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Correlations between clinical and laboratory findings and prognostically unfavorable CMR-based characteristics of acute ST-elevation myocardial infarction

Aim — To evaluate factors associated with unfavorable predictive characteristics of ST-segment elevation acute myocardial infarction (STEMI) as per data of magnetic resonance imaging (MRI).

Material and methods — The study included 52 patients with STEMI who underwent a primary percutaneous coronary intervention (pPCI). Contrast-enhanced cardiac MRI was performed for all patients on days 3-7. Delayed contrast-enhancement images were used for assessing infarct size, presence of microvascular obstruction (MVO) areas, and heterogeneity zones.

Results — Multifactorial analysis showed that independent predictors of MVO were type 2 diabetes mellitus (DM) (relative risk (RR) 1.9, confidence interval (CI): 1.1–3.26, p=0.012), increased levels of brain natriuretic peptide (BNP) (RR 2.04, CI: 1.39–2.99, p=0.004) and creatine kinase (CK) (RR 2.06, CI: 0.52–0.80, p=0.02), and infarct size (IS) (RR 2.81; CI: 1.38–5.72, p=0.0004). Construction of ROC curves provided the quantitative values of study indexes, at which the risk of MVO increased. For BNP, this value was ≥276 pg/ml (sensitivity, 95.7%; specificity, 37.9%); for CK ≥160 U/l (sensitivity, 74.1%; specificity, 61.9%); and for IS ≥18.8% (sensitivity, 79.3%; specificity, 69.6%). Correlation analysis of risk factors for increased size of the heterogeneity zone showed significant correlations of the heterogeneity zone size with older age of patients (r=0.544, p<0.0001), higher concentrations of BNP (r=0.612, p<0.0001), CK (r=0.3, 95% CI: 0.02–0.5, p=0.03), and C-reactive protein (CRP) (r=0.59, CI: 0.3–0.7, p=0.0001). Increased levels of CK (r=0.53, 95% CI: 0.29–0.70, p=0.0001) and BNP (r=0.55, 95% CI: 0.28–0.70, p=0.0003) significantly correlated with increased IS.

Conclusion — Risk of MVO formation as per MRI data increased in the presence of type 2 DM and IS ≥18.8% (p<0.05). Formation of MVO in patients with STEMI was associated with increased levels of BNP ≥276 pg/ml and CK ≥160 U/l (p<0.05). Increased levels of BNP, CK, and CRP were associated with a larger size of heterogeneity zone according to data of the correlation analysis. A larger heterogeneity zone was more typical for older patients. Increased levels of CK and BNP were also associated with larger IS. The correlation analysis did not show any significant interactions between the size of heterogeneity zone, IS, and MVO size (p>0.05).

Keywords — ST-segment elevation acute myocardial infarction; contrast-enhanced magnetic resonance imaging; infarct size; microvascular obstruction; heterogeneity zone

For citation — Terenicheva M.A., Shakhnovich R.M., Stukalova O.V., Pevzner D.V., Arutyunyan G.K., Demchenkova A.Yu., et al. Correlations between clinical and laboratory findings and prognostically unfavorable CMR-based characteristics of acute ST-elevation myocardial infarction. Kardiologiia. 2021;61(1):44–51. [Russian: Тереничева М.А., Шахнович Р.М., Стукалова О.В., Певзнер Д.В., Арутюнян Г.К., Демченкова А.Ю. и др. Взаимосвязь клинических и лабораторных показателей с развитием прогностически неблагоприятных характеристик инфаркта миокарда с подъемом сегмента ST по данным магнитно-резонансной томографии сердца с контрастированием. Кардиология. 2021;61(1):44–51]

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Introduction

Despite recent significant progress in the treatment of myocardial infarction (MI) and noticeable improvement in post-MI prognosis, mortality remains high and persists at 7.3% during the first year [1]. New cardiac magnetic resonance imaging (MRI) with contrast enhancement allowed detecting several structural MRI characteristics of myocardial infarction, which contributed to a more accurate estimation of the prognosis for patients [2].

