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Predictors of pulmonary hypertension in the subacute period of myocardial infarction in young and middle-aged males

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ABSTRACT

Aim. To identify predictors of the development of pulmonary hypertension (PH) in the subacute period of myocardial infarction (MI) in young and middle-aged males to improve preventive measures.

Materials and methods. We studied the results of treatment of male patients aged 32–60 years with a verified diagnosis of MI. Based on echocardiography findings and detection of PH at the end of the third week of MI, the patients were divided into the study group (patients with PH) and the comparison group (patients with a normal pressure in the pulmonary artery). In the studied groups, a comparative assessment of various parameters was performed, and an analysis of the risks of developing PH using the Pearson's chi-squared test was conducted.

Results. We found that the risk of developing PH in the subacute period of MI was significantly affected by certain parameters of peripheral hemodynamics, the presence of bradycardia, and the calculated value of total pulmonary resistance. The main parameters of the lipid profile were found to be significant predictors of PH in the subacute period of MI, along with some parameters of electrolyte metabolism (sodium and magnesium in the first 48 hours of MI, potassium and calcium at the end of the third week of the disease). We established the presence of a reliable relationship between several parameters of the structural and functional state of the myocardium both in the first 48 hours of MI and the end of the third week of the disease with the risk of developing PH in the subacute period of MI.

Conclusion. The identified predictors make it possible to determine patients with MI who are at an increased risk of PH to timely diagnose and treat the disease and improve the prognosis.

Keywords: pulmonary hypertension, predictors, myocardial infarction, cardiovascular disease risk factors, pulmonary artery pressure, systolic dysfunction, echocardiography, men, young and middle age

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Предикторы легочной гипертензии в подостром периоде инфаркта миокарда у мужчин молодого и среднего возраста

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РЕЗЮМЕ

Цель. Выявить предикторы развития легочной гипертензии (ЛГ) в подостром периоде инфаркта миокарда (ИМ) у мужчин молодого и среднего возраста для совершенствования профилактических мероприятий.

Материалы и методы. Изучены результаты лечения мужчин 32–60 лет с верифицированным диагнозом ИМ. По итогам выполнения эхокардиографии и выявления ЛГ в конце третьей недели ИМ пациентов разделяли на исследуемую группу (с ЛГ) и группу сравнения (с нормальным уровнем давления в легочной артерии). В изучаемых группах проведена сравнительная оценка различных параметров, а также выполнен анализ рисков развития ЛГ с помощью критерия $\chi 2$ Пирсона.

Результаты. На риск развития ЛГ в подостром периоде ИМ оказывают статистически значимое влияние некоторые параметры периферической гемодинамики, наличие брадикардии, расчетная величина общего легочного сопротивления. Значимыми предикторами ЛГ в подостром периоде ИМ оказались основные параметры липидограммы, а также некоторые показатели электролитного обмена (натрий и магний в первые 48 ч ИМ, калий и кальций в конце третьей недели заболевания). Установлено наличие статистически значимой взаимосвязи ряда показателей структурно-функционального состояния миокарда как первых 48 ч ИМ, так и конца третьей недели заболевания, с риском развития ЛГ в подостром периоде ИМ.

Заключение. Выявленные предикторы позволят формировать группы повышенного риска ЛГ среди пациентов с ИМ с целью своевременной диагностики и лечения для улучшения прогноза.

Ключевые слова: легочная гипертензия, предикторы, инфаркт миокарда, факторы риска кардиоваскулярных заболеваний, давление в легочной артерии, систолическая дисфункция, эхокардиография, мужчины, молодой и средний возраст

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Pulmonary hypertension (PH) is a pathological condition that is often a complication of a significant number of diseases, which underlies the modern classification of this pathology. PH is considered separately in diseases of the left chambers of the heart, especially in myocardial infarction (MI) [1, 2], since this complication significantly aggravates its course and worsens the prognosis [1, 3]. This statement has been proven to a greater extent in relation to elderly patients [4, 5]; however, there is currently a clear trend toward MI incidence in young individuals [6, 7].

