ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

ORIGINAL STUDY

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ОЦЕНКА ФУНКЦИИ ЭНДОТЕЛИЯ, ЭЛАСТИЧНОСТИ СОСУДИСТОЙ СТЕНКИ И ИХ ВЛИЯНИЯ НА ГОДОВОЙ ПРОГНОЗ У БОЛЬНЫХ С ИНФАРКТОМ МИОКАРДА ПРИ ОБСТРУКТИВНОМ И НЕОБСТРУКТИВНОМ ПОРАЖЕНИИ КОРОНАРНЫХ АРТЕРИЙ

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Цель. Провести сравнительный анализ состояния функции эндотелия (ФЭ), эластичности сосудистой стенки и их влияния на годовой прогноз у больных с инфарктом миокарда (ИМ) при обструктивном и необструктивном поражении коронарных артерий (КА).

Материалы и методы. На первом этапе было отобрано 206 пациентов с диагнозом ИМ, из них 103 пациента без обструктивного поражения КА (ИМБОКА) по результатам коронароангиографии и 103 пациента – с ИМ и обструктивным поражением КА (ИМОКА). Методом случайных чисел было отобрано 59 пациентов (34 пациента – из первой группы, 25 – из второй), у которых проведена оценка ФЭ и эластических свойств артериальной стенки. Исходно пациенты обеих групп были сопоставимы по возрастно-половой и клинико-анамнестическим характеристикам, а также по частоте применения основных групп лекарственных препаратов, влияющих на прогноз. Изучался годовой прогноз пациентов двух групп в зависимости от наличия/отсутствия функциональных и морфологических изменений сосудистой стенки.

Результаты. У больных ИМБОКА при оценке ФЭ индекс окклюзии по амплитуде (ИОА) ниже пороговых значений зарегистрирован в 22 из 34 (64,7%) случаев ИМБОКА и в 22 из 25 – при ИМОКА (88,0%, $p<0,05$). При этом, средние значения ИОА составили 1,7 (1,5; 2,3) и 1,4 (1,2; 1,8) соответственно ($p<0,05$). Значения сдвига фаз между каналами в двух группах ниже нормальных значений встречались одинаково часто (88,2 и 88,0%, $p>0,05$) и сравнение средних величин данного показателя статистического значимого различия также не выявило. Расчетный индекс аугментации, приведенный к пульсу 75 ударов в минуту (AIp75), в изучаемых группах составил 12,5 (9,9; 17,9) и 18,8 (12,9; 20,8) соответственно ($p>0,05$). Снижение эластичности сосудистой стенки в группе ИМБОКА встречалось у 82,4% пациентов, при ИМОКА – в 100% случаев, ($p<0,05$). Статистически значимых различий в частоте сердечно-сосудистых событий в течение года в группах зарегистрировано не было ($p>0,05$).

Заключение. Функциональные изменения сосудистой стенки (эндотелиальная дисфункция и снижение эластичности сосудистой стенки) у пациентов с ИМБОКА были зарегистрированы почти в 2/3 случаев, однако при ИМОКА их частота еще выше (88,0%). Годовой прогноз в изучаемых группах с ИМБОКА и ИМОКА не различался.

Ключевые слова: *инфаркт миокарда; ИМБОКА; функция эндотелия; эластичность сосудистой стенки; прогноз.*

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EVALUATION OF ENDOTHELIAL FUNCTION, OF ELASTICITY OF VESSEL WALL AND THEIR INFLUENCE ON ONE-YEAR PROGNOSIS OF PATIENTS WITH MYOCARDIAL INFARCTION WITH OBSTRUCTIVE AND NON-OBSTRUCTIVE CORONARY ARTERIES

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Aim. To carry out comparative analysis of the state of the endothelial function (EF), elasticity of the vessel wall and their influence on one-year prognosis of patients with myocardial infarction (MI) with obstructive and non-obstructive coronary arteries (CA).

