

Effect of intramyocardial haemorrhage on structural and functional echocardiographic parameters of myocardium after ST-segment elevation myocardial infarction with

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Aim. To analyze the effect of intramyocardial haemorrhage (IMH) on the structural and functional echocardiographic parameters of myocardium in patients with primary ST-segment elevation myocardial infarction (STEMI).

Material and methods. The study included 60 patients with primary STEMI reperused within 12 hours after symptom onset. On the second day after the event, all subjects underwent gadolinium-enhanced cardiac magnetic resonance imaging (MRI). IMH was visualized as T2-weighted hypointense areas. Subsequently, all patients underwent the standard echocardiography on the 7th day after MI.

Results. IMH was revealed in 31 patients (51,6%). In 22 patients (70,9%), IMH was accompanied by microvascular obstruction (MVO). In the remaining 9 patients (29%), an isolated IMH phenomenon was visualized. Lower values of left ventricular ejection fraction (LVEF) and LV volume parameters were associated with a combination of MVO and IMH. At the same time, the indices of volumetric characteristics and LVEF in isolated IMH were the same as in the group without IMH and MVO. It was demonstrated that the IMH occupies 1% (1-3%) of the LV myocardium. Correlation analysis showed a moderate inverse correlation between the IMH area and LV contractile function: the larger the area, the lower the LVEF ($R=-0,35$; $p=0,007$).

Conclusions. The analysis of the influence of different IMH phenotypes on the structural and functional echocardiographic parameters of myocardium in the short-term period after STEMI has shown that the combination of IMH with MVO and isolated IMH have different effects on LV contractile function. The combination of IMH with MVO is a predictor of a decrease in LVEF and increase of end-

systolic volume (ESV), while an isolated IMH does not affect these parameters. Correlations between the IMH area and a decrease in LVEF, as well as an increase in ESV, have been demonstrated.

Keywords: microvascular injury, intramyocardial haemorrhage, STEMI, myocardial infarction.

Relationships and Activities. This work was supported by a fellowship of the President of the Russian Federation for young scientists and post-graduate students "The influence of microvascular myocardial injury on the course of the inflammatory response in myocardial infarction".

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The absence of microvascular perfusion, despite the restoration of blood flow in the epicardial coronary artery, is a limiting factor in reperfusion therapy in ST-segment elevation myocardial infarction (STEMI) [1]. The actualization of the problem of microvascular injury is largely associated with the magnetic resonance imaging (MRI) in patients after an acute coronary event. According to the studies conducted, contrast-enhanced cardiac MRI is a highly sensitive and specific method visualizing injury at damage at microvascular level [2].

To date, it is known that microvascular injury is heterogeneous and includes several phenomena: isolated microvascular obstruction (MVO), a combination of MVO with intramyocardial haemorrhage (IMH), and, according to recent data, isolated IMH. It should be noted that until recently IMH has always been associated with MVO [2]. However, recently Reinstadler SJ, et al. demonstrated the heterogeneity of IMH, since in addition to its combination with MVO, a group with isolated IMH was described [3]. Previously, we have also shown different phenotypes of the IMH in patients with primary STEMI [4].

If MVO refers to the generally accepted predictors of pathological remodeling and progression of heart failure, then opinions on IMH are contradictory [5-9]. According to a meta-analysis with 9 studies, the prevalence of IMH is considered as more unfavorable a prognostic factor associated with decreased contractile function and pathological myocardial remodeling. In the studies, all patients had a combination of IMH with MVO [7]. There is also an opposite point of view, according to which IMH does not have a significant effect on myocardial remodeling [6]. The ambivalence of the obtained results shows that to date deficient knowledge regarding this phenomenon in an urgent issue. The question remains debatable whether IMH is only a 'satellite' or the cause of severe myocardial injury. In addition, it is of interest to study the heterogeneity of this phenomenon and assess the structural and functional cardiac parameters depending on the IMH phenotype.

