

Risk Factors for Adverse One-Year Prognosis in Patients with Chronic Cerebral Ischemia After Myocardial Infarction Complicated by Heart Failure with Reduced Ejection Fraction

N.B. Lebedeva ^{1*}, L.Yu. Chesnokova ²

¹ Associate Professor, a senior researcher at the Laboratory of Rehabilitation, Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Disease", Kemerovo, Russia; ORCID 0000-0003-2769-3807.

² A Researcher at the Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Disease", Kemerovo, Russia; ORCID 0000-0002-7471-786X.

***Corresponding Author:** Nataliya B. Lebedeva, Associate Professor, a senior researcher at the Laboratory of Rehabilitation, Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Disease", Kemerovo, Russia.

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Abstract

Aim: To determine the predictors of poor long-term survival in patients with chronic cerebral ischemia after myocardial infarction complicated by heart failure with reduced ejection fraction.

Methods: 182 patients with left ventricular failure and chronic cerebral ischemia presented with Q-wave MI were recruited in a observational study. Of them, 149 (81.9%) were men and 33 (18.1%) were women. Their median age was 60.4 (53; 69) years. All patients underwent echocardiography, coronary angiography, carotid color duplex scanning, and were consulted by an interventional neurologist at the acute phase of MI. One year after MI, the hard endpoints were collected. Univariate and multivariate regression analyzes were performed.

Results: Cerebral arteriopathy was confirmed in all patients from the study group. The thickness of the intima-media was over 1.0 mm. The mean carotid intima-media thickness was 1.8 ± 0.6 mm. The majority of patients had mild to moderate encephalopathy. Carotid atherosclerotic plaques were found in 37.4% of patients. The degree of stenosis did not exceed 50% in all cases. One-year after MI, 77 (46.1%) patients reached hard endpoints. The multivariate regression model showed that previous stroke (RR 7.33 [95% CI 1.97-27.32], $p = 0.003$) was the most unfavorable predictor of mortality, whereas the most unfavorable predictors of endpoints were prior stroke (RR = 1.92 [95% CI 1.09-3.38], $p = 0.025$) and the presence of carotid atherosclerotic plaque (RR = 2.12 [95% CI 1.34-3.37], $p = 0.001$).

Conclusion: The presence of carotid atherosclerotic plaques and previous stroke affect the one-year prognosis in patients with chronic cerebral ischemia after myocardial infarction, complicated by heart failure with reduced ejection fraction.

Key Words: myocardial infarction; chronic cerebral ischemia; heart failure; reduced ejection fraction; prognosis

List of abbreviations

ARB - angiotensin receptor blockers

LVEF - left ventricular ejection fraction

ACEI - angiotensin-converting enzyme inhibitors

PCI - Percutaneous coronary intervention

CCI - chronic cerebral ischemia

1.1 Background

Coronary artery disease (CAD) and stroke being the most common cardiovascular diseases caused by atherosclerosis remain the leading causes of death worldwide [1,2]. Recent studies have provided evidence suggesting the presence of the association between coronary artery diseases and stroke risk factors due to the systemic nature of the

atherosclerotic process [3,4]. The carotid intima-media thickness arteriopathy predicts the risk of new-onset coronary artery disease and its severity. A significant relationship between the presence of non-stenotic carotid atherosclerotic plaques and silent myocardial ischemia has been reported. The overall prevalence of CAD along with carotid artery stenosis is over 50% [5-8].

Half of the patients with acute coronary syndrome report carotid plaque ultrasonic heterogeneity suggesting their instability [9,10]. This fact confirms the existence of common underlying pathological mechanisms that contribute to the development of adverse cardiovascular and cerebral events.