Materials and Methods. In the first stage, 206 patients were selected diagnosed with MI, of them 103 patients with MI with non-obstructive CA (MINOCA) according to the results of coronaroangiography, and 103 patients with MI with obstructive CA (MIOCA). Using the method of random numbers, 59 patients were selected (34 patients of the first group and 25 of the second group), in whom EF and elastic properties of the arterial wall were evaluated. Patients of both groups were initially comparable in age, gender, clinical and anamneustic characteristics, and also in frequency of application of the main groups of medical drugs that influence prognosis. One-year prognosis of the two groups of patients was studied depending on the presence/absence of functional and morphological alterations of the vessel wall.

Results. In evaluation of EF in patients MINOCA, the occlusion index by amplitude (OIA) below threshold values was recorded in 22 of 34 (64.7%) cases of MINOCA and in 22 of 25 (88.0%, $p<0.05$) cases of MIOCA. Here, the average values of OIA were 1.7 (1.5; 2.3) and 1.4 (1.2; 1.8), respectively ($p<0.05$). The values of phase shifts between the channels below the norm were equally frequent in two groups (88.2 and 88.0%, $p>0.05$), and comparison of the average values of this parameter did not show any statistically significant difference. The calculated augmentation index normalized to the pulse rate 75 beats per minute (AIp75), in the study groups was 12.5 (9.9; 17.9) and 18.8 (12.9; 20.8), respectively ($p>0.05$). Reduction of the elasticity of the vessel wall in the group with MINOCA was noted in 82.4% of patients, in the group MIOCA – in 100% of cases ($p<0.05$). No statistically significant differences were found in the frequency of cardiovascular events between the groups during a year ($p>0.05$).

Conclusion. Functional alterations of the vessel wall (endothelial dysfunction and reduction of elasticity of the vessel wall) in patients with MINOCA were recorded almost in 2/3 of cases, however, their incidence in MIOCA was still higher (88.0%). The one-year prognosis in the study groups MINOCA and MIOCA showed no differences.

Keywords: *myocardial infarction, MIOCA; MINOCA; endothelial function; elasticity of vessel wall; prognosis.*

Endothelial function (EF) is an integral indicator of atherogenic and atheroprotective factors that play key roles in all phases of atherosclerosis [1]. One of the signs of endothelial dysfunction (ED) is the derangement of vessel tone regulation because of an imbalance in the release of vasodilators and vasoconstrictors in response to different stimuli [2], This phenomenon has been demonstrates in a study involving an ischemia model of laboratory rats [3]. In humans, similar data have shown that the

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incidence of cardiovascular events in patients with disorders in vessel wall elasticity is higher than that in patients with preserved vessel wall elasticity [4].

Coronary heart diseases are diagnosed and treated with X-ray endovascular methods, which have high medical efficiency and social value [5]. Thus, in the majority of myocardial infarction (MI) cases, coronary angiography (CAG) results reveal an obstructive lesion (more than 50% stenosis) of infarction-associated coronary arteries (CA) [6]. In other studies [6-8], MI develops with unchanged CAs or nonstenotic lesions (less than 50% stenosis), i.e., MI with non-obstructive CA (MINOCA), in an average of 6% of cases. The pathogenetic basis of MI caused by the atherosclerotic lesion of CA is the disorder in the morphological and functional states of vessel walls. Even in the absence of an evident lesion of CA in CAG, an independent predictor of the development of cardiovascular events (including lethality from cardiovascular causes, MI, stroke, and unstable angina) is the ED of CA in the epicardium and microcirculatory bed [9,10]. However, studies have yet to comparatively analyze the EF of patients with MINOCA and MI with obstructive CA (MIOCA). Therefore, the main parameters of EF and the elasticity of vessel wall in patients with MI should be explored in terms of the extent of CA obstruction.

The non-invasive determination of EF is based on the evaluation of the influence of nitric oxide as the main vasodilatory mediator in the smooth muscles of vessel walls in response to ischemia. ED has a generalized character, the condition of EF in CA in the epicardium and microvasculature can be determined by evaluating the condition of the endothelium in any part of the vascular bed permits [1,11].

This study *aimed* to comparatively analyze the function of the endothelium and elasticity of vessel walls and their influence on the 12-month prognosis of patients with MIOCA and MINOCA.