Since young and middle-aged males are exposed to such common risk factors for the development of cardiovascular pathology as unhealthy diet, low physical activity, overweight, psychological stress, smoking, and arterial hypertension, the incidence of MI in this group of patients increases. In the long run, this will make PH a relevant problem in males of working age [6–8]. Echocardiography (ECHO) is the most accessible noninvasive method for detecting

increased pressure in the pulmonary artery, which, however, does not always allow for timely diagnosis of PH, despite its widespread use [1, 5, 8]. PH is characterized by a steadily progressive course. As a rule, it does not have clear clinical manifestations for a long time, which makes it difficult to diagnose and leads to disability of patients, as well as a decrease in the effectiveness of therapy [1, 2, 8].

The aim of the study was to identify predictors of the development of PH in the subacute period of MI in males under 60 years of age among the most accessible clinical and test parameters to improve its prevention.

MATERIALS AND METHODS

The main inclusion criteria were the following: male; age from 18 to 60 years; verified type 1 MI (Fourth Universal Definition of Myocardial Infarction, 2018) [9]. The exclusion criteria were as follows: female; age younger than 18 and older than 60 years; at baseline, reduced glomerular filtration rate (CKD-EPI, 2011) of less than 30 ml / min / 1.73 m^2; type 2, 3, 4, and 5 MI; presence of concomitant pathology capable of independently influencing the development of PH (viral hepatitis B and C, cirrhosis, other portal hypertension syndromes, HIV infection; systemic connective tissue diseases with constant immunosuppressive therapy; congenital heart disorders); verified cancers; endocrine pathology (except diabetes mellitus); pronounced deviations in the complete blood count (hemoglobin level of less than 130 g / l, platelet count of less than 100×10^9 / l, leukocyte count of less than 3.0×10^9 / l).

The study was approved by the Independent Ethics Committee at S.M. Kirov Military Medical Academy (Protocol No. 258 of 21.12.2021). All the examined persons or their relatives signed an informed consent to participate in this study before undergoing the procedures.

Thus, the study included 570 males aged 32–60 years, among whom Q-wave MI and the presence of complications were detected in 53.5% (305 patients) and 56.5% (322 patients) of cases, respectively. Reinfarction and recurrent MI were registered in 49.7% (283 patients) and 4.4% (25 patients) of cases, respectively. Depending on the location of MI, patients were distributed as follows: anterior MI in the left ventricle (LV) was detected in 47.0% (268 people) of cases, LV inferior wall MI – in 39.5% (225 people), and MI in other locations – in 13.5% (77 people). When divided into the study and the comparison group, the patients did not significantly differ in these characteristics. A fatal outcome was observed in 5.1% of cases (29 patients) – only among patients of the comparison group ($p = 0.012$).

In the first 48 hours (I) and at the end of the third week of MI (II), all patients underwent a set of clinical examinations and tests in accordance with approved clinical guidelines, including ECHO, during which the sizes of the heart chambers and the mean pulmonary artery pressure were recorded (mPAP) [1, 10], and LV systolic function was assessed (according to the Simpson method) [11–13]. The value of total pulmonary resistance (TPR) was calculated by the Shishmarev method [13–15]. ECHO was used to determine the following parameters in all patients: the dimensions of the left atrium (LA), the thickness of the LV posterior wall (PW), right ventricular end-diastolic volume (RVEDV), LV ejection fraction (EF), including cardiac index (CI), LV myocardial mass index (LVMMI), LV end-systolic (ESV/S) and end-diastolic (EDV/S) volumes. Indexing was estimated by body surface area (proposed by D. Du Bois and E.F. Du Bois) [10, 11]. Depending on the values of mPAP, the patients were divided into two groups: the study group, in which the level of $mPAP_I$ was within the normal range (less than 20 mm Hg) and elevated to 21 mm Hg and more – 102 patients (average age 51.0 ± 7.0 years); and the comparison group – patients with normal or elevated levels of $mPAP_I$ and normal levels of $mPAP_{II}$ – 468 patients (51.4 ± 6.0 years, $p = 0.978$).

