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Impact of Microvascular Injury Various Types on Function of Left Ventricular in Patients With Primary Myocardial Infarction With ST Segment Elevation

Aim	To compare long-term effects of different phenotypes of myocardial microvascular damage on left ventricular (LV) contractility by echocardiography (EchoCG) data in patients with primary ST segment elevation myocardial infarction (STEMI).
Material and methods	This study included 60 patients with primary STEMI. On the 2nd day after acute coronary complication, paramagnetic contrast-enhanced magnetic resonance imaging (MRI) was performed for all patients. Hemorrhagic suffusion of the myocardium (HSM) was visualized as areas of low signal intensity on the background of the myocardium with a high T2-weighed signal intensity. Microvascular obstruction (MVO) was determined as an area with low signal intensity during the late phase of contrasting in an inversion recovery sequence. Then a standard EchoCG protocol was used for all patients on day 7 and at 3 months after myocardial infarction (MI).
Results	According to data of contrast-enhanced MRI, patients with primary MI had various phenotypes of myocardial microvascular injury, including the absence of injury (n=19), isolated MVO (n=10), isolated HSM (n=9), and a combination of MVO and HSM (n=22). The presence of MVO+HSM combination was associated with impaired LV contractility and dilation of heart chambers. Isolated MVO was also associated with a lower LV ejection fraction (EF) compared to patients without microvascular myocardial injury. Isolated HSM did not affect the LV contractility in the late postinfarction period. The size of MVO expressed in per cent of LV size predicted a decrease in LV EF both in the early and the late postinfarction period.
Conclusion	The combination of MVO and HSM in primary STEMI directly correlates with the impairment of LV contractility at 3 months after the event. Isolated MVO was also associated with a lower LV EF in contrast to patients without microvascular myocardial injury; furthermore, the size of MVO directly correlated with the decrease in LV contractility. In isolated HSM, LV structure and function values were in the normal range in the late postinfarction period.

Keywords	ST segment elevation myocardial infarction; myocardial microvascular injury; microvascular obstruction; no-reflow phenomenon; hemorrhagic suffusion of the myocardium
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Introduction

The treatment of patients with myocardial infarction (MI) is one of the best studied problems in cardiology. The available treatment algorithms have improved quality of life and prognosis for patients after MI, as well as significantly reducing mortality. Given this background, a natural question arises concerning the extent of further potential to limit necrosis size and improve myocardial function in patients during and after MI.

Despite the effectiveness of current coronary reperfusion techniques (primary percutaneous coronary intervention (PCI) and pharmacoinvasive management) in restoring blood flow in the epicardial artery, the efficacy of the procedure is significantly reduced by a lack of microvascular perfusion. Recent improvements in cardiovascular imaging technology raised the problem of myocardial microvascular damage in patients with ST-segment elevation MI (STEMI), showing that it is both underdiagnosed and heterogeneous [1]. Numerous studies have showed that more than 50% of patients with STEMI had myocardial microvascular damage following primary PCI [2, 3], which is known to be based on microvascular obstruction (MVO) and myocardial bleedinging [4, 5].

MVO, also known as the no-reflow phenomenon, is the best-studied form of myocardial microvascular damage. According to a meta-analysis, MVO, as shown by magnetic resonance imaging (MRI), was detected in 40–80% of patients with STEMI following the successful revascularization of an infarct-related coronary artery. The presence of MVO, which is associated with maladaptive postinfarction remodeling, is a predictor of cardiovascular events regardless of reducing left ventricular (LV) function [6].

There has recently been a growing interest in the phenomenon of myocardial bleeding, which is reported in major studies in 40% of STEMI patients following mechanical reperfusion. The prognostic role of myocardial bleeding has been studied extensively. According to a prevailing opinion, myocardial bleeding is associated with the more severe microvascular dysfunction involving a larger volume of myocardial damage and poorer prognosis than in MVO [3, 5]. Carrick et al. [7] demonstrated that the myocardial bleeding is a robust independent predictor of adverse LV remodeling. The majority of studies show that myocardial bleeding is found only in patients with MVOs. However, several trials identified a few patients who developed an isolated myocardial bleeding phenomenon [8, 9]. Due to the heterogeneity of microvascular myocardial damage associated with isolated MVOs or myocardial bleeding and their combination, the question of their impact on the structural and functional changes occurring in the myocardium in the later postinfarction period appears to be of relevance.

Objective

Compare the long-term effects of myocardial microvascular damage of different phenotypes on the LV wall motion as estimated by echocardiogram in patients with primary STEMI.

Material and methods

From March 2018 to February 2019, 60 patients with primary STEMI admitted to the Institute of Cardiology of the Tomsk National Research Medical Center within 12 hours following onset were successively included in the study. All patients were subjected to emergency reperfusions of the infarct-related coronary artery. Coronary reperfusion was carried out using two methods: primary PCI (n=21) and pharmacoinvasive reperfusion (n=39). Reperfusion methods were selected before hospitalization following the ESC Clinical Practice Guidelines for STEMI patients [10]. Exclusion criteria comprised patient's refusal, recurrent MI, history of coronary revascularization, unstable hemodynamics (Killip III–IV), acute mental disorders, severe comorbidities, and contraindication for heart MRI. All patients signed the informed consent prior to being included in the study. The study protocol was approved by the Ethics Committee of the Research Institute of Cardiology. The study has been registered with ClinicalTrials.gov under the identification number NCT03677466.

