidogrel	49 (79%)	32 (67%)	0.14
Beta-blocker	47 (76%)	40 (83%)	0.3
Ca-blocker	11 (18%)	16 (33%)	0.060
ACE inhibitor	46 (74%)	34 (71%)	0.7
Angiotensin receptor blocker	3 (4.8%)	2 (4.2%)	> 0.9
Diuretic	13 (21%)	11 (23%)	0.8
Trimetazidine	2 (3.2%)	0 (0%)	0.5
Nitrates	36 (58%)	25 (52%)	0.5
Vitamin K antagonist	8 (13%)	5 (10%)	0.7
Novel oral anticoagulant	3 (4.8%)	1 (2.1%)	0.6
Statin	56 (90%)	45 (94%)	0.7

ASA — aspirin, ACE — angiotensin-converting enzyme

Discussion

This study is the first to show CSF's impact among patients with MINOCA at a 5-year follow-up. MINOCA patients presenting with CSF did not have worse clinical outcomes than patients with the normal coronary flow.

Recently, it has become acknowledged that MINOCA is not a rare entity and accounts for 5–15% of all acute MI cases [1, 16-18]. In the present paper, the authors also observed MINOCA frequency at 5.8%. This is also in agreement with the recent report on MINOCA frequency in Poland just before the COVID-19 pandemic (6.3%) and during the COVID-19 pandemic (5.9%) [2]. In 9466 patients with MINOCA during the 4-year follow-up, Lindahl et al. observed a MACE rate of 23.9%, all-cause death of 13.4%, MI of 7.1%, ischaemic stroke of 4.3% and heart failure hospitalization of 6.4% [19]. In the present study, it was observed that the MACE

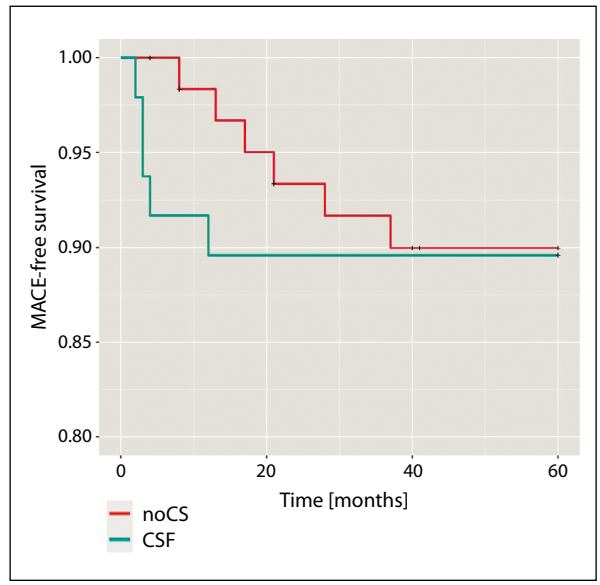

Figure 2. Kaplan-Meier curves for MACE at 5 years for MINOCA patients with the normal coronary flow or with coronary slow flow

Table 4. 5-year outcomes no coronary slow flow *vs.* coronary slow flow

Parameter	No CSF N = 62	CSF N = 49	HR	95% CI	P-value
All-cause death	3 (4.8%)	3 (6.1%)	0.93	0.67–1.94	0.8
Cardiac death	1 (1.6%)	0	0.99	0.65–2.01	0.9
Myocardial infarction	2 (3.2%)	2 (4.1%)	0.90	0.76–1.32	0.7
Percutaneous intervention	1 (1.6%)	1 (2%)	0.95	0.78–1.11	0.9
Hospitalization due to angina	4 (6.5%)	5 (10.2%)	0.84	0.45–1.99	0.6
MACE	6 (9.6%)	7 (14.3%)	0.80	0.28–2.96	0.7

MACE — major adverse cardiovascular event

rate was 11.6% among total MINOCA patients (0.9% cardiac death, 3.6% non-fatal MI, 8.1% angina rehospitalization), stressing the need for physicians to look closely at this population. Interestingly, when the study group was divided depending on the presence of CSF, the authors recorded MACE of 9.6% in normal coronary flow and a MACE rate of 14.3% in the CSF subgroup. Nevertheless, there was no statistical significance between those two groups (HR 0.90, 95% CI 0.28–2.96, p = 0.7). The management strategy of these patients should consider the underlying mechanisms; therefore, it is crucial to learn the specific ones. This may help in choosing the most appropriate therapy, which can translate into improved quality of life as well as improved outcomes [20, 21].