Materials and Methods

A retrospective study with elements of a prospective study was conducted, as approved by the Local Ethics Committee of Regional Clinical Cardiologic Dispensary on November 15, 2017 (Protocol No. 11). At the first stage, 206 patients who were admitted to hospitals in Ryazan and diagnosed with MI established on the basis of the fourth universal definition of MI [12] were selected in this study. According to the CAG results, two groups of patients were formed: group 1 had 103 patients without an obstructive lesion of CA (stenosis of less than 50% or without signs of atherosclerotic lesions), and group 2 was composed of patients with an obstructive lesion of CA. The myocardium of the patients in the second group (MIOCA) was revascularized. The second group was selected via the «copy-pair» method relative to the first group.

Through the random number methods, 34 and 25 patients were selected from the first and second groups, respectively. The groups were comparable in terms of age, gender, classification form of MI (Q-MI and non-Q-MI), ischemic history, risk factors, and medication frequency (except salicylic acid, Table 1). The management of patients were in accordance with the procedures recommended for the given pathology. The patients (or their legal representatives) were asked to sign their informed consent upon hospital admission.

During hospitalization, 5 days after the establishment of the diagnosis of MI, the patients were subjected to an occlusion test to evaluate EF through photoplethysmography; the elastic properties of the arterial wall were studied through the contour analysis of pulse wave (CAPW) on an Angioscan-01 hardware-software complex (OOO Angioscan-Electronics, Russia) [10]. This study was performed in accordance with the standard method: in a warm, quiet, and darkened room in the morning, on an empty stomach, after 10-15 min rest, in a sitting position after the

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Table 1

Clinical and Demographic Characteristics of the Study Groups

Parameters	MINOCA	MIOCA
n	34	25
Age, M (Q1; Q3), years	58.6 (48.5; 67.7)	59.7 (53.2; 66.6)
Men, n (%)	23 (67.6)	13 (52.0)
Clinical Diagnosis on Admission		
MI with the elevation of the ST segment on ECG, n (%)	22 (64.7)	13 (52.0)
MI without the elevation of the ST segment on ECG, n (%)	12 (35.3)	12 (48.0)
Final Clinical Diagnosis		
MI with the formation of the Q wave, n (%)	15 (44.1)	13 (52.0)
MI without the formation of the Q wave, n (%)	19 (55.9)	12 (48.0)
Ischemic History		
Exertional angina, n (%)	16 (47.1)	8 (32.0)
Postinfarction cardiosclerosis, n (%)	5 (14.7)	4 (16.0)
Fibrillation of atria, n (%)	8 (23.5)	2 (8.0)
Chronic heart failure, n (%)	5 (14.7)	1 (4.0)
Risk Factors		
Arterial hypertension, n (%)	27 (79.4)	20 (80.0)
Smoking, n (%)	13 (38.2)	12 (48.0)
Diabetes mellitus, n (%)	7 (20.6)	4 (16.0)
Obesity, n (%)	12 (35.3)	4 (16.0)
Positive heredity, n (%)	7 (20.6)	8 (32.0)
Medication Used		
Statins, n (%)	29 (85.2)	23 (92.0)
iACE or ATII receptor blockers, n (%)	25 (73.5)	22 (88.0)
Beta-adrenoblockers, n (%)	23 (67.6)	18 (72)
Acetylsalicylic acid, n (%)	24 (70.6)	25 (100)

Note: Statistical significance level (p) except salicylic acid; $p>0.05$ in all cases; iACE – inhibitor of angiotensin converting enzyme, AT II – angiotensin II

preliminary measurement of the arterial pressure via a standard oscillometric method. During an occlusion test, LED sensors were placed on the phalangettes of the index fingers of both hands positioned on the heart level, the channel 1 sensor on the finger of the right hand and the channel 2 sensor on the finger of the left hand. The initial signal of pulse waves was recorded. Afterward, the right brachial artery was occluded by inflating the cuff of the tonometer to a pressure above 50 mm Hg from the initial level and keeping it for 5 min.