In order to conduct early monitoring of manifestations of heart failure (HF), in the first 48 hours and at the end of the third week of MI, the severity of its symptoms (shortness of breath, palpitations, weakness, cough, fatigue) were assessed by calculating the index of subjective manifestations of HF (SMHFI) [15]. The main parameters of peripheral hemodynamics were used as parameters of the clinical examination: heart rate (HR) per minute, levels of systolic (systBP), diastolic (diastBP) and mean (meanBP) blood pressure (meanBP = diastBP + 1/3 × (systBP – diastBP)). Among the test parameters, the main parameters of the lipid profile were studied: the concentration of total cholesterol (TC) in the blood, lipoproteins ranked by density (high (HDL), very low (VLDL) and low (LDL)), their ratio (LDL/HDL and TC/HDL), and atherogenic coefficient (AC). In addition, parameters of electrolyte metabolism were determined, including the levels of potassium, sodium, total calcium, and magnesium.

All patients included in the study received drug therapy in accordance with clinical guidelines for the management of patients with MI, including anticoagulants, antiplatelets, and lipid-lowering agents, as well as renin – angiotensin – aldosterone system inhibitors, beta-blockers, and nitrates. Patients in the study group and the comparison group did not have significant differences in terms of drug therapy. The proportion of patients who underwent revascularization was 25.5% (26 people) and 21.8% (102 people, $p = 0.263$) in the study and comparison groups, respectively. The selected groups did not have significant differences in the number of arteries affected in coronary artery disease (CAD), the extent and severity of the identified CAD, as well as in the frequency and the volume of revascularization. The low proportion of patients who underwent coronary angiography and early myocardial revascularization is mainly due to their refusal to undergo the procedure and / or delayed hospitalization due to late presentation.

The obtained data of the clinical and test examinations were organized using a formalized medical history, presented in the form of an electronic database (Microsoft Excel 2016). The research results were statistically processed using the Microsoft Excel 2016, Statistica 10.0, and SAS JMP 11 software. The obtained parameters were compared between the selected groups using the Mann – Whitney test and the Pearson's chi-squared test. In addition, the latter was used to assess the statistical significance of the influence of factors on a binary target variable when calculating the risks of PH at the second time point (II) – absolute risk (AR, %) and relative risk with a 95% confidence interval (RR, abs. [95% CI]). The cut-off levels of these factors were determined by their maximum statistical significance. The value of $p < 0.05$ was considered to be statistically significant.

RESULTS

When assessing the influence of peripheral hemodynamic parameters on the risk of PH development at the second measurement point (II), it turned out that parameters determined during this period (II), such as $meanBP_{II}$ levels of 93.3 mm Hg or more (AR: 11.2%; RR: 1.98 [1.23; 3.19]; $p = 0.003$) and $diastBP_{II}$ of 75 mm Hg or more (AR: 10.9%; RR: 1.98 [1.19; 3.30]; $p = 0.005$), as well as $systBP_{I}$ level of 160 mm Hg or more (AR: 9.3%; RR: 1.58 [1.07, 2.33]; $p = 0.023$) and HR_{I} of less than 75 bpm (AR: 20.5%; RR: 3.71 [2 .19; 6.28]; $p < 0.001$) in the first hours (I) of MI had a significant relationship. It was revealed that the risk of developing PH after MI increases if the patient has bradycardia during ECG (AR: 17.3%; RR: 2.04 [1.33; 3.14]; $p = 0.020$) and decreases if sinus tachycardia is registered (AR: -17.9%; RR: 0.18 [0.06, 0.57]; $p < 0.001$). The risk of PH development in the subacute MI period increases in patients with a TPR_{I} value of less than 421 dyn. × s × cm^{-5} (AR: 20.1%; RR: 3.29 [2.03; 5.32]; $p < 0.001$) and TPR_{II} of 237.3 dyn. × s × cm^{-5} or more (AR: 17.6%; RR: 4.03 [1.81; 8.97]; $p < 0.001$). The risk of PH development after MI was associated with an estimated level of SMHFI of less than 19.3%, determined at the end of the third week of MI (AR: 12.1%; RR: 2.16 [1.02; 4.58]; $p = 0.033$).

Figures 1 and 2 present data on the relationship between lipid metabolism parameters and the risk of PH development after MI.