The aim was to analyze the IMH effect on the structural and functional echocardiographic parameters of myocardium in patients with primary STEMI.

Material and methods

For the period from March 2018 to February 2019, 60 patients with primary STEMI who were admitted to the Cardiology Research Institute of the Tomsk National Research Medical Center in the first 12 hours from the onset were included in the study. All

patients underwent urgent reperfusion of the infarct-related coronary artery. For coronary reperfusion, 2 methods were used — primary percutaneous coronary intervention (n=21) and pharmacoinvasive treatment (n=39). The choice of the reperfusion strategy was carried out at the prehospital stage according to the guidelines on STEMI [1]. The exclusion criteria were patient refusal, repeated MI, previous coronary revascularization, unstable hemodynamics, acute psychiatric disorders, severe comorbidities, and contraindications to cardiac MRI. All patients signed informed consent before inclusion. The study protocol was approved by the Biomedical Ethics Committee of the Cardiology Research Institute.

On the second day after the acute coronary event, all subjects underwent contrast-enhanced cardiac MRI on a Toshiba Vantage Titan scanner, with a magnetic induction of 1.5 T. MRI was performed on the basis of cardiac package Cardiac with obtaining myocardial images in synchronization of electrocardiography and respiration. For contrast study, a gadolinium-based contrast agent was used. The cardiac MRI protocol included standard pulse sequences (PIs) (T2-weighted dark blood sequence; fat-suppressed T1-weighted sequence) — along the short axis in a two-chamber view; dynamic sequences (GRE-SSFP 'bright blood' technique) — along the short axis in a two-chamber view, along the long axis in a two-, four-chamber view; delayed contrast-enhanced MRI (8-15 minutes after intravenous administration of a contrast agent) (GRE IR with selection of inversion time, TSE T1) — along the short axis in a two-chamber view, along the long axis in a two-, four-chamber view.

MI was assessed according to the following criteria: focal enhancement of the signal intensity on T2-weighted images, subendocardial contrasting of the myocardium or in varying degrees of transmural of the left ventricular (LV) wall, on delayed contrast-enhanced and accumulation of contrast agent in myocardial segments of corresponding coronary arteries. IMH was visualized as hypointense areas against the background of the myocardium with increased signal intensity in the T2 weighted mode (Figure 1). MVO was defined as hypointense areas in the delayed contrasting phase.

Echocardiography was performed on a Vivid E9 ultrasound system (GE, Healthcare) in a two-dimensional mode according to the standard technique from the parasternal and apical views using a M5S matrix sector probe (1,5-4,6 MHz). Standard echocardiography was assessed 7 days after MI.

Statistical data processing. Statistical analysis of the data obtained was carried out using the