The infarction size, the presence and size of the microvascular obstruction (MO) sites, and heterogeneity size are among the main MRI predictors of unfavorable prognosis in acute MI patients (Table 1). The first two parameters have an effect on all-cause mortality rates and the rate of hospitalizations for heart failure (HF) [3, 4]. The

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1373

latter is a risk factor in ventricular arrhythmias and sudden cardiac death [5].

Clinical and laboratory indicators which can lead to the appearance or aggravation of adverse MRI characteristics of acute myocardial infarction (AMI) have not been sufficiently studied.

Objective

To evaluate factors associated with prognostic adverse MRI characteristics of ST-segment-elevation acute myocardial infarction (STEAMI).

Material and methods

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and approved by the ethics committee of the Russian National Cardiology Research Center. All patients signed informed consent to participate in the study.

The study included 52 patients with first-onset STEAMI within 48 hours from disease onset. AMI was diagnosed following the Fourth Universal Definition of Myocardial Infarction [6].

ECG criteria given in the 2017 Guidelines of the European Society of Cardiology were used for STEAMI [7].

All patients underwent urgent coronary angiography (CAG) and primary percutaneous coronary intervention (pPCI) for infarct-related artery (IRA). Contrast-enhanced cardiac MRI was performed on days 3–7 in a superconducting MR scanner with a 1.5T magnetic field strength (Siemens Avanto).

Non-contrast scanning included:

- cine-MRI in standard views (2- and 4 chamber long axes, LV short axis) evaluating left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), ejection fraction (EF), local myocardial contractility abnormalities in 17 LV segments;
- T2 weighted images in the same views to estimate myocardial edema (considered as more than 2-fold signal intensity (SI) compared to the normal myocardium.
- Gadolinium-based contrast agent (Magnevist, Bayer AH) was used at a dose of 0.15 mmol/kg body weight.

The contrast-enhanced scanning included:

- early contrast enhancement (2 minutes after intravenous contrast injection);
- delayed contrast enhancement (10–20 minutes after intravenous contrast injection).

Contrast-accumulating sites were regarded as acute or chronic myocardial injury (depending on the presence of edema in T2 weighted images).

The reduced intensity zones located inside the contrast accumulating site were considered as MO.

The region with signal intensity of 25–50% of the contrast accumulating site was regarded as a heterogeneous zone.

The CVI-42 (circle cardiovascular imaging) program was used to perform tissue analysis. The size of MI, MO, heterogeneous zone, and LVEF were estimated. Based on the signal intensity analysis, a necrosis part (more than 5 standard deviations compared to the normal myocardium) and a heterogeneous zone (2 to 5 standard deviations) were identified in the injury area. The masses of necrosis and heterogeneous zones were quantified, and their percentage of the LV myocardial mass was determined.

Brain natriuretic peptide (BNP) was analyzed by chemiluminescent immunoassay (Abbott, USA). Creatine phosphokinase (CPK) was determined by photometric enzymatic assay (Abbott, Architect C 8000), and C-reactive protein (CRP) was measured by turbidimetry (Abbott).

Table 1. Main MRI characteristics of AMI

Parameter/definition	MRI signs
Infarction size	The myocardial volume or mass that accumulates the contrast agent in the delayed contrast-enhancement phase
MO is an area in the IRA bed where coronary microcirculation is still abnormal while the blood flow in IRA is recovered	The reduced intensity zones located inside the contrast accumulating site
Heterogeneity is a peri-infarct zone with a histopathological combination of necrotized tissue, ischemic and intact cardiomyocytes, and fibroblasts	The area with SI of 25–50% of the maximum in the delayed contrast-enhanced images

MO, microvascular obstruction;
IRA, infarct-related artery; SI, signal intensity.