The long-term prognosis after myocardial infarction (MI) is usually determined by many factors. Impaired left ventricular systolic function contributes greatly to poor survival [11]. Half of MI patients with left ventricular ejection fraction (LVEF) less than 40% die within 3 years. These patients have a 5-fold increased risk of sudden cardiac death than the general population [12-14]. Reduced LVEF in CAD patients is associated with both, multivessel coronary lesions and carotid stenosis [3]. Recent studies have reported the correlation between left ventricular dysfunction and asymptomatic carotid artery stenosis [9]. Besides, cerebral blood reduced, especially in the presence of carotid stenosis, is largely determined by central hemodynamics with the cardiac output playing the key role. The presence of cerebral ischemia and its aggravation can further worsen the course of coronary artery disease, MI, and left ventricular failure [15,16]. There are frequent cases of MI in patients with strokes. Undoubtedly, it worsens the prognosis for this group of patients and necessitates the need for further studies to determine the new strategies for diagnosis and treatment [17]. Chronic cerebral ischemia (CCI) is now considered as an additional extracardiac factor contributing to a more severe course of acute and chronic CAD [18,19].

Our study is aimed at determining the predictors of an adverse one-year prognosis in patients with chronic cerebral ischemia after MI complicated by heart failure with reduced ejection fraction.

1.2 Methods

182 patients with left ventricular failure after Q-wave MI and CCI were recruited in a observational study. All patients suffered from left ventricular failure and chronic cerebral ischemia before the indexed event. All patients with suspected MI were admitted to the hospital within 7.6 (5.3; 15.2) hours from the chest pain onset. Of them, 149 (81.9%) were men and 33 (18.1%) were women. The mean age of recruited patients was 60.4 (53; 69) years.

The inclusion criteria were as folreduceds: Q-wave MI, left ventricular ejection fraction (LVEF) $\leq 40\%$, a positive history of chronic cerebral ischemia diagnosed before the onset of MI, Killip II-III. The exclusion criteria were as folreduceds: non-Q-wave MI, persistent rhythm and conduction disturbances, Killip IV, valvular heart disease, severe diabetes, the refusal to sign written informed consent. MI was diagnosed based on (2012) [20].

The study was conducted folreducing Good Clinical Practice and the principles of the World Association's Declaration of Helsinki "Ethical

Principles for Medical Research Involving Human Subjects", 1975. The study protocol and informed consent were approved by the Local Ethics Committee. Written informed consent was obtained from each patient.

At admission, all patients underwent a standard clinical and instrumental examination. Left ventricular function was assessed with M-mode, B-mode, and Doppler echocardiography using including an assessment of the functional state of the LV according to ECHO-CG data in M-, B- and Doppler modes on an Acuson 128/XP10 ultrasound machine (USA). The measurements were performed according to the generally accepted protocol. All patients underwent selective coronary angiography (CAG) undertaken on Siemens Angioscop equipment (USA) and INNOVA 3100 (GE, USA). On days 2-3 after myocardial infarction, color freduced duplex scanning of the brachiocephalic arteries and pulsed Doppler ultrasonography were performed on a Sonos-2500 ultrasound machine (Hewlett Packard). All patients underwent the MMSE test. Pre-existing chronic cerebral ischemia and the severity of encephalopathy before the onset of myocardial infarction were confirmed by an interventional neurologist based on the clinical examination, the MMSE scores (28-30 points: normal cognition; 24-27 points: pre-dementia; 20-23 points: mild dementia; 11-19 points: moderate dementia; 0 - 10 points - severe dementia) and echocardiography and ultrasonography findings.

All patients included in the study received standard medical therapy: antiplatelet agents (after a loading dose of aspirin at a dose of 75-100 mg and clopidogrel 75 mg), enoxaparin, nitrovasodilators, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), or angiotensin receptor blockers (ARB), diuretics, mineralocorticoid receptor antagonists, statins, and individual calcium antagonists.

One year after MI, the folreducing hard endpoints were collected: recurrent MI, progressive angina pectoris, need for revascularization, acute decompensated heart failure (HF), readmission to hospital, cerebrovascular events, deaths (cardiovascular mortality and overall mortality).