All subjects underwent heart MRI with paramagnetic enhancement performed on a Toshiba Vantage Titan 1.5 T scanner on the second day following acute coronary complication. MRI was performed using the basic Cardiac cardiological software suite to view the myocardium with the ECG and respiration synchronization. A gadolinium chelating agent was used for contrast enhancement. The heart MRI protocol included standard impulse sequences (dark blood TSE T2 weighted sequence, fat suppression T1 weighted sequence) in a short-axis two-chamber view; dynamic sequences (bright blood GRE-SSFP) in short-axis two-chamber-, as well as long-axis two-chamber- and four-chamber views; MRI with delayed enhancement in 8–15 minutes after the intravenous administration of a contrast enhancement agent (GRE IR with selectable inversion time, TSE T1) in short-axis two-chamber-, as well as long-axis two-chamber- and four-chamber views.

MI was evaluated by the following criteria: focal increase in T2 weighted signal intensity, inversion recovery delayed contrast enhancement, and accumulation of a contrast-enhancement medium in the myocardial segments corresponding to the coronary systems. Myocardial bleeding was visualized as a low-intensity area against the myocardium with the increase in T2 weighted signal intensity. MVO was defined as a low-intensity area in a delayed contrast enhancement inversion recovery.

An echocardiogram was performed in a Vivid E9 ultrasound system (GE Healthcare, USA) in two-dimensional mode using the standard procedure from the parasternal (short ventricular axis at the levels of the mitral annulus, papillary muscles, and top) and apical views (in two-chamber and four-chamber views and the LV long axis) using an M5S matrix sensor (1.5–4.6 MHz). Standard echocardiography was performed on day 7 following MI and within 90±10 days. the echocardiography protocol was based on the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. LV end-systolic volume (LVESV), end-diastolic (LVEDV), and ejection fraction (LVEF) were calculated from the apical two-chamber- and four-chamber views usi ng

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Simpson's method. When LVESV and LVEDV increased by 20% or more in 3 months after acute MI, LV remodeling was assessed as unfavorable.

The statistical analysis of findings was carried out using the Statistica 10.0 suite. The results are presented as the median and interquartile range (Me [25th percentile; 75th percentile]). The statistical significance of the differences between independent quantitative variables was assessed using the Mann–Whitney U-test. The significance of differences in multiple comparisons was determined using the Kruskal-Wallis test. The statistical significance of differences between qualitative variables was evaluated using Pearson's χ^2 test and the Fisher test. The correlations between the signs of interest were evaluated using Spearman's correlation coefficient. The relevance of the various factors was assessed using logistic regressions. The prognostic value of the logistic analysis for a reduction of LV wall motion was estimated by the area under the ROC curve (AUC). The intergroup differences were statistically significant at $p<0.05$.

Results

According to the contrast-enhanced cardiac MRI, 41 (68.3%) patients had myocardial microvascular damage. Patients were divided into four groups depending on a phenotype of myocardial microvascular damage: Group 1 included 19 (31.7%) patients in whom myocardial microvascular damage was absent; Group 2 was formed by 10 (16.7%) patients exhibiting isolated MVO phenomena; Group 3 included 9 (15%) patients with isolated myocardial bleeding phenomena; Group 4 comprised 22 (36.6%) patients with a combination of MVO and myocardial bleeding.

Table 1. Clinical and anamnestic characteristics of patients included in the study depending on phenotype of myocardial microvascular damage

Parameter	Group I (n=19; no myocardial microvascular damage)	Group 2 (n=10; isolated MVO)	Group 3 (n=9; isolated myocardial bleeding)	Group 4 (n=22; a combination of MVO and myocardial bleeding)
Age, years	59 [49; 66]	63 [59; 67]	65 [62; 69]	62 [55; 65]
Sex, M/F	15/4	8/2	6/3	17/5
BMI, kg/m²	26 [24; 30]	34.6 [27.3; 36.3]	25.01 [21.5; 29.05]	28.23 [26.7; 31]
GRACE, %	2 [1; 3]	3 [1; 5]	4 [2; 5.5]	2 [1; 4]
Pain-to-reperfusion time, min	130 [91; 160]	205 [140; 227]	113 [100; 179]	193 [95; 400]
Reperfusion methods (pharmacoinvasive management/primary PCI)	14/5	7/3	5/4	10/12
Localization of MI, n (%)				
• Anterior	10 [52.6]	4 [40]	4 [44.4]	16 [72.7]
• Inferior	9 [47.4]	6 [60]	5 [55.6]	6 [27.3]
Hypertensive heart disease, n (%)	18 [94.7]	8 [80]	8 [88.9]	20 [90.9]
Diabetes mellitus, n (%)	2 [10.5]	2 [20]	2 [22.2]	7 [31.8]
Obesity, n (%)	6 [31.6]	6 [60]	9 [100]	7 [26.3]
Dyslipidemia, n (%)	18 [94.7]	9 [90]	9 [100]	21 [95.5]
Smoking	16 [84.2]	5 [50]	7 [77.8]	15 [68.2]
CPK-MB, U/L	60 [25; 77]	121 [92; 166]*	59 [30.1; 219]	138 [68; 389]†
Troponin I, ng/mL	4.66 [2.2; 34.7]	25.5 [15.2; 87.8]*	20.9 [18; 42.2]	46.5 [14.3; 96.8]†
Killip, n (%)				
• I	15 [78.9]	7 [70]	8 [88.9]	16 [72.7]
• II	4 [21.1]	3 [30]	1 [11.1]	6 [27.3]
TIMI flow ≤1 before PCI, n (%)	1 [5.5]	3 [30]	2 [22.2]	8 [36.4]
TIMI flow 3 after PCI, n (%)	18 [94.7]	9 [90]	9 [100]	17 [77.3]
One-/two-/three-vessel disease, n	3/7/9	5/3/2	0/4/5	4/10/8
No-reflow according to CAG after PCI, n (%)	–	–	–	3 [13.6]
Volume of the damaged tissue according to MRI, %	10 [8; 18]	17.3 [12; 30]	23.2 [9; 25]	24.8 [17.5; 35]†

The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]) or the absolute number and percentage (n (%)). The differences are statistically significant ($p<0.05$) † between the group of combined MVO and myocardial bleeding and the group without myocardial microvascular damage; * between the group with isolated MVO and the group without myocardial microvascular damage.
MVO – microvascular obstruction; BMI – body mass index; PCI – percutaneous coronary intervention; MI – myocardial infarction; CPK – creatine phosphokinase; CAG – coronary angiography; MRI – magnetic resonance imaging.