Statistical analysis

Statistical data analysis was performed using MedCalc 15.8 Portable and Stat Research V 7.32.1 light software programs. The data obtained was tested for distribution normality using the Kolmogorov-Smirnov test. Mean and standard deviation or 95% confidence interval was provided for the quantitative characteristics with normal distribution. Relative risk was determined using a multivariate analysis by binary dependent logistic regression, in order to determine the outcome rate ratios among the subjects. ROC-curve was built, and the sensitivity and specificity were analyzed to calculate an optimal cut-off value of the parameters of interest. Spearman's correlation analysis was used to determine the dependence of quantitative variables. Differences were regarded as statistically significant at $p<0.05$ for each of the hypotheses tested.

Results

The percentage of male patients was 85%, and the median age was 59.09±7.7 years. All patients were subjected to reperfusion therapy by pPCI. The median time of pPCI from the onset of symptoms was 3 hours. Characteristics of the groups are provided in Table 2.

Clinical and laboratory factors and risk of developing MO

A multivariate analysis was conducted to assess the risk factors of MO in patients with MI. The results are presented in Table 3. The analysis of clinical factors did not find any statistically significant correlation between the age of patients, history of arterial hypertension (AH), smoking, obesity, and MO (p>0.05). The presence of type 2 DM turned out to be an independent predictor of developing MO (OR 1.9, 95% CI: 1.10–3.26; p=0.012). Elevated levels of BNP (OR 2.04, 95% CI: 1.39–2.99, p=0.004) and CPK (OR 2.06, 95% CI: 0.52–0.80, p=0.02) were identified as independent predictors of the risk of MO. No significant correlation was established between CRP levels and the risk of developing MO (p=0.6).

When the ROC-curves were constructed, the levels of laboratory indicators of interest associated with the highest risk of developing MO were determined. BNP was ≥276 pg/mL with high specificity (95.7%) and low sensitivity (37.9%). CPK was ≥160 U/L clip with a sensitivity and specificity equal to 74.1 and 61.9%, respectively.

The analysis of the effects of MR characteristics of AMI on the risk of developing MO showed that the independent predictor of this phenomenon was the size of MI (OR 2.81, 95% CI 1.38–5.72, p=0.0004). When the ROC curve was constructed, the size of MI associated with the increased risk of developing MO was 18.8% (sensitivity 79.3%, specificity 69.6%) (Figure 1). No significant correlation was established between the size of the heterogeneity and the risk of developing MO (p=0.07).

Clinical and laboratory factors and heterogeneity size

A correlation analysis was conducted to assess the correlation between quantitative indicators (clinical and laboratory indicators and heterogeneity size; Table 4). The analysis of clinical characteristics of patients detected a statistically significant correlation between the heterogeneity size and the age of patients (r=0.544, p<0.0001).

The correlation analysis of the heterogeneity size and the laboratory indicators showed a statistically significant correlation between the heterogeneity size and the levels of BNP (r=0.612, r < 0.0001) and CPK (r=0.3, 95% CI: 0.02–0.50; p=0.03). Increased CRP was also significantly correlated with the size of heterogeneity (r=0.59, CI: 0.3–0.7; p=0.0001).

Table 2. Group characteristics

Indicator	Value
Male, n (%)	44 (84.6)
Mean age, years	59.09 ± 7.70
Active smokers, n (%)	34 (65.4)
Hypertensive heart disease, n (%)	40 (77)
Obesity (BMI≥30 kg/m²), n (%)	22 (42)
History of myocardial revascularization, n (%)	0
Burdened family history (CHD in first degree relatives: male <55 years old and female <60 years old), n (%)	2 (3.9)
Diabetes mellitus type 2, n (%)	26 (50)
History of stable angina, n (%)	7 (13.5)
Angina within 1 month before AMI, n (%)	10 (19.2)
No history of CHD, n (%)	38 (73.1)
Median time from the disease onset to pPCI	3 h
Prehospital thrombolytic therapy, n (%)	1 (1.9)
IRA: LAD, n (%)	28 (53.8)
IRA: RCA, n (%)	16 (30)
IRA: LCX, n (%)	4 (7)
LVEF >40%, n (%)	50 (96)
Hospital mortality, n (%)	1 (1.9)

BMI, body mass index; pPCI, primary percutaneous coronary intervention; IRA, infarct-related artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; LVEF, ejection fraction.