Statistical analysis was performed using the STATISTICA 10.0 and SPSS software packages. The Shapiro-Wilk test was used to test the normality of data. Continuous variables are presented as the median and interquartile range (Me (25; 75)). The Mann - Whitney U test was used to compare two groups where the variable of interest was continuous. The two-sided Fisher's exact test and Yates's chi-squared test were used to comparing the frequencies. Univariate and multivariate logistic regression was used to determine independent predictors of adverse outcomes. To assess each factor in predicting the event under study, the risk ratio (RR) and odds ratio (OR) were calculated with a 95% confidence interval (CI). Differences were considered statistically significant at $p < 0.05$.

1.3 Results

Clinical and demographic data of the study population are presented in Table 1. The vast majority of patients were men with pre-existing arterial hypertension, angina pectoris, and heart failure. Patients with anterior MI, multivessel coronary artery disease, and Killip II prevailed, 81.2% of patients underwent the revascularization of the infarct-related artery.

Parameter	n=182
Age, year, Me (Q25; Q75)	59 (52; 69)
Male, n (%)	148 (81.3)
Arterial hypertension, n (%)	149 (81.9)
Stroke, n (%)	19 (10.4)
Diabetes mellitus type 2, n (%)	45 (24.7)
Angina pectoris, n (%)	134 (73.6)
Heart failure, n (%)	152 (83.5)
Recurrent myocardial infarction, n (%)	69 (37.9)
Anterior myocardial infarction, n (%)	112 (61.5)

Killip II, n (%)	128(70.3)
Killip III, n (%)	54 (29.6)
Grade 1 chronic cerebral ischemia, n (%)	38 (20.8)
Grade 2 chronic cerebral ischemia, n (%)	122 (67.0)
Grade 3 chronic cerebral ischemia, n (%)	22 (12.1)
Left ventricular ejection fraction, Me (Q25; Q75)	38 (31; 44)
Coronary angiography, n (%)	156 (85.7)
SYNTAX, Me (Q25; Q75)	23 (18; 28.5)
Coronary artery lesions, n (%)	3-vessel disease 2-vessel disease 1-vessel disease
	69 (37.9) 50 (27.4) 27 (14.8)
Percutaneous coronary intervention, n (%)	121 (66.4)
Thrombolysis, n (%)	27 (14.8)

Table 1: Clinical and demographic data of the study cohort

The interventional neurologist reported that 20.9% (group 1) of patients had emotional lability, anxiety, phobias, slight reflex instability, and incoordination corresponding to mild encephalopathy. 67.6% of patients (group 2) had complaints about decreased memory and mental abilities, increased fatigue and decreased performance, emotional lability, headache, dizziness, sleep disturbance). Group 2 patients had mild neurological disorders corresponding to moderate encephalopathy. 11.5% of patients (group 3) had a positive history of ischemic stroke. The severity of cognitive deficit measured with the MMSE corresponded to the severity of encephalopathy: group 1 - 25

(24; 27) points (pre-dementia), group 2 - 25 (24; 26) points (pre-dementia), and group 3 - 23.5 (21; 25) points (mild dementia) ($p_{2-3} = 0.006$, $p_{1-3} = 0.017$).

According to the echocardiography and ultrasonography findings, all patients reported carotid intima-media thickness arteriopathy of >1 mm (the mean carotid intima-media thickness was 1.8 ± 0.6 mm). 37.4% of patients had carotid atherosclerotic plaques. The severity of stenosis did not exceed 50% in all cases (Table 2).

Parameter, n (%)	Study population, n=182 (100%)
Carotid IMT ^a >1.0 cm	182 (100)
Extracranial stenosis up to 50%	68 (37.4)
Unilateral carotid stenosis up to 50 %	47 (25.8)
Bilateral carotid stenosis up to 50 %	21 (11.5)

^aIMT – intima-media thickness

Table 2: Carotid atherosclerotic lesions in the study cohort, n (%)

Five (2.7%) patients died due to recurrent myocardial infarction during the hospitalization. Thus, clinical data of 177 (91.7%) patients were used to predict the one-year prognosis.

cases of ACS, of them 22 recurrent MI and 30 cases of unstable angina, 8 ischemic strokes, and 31 cases of acute decompensated chronic heart failure. 19 patients underwent percutaneous coronary intervention with stenting and 20 patients were referred to coronary artery bypass grafting within the folreduced-up period.