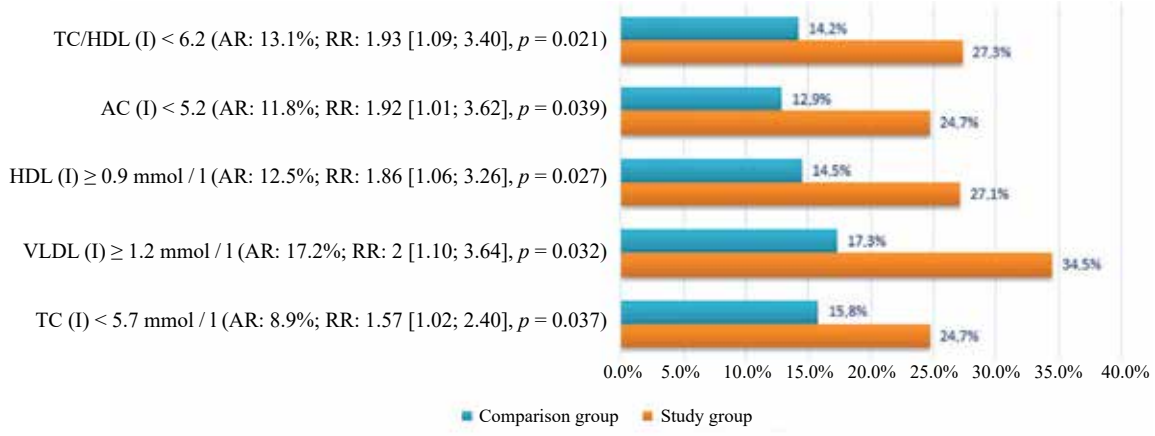

Fig. 1. Relationships between lipid metabolism parameters in the first hours of myocardial infarction and the risk of developing pulmonary hypertension in its subacute period: p – level of significance, the chi-squared test

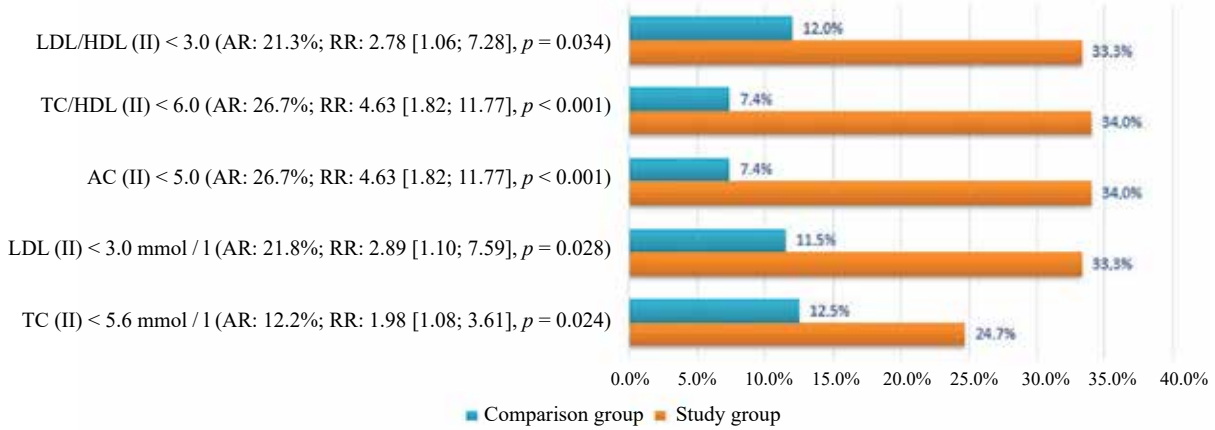

Fig. 2. Relationships between lipid metabolism parameters at the end of the third week of myocardial infarction and the risk of developing pulmonary hypertension during this period: *p* – level of significance, the chi-squared test

Significant patterns of changes in the risks of developing PH in the examined patients depending on the concentration of the main electrolytes in the blood plasma were obtained both during the first hours (Fig. 3) and at the end of the third week of the disease (Fig. 4).