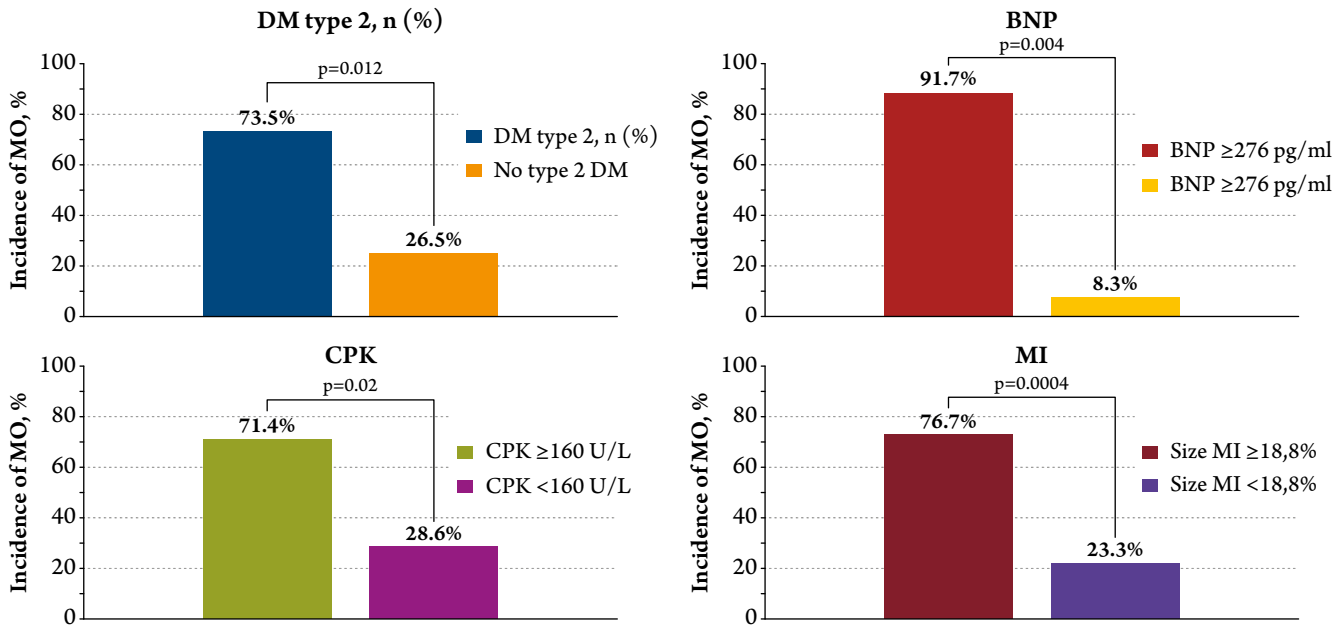
Table 3. Results of multivariate analysis of MO risk factors

Risk factor	Odds ratio	95% confidence interval	p
Clinical anamnestic factors			
Age	1.15	0.62; 2.15	0.6464
Obesity (BMI>30 kg/m²)	0.83	0.5–1.39	0.16
Smoking	1.01	0.32–3.20	0.9
AH	2.1	0.57–7.79	0.2
DM type 2, n (%)	1.9	1.1–3.26	0.012
Laboratory indicators			
BNP ≥276 pg/mL	2.04	1.39–2.99	0.004
CRP	0.55	0.376–0.71	0.6
CPK ≥160 U/L	2.06	0.52–0.8	0.02
MRI characteristics of AMI			
Size of heterogeneity, %	1.7	0.86; 3.36	0.0770
Size of AMI, %	2.81	1.38; 5.72	0.0004

Note: BMI, body mass index; AH, arterial hypertension; DM type 2, – type 2 diabetes mellitus; BNP, brain natriuretic peptide, CRP, C-reactive protein; CPK, creatine phosphokinase.