Clinical and anamnestic characteristics of patients depending on the microvascular damage phenotype have been previously described in detail (Table 1) [9].

Since three patients were lost to follow-up by visit in the three months following index coronary complication, echocardiogram was carried out in the remaining 57 patients. LV structural and functional parameters as assessed by echocardiogram depending on myocardial microvascular damage phenotype in the late postinfarction period are described in Table 2. Regardless of the presence of microvascular lesions, the integrated echocardiogram indicators did not significantly differ from the normal levels. This can be explained by the exclusion of severe patients from the study and all examined patients having undergone reperfusion therapy early after the onset of the disease [11].

Comparative analysis of volumetric echocardiographic indicators three months following MI revealed statistically significant differences in the MVO/myocardial bleeding combination group and patients without myocardial microvascular damages. Patients with a combination of MVO and myocardial bleeding had the most severe LV dilatation: LVESI (29.3 [26; 40.9] mL/m^2 versus 17.7 [14.4; 24.6] mL/m^2; p=0.001) (Figure 1) and LVEDI (68.1 [60.3; 76.3] mL/m^2 versus 61.2 [45.6; 70.7] mL/m^2; p=0.08). LVESI was significantly higher in the group of patients with isolated MVO than in patients without myocardial microvascular damage: 26.9 [21.5; 40.2] mL/m^2 versus 17.7 [14.4; 24.6] mL/m^2 (p=0.04), respectively. Comparable LV volumes in the group of patients with isolated myocardial bleeding and those without myocardial microvascular

Table 2. Echocardiographic indicators three months after primary STEMI depending on microvascular damage in primary STEMI

Parameter	All patients (n=57)	No myocardial microvascular damage (n=18)	Isolated MVO (n=10)	Isolated myocardial bleeding (n=9)	Combination of myocardial bleeding and MVO (n=20)
LVEDD, mm					
baseline	48 [45; 51]	46 [45; 50]	50 [46; 53]	49 [46.5; 50.5]	48 [44; 51]
in 90 days	50 [46; 53]	47 [41; 51]	51.5 [48; 55]	47 [43; 50]	51 [46.5; 54]
Δ% in 90 days	2.12 [–3.1; 8.3]	0 [–6.6; 2.1]	0.9 [–0.5; 13.3]	1.04 [–3.5; 4.7]	2.2 [0; 13.3]
LVESD, mm					
baseline	31 [30; 34]	31.5 [30; 36]	31.5 [30; 39]	30 [28; 31.5]	32 [30; 34]
in 90 days	33 [31; 36]	32.5 [23; 36]	31 [29; 39]	30 [27; 33]§§	35 [32; 43]††
Δ% in 90 days	3.2 [–2.8; 13.4]	0 [–11.1; 3.1]	–1.2 [–4.6; 3.7]	3.5 [–6; 12.3]	9.3 [3.2; 27.5]
LVEDV, mL					
baseline	100 [88; 120]	95 [81; 109]	104.5 [85; 124]	99 [88.5; 105]	105 [92; 124]
in 90 days	118.5 [99; 140]	114 [93; 126]	129 [113; 144]	101.5 [87; 115]§§	124 [109; 144]
Δ% in 90 days	8.8 [–1.73; 36.6]	0 [–5.3; 22.5]	11.1 [–0.2; 39.6]	4.08 [–8.7; 13.6]	26.2 [1.2; 42.6]
LVESV, mL					
baseline	42 [35; 53]	35.5 [30; 44]	40 [36; 60]	33.5 [31; 45]§	53 [43; 61]†
in 90 days	50 [37.5; 60]	34 [31; 41]	58 [44.5; 85.5]*	43 [28; 50]§§	55 [50; 76]††
Δ% in 90 days	8.5 [–11.4; 37.5]	0 [–26.6; 25.5]	28.7 [0.8; 103]	5.8 [–9.1; 23.7]	4.25 [–5.4; 45.6]
LVEDI , mL/m^2					
baseline	53 [45.9; 58.1]	49.9 [43.5; 54.7]	53.9 [45.3; 65.7]	51.5 [45.05; 56.8]	54.3 [50; 64.9]
in 90 days	64.9 [54; 75]	61.2 [45.6; 70.7]	67 [57.4; 87.6]	54.9 [46.2; 66.7]§§	68.1 [60.3; 76.3]
Δ% in 90 days	20.23 [0.34; 46.2]	15.1 [–10.2; 38.6]	25.5 [5.5; 45.5]	6.2 [–7.4; 17]	43.2 [2.9; 63.9]
LVESI , mL/m^2					
baseline	22.2 [18.6; 27.9]	18.9 [16.1; 22.7]	19.9 [18.6; 29.8]	19.1 [15.7; 24.1]§	27.9 [24; 33.4]†
in 90 days	26.2 [19.6; 32.9]	17.7 [14.4; 24.6]	26.9 [21.5; 40.2]*	23.9 [14.2; 28.2]§§	29.3 [26; 40.9]††
Δ% in 90 days	10.8 [–10.7; 47.3]	1.21 [–26.7; 46.9]	29.6 [2.1; 45.2]	7.4 [–8.7; 28.6]	8.2 [–6.2; 57.7]
LVEF, %					
baseline	58 [51; 65]	64 [60; 68]	56 [51; 61]*	62.1 [58; 66]§	49 [47; 56]†
in 90 days	59 [51; 66]	65 [62; 70]	55 [54; 66]	61.5 [54; 71]§§	51 [46; 59]††
Δ% in 90 days	1.83 [–7.9; 14.7]	7.5 [0; 15]	0.94 [–7.4; 5.5]	2.3 [–7.1; 4.7]	1.9 [–4.6; 21.6]