The pressure in the cuff was reduced, and volume pulse waves were recorded within 3 min after occlusion. The increase in the amplitude of the signal from the finger of the right arm subjected to occlusion was evaluated. The occlusion index by amplitude (OIA) was calculated with adjustments for the signal from channel 2, which was the control signal. The threshold value of this parameter (2.0 and more) indicated the preserved EF on the level of small-resistance arteries and arterioles. In physiological aspects, OIA characterizes the blood filling of arteries in response to nitric monoxide production after occlusion. For the evaluation of the EF on the level of medium muscular type arteries, the occlusion index with a phase lag (phase shift) was determined, and its norm was ≥10 msec. This parameter was calculated on the basis of the decelerating propagation of the pulse wave distal to the occlusion site (medium-caliber arteries) because of the reduction of the tone of the smooth muscle elements of vessel walls under the action of nitric monoxide.

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During CAPW after the measurement of the arterial pressure, an optic sensor of channel 1 was placed on the phalangette of the index finger of the right hand. The elastic properties of the arterial wall were evaluated in terms of the augmentation index (AIp) as an integral parameter of the rigidity of the arterial wall. AIp shows the contribution of the late systolic wave to the arterial pulse pressure and permits the quantitative evaluation of the type of the pulse wave curve. When a vessel wall is highly rigid, the velocity of pulse wave increases, and AIp has a positive value (type A or B pulse wave). When the elasticity of the arterial wall is preserved, AIp has a negative value (type C pulse wave). In this study, theoretical AIp was used to normalize the pulse rate of 75 per min (AIp75) to obtain comparable values.

The 12-month prognosis was evaluated in the two groups of patients with the preserved and disordered EF of medium-caliber arteries, the microcirculation level, the preserved elasticity of the vessel wall, and the enhanced rigidity of the vessel wall. The combined end point (CEP) was studied on the basis of the following parameters: lethality from cardiovascular causes, MI, cerebro-vascular event, and unstable angina.

Data were processed in Microsoft Excel 2016 and statistically analyzed with IBM SPSS Statistics 10.0. The mean values of the quantitative parameters other than the normal distribution were presented in the form of median (M), upper (Q3), and lower (Q1) quartiles and compared via a Mann-Whitney test. Qualitative characteristics were presented in absolute values (n) and percentages of the total number of patients in the groups; in comparative analysis, the statistical significance level (p) was evaluated through chi-square distribution with the construction of contingency tables. When the values of at least one of the criteria were <10, Yates adjustments were made. When values were <5, Fisher's exact test was conducted. For adverse outcome analysis, Cox proportional hazard model was used. Differences were considered statistically significant at $p<0.05$.

Results and Discussion

In the occlusion test, an IOA of <2.0 (indicating ED on the level of small-resistance arteries and arterioles) was recorded in 22 of 34 (64.7%) patients with MINOCA and 22 of 25 (88%) patients with MIOCA ($p=0.04$). In the quantitative evaluation of OIA in the patients in both groups, the mean values were below the normal; however, IOA of the patients with MINOCA was higher than that of the patients with MIOCA ($p=0.02$, Table 2).

The comparison of the functional condition of the endothelium in terms of the level of the epicardial arteries revealed disorders in both groups. The analysis of the phase shift between the channels showed that its values were lower in patients with MI regardless of the extent of the lesion of CA in an atherosclerotic process ($p=0.5$, Table 2). ED in the medium-caliber arteries was recorded in 30 of 34 (88.2%) patients with MINOCA and in 22 of 25 (88.0%) patients with MIOCA ($p>0.05$).

Table 2

Comparison of IOA and Phase Shift between Channels in the Study Groups

Parameters	MINOCA	MIOCA	p
n	34	25	-
IOA, M (Q1; Q3)	1.7 (1.5; 2.3)	1.4 (1.2; 1.8)	0.02
Occlusion index, channel 1, M (Q1; Q3)	2.1 (1.8; 2.7)	1.6 (1.3; 2.1)	0.01
Occlusion index, channel 2, M (Q1; Q3)	1.2 (1.0; 1.4)	1.2 (1.0; 1.3)	0.90
Phase shift between channels, ms, M (Q1; Q3)	-4.9 (-8.5; 0.3)	-5.7 (-8.6; -3.0)	0.50

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In the contour analysis of pulse waves, AIp75 was evaluated as the main parameter of vessel wall elasticity. In the study groups, AIp75 had medium positive values (which indicated a reduction of the elastic properties and increase in the rigidity of the vessel wall) without statistically significant differences ($p>0.05$). In most cases in both groups, the type A curve was recorded in 79.4% and 92.0% of the cases, respectively (Table 3). However, vessel wall elasticity decreased in 82.4% of patients with MINOCA. By comparison, vessel wall elasticity decreased in 100% of patients with MIOCA ($p<0.05$).