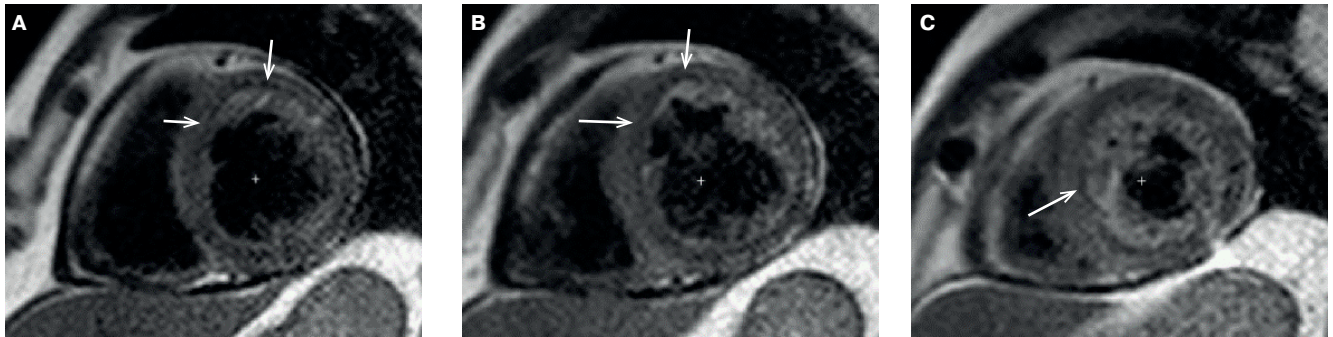


Figure 1. Intramyocardial haemorrhage by cardiac MRI. The short axis of the basal, middle, and apical (A, B, C) LV levels.
Note: arrows show hypointense areas in the projection of the LV anterior wall (A, B) and inferior lateral wall (B, C) in the T2-WI mode.

STATISTICA 10 software package. The obtained values are presented as the median (Me) and 25 and 75 percentiles (Q_{25} ; Q_{75}). The statistical significance of the differences between the two independent quantitative variables was assessed using the Mann-Whitney U test. The Kruskal-Wallis test was used to determine the significance of differences in multiple comparisons. The statistical significance of differences in qualitative traits was assessed using the Pearson's chi-squared test and Fisher's F-test. The strength of the relationship was determined using Spearman R correlation analysis. To assess the relationship of various factors, we used logistic regression methods. Differences between groups were considered significant at $p < 0,05$.

Results

According to contrast-enhanced cardiac MRI performed on the second day after MI, the overall incidence of microvascular injury was 68,3% ($n=41$). In 10 patients, an injury was represented by an isolated MVO, which amounted to 16,7%. The IMH occurred in 31 patients (51,6%). Moreover, most often, in 22 patients (70,9%), IMHT was detected in combination with MVO. An isolated IMH was visualized in 9 patients (29%) out of 31. In 19 patients, there was no microvascular injury (31,7%), and these patients were selected as a comparison group (Figure 2).

Clinical and medical history characteristics of patients, depending on the presence of IMH, are presented in Table 1.

Earlier, we described in more detail the characteristics of groups depending on the phenotype of microvascular injury [4]. With enlarged sample and detailed IMH analysis, we obtained a similar result: large values of troponin I and myocardial injury area were observed in the IMH group. When dividing IMH into isolated and combination with MVO, it was the combination that contributed to the change of listed indicators. The previously described tendency to longer ischemia in IMH+MVO group

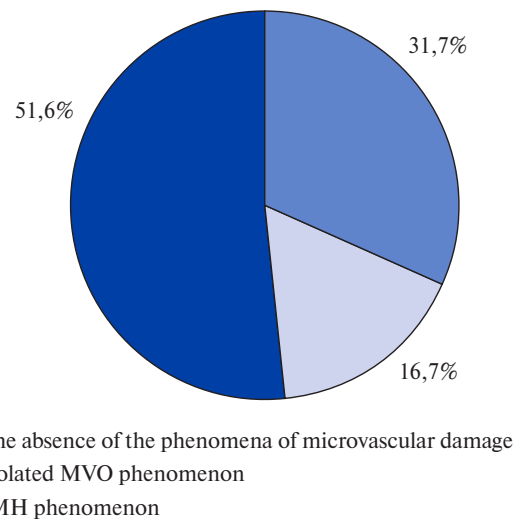


Figure 2. Prevalence of microvascular injury in patients with primary STEMI.

Abbreviations: IMH — intramyocardial haemorrhage, MVO — microvascular obstruction.

also persists. According to coronary angiography, the no-reflow phenomenon occurred in three patients. All these cases belonged to IMH+MVO group according to MRI data. In addition, there was a tendency for more frequent no-flow in the epicardial artery ($TIMI \leq 1$) before angioplasty in IMH+MVO group compared with patients with no microvascular injury. A comparative analysis of the group with isolated IMH and without microvascular injury revealed significant differences in age and body mass index: the patients were older and with lower body weight.