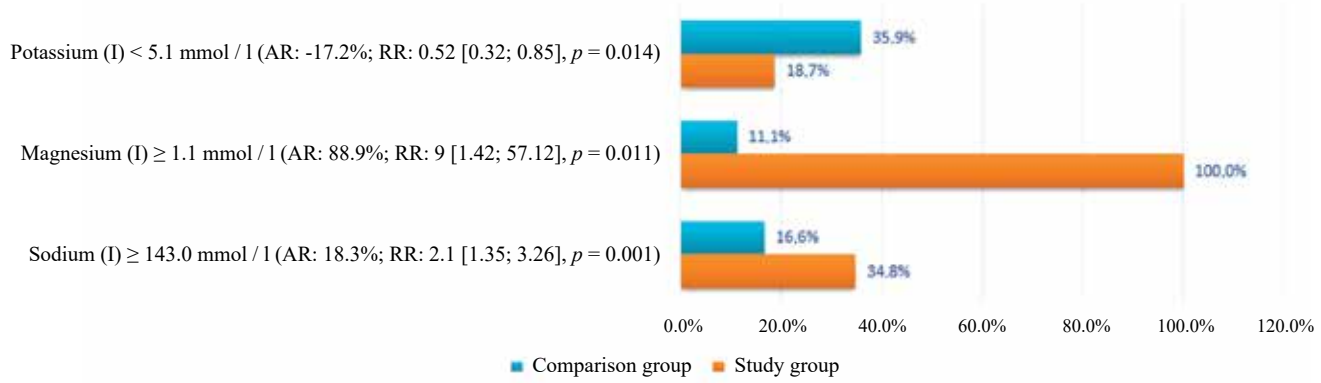

Fig. 3. Relationships between blood plasma electrolyte concentrations in the first hours of myocardial infarction and the risk of pulmonary hypertension at the second measurement point: *p* – level of significance, the chi-squared test

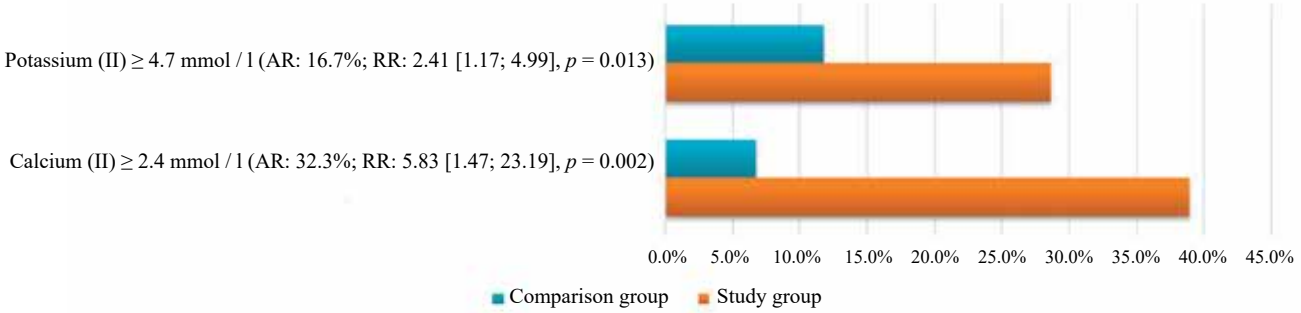

Fig. 4. Relationships between blood plasma electrolyte concentrations at the end of the third week of myocardial infarction and the risk of developing pulmonary hypertension in its subacute period: *p* – significance level, the chi-squared test

Of all the studied factors, the parameters of the structural and functional state of both the left and right heart chambers were found to have the largest number of relationships with the risk of PH development at the end of the subacute MI period (Fig. 5, 6). In the first 48 hours of the disease, the following parameters turned out to be significant: CI, LVMMI, LV ESV/S and LV EDV/S, LA sizes and LVPW thickness, LVEF, and RVEDV.

At the end of the third week of MI, a relationship with the risk of PH development was identified for the following parameters: right atrium (RA) size, LVMMI, LV PW thickness, and LA transverse size.