Differences are statistically significant (p<0.05) between the group without myocardial microvascular damage and † the group of baseline myocardial bleeding with MVO, †† the group of myocardial bleeding with MVO in 90 days, * the group of isolated MVO; between the group of the combination of myocardial bleeding with MVO and § the group of baseline isolated myocardial bleeding; §§ the group of isolated myocardial bleeding in 90 days. MVO – microvascular obstruction; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension; LVESV – left ventricular end-systolic volume; LVEDV – left ventricular end-diastolic volume; LVEDI – left ventricular end-diastolic index; LVESI – left ventricular end-systolic index; LVEF – left ventricular ejection fraction.

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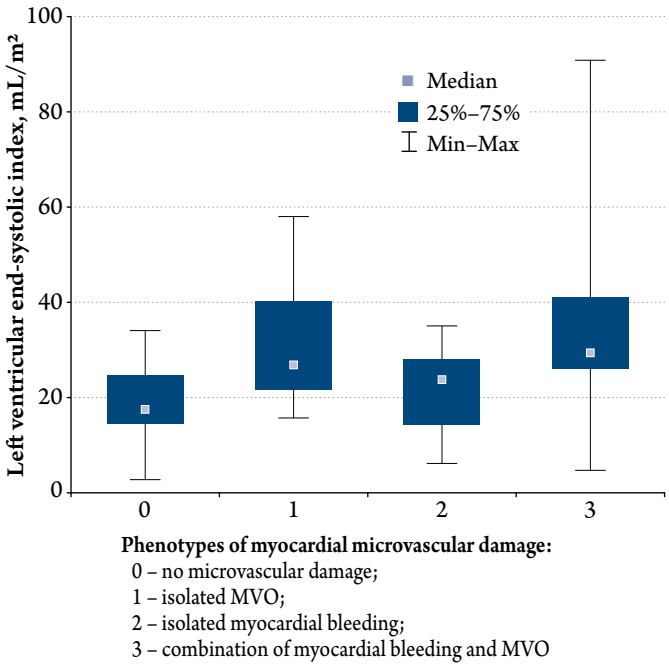
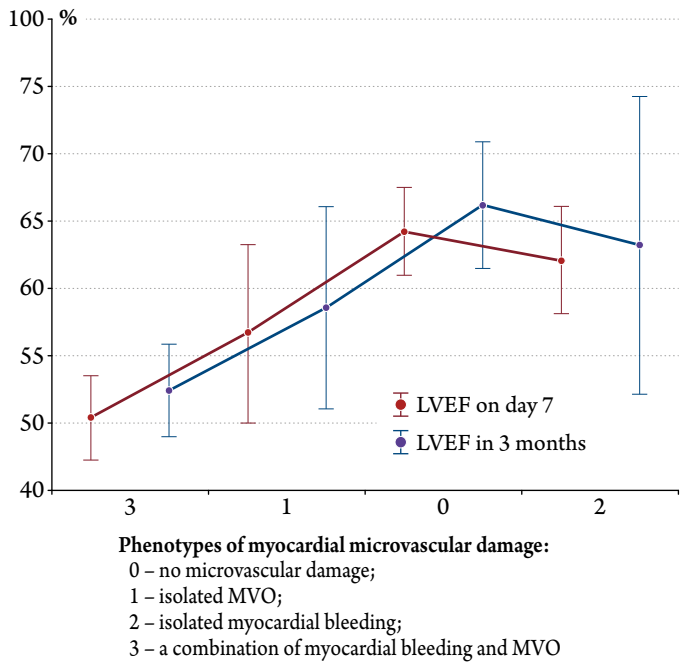
Figure 1. Comparison of the echocardiographic LVESI in 90 ± 10 days after acute MI depending on myocardial microvascular damage phenotype



LVESI – left ventricular end-systolic index; MI – myocardial infarction; MVO – microvascular obstruction.

Figure 2. Echocardiographic changes in LVEF depending on myocardial microvascular damage phenotype



LVEF – left ventricular ejection fraction; MVO – microvascular obstruction.

damage were significantly lower than in the group of patients having a combination of MVO and myocardial bleeding, in particular, LVESI was lower (23.9 [14.2; 282] mL/m² versus 29.3 [26; 40.9] mL/m²; p=0.01) (Table 2).

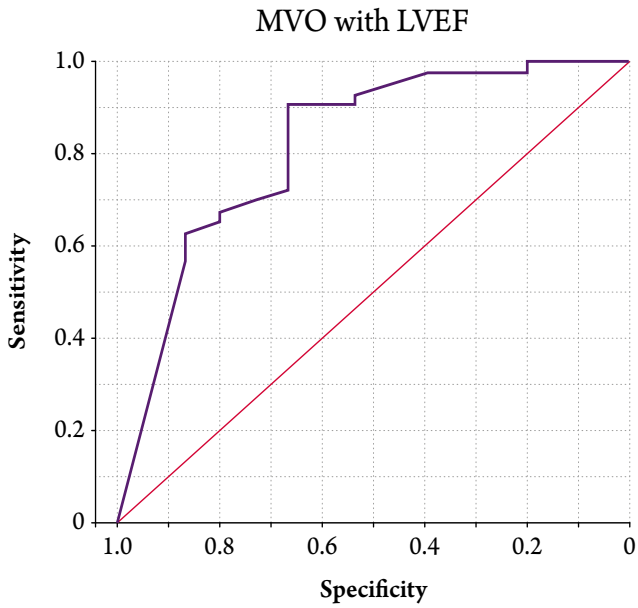
Changes in LV volumes in the early and late postinfarction periods are presented depending on myocardial microvascular damage phenotypes in Table 2. The analysis of changes in LVESV and LVEDV of all included patients detected adverse LV remodeling in 19 (33.3%) patients. The study of the correlation between the development of adverse myocardial remodeling and different phenotypes of microvascular damage showed that 8 (42.1%) patients had a combination of myocardial microvascular damage phenomena, 5 (26.3%) patients had isolated MVO, 2 (10.5%) patients had isolated myocardial bleeding, and 4 (21.1%) patients had no myocardial microvascular damage. Despite the fact that the most widespread adverse LV remodeling occurred in patients with a combination of MVO and myocardial bleeding, the correlation between these processes was not statistically significant.