The structural and functional LV parameters according to echocardiography, depending on IMH presence in the early postinfarction period, are presented in Table 2. Regardless of the presence of microvascular injury, the integral indicators of echocardiography did not significantly differ from normal values. Perhaps this is due to the inclusion of non-severe patients and the early reperfusion therapy.

Table 1

**Clinical and medical history characteristics of the patients included
in the study depending on the presence of microvascular injury**

Parameter	No microvascular injury, n=19	IMH, n=31	IMH	
			Isolated, n=9	Combination with MVO, n=22
Age (years)	59 (49-66)	60 (55-68)	65 (62-69)*	62 (55-65)
Sex (m/f)	15/4	23/8	6/3	17/5
BMI (kg/m ²)	26 (24-30)	27,4 (24,2-31)	25,01 (21,5-29,05)*	28,23 (26,7-31)
GRACE (%)	2 (1-3)	2 (1-4)	4 (2-5,5)	2 (1-4)
Onset-to-reperfusion time (min)	130 (91-160)	162 (100-275)	113 (100-179)	193 (95-400)
Reperfusion technique (PIS/primary PCI)	14/5	15/16	5/4	10/12
Localization of MI (n, %)				
Anterior	10 (52,6)	20 (64,5)	4 (44,4)	16 (72,7)
Inferior	9 (47,4)	11 (35,5)	5 (55,6)	6 (27,3)
Killip (n, %)				
I	15 (78,9)	24 (77,4)	8 (88,9)	16 (72,7)
II	4 (21,1)	7 (22,6)	1 (11,1)	6 (27,3)
Q-wave MI (n, %)	10 (52,6)	16 (51,6)	6 (66,7)	10 (52,6)
TIMI grade ≤1 blood flow before PCI, (n, %)	1 (5,5)	10 (32,6)	2 (22,2)	8 (36,4)
No-reflow by CA after PCI, (n, %)	-	3 (9,6)	-	3 (13,6)
Throponin I, ng/l	4,66 (2,2-34,7)	38,2 (17,3-95,2) [§]	18,7 (17,3-22,8)	46,5 (14,9-98,8) [†]
Myocardial injury area according to cardiac MRI, %	10 (8-18)	24 (17,5-29) [§]	23,2 (9-25)	24,8 (17,5-35) [†]
Risk factors of CAD				
Hypertension (n, %)	18 (94,7)	28 (90,3)	8 (88,9)	20 (90,9)
Diabetes (n, %)	2 (10,5)	9 (29)	2 (22,2)	7 (31,8)
Dyslipidemia (n, %)	18 (94,7)	30 (96,7)	9 (100)	21 (95,5)
Obesity (n, %)	6 (31,6)	9 (29)	2 (22,2)	7 (26,3)
Smoking (n, %)	16 (84,2)	22 (70,9)	7 (77,8)	15 (68,2)
In-hospital therapy				
ASA+Clopidogrel (n, %)	7 (36,9)	14 (45,2)	5 (55,6)	9 (40,9)
ASA+ Ticagrelor (n, %)	12 (63,1)	18 (58)	4 (44,4)	14 (63,6)
ACE inhibitors (n, %)	17 (89,5)	29 (93,5)	7 (77,8)	22 (100)
β-blockers (n, %)	15 (78,9)	28 (90,3)	6 (66,7)	22 (100)
Statins (n, %)	19 (100)	31 (100)	9 (100)	22 (100)

Note: * — $p < 0,05$ — difference between the group with isolated IMH and the group without microvascular injury; [§] — difference between the group of IMH (total) and the group without microvascular injury; [†] — difference between IMH+MVO combination and the group without microvascular injury.

Abbreviations: ASA — acetylsalicylic acid, IMH — intramyocardial haemorrhage, ACE — angiotensin converting enzyme, MI — myocardial infarction, BMI — body mass index, CA — coronary angiography, MVO — microvascular obstruction, MRI — magnetic resonance imaging, PIS — pharmacoinvasive strategy, PCI — percutaneous coronary intervention.