Patients demonstrated high adherence to medical therapy within the year. 87% of patients continued to receive ACEI or ARB. 96% regularly took beta-blockers, 70% - diuretics, 64% - double antiplatelet therapy, and 63% - statins.

Univariate regression reported that a history of stroke and carotid atherosclerotic plaques in the acute MI phase were the most significant individual risk factors associated with one-year mortality (Table 3).

77 (43.5%) patients reached the hard endpoints within one year after MI. A total of 141 hard endpoints were collected, including 11 deaths, 52

Parameter	Survived (n=166)	Dead (n=11)	OR, 95% CI	p
Age >65 years	66 (39.8)	6 (54.5)	3.09 (0.75-12.79)	0.1
Male gender	136 (81.9)	9 (81.8)	1.07 (1.02-1.11)	0.15
Smoking	74 (44.5)	6 (54.5)	2.51 (1.61-3.39)	0.19
Diabetes mellitus	45 (27.1)	0	0.93 (0.89-0.98)	0.072
Prior MI	60 (36.1)	5 (45.5)	2.25 (0.58-8.7)	0.23
Prior Stroke	15 (9.0)	4 (36.4)	9.81 (1.98-33.68)	0.001
Carotid artery plaque	62 (37.3)	6 (54.5)	3.92 (2.91-16.97)	0.049
Killip II	121 (72.9)	4 (36.4)	0.31 (0.08-1.21)	0.077
Killip III	47 (28.3)	5 (45.5)	3.22 (0.83-12.5)	0.077
PCI of the IRA ^a	97 (58.4)	3 (27.3)	0.37 (0.09-1.51)	0.15

^aIRA – infarct-related artery

Table 3: Univariate regression analysis of the association of clinical and demographic data with one-year mortality, n (%)

Multivariate logistic regression reported prior stroke was the most unfavorable predictor of death within one year after MI (RR 7.33 [95% CI 1.97-27.32], $p = 0.003$).

We then performed univariate regression to determine the most likely predictors of adverse outcomes associated with the development of

cardiovascular events in patients who reached hard endpoints and those who did not (Table 4).

Parameter	Patients without endpoints (n=100)	Patients with endpoints (n=77)	OR, 95% CI	p
Age >65 years	35 (35.0)	37 (48.1)	1.72 (0.94-3.15)	0.08
Male gender	86 (86.0)	59 (76.6)	0.54 (0.25-1.16)	0.11
Smoking	42 (42.0)	38 (49.4)	1.38 (0.76-2.52)	0.29
Diabetes mellitus	28 (28.0)	17 (22.1)	0.73 (0.36-1.46)	0.37
Prior MI	35 (35.0)	30 (39.0)	1.19 (0.64-2.19)	0.59
Prior Stroke	6 (6.0)	16 (20.8)	4.11 (1.52-11.01)	0.003
Carotid artery plaque	29 (29.0)	39 (50.6)	2.51 (1.35-4.68)	0.003
Killip II	76 (76.0)	49 (63.6)	0.55 (0.29-1.1)	0.073
Killip III	24 (24.0)	28 (36.4)	1.81 (0.94-3.48)	0.073
PCI of the IRA ^a	63 (63.0)	37 (48.1)	0.54 (0.3-0.99)	0.047

^aIRA – infarct-related artery

Table 4: Univariate regression analysis of the association of clinical and demographic data with a risk of cardiovascular events, n (%)

The risk factors associated with the development of cardiovascular events within the folreduced-up included the presence of carotid atherosclerotic plaques confirmed during the hospitalization and a positive history of stroke. Percutaneous coronary intervention (PCI) of the infarct-related artery was associated with a favorable prognosis.

Similar results were demonstrated by multivariate regression models. A positive history of stroke (RR = 1.92 [95% CI 1.09-3.38], $p = 0.025$) and the presence of carotid atherosclerotic plaque (RR = 2.12 [95% CI 1.34-3.37], $p = 0.001$) were the most significant predictors of adverse one-year annual prognosis. PCI of the infarct-related artery significantly improved one-year prognosis (RR = 0.6 [95% CI 0.38-0.95], $p = 0.03$).