Figure 2 shows LVEF on day 7 after MI day and 3 months following the index coronary complication. It can be seen that LV wall motion improved in all groups regardless of myocardial microvascular damage phenotype. However, LV wall motion was significantly lower in patients with a combination of MVO and myocardial bleeding than in patients with isolated microvascular myocardial damages or without any damages: 51 [46; 59] % versus 55 [54; 66] and 61.5% [54; 71] % in isolated MVO and myocardial bleeding, respectively.

The combination of myocardial bleeding and MVO was found to be an independent predictor of wall motion depression according to the logistic regression analysis in the late postinfarction period (odds ratio (OR) 0.92; 95% confidence interval (CI) 1.5–18.87 (p=0.01)). Isolated myocardial bleeding had no effect on LVEF (OR 1.08; 95% CI 0.99–1.18, p=0.07). According to the comparative analysis, isolated MVO was statistically significantly correlated with decreased LVEF. However, the logistic regression analysis did not show such correlations.

MVO percentage of LV area was 1 [0.9; 3] %. This did not significantly vary depending on the phenotype: 1 [0.8; 3] % in isolated MVO and 1.5 [0.7; 6.3] % in the combination of MVO and myocardial bleeding. However, there was a trend to greater MVO when it was combined with myocardial bleeding. Myocardial bleeding area percentage was comparable to MVO and equal to 1 [1; 3] %. There was no difference in the area of myocardial bleeding whether isolated or combined with MVO: 1 [0.7; 1.4] and 1 [0.6; 2.2] %, respectively.

Figure 3. ROC-analysis of the correlation between MVO area and LVEF as measured by echocardiography three months following acute MI (AUC = 0.82)



LVEF – left ventricular ejection fraction;
MVO – microvascular obstruction; MI – myocardial infarction.

The effects of MVO and myocardial bleeding areas on the LV wall motion were assessed in the late post-infarction period. Correlation analysis showed moderate inverse correlation between the area of myocardial bleeding and LVEF (R=–0.43; p=0.0007), as well as correlation between area of MVO and LVEF (R=–0.60; p=0.000002). According to the logistic regression analysis, MVO area was significantly correlated with decreased LV wall motion both in early (OR 1.6; 95% CI 0.3–2.28; p <0.05) and late postinfarction periods (OR 1.6; 95% CI 0.3–2.28; p<0.05). The ROC analysis showed that the MVO area is predictive of decreased LVEF with 91% sensitivity and 67% specificity (Figure 3).

Discussion

In the Russian literature, there are single publications on the heterogeneity of myocardial microvascular damage in MI as shown by contrast-enhanced cardiac MRI [9, 12]. In previous publications, we provided a detailed description of the clinical and laboratory characteristics of patients having different phenotypes of myocardial microvascular damage and presented a comprehensive assessment of the LV wall motion in the early postinfarction period in cases of myocardial bleeding [13]. Thus, the present work is a continuation of an investigation into the prognostic role of different phenotypes of myocardial microvascular damage in patients with STEMI.

According to the results of this study, a combination of myocardial bleeding and MVO makes the most significant contribution to LV wall motion depression and subsequent adverse LV remodeling. There also data in the literature on the combination of myocardial bleeding and MVO correlating with the most unfavorable long-term prognosis in patients with STEMI. Mather et al. [14] demonstrated that LV dilation three months following index coronary complication in patients experiencing a combination of myocardial bleeding and MVO was mainly due to LVEDV and involved no LV wall motion improvements.

A less pronounced decrease in LVEF and LV dilation during the late postifarction period was caused by iso lated MVO. Here, our findings are consistent with the available published works. For example, Carrick et al. [7] reported that isolated MVO in STEMI was rarer than its combination with myocardial bleeding (32 and 101 patients, respectively). The authors demonstrated the more significant effect of a combination of MVO and myocardial bleeding on wall motion and LV dimensions than that of isolated MVO. Reinstadler et al. [8] also described a trend towards a higher incidence of adverse outcomes in patients experiencing a combination of MVO and myocardial bleeding as compared to patients with an isolated form of MVO.

The phenomenon of isolated myocardial bleeding is among the least studied areas. Myocardial bleeding has been previously associated with the presence of MVO, which can be explained by the development of RBC extravasation in the myocardium being due to more severe microvascular damage [5]. However, Reinstadler et al. [8] showed that 2% of patients had isolated myocardial bleeding. In our study, this phenotype of myocardial microvascular damage was detected in 15% of cases. In a previous work, we demonstrated that isolated myocardial bleeding has no significant effect on the structural and functional changes in LV myocardium in the early postinfarction period. [13] In this work, LV wall motion and dimensions three months following index coronary complication were estimated for the first time in patients with isolated myocardial bleeding. The phenotype of isolated myocardial bleeding in the early and late postinfarction period does not depress LV wall motion or cause cardiac cavity dilatation. Conversely, LV structural and functional indicators in isolated myocardial bleeding in the late post-infarction period were comparable to those in patients without microvascular myocardial damage.