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1373

Figure 1. Rate of MO



A multivariate analysis was conducted, in order to assess the risk factors of enlarged heterogeneity size. The median size of heterogeneity, 15% in the study group, was used as a binary dependent variable. However, there was no significant correlation between the factors of interest and the size of heterogeneity of less than 15% and more than 15% (p>0.05).

Clinical and laboratory factors and infarction size

The correlation analysis of factors associated with the increased size of myocardial infarction (Table 4) did not detect any significant correlation with age and body mass index (BMI) (p>0.05). In the laboratory analysis, the increased size of MI was significantly correlated with increased levels of CPK (r=0.53, 95% CI: 0.29–0.70, p=0.0001) and BNP (r=0.55, 95% CI: 0.28–0.70; p=0.0003). In the multivariate analysis, the size of MI equal to 15% was regarded as the binary dependent variable (since this value had been previously used as a measurer of large MI [8]), as well as the median size of MI in the study group (15.9%), and the value obtained by ROC-analysis as a predictor of MO (18.8%). There was no significant correlation between clinical and laboratory indicators and the above values (p > 0.05).

Estimation of correlation of MRI characteristics of AMI

The correlation analysis did not detect any statistically significant correlations between the sizes of heterogeneity, MI, and MO (p > 0.05; Table 5).

Discussion

Recent years have witnessed active development of cardiac MRI technique. It allows MRI to be used for differential diagnosis of acute and chronic myocardial injury, visualization of thrombi in the cavities of the heart, diagnosis of mechanical complications of AMI, etc., as well as being a promising tool for assessing the prognosis for AMI patients and identifying groups of risk for the adverse course. Several essential characteristics of AMI can be determined with delayed contrast-enhanced MRI. The main contrast-enhanced MRI parameters of MI include the size of MI, myocardial edema, MO, intramyocardial hemorrhage, heterogeneity [1].

Table 4. Correlation analysis of clinical and laboratory indicators and MR characteristics of AMI

Indicator		Size of heterogeneity, %	Size of MI, %
BNP	r	0.612	0.55
	p	<0.0001	0.0003
Age	r	0.544	0.016
	p	<0.0001	0.9121
BMI	r	–0.136	0.027
	p	0.3349	0.8499
CPK	r	0.3	0.53
	p	0.03	<0.0001
CRP	r	0.59	0.2437
	p	0.0001	0.2

Infarction size

The size of infarction is defined as the volume or mass of acute focal injury developing into fibrosis which accumulates the contrast agent [9]. The method is based on the tissue distribution of a gadolinium-based contrast agent, which can penetrate only into cells with compromised membrane integrity, thus accumulating in the zone of myocardial necrosis [10]. Contrast-enhanced MRI is now considered the most

accurate method of estimating the size of MI [11, 12]. The size of MI allows for more accurate judgments about myocardial injury compared to LVEF. This can change, especially in the acute period of MI, due to myocardial hibernation and stunning, as well as external causes (volemic status, heart rate disorders, etc.). The role of accurate measurement of MI size using cardiac MRI was shown by Stone et al. [3], who found that a 5% increase in MI size caused an increase in the 12-month rate of hospitalizations for HF and all-cause mortality by 20%. The correlation between the MRI size of MI and clinical outcomes was demonstrated by Klem et al., who detected a direct correlation between the increased fibrosis size by >5% of LV mass and the rate of adverse cardiovascular events (odds ratio (OR) 5.2, 95% CI: 2.0–13.3; p<0.0006). Scarring size >5% was defined as an independent predictor of endpoint outcome (all-cause death, activation of an implantable cardioverter-defibrillator (ICD) for ventricular tachycardia (VT)/ventricular fibrillation (VF) (OR 4.6, 95% CI: 1.8–11.8, p<0.002). However, LVEF did not have a significant effect on the development of VT/VF and the number of ICD activations (OR 0.1, 95% CI: 0.97–1.20; p < 0.58) [13]. The size of AMI is also a more significant predictor of developing abnormal remodeling than LVEF. According to Wu et al., increased size is accompanied by a more pronounced increase in EDV and ESV in the long-term period of MI (p < 0.001) [14].