The presence of IMH was independently associated with lower LV ejection fraction (LVEF) values (53,9% [48-60] vs. 64,5% [60-68]; $p=0,002$), an increase in end-systolic volume (ESV) (47 ml [35-61] vs. 35,5 ml [28,5-43]; $p=0,02$) and end-systolic volume index (ESVI) (25,3 ml/m² [19,4-32,9] vs. 19,5 ml/m² [16,1-22,4], $p=0,005$), in contrast to patients without microvascular injury (Table 2). When assessing end-diastolic dimension, significant differences between the groups were not

found. The values of the impaired local contractility index were higher in the group with IMH (2,22 [2,0-2,5] vs. 2,44 [2,25-2,75]; $p=0,007$).

When dividing patients into groups of isolated IMH and a combination of IMH with MVO, a different effect on myocardial contractile function and LV volume was found. Lower values of LVEF (52% [48-58] vs. 64,5% [60-68]) and an increase in ESV (53 ml [40-66] vs. 35,5 ml [28,5-43]), ESVI (28,2 ml/m² [22,3-33,7] vs. 19,5 ml/m² [16,1-22,4])

Table 2

**Echocardiographic data on the seventh day
from primary STEMI, depending on IMH presence**

Parameter	No microvascular injury, n=19	IMH, n=31	IMH	
			Isolated, n=9	Combination with MVO, n=22
LVEF, %	64,5 (60-68)	53,9 (48-60) [†]	64 (58,5-66)	52 (48-58)*
EDV, ml	93,5 (80,5-108)	100 (89-120)	92 (86-105)	115 (95-133)
ESV, ml	35,5 (28,5-43)	47 (35-61) [†]	33,5 (31,5-39,5)	53 (40-66)*
EDVI, ml/m ²	49,9 (43,5-54,3)	54,2 (46,8-60,6)	49,3 (45,2-56,6)	57,2 (50,9-67,7)
ESVI, ml/m ²	19,5 (16,1-22,4)	25,3 (19,4-32,9) [†]	19,1 (16,6-23,3)	28,2 (22,3-33,7)*
ILCI, CU	1,22 (1,0-1,5)	1,44 (1,25-1,75) [†]	1,19 (1,19-1,44)	1,44 (1,12-1,75)*
SV, ml	58 (48-67)	58 (47-65)	57 (53-66,5)	60 (49-75)
MM, g	197,5 (167-232)	204 (174-240)	176,5 (169-206)	208 (181-243)
MI, g/m ²	97 (93-123)	107 (96-127)	103 (92-109)	113 (98-133)

Note: [†] — $p < 0,05$ — difference between the group without microvascular injury and the IMH group (total); * — $p < 0,05$ — difference between the group without microvascular injury and the isolated IMH group.

Abbreviations: IMH — intramyocardial haemorrhage, MVO — microvascular obstruction, LVEF — left ventricular ejection fraction, EDV — end-diastolic volume, ESV — end-systolic volume, EDVI — end-diastolic volume index, ESVI — end-systolic volume index, ILCI — impaired local contractility index, SV — stroke volume, MM — myocardial mass, MI — mass index.

were associated with a combination of MVO and IMH. At the same time, volume characteristics and LVEF in isolated IMH were comparable with the group without microvascular injury. Similar results were demonstrated in the analysis of impaired local contractility index. The impaired local contractility index was significantly higher in the MVO+IMH group; with isolated IMH, such a correlation was not observed.

Using logistic regression analysis, it was shown that IMH+MVO combination is a predictor of decreased LV contractile function in the early postinfarction period (odds ratio, 2,1; 95% confidence interval, 2,02-2,19; $p=0,005$). The effect of isolated IMH on LVEF did not reach statistical significance (2,08; 0,99-2,18; $p=0,07$).