Quantification of MVO and myocardial bleeding demonstrated that, despite a small damaged surface, myocardial bleeding and MVO areas are correlated

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ВКЛЮЧЕН В РЕКОМЕДАЦИИ ПО ХСН[2]

1 таблетка 10 мг[1] | **1 раз в сутки[1]** | **без титрации[1]** | **включен в ЖНВЛП[4] и ОНЛС[5]**

КРАТКАЯ ИНСТРУКЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ФОРСИГА®: РЕГИСТРАЦИОННЫЙ НОМЕР: ЛП-002596 **ТОРГОВОЕ НАЗВАНИЕ:** ФОРСИГА (FORXIGA)®. **МЕЖДУНАРОДНОЕ НЕПАТЕНТОВАННОЕ НАЗВАНИЕ:** ДАПАГЛИФЛОЗИН. **ЛЕКАРСТВЕННАЯ ФОРМА:** таблетки, покрытые плёночной оболочкой. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ: САХАРНЫЙ ДИАБЕТ 2 ТИПА** у взрослых пациентов в дополнение к диете и физическим упражнениям для улучшения гликемического контроля в качестве: монотерапии, когда применение метформина невозможно ввиду непереносимости; комбинированной терапии с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами дипептидилпептидазы 4 (ДПП-4) (в том числе, в комбинации с метформином); агонистом рецепторов глюкагоноподобного полипептида-1 (ГПП-1) эксенатидом пролонгированного действия в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения) при отсутствии адекватного гликемического контроля на данной терапии; стартовой комбинированной терапии с метформином, при целесообразности данной терапии. Сахарный диабет 2 типа у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска (возраст у мужчин ≥ 55 лет или ≥ 60 лет у женщин и наличие не менее одного фактора риска: дислипидемия, артериальная гипертензия, курение) для снижения риска госпитализации по поводу сердечной недостаточности. **СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ (II-IV функциональный класс по классификации NYHA) со сниженной фракцией выброса у взрослых пациентов для снижения риска сердечно-сосудистой смерти и госпитализации по поводу сердечной недостаточности. ПРОТИВОПОКАЗАНИЯ:** повышенная индивидуальная чувствительность к любому компоненту препарата; сахарный диабет 1-го типа; диабетический кетоацидоз; нарушение функции почек при расчетной СКФ (рСКФ) стабильно менее 45 мл/мин/1,73 м², включая нарушение функции почек тяжелой степени и терминальную стадию почечной недостаточности, при применении по показанию «сахарный диабет 2 типа»; нарушение функции почек тяжелой степени и терминальная стадия почечной недостаточности (рСКФ < 30 мл/мин/1,73 м²), при применении по показанию «сердечная недостаточность»(в связи с ограниченным опытом применения в клинических исследованиях); наследственная непереносимость лактозы, дефицит лактазы или глюкозо-галактозная мальабсорбция; беременность и период грудного вскармливания; детский возраст до 18 лет (безопасность и эффективность не изучены). **С ОСТОРОЖНОСТЬЮ:** печеночная недостаточность тяжелой степени, инфекции мочевыделительной системы, повышенное значение гематокрита. **ПРИМЕНЕНИЕ В ПЕРИОД БЕРЕМЕННОСТИ И ГРУДНОГО ВСКАРМЛИВАНИЯ** В связи с тем, что применение дапаглифлозина в период беременности не изучено, препарат противопоказан в период беременности. В случае диагностирования беременности терапия дапаглифлозином должна быть прекращена. Неизвестно, проникает ли дапаглифлозин и/или его неактивные метаболиты в грудное молоко. Нельзя исключить риск для новорожденных/младенцев. Дапаглифлозин противопоказан в период грудного вскармливания. **СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ:** Внутрь, независимо от приёма пищи, не разжевывая. Сахарный диабет 2 типа. Монотерапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. Комбинированная терапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки в комбинации с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами ДПП-4 (в том числе, в комбинации с метформином); агонистом рецепторов ГПП-1 – эксенатидом пролонгированного действия, в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения). С целью снижения риска гипогликемии при совместном назначении препарата Форсига с препаратами инсулина или препаратами, повышающими секрецию инсулина (например, с производным сульфонилмочевины), может потребоваться снижение дозы препаратов инсулина или препаратов, повышающих секрецию инсулина. Стартовая комбинированная терапия с метформином: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки, доза метформина – 500 мг один раз в сутки. В случае неадекватного гликемического контроля дозу метформина следует увеличить. СД2 у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска для снижения риска госпитализации по поводу сердечной недостаточности: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. **Сердечная недостаточность: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. ПОБОЧНОЕ ДЕЙСТВИЕ.** Краткий обзор профиля безопасности. В клинических исследованиях СД2 более 15000 пациентов получали терапию дапаглифлозином. Первичная оценка безопасности и переносимости проводилась в заранее запланированном анализе объединенных данных 13 краткосрочных (до 24 недель) плацебо-контролируемых исследований, в которых 2360 пациентов принимали дапаглифлозин в дозе 10 мг и 2,295 пациентов получали плацебо. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов при СД2 (DECLARE) 8574 пациента получали дапаглифлозин 10 мг и 8569 получали плацебо (медиана воздействия 48 месяцев). В общей сложности экспозиция дапаглифлозина составила 30623 пациенто-лет. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов у пациентов с сердечной недостаточностью со сниженной фракцией выброса (DAPA-HF) 2368 пациентов получали дапаглифлозин 10 мг и 2368 получали плацебо (медиана воздействия 18 месяцев). Популяция включала пациентов с СД2 и без него, и пациентов с рСКФ ≥ 30 мл/мин/1,73 м². Профиль безопасности дапаглифлозина в исследованиях был в целом схожим по изучаемым показаниям. Тяжелую гипогликемию и диабетический кетоацидоз отмечали только у пациентов с сахарным диабетом. Ниже представлены НР, отмечавшиеся в плацебо-контролируемых клинических исследованиях и при пострегистрационном применении. Ни одна из них не зависела от дозы препарата. НР классифицированы по частоте и классу систем и органов. Частота НР представлена в виде следующей градации: очень часто (≥ 1/10), часто (≥ 1/100, < 1/10), нечасто (≥ 1/1000, < 1/100), редко (≥ 1/10000, < 1/1000), очень редко (< 1/10000) и неуточненной частоты (невозможно оценить по полученным данным). Инфекционные и паразитарные заболевания: часто – вульвовагинит, баланит и связанные с ними генитальные инфекции, инфекция мочевыводящих путей; нечасто – вульвовагинальный зуд, грибковые инфекционные заболевания; очень редко – некротизирующий фасциит промежности (гангрена Фурнье). Нарушения со стороны обмена веществ и питания: очень часто – гипогликемия (при применении в комбинации с производным сульфонилмочевины или инсулином); нечасто – снижение ОЦК, жажда; редко – диабетический кетоацидоз (при применении при СД2). Нарушения со стороны нервной системы: часто – головокружение. Нарушения со стороны желудочно-кишечного тракта: нечасто – запор, сухость во рту. Нарушения со стороны кожи и подкожных тканей: часто – сыпь; очень редко – ангионевротический отек. Нарушения со стороны костно-мышечной системы и соединительной ткани: часто – боль в спине. Нарушения со стороны почек и мочевыводящих путей: часто – дизурия, полиурия; нечасто – никтурия. Лабораторные и инструментальные данные: часто – дислипидемия, повышение значения гематокрита, снижение почечного клиренса креатинина на начальном этапе терапии; нечасто – повышение концентрации мочевины в крови, повышение концентрации креатинина в крови на начальном этапе терапии.