The time from the onset of symptoms to reperfusion therapy is the most well-known factor which affects changes in MI size. The post-pPCI retention of ST-segment elevation at more than 50% of the baseline is the predictor of a larger necrosis zone [15, 16]. Our goal was to identify additional factors unrelated to myocardial revascularization which may be associated with the increased size of AMI and deterioration of prognosis. We assessed the size of MI using MRI in the acute period (day 3–7 after AMI). The correlation analysis of MI size and markers of acute myocardial injury showed that there was a significant medium correlation with the levels of CPK (r=0.53, 95% CI 0.29–0.70, p=0.0001) and BNP (r=0.55, 95% CI 0.28–0.70, p=0.0003). This was expected, since CPK is an intracellular enzyme released from the cytosol into the systemic circulation when cell membranes are damaged due to hypoxia [17]. We used CPK to perform additional quantification of myocardial necrosis.

BNP is a cardiac neurohormone secreted by LV cardiomyocytes in response to increased wall stress due to volume or pressure overload. Its plasma concentration reflects the degree of LV dysfunction and is an important prognostic factor in patients with acute coronary syndrome and chronic heart failure [18]. Our findings are consistent with previous studies, in which a significant correlation of N-terminal pro-brain natriuretic peptide (NT-proBNP) with the size of MI had already been revealed by contrast-enhanced MRI [19].

Table 5. Correlation analysis of MRI characteristics of AMI

Indicator		Size of MO	Size of heterogeneity	Size of MI
Size of MO	r	–	0.277	–0.144
	p		0.1458	0.4574
Size of heterogeneity	r	0.277	–	0.067
	p	0.1458		0.6381
Size of MI	r	–0.144	0.067	–
	p	0.4574	0.6381	

Microvascular obstruction

Microvascular obstruction (MO) is an area in the IRA bed, where coronary microcirculation is still abnormal while the blood flow in IRA is recovered. MO results from impaired coronary microcirculation in the IRA basin despite the recovery of blood flow. The pathophysiology of MO includes microcirculatory vasoconstriction, distal embolization by the atherosclerotic plaque particles, complexes of fibrin, platelets, and RBCs [21]. The mechanisms of vasoconstriction have not been sufficiently studied. Ischemic damage to the endothelium shown in animal models of STEAMI is possible [22]. Microembolization also stimulates an inflammatory response. Thus, the aggregation of leukocytes is noted in the MO zones, creating an additional mechanical barrier to blood flow and disrupting capillary vasodilation by triggering oxidative stress [23]. In the contrast-enhanced MRI, MO is dark hypointense zones within the area where the contrast agent (infarction zones) accumulates. Despite successful reperfusion therapy, the incidence of MO in STEAMI patients is about 50% [24–26]. Both the very presence and the severity of MO are associated with the deterioration of systolic and diastolic LV function, a larger size MI, and diffuse changes in intact myocardial tissues. MO is one of the most important prognostic factors for patients with STEMI. Thus, MO is an independent predictor of all-cause death and hospitalizations for HF in this patient category. The size of MO > 1.4% of the LV mass is an independent predictor of all-cause death, recurrence of MI, and the increased number of hospitalizations for HF within 12 months (p < 0.001) [4]. It should be noted that MO is an unfavorable prognostic sign, even if myocardial contractility is preserved (LVEF >50%) [27]. The meta-analysis by Van Kranenburg et al. of more than 1,025 patients with STEMI, showed that MO was also an independent predictor of cardiovascular mortality, HF, and the recurrence of MI within two years [21]. Delayed reperfusion therapy is a well-known risk factor for MO, as is the increased size of AMI. An incomplete resolution of the ST segment after PCI is a sign of the suboptimal outcome of revascularization [3]. According to Ndrepepa et al. [28], the onset of MO is associated with an increased volume of myocardial necrosis. Our study confirmed these findings. The multivariate analysis showed a direct correlation between the

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1373

increased size of MI and the risk of developing MO. The risk of MO increased when the size of MI was ≥ 18.8% of the LV mass. These findings were consistent with the results of the correlation analysis between MO and laboratory indicators, showing a significant correlation between the markers of myocardial injury (CPK, BNP) and the risk of developing MO. The analysis of anamnestic factors and the incidence of MO showed that there was a significant correlation between type 2 DM and the risk of developing MO. It has already been suggested above that MO develops, if the microvascular bed is initially compromised. Thus, this phenomenon may result from endothelial dysfunction, with type 2 DM being its common cause.