In addition to the very fact of IMH presence, the effect of its area on LV contractility was assessed. IMH to LV area was 1% (1-3%). The IMH area was comparable both in combination with MVO and in the isolated type: 1% (0,6-2,2) vs. 1% (0,7-2,4).

Correlation analysis showed a moderate inverse correlation between the IMH area and LV contractile function: the larger the IMH area, the lower the LVEF ($R=-0,35$; $p=0,007$) (Figure 3). Evaluating separately the effect of IMH area on LVEF in the isolated type, such a dependence was not revealed, however, this may be due to the small sample. Direct positive correlations of IMH with ESVI ($R=0,29$; $p=0,02$) were established, which were also not confirmed in patients with isolated IMH (Figure 4).

Discussion

Despite the fact that microvascular injury in myocardial infarction has been studied in many aspects, the study of the IMH phenomenon remains relevant. Until now, the mechanism of its phenomenon remains unclear, and discussions continue whether it is the cause or the result of ischemia-reperfusion injury. According to the most common point of view, the development of IMH is associated with irreversible MVO, and therefore it is associated with severe microvascular dysfunction [7, 10-13].

The prevalence of the IMH, according to the studies, is wide. This phenomenon is observed in 30-60% of patients with STEMI [10, 13]. According to our study, IMH was detected in 51,6% of cases. It has been demonstrated that IMH is heterogeneous and is most often associated with MVO. However, in 15% of cases, an isolated IMH was encountered. Similar data on the imaging of isolated IMH were described in the only recently published study by Reinstadler SJ, et al., where IMH without MVO was detected in 2% of patients [3]. A targeted study of this IMH phenotype has not been carried out. Analyzing the cause for higher prevalence of isolated IMH in the study performed, the relationship was suggested between the use of a pharmacoinvasive treatment and development of isolated IMH, but no correlations were obtained, which may be due to a small sample. The second possible explanation is the limitation of the T2 mode, which was used in our

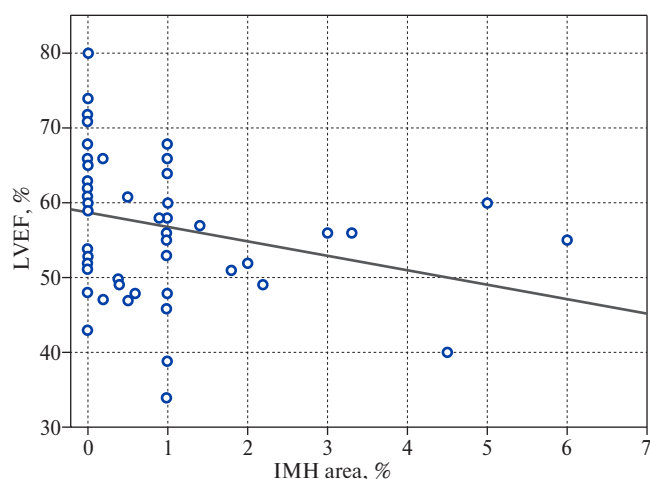


Figure 3. Relationship between the IMH area and LVEF according to echocardiography 7 days after MI.

Abbreviations: IMH — intramyocardial haemorrhage, LVEF — left ventricular ejection fraction.

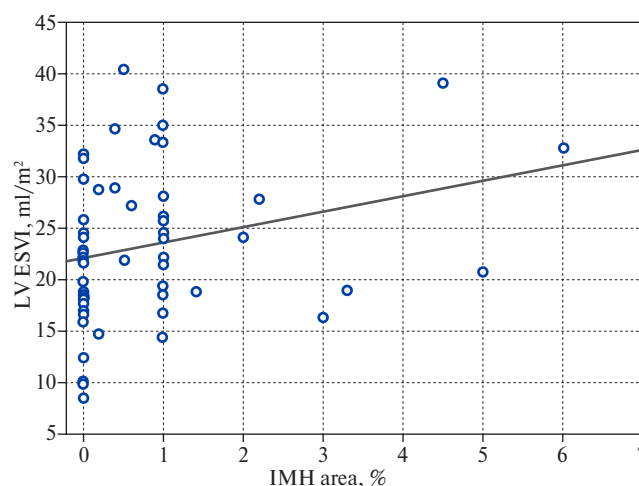


Figure 4. Relationship between the IMH area and LV ESVI according to echocardiography 7 days after MI.