Ссылка на полную инструкцию: Инструкция по медицинскому применению лекарственного препарата Форсига ® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение ЛП-002596 от 21.08.2014

ХСНнФВ – хроническая сердечная недостаточность со сниженной фракцией выброса; СС – сердечно-сосудистый; СН – сердечная недостаточность.

* Включая неотложные обращения по причине СН. # Снижение относительного риска сердечно-сосудистой смерти и смерти от всех причин в группе дапаглифлозина по сравнению с плацебо в исследовании DAPA HF.

1. Инструкция по медицинскому применению лекарственного препарата Форсига® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение № ЛП 002596 от 21.08.2014.
2. Клинические рекомендации Хроническая сердечная недостаточность 2020. https://scardio.ru/content/Guidelines/2020/Clinic_rekom_HSN.pdf (дата обращения 04.05.2021)
3. McMurray JJV et al., N Engl J Med. 2019;381(21):1995–2008.
4. Перечень жизненно необходимых и важнейших лекарственных препаратов для медицинского применения.
5. Перечень лекарств для обеспечения отдельных граждан.

Материал предназначен для специалистов здравоохранения. Имеются противопоказания. Перед назначением ознакомьтесь, пожалуйста, с полной инструкцией по медицинскому применению лекарственного препарата.

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with decreased LV wall motion. The especially good prognostic value of MVO area makes it possible to predict a decrease in LVEF high sensitivity and specificity according to ROC-curve analysis.

On the basis of the foregoing, it may be stated that the assessment of microvasculature taking into account the presence/absence of myocardial microvascular damage after removing an epicardial coronary obstruction is one of the most promising directions in developing a personalized approach to patients with myocardial infarction.

Thus, myocardial microvascular damage after coronary reperfusion (MVO, especially in combination with myocardial bleeding) comprises an important pathogenic factor in the postinfarction decrease in LVEF and cardiac remodeling. In future, this may serve as an additional marker for early adverse outcome risk stratification and the selection of the best possible treatment strategy taking into account the risk of thrombotic and hemorrhagic complications. The study of myocardial microvascular damages suggests that their potential impact on postinfarction remodeling is not exhausted. Since there are no mechanisms for preventing myocardial microvascular damage, more than 50% of patients with STEMI have a worse prognosis due to the lack of adequate myocardial perfusion and the development of excessive and/or long-term inflammatory response in the infarcted myocardium, which leads to severe structural changes with reduced wall motion [15, 16].

Conclusions

1. The combination of microvascular obstruction with myocardial bleeding in patients with primary ST-segment elevation myocardial infarction three months following the index event is directly correlated with an increase in left ventricular volumes and a decrease in wall motion. This combination can also serve as a prognostic factor for adverse left ventricular remodeling.
2. Unlike in patients without myocardial microvascular damage, isolated microvascular obstruction is also associated with reduced left ventricular ejection fraction. The area of microvascular obstruction directly correlates with left ventricular function depression.
3. Structural and functional parameters of the left ventricle in isolated myocardial bleeding in the long-term postinfarction period are within the normal range and comparable with parameters in patients without microvascular myocardial damage.