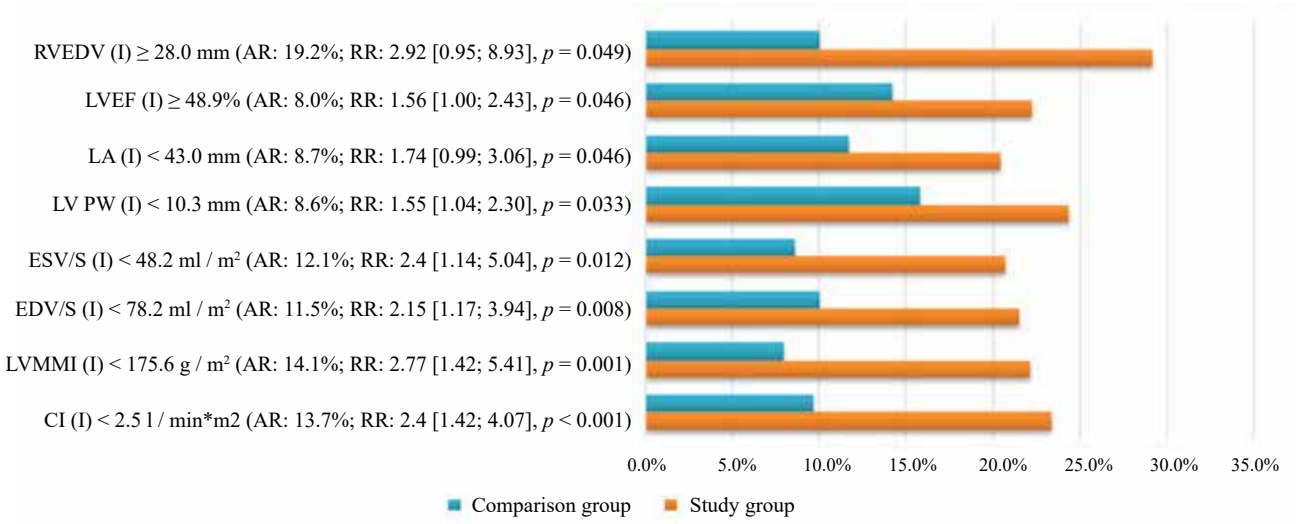

Fig. 5. Relationships between the parameters of the structural and functional state of the heart in the first hours of myocardial infarction and the risk of pulmonary hypertension development in the second period of the study: *p* – level of significance, the chi-squared test

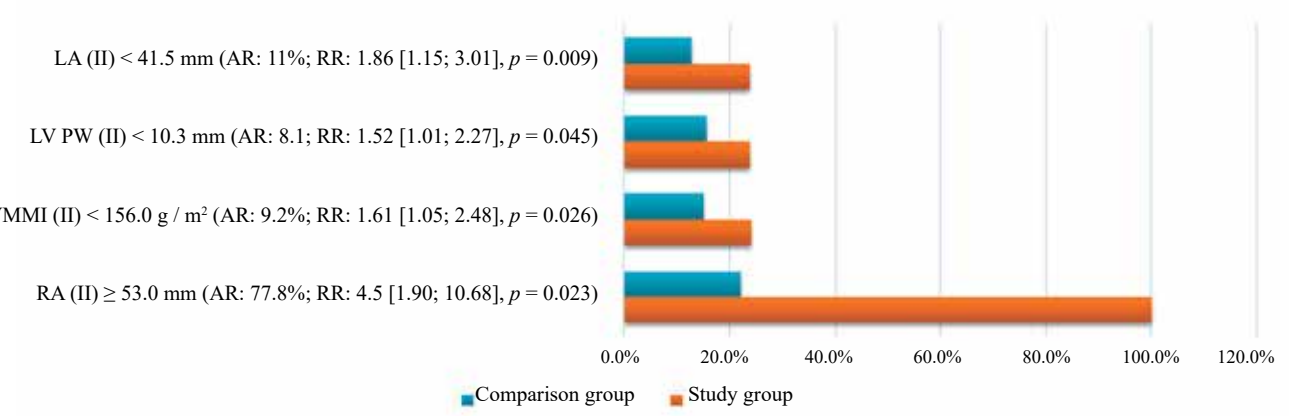

Fig. 6. Patterns of changes in parameters of the structural and functional state of the heart at the end of the third week of myocardial infarction and the risk of pulmonary hypertension development during this period: *p* – level of significance, the chi-squared test