Table 3

Comparison of the Parameters of CAPW in the Study Groups

Parameters	MINOCA	MIOCA	p
n	34	25	-
AIp75, M (Q1; Q3)	12.5 (9.9; 17.9)	18.8 (12.9; 20.8)	0.06
Type A pulse wave, n (%)	27 (79.4)	23 (92.0)	0.17
Type B pulse wave, n (%)	0	0	-
Type C pulse wave, n (%)	7 (20.6)	2 (8.0)	0.17

In the evaluation of the 12-month prognosis of patients with MINOCA with preserved and impaired EF on the microcirculatory level, the CEP was recorded in 7 of 12 (58.3%) patients with preserved EF compared with that of 11 of 22 (50%) patients with disordered EF ($p>0.05$). In patients with MIOCA, the CEP within a year was found in 1 of 3 (33.3%) patients with unchanged EF and in 13 of 22 (59.1%) with ED ($p>0.05$). In the analysis of 1-year prognosis of patients with MINOCA with preserved and disordered EF on the level of epicardial arteries, cardiovascular events were detected in 50.0% and 53.3% of patients, respectively ($p>0.05$). Similar parameters were observed in the second group; that is, the CEP was recorded in 66.7% of patients with preserved EF and in 50.0% of cases with ED ($p>0.05$).

In 4 of 6 (66.7%) patients with MINOCA with preserved vessel wall elasticity, the CEP did not significantly differ from that of patients with enhanced vessel wall rigidity (in 14 of 28 [50.0%], $p>0.05$). In all patients with MIOCA and vessel wall rigidity, cardiovascular events were recorded with comparable frequency (in 14 patients of 25 [56.0%], $p>0.05$).

Despite the absence of lesions or an insignificant lesion of CA via an atherosclerotic process (stenosis of less than 50%), EF was disordered in patients with MINOCA in epicardial arteries and microcirculatory vessels (88.2% and 64.7% of cases, respectively). The incidence of ED of small-resistance arteries and arterioles of the patients with MIOCA was higher than that of the patients with MINOCA possibly because of the dramatic structural changes in CA of the given patients.

The results of CAPW evidence increased the arterial wall rigidity in patients with MINOCA and MIOCA. However, the vessel wall elasticity of 82.4% of the patients with MINOCA was significantly rarer ($p<0.05$) than that of the patients with MIOCA (100%). Therefore, *the morphological and functional alterations of the vessel wall were more pronounced in patients with MIOCA than in patients with MIOCA.*

In our study, the influence of ED and the reduction of vessel wall elasticity on the prognosis was evaluated. The results showed that ED on the levels of microcirculation and epicardial arteries did not influence the prognosis of patients with MINOCA

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(p>0.05). No interrelation was established between the reduction of vessel wall elasticity and the prognosis of patients (p>0.05). The influence of ED and the rigidity of the vessel wall on the incidence of CEP in the patients with MIOCA was not significantly different (p>0.05). However, other studies have shown that ED in patients with a hemodynamically mild lesion of CA significantly affects the prognosis of patients in comparison with that of normal EF [9,10]. This contradiction may occur because of the limited number of patients from whom prognosis was determined.

Conclusion

In patients with MINOCA and MIOCA, signs of ED were revealed along the entire length of their CA, the level of microcirculation to a lesser extent, and the level of epicardial arteries to a comparable extent. In both groups, the elasticity of the vessel wall decreased. However, with the non-obstructive lesion of CA, the rigidity of the arterial wall was significantly rare.

The ED and reduction of the elasticity of vessel walls are possible pathophysiological mechanisms in MINOCA but less often in MIOCA. The ED on the level of microcirculatory vessels and epicardial arteries did not independently influence the prognosis of patients with MIOCA and MINOCA in our study.

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