Abbreviations: IMH — intramyocardial haemorrhage, LVEF — left ventricular ejection fraction.

study, since it was proved that T2* is more sensitive and specific for IMH imaging [11].

When planning this study, we expected that IMH would lead to a significant deterioration in contractility and a rapid progression of pathological myocardial remodeling. Analysis of the results showed that a decrease in LVEF and an increase in LV volume parameters independently correlate with combination of IMH with MVO. The revealed regularities confirm the published data on the effect of IMH on LV contractility, since in the conducted studies IMH was found in all cases in combination with MVO; therefore, IMH predicted decreased LVEF, as well as with progressive structural abnormalities [2, 11-13]. Fundamentally new is that in the group of isolated IMH, on the contrary, there was no effect on LV contractility and volume parameters. In addition, the structural and functional cardiac parameters according to echocardiography in isolated IMH group were comparable to the group without microvascular injury.

It has been demonstrated that IMH to LV area is 1% (1-3%). However, despite the small size of IMH, studies have shown that the very fact of IMH is associated with a large MI size, pathological remodeling, systolic dysfunction, and an unfavorable clinical outcome. It is important to note that these patterns were also established when studying the IMH with MVO combination [2, 7, 13]. In this connection, a number of authors believe that the assessment of MVO and its area play a more significant role in healing of the infarcted area and myocardial remodeling. Thus, Ma M, et al. showed that the MVO size, regardless of IMH presence

and size, has a more pronounced correlation with damaged myocardial size [6]. The effect of isolated IMH area on LVEF was not evaluated in any of the studies. According to our work, it has been shown that if the phenomena are not divided into isolated and combination, the IMH area correlates with decreased LVEF and increased LV ESVI. However, with a targeted examination of isolated IMH area on LV structure and function, similar dependences are not shown.

The study of cardiac MRI in patients with MI as a diagnostic tool is a relatively new direction in cardiology. The ability of this method to non-invasively visualize different phenotypes of microvascular injury *in vivo* demonstrated the existing barrier to studying the myocardial remodeling. In this regard, the following questions are relevant: an isolated IMH and a combination of IMH with MVO are links of one process and the appearance of which of the phenomena of microvascular injury or just their combination is more associated with pathological myocardial remodeling, as well as how we can influence microvascular injury? It is likely that the extravasation of erythrocytes into the myocardium, which is the basis of IMH, is only a trigger mechanism that provokes a cascade of reactions leading to pronounced structural and functional cardiac changes. Therefore, it is of interest to further study the IMH, especially in terms of its effect on chronic sterile inflammation.

Study limitations. A small number of subjects in the group of isolated IMH; no technical feasibility of using T2* MRI mode.

Conclusion

The analysis of the influence of different IMH phenotypes on the structural and functional echocardiographic parameters of myocardium in the short-term period after STEMI has shown that the combination of IMH with MVO and isolated IMH have different effects on LV contractile function. The combination of IMH with MVO is a predictor of a decrease in LVEF and increase of ESV, while an isolated IMH does not affect these parameters.

Correlations between the IMH area and a decrease in LVEF, as well as an increase in ESV, have been demonstrated.

Relationships and Activities. This work was supported by a fellowship of the President of the Russian Federation for young scientists and post-graduate students “The influence of microvascular myocardial injury on the course of the inflammatory response in myocardial infarction”.

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