1.4 Discussion

Risk assessment of developing an adverse prognosis is crucial for understanding the medical and social significance of the disease and determining the intensity of subsequent treatment and secondary prevention. However, there are very few studies describing the effects of concomitant chronic cerebral ischemia on the prognosis after MI.

Systolic dysfunction developing after MI in patients with pre-existing carotid stenosis worsens chronic cerebral ischemia due to both, cardioembolic risk and hypoperfusion aggravation [18]. However, recent studies showed that the presence of significant brachiocephalic stenosis is not necessary in this case [21]. The presence of heart failure is known to contribute to the emergence or aggravation of autonomic, cognitive, and neuropsychological deficits due to a decrease in the thickness of the cerebral cortex, regardless of carotid stenosis [22]. A regional decrease in cerebral blood flow occurs in patients with heart failure. This decrease is particularly pronounced in those patients who have pre-existing cerebral ischemia [23]. However, there is no clear relationship of the presence and severity of carotid stenosis and with the clinical manifestations of cerebral ischemia in patients with heart failure [21-23]. No doubt, the interaction between the damaged myocardium and altered cerebral functions in chronic cerebral ischemia affects the prognosis. Non-stenotic cerebral atherosclerosis in its turn can further worsen the prognosis in patients after myocardial infarction due to the risk of cerebral atherothrombotic events [19].

We found that carotid intima-media thickening was the main manifestation of carotid artery arteriopathy. The prevalence of carotid atherosclerotic plaques was reduced. The one-year mortality rate was 6.2% in the study group. Complete myocardial revascularization and optimal drug therapy in most patients resulted in improved survival. Logistic regression analysis showed the high significance of cerebral atherosclerosis, in particular, the presence of carotid atherosclerotic plaque and prior stroke contributed greatly to one-year prognosis in patients with CCI after MI. The onset of acute coronary syndrome is

accompanied by morphological changes in atherosclerotic plaques and other vascular areas. This argument is confirmed by the ultrasonography findings reporting carotid plaque heterogeneity in the internal carotid arteries, their transition to an unstable state, "activation" in half of the patients several days after MI [14]. This transition from stable plaques to unstable plaques confirms the presence of common pathological mechanisms contributing to the development of adverse events. Our findings suggest that cerebral vascular events were more significant for long-term prognosis than reduced LVEF in patients with chronic cerebral ischemia.

Our findings are consistent with the results of the prospective CAFES-CAVE study suggesting the presence of a significant relationship between carotid atherosclerotic lesions and the incidence of cardiac complications [24]. Thus, the presence of even non-stenotic carotid atherosclerotic plaques significantly increased the risk of adverse cardiovascular events [24]. Thus, chronic cerebral perfusion can be considered as an additional extracardiac factor contributing to poor prognosis in patients with reduced LVEF after MI, including the risk of stroke. Large-scale studies showed that progressive impairment of left ventricular systolic function is associated with a 4-fold increase in the risk of stroke [25].

1.5 Conclusion

The presence of carotid atherosclerotic plaques and previous stroke affect the long-term prognosis in patients with chronic cerebral ischemia after myocardial infarction, complicated by heart failure. Our findings necessitate the development of target multidisciplinary approaches in secondary prevention and outpatient monitoring of patients with reduced left ventricular ejection fraction and concomitant chronic cerebral ischemia.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from each patient. The study was approved by the Joint Local Ethics Committee of the Kemerovo Cardiological Dispensary and Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases" (Protocol No. 50 issued on 25.01.10).

Consent for publication/ Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The Authors declare that there is no competing of interest.

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Authors' contributions

Lebedeva N.B. developed the concept and design of the study, contributed to the analysis, interpretation and synthesis of the data obtained, approved the final version of the article before submitting it for publication;

Chesnokova L.Yu. made a significant contribution to the receipt of data, their analysis and interpretation, wrote the first version of the article

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