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REFERENCES

1. Durante A, Laricchia A, Benedetti G, Esposito A, Margonato A, Rimoldi O et al. Identification of High-Risk Patients After ST-Segment–Elevation Myocardial Infarction: Comparison Between Angiographic and Magnetic Resonance Parameters. Circulation: Cardiovascular Imaging. 2017;10(6):e005841. DOI: 10.1161/CIRCIMAGING.116.005841
2. Kandler D, Lücke C, Grothoff M, Andres C, Lehmkuhl L, Nitzsche S et al. The relation between hypointense core, microvascular obstruction and intramyocardial haemorrhage in acute reperfused myocardial infarction assessed by cardiac magnetic resonance imaging. European Radiology. 2014;24(12):3277–88. DOI: 10.1007/s00330-014-3318-3
3. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of Microvascular Obstruction and Intramyocardial Hemorrhage by CMR on LV Remodeling and Outcomes After Myocardial Infarction: a systematic review and meta-analysis. JACC: Cardiovascular Imaging. 2014;7(9):940–52. DOI: 10.1016/j.jcmg.2014.06.012
4. Sezer M, van Royen N, Umman B, Bugra Z, Bulluck H, Hausenloy DJ et al. Coronary Microvascular Injury in Reperfused Acute Myocardial Infarction: A View From an Integrative Perspective. Journal of the American Heart Association. 2018;7(21):e009949. DOI: 10.1161/JAHA.118.009949
5. Betgem RP, de Waard GA, Nijveldt R, Beek AM, Escaned J, van Royen N. Intramyocardial haemorrhage after acute myocardial infarction. Nature Reviews Cardiology. 2015;12(3):156–67. DOI: 10.1038/nrcardio.2014.188
6. Galea N, Dacquino GM, Ammendola RM, Coco S, Agati L, De Luca L et al. Microvascular obstruction extent predicts major adverse cardiovascular events in patients with acute myocardial infarction and preserved ejection fraction. European Radiology. 2019;29(5):2369–77. DOI: 10.1007/s00330-018-5895-z
7. Carrick D, Haig C, Ahmed N, McEntegart M, Petrie MC, Eteiba H et al. Myocardial Hemorrhage After Acute Reperfused ST-Segment–Elevation Myocardial Infarction: Relation to Microvascular Obstruction and Prognostic Significance. Circulation: Cardiovascular Imaging. 2016;9(1):e004148. DOI: 10.1161/CIRCIMAGING.115.004148
8. Reinstadler SJ, Stiermaier T, Reindl M, Feistritzer H-J, Fuernau G, Eitel C et al. Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. European Heart Journal - Cardiovascular Imaging. 2019;20(2):138–46. DOI: 10.1093/ehjci/jey101
9. Alexeeva Ya.V., Vyshlov E.V., Ryabov V.V., Mochula O.V., Usov V.Yu., Markov V.A. et al. Phenomenons of microvascular injury in primary myocardial infarction with ST-segment elevation. Cardiological Bulletin. 2019;14(2):54–60. [Russian: Алексеева Я.В., Вышлов Е.В., Рябов В.В., Мочула О.В., Усов В.Ю., Марков В.А. и др. Феномены микрососудистого повреждения миокарда при первичном инфаркте миокарда с подъемом сегмента ST. Кардиологический вестник. 2019;14(2):54-60]. DOI: 10.17116/Cardiobulletin20191402154
10. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction

ISSN 0022-9040. Kardiologiia. 2021;61(5). DOI: 10.18087/cardio.2021.5.n1500

in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;39(2):119–77. DOI: 10.1093/eurheartj/ehx393
11. Prasad A, Gersh BJ, Mehran R, Brodie BR, Brener SJ, Dizon JM et al. Effect of Ischemia Duration and Door-to-Balloon Time on Myocardial Perfusion in ST-Segment Elevation Myocardial Infarction. JACC: Cardiovascular Interventions. 2015;8(15):1966–74. DOI: 10.1016/j.jcin.2015.08.031
12. Sharafeev A.Z., Malov A.A., Alkhazurov A.I., Khalirakhmanov A.F., Gabdulkhakov E.F. The features of myocardium reperfusion in smokers in acute myocardial infarction according to MRI. The Bulletin of Contemporary Clinical Medicine. 2018;11(3):76–81. [Russian: Шарафеев А.З., Малов А.А., Алхазуров А.И., Халирахманов А.Ф., Габдулхаков Э.Ф. Особенности реперфузионного повреждения миокарда у курильщиков во время острого инфаркта миокарда по данным МРТ. Вестник современной клинической медицины. 2018;11(3):76-81]. DOI: 10.20969/VSKM.2018.11(3).76-81
13. Alekseeva Ya.V., Vyshlov E.V., Mochula O.V., Ussov V.Yu., Ryabov V.V. Effect of intramyocardial haemorrhage on structural and functional echocardiographic parameters of myocardium after ST-segment elevation myocardial infarction with. Russian Journal of Cardiology. 2020;25(12):32–8. [Russian: Алексеева Я.В., Вышлов Е.В., Мочула О.В., Усов В.Ю., Рябов В.В. Анализ влияния геморрагического пропитывания миокарда на структурно-функциональные показатели миокарда по данным эхокардиографии у пациентов с первичным инфарктом миокарда с подъемом сегмента ST. Российский кардиологический журнал. 2020;25(12):32-8]. DOI: 10.15829/1560-4071-2020-4032
14. Mather AN, Fairbairn TA, Ball SG, Greenwood JP, Plein S. Reperfusion haemorrhage as determined by cardiovascular MRI is a predictor of adverse left ventricular remodelling and markers of late arrhythmic risk. Heart. 2011;97(6):453–9. DOI: 10.1136/hrt.2010.202028
15. Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular Magnetic Resonance in Acute ST-Segment–Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. Circulation. 2018;137(18):1949–64. DOI: 10.1161/CIRCULATIONAHA.117.030693
16. Markov V.A., Ryabov V.V., Vyshlov E.V., Ryabova T.R., Shurupov V.S., Oyunarov E.O. et al. Postinfarction heart remodeling after acute myocardian infarction and pharmakoinvasive reperfusion and enhanced external counterpulsation. -Tomsk: STT;2014. - 244 p. [Russian: Марков В.А., Рябов В.В., Вышлов Е.В., Рябова Т.Р., Шурупов В.С., Оюнаров Э.О. и др. Особенности ремоделирования сердца после инфаркта миокарда при фармакоинвазивных методах реперфузии и усиленной наружной контрпульсации. – Томск: STT; 2014. – 244с]. ISBN 978-5-93629-516-4