Coronary slow flow phenomenon prevalence ranges from 0.2% to even 34% among patients with normal or near-normal coronary arteries. This is mainly associated with the study population as well as the heterogeneously used definitions [22, 23]. In studies with patients with non-obstructive arteries and acute coronary syndrome or takotsubo, the CSF rates were 34% and 17.8%, respectively [7, 24].

The pathomechanisms of CSF are not fully understood, and one can mention factors such as microcirculation dysfunction, inflammatory state, fibromuscular hypertrophy, or endothelial injury [25]. Nevertheless, the co-existence of anatomical and functional abnormalities of coronary microcirculation is probably the most convincing mechanism [26]. Consequently, coronary microcirculation dysfunction and CSF are suspected of playing a key role in many MINOCA patients [1, 20, 27]. The CSF presence in MINOCA patients ranges in recent papers between 16.8% to even 57% [12, 14, 28]. In the present study, the authors showed that CSF was present in 44.1% of patients with MINOCA proving that CSF is a pretty common abnormality and might be one of the key pathways predisposing to MINOCA pathogenesis.

In some clinical research studies, authors showed that CSF might negatively affect outcome rates. Patients with takotsubo syndrome and CSF had an increased risk of in-hospital complications as well as poorer long-term outcomes than no CSF patients [7]. Wang et al. showed that CSF patients characterized a significantly elevated MI type 4a risk during PCI [29]. Other researchers demonstrated that CSF is not a benign phenomenon, and CSF patients are more prone to the development of atherosclerosis and obstructive coronary artery disease [30]. Also, in other papers, patients with CSF were characterized as having a higher risk of future cardiovascular events [31].

However, there are scarce papers evaluating the prognostic impact of CSF in MINOCA patients. Up to now, the authors have identified only one paper assessing the impact of CSF on the prognosis of patients with MINOCA. In the paper by Mareai et al., the CSF incidence was 34.2% [14]. The authors revealed that the two-year MACE rate was higher among CSF patients than in the no-CSF group (35.2% vs. 20.2%, p = 0.040). Moreover, the multivariable Cox regression analysis reported that CSF was an independent MACE predictor (HR 2.76; 95% CI 1.34–5.67; p = 0.006). The results of the paper are opposite to ours. Several factors might cause this discrepancy. The authors' observation lasted much longer (5 years), and most events were indeed within the first two years. This might suggest that vasomotor disturbances might have a transient character. Also, there might be other confounding factors such as race (Caucasian vs. Asian), genetic susceptibility, and in consequence, different treatment strategies.

Study limitations

This study has several limitations. First, this was a retrospective study; therefore, residual confounding factors may exist. Second, angiographic data were available only at the index hospitalization; consequently, the authors could not provide any details on the CSF recovery over the follow-up period. Third, CSF was measured only by semi-quantitative indicators of angiography such as cTFC; a comprehensive assessment of both epicardial and microvascular chambers would have provided further information. And finally, the authors included all MINOCA patients that could be identified; therefore, no sample size calculation was performed; however, relatively small populations might have caused no evident statistically significant differences in the outcomes between CSF and no CSF MINOCA patients.

Conclusions

For the first time, the authors showed data on the impact of CSF on prognosis in MINOCA patients at a 5-year follow-up. These results showed no statistically significant differences in MINOCA patients with or without CSF.

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Ethical statement: *The study protocol was reviewed and approved by the Institutional Review Board (or Ethics Committee) of the District Physician Chamber in Plock (No 1/2020 of 20.11.2020). Patient consent was waived due to the retrospective nature of the study.*

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