DISCUSSION

Hemodynamic parameters, such as blood pressure and heart rate, as well as a significant increase in TPR in the patients of the study group, significantly affect the development of PH, which confirms that persistent narrowing of pulmonary vessels in addition to a passive retrograde increase in the pulmonary artery pressure participate in the pathogenesis of PH during MI [2, 8, 13]. It was found that the risk of PH development in the subacute MI period is higher in patients with bradycardia, which is most likely due to a long history of cardiovascular diseases accompanied by the development of atherosclerotic and/or postinfarction cardiosclerosis, leading to a decrease in the automaticity of the sinoatrial node [16]. The effect of the SMHFI value on the risk of developing the studied complication has no independent prognostic value; however, it indirectly reflects the degree of functional myocardial insufficiency. In the patients of the study group, the calculated SMHFI value was less than 19.3%, which corresponds to a minimal or moderate degree of myocardial insufficiency [16].

The identified relationship between the risk of developing PH in MI and lipid metabolism parameters is reflected in the literature. It has been shown that apolipoprotein AI- and E-dependent mechanisms employ the patterns of interrelated changes in pulmonary hemodynamics and lipid levels [17], with the involvement of specific regulatory elements, such as microRNA [18], protein associated with transforming growth factor beta [19], and exosomes [20]. Electrolyte changes found in the patients of the study group, in particular an increase in sodium concentration, indicate increased activity of hormones of the renin – angiotensin –aldosterone system, water

retention in the body, an increase in pre- and afterload on the myocardium, the occurrence and subsequent increase in diastolic dysfunction, and also hypertrophy of vascular smooth muscle cells and fibrosis of their walls [1, 14, 20]. An increase in the concentration of total calcium in the blood serum in the patients of the study group confirms the separate role of this ion and numerous calcium channels in the PH development due to the regulation of pulmonary vasoconstriction and remodeling of pulmonary vessels [21].

The parameters of the structural and functional state of the myocardium in the first hours of the disease significantly affect the risk of PH development, which indicates the presence of more pronounced LV systolic dysfunction in patients with PH, as well as dilatation and remodeling of the left heart [8, 14], which reflects the pathogenesis of PH in diseases of the left chambers of the heart [1]. The baseline increase in RVEDV in the patients of the study group indicates a smaller adaptive reserve of the right chambers of the heart and is a prerequisite for the PH development during the studied MI period and acts as a predictor of an unfavorable prognosis [22].

The result of the study confirms a statistically significant relationship between PH and LV dysfunction, and changes in electrolyte and lipid metabolism. However, we should not exclude the effect of other probable causes of PH, given their ability to additionally contribute to the development and progression of this pathology. In order to determine the presence of LV myocardial dysfunction as the main etiological factor of PH, as well as to conduct differential diagnosis with rare syndrome-like conditions as causes of increased pressure in the pulmonary arteries, it is recommended to determine the concentration of N-terminal pro–B-type natriuretic peptide [23]. It is important to establish the hemodynamic mechanisms of PH depending on the degree of pulmonary vascular resistance to initiate optimal therapy, which dictates the need for early diagnosis of increased pulmonary artery pressure [1, 8, 24]. When conducting the differential diagnosis of PH in MI, it is recommended to exclude right ventricular and atrial MI, ruptures of the interventricular septum, previously undiagnosed congenital heart disorders, as well as severe mitral regurgitation requiring surgical correction [3, 4, 25].

CONCLUSION

The study established the presence of a number of anamnestic, clinical, and test markers associated with the development of PH in the subacute period of MI. Their early detection at the stage of admission to hospital makes it possible to form a group of patients at high risk of developing this complication for timely and necessary diagnostic and therapeutic measures in accordance with the algorithm. ECHO is the most convenient, reliable, non-invasive, and currently available technique that allows to verify PH at early stages, as well as to predict the risk of its development. This explains the need to determine the level of mPAP over time in patients at high risk of developing PH in early phases of MI.

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