When assessing the effects of laboratory indicators on the risks of developing MO, its probability increased significantly with BNP ≥ 276 pg/mL and CPK ≥160 U/L ($p < 0.05$). In earlier studies, elevated levels of BNP and D-dimer were regarded as independent predictors of MO (estimated by the invasive measurement of microvascular resistance index) [29].

Heterogeneity

Several pathomorphological studies have shown that the myocardial infarction zone is morphologically inhomogeneous. Its structure includes a nucleus represented by necrotized cardiomyocytes in acute MI and fibrous tissue as the scar forms, as well as a heterogeneous zone, which is a boundary between the MI zone and the normal myocardium consisting of necrotized, ischemic and intact cardiomyocytes [30–32]. In delayed contrast-enhanced MR images, a heterogeneous zone is defined as an area with a SI less than 50% of the maximum in the infarction area but higher than the maximum SI in the remote area [33]. Initially, heterogeneity was of interest as an area with high arrhythmogenic potential. Conduction in the peri-infarction heterogeneous zone is altered by a short refractory period and slower electrical conduction, thus forming a substrate for the development of ventricular arrhythmias [34–36]. As early as the end of the 1970s during electrophysiological studies in patients with postinfarction cardiosclerosis (PICS), several authors revealed the existence of both macro re-entry foci around the scarring tissue and multiple micro re-entry foci at the border of the scar and the healthy myocardium [37, 38].

Later studies confirmed that the mechanism of paroxysmal VT in PICS patients was the formation of re-entry foci by a combination of viable cardiomyocytes and fibrous tissue, mainly at the scarring border [39]. It was later shown that increasing heterogeneity leads to a higher incidence of ventricular arrhythmias [5]. These findings have been confirmed by several studies in patients with PICS [32, 40–42]. There is no published data on the risk factors of the increased size of heterogeneity. A significant correlation was found in our study between the increased size of heterogeneity and patient's age. This is probably due to age-related degenerative processes in the myocardium and the appearance of fibrosis sites [43], leading to greater myocardial heterogeneity. According to our findings, the increased size of heterogeneity correlated to all the biomarkers of interest (BNP, CRP, CPK). Previous studies of CRP in patients with a history of MI have shown that this marker is associated with the rate of arrhythmic events and the number of ICD activations [44, 45]. The levels of markers of LV dysfunction BNP and CPK and volume of the myocardial injury may reflect the size of a zone combining necrotized, reversibly damaged and intact cardiomyocytes, i.e., heterogeneity zone.

New cardiac MRI techniques have revealed certain characteristics of the myocardial infarction zone which can affect the prognosis for patients, as confirmed by many trials and meta-analyses. Estimation of a combination of clinical anamnestic and laboratory indicators significantly correlated to individual MRI characteristics of AMI can provide additional information of interest for prognosis after discharge from the hospital. Larger studies are needed to analyze the effects of different factors on the adverse MRI characteristics of AMI.

Conclusion

According to our findings, type 2 DM, the size of MI≥18.8%, BNP≥276 pg/mL, and CPK≥160 U/L are the independent predictors of developing MO. The increased the size of heterogeneity (a risk factor for sudden cardiac death) correlated to more advanced age and increased levels of BNP, CPK, and CRP. Elevated levels of CPK and BNP were also correlated to the larger size of MI. There were no statistically significant correlations between the sizes of heterogeneity, MI, and MO ($p>0.05$).

No conflict of interest is reported.

The article was received on 21/09/2020

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