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Sex characteristics of cognitive functions assessed by the MMSE and MoCA scores in patients with coronary artery disease

Tarasova I. V., Trubnikova O. A., Sosnina A. S., Syrova I. D., Kukhareva I. N., Kupriyanova D. S., Barbarash O. L.

Aim. To study the sex characteristics of cognitive functions in a cohort of patients undergoing coronary artery bypass grafting (CABG) by comparing the results of Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores.

Material and methods. The prospective cohort study included 272 people, including 74 women aged 41 to 82 years, who were admitted to the Research Institute of Complex Issues of Cardiovascular Diseases for CABG surgery. All patients underwent clinical, laboratory, electrophysiological and ultrasound examinations. The Charlson comorbidity index (CCI) was calculated. Assessment of cognitive functions was carried out using the MMSE and MoCA scores. All types of statistical analysis were performed using the STATISTICA 10 program (StatSoft Inc., USA).

Results. It was found that women scheduled for CABG have an older age and a higher CCI score compared to men (p=0,008). According to the MMSE, the likelihood of moderate and severe cognitive impairment in men compared with women was 1,36 times higher (odds ratio (OR), 1,35; 95% confidence interval (CI), 0,79-2,32, Z=1,11, p=0,27). The MoCA scores showed that half of the male (49%) and female (50%) participants had severe cognitive impairment. The likelihood of moderate and severe cognitive impairment in men compared with women was 1,33 times higher (OR, 1,33; 95% CI, 0,68-2,59, Z=0,841, p=0,40). According to subtests of the MoCA, men were better in naming (p=0,002), abstraction (p=0,005), and women outperformed men in verbal fluency (p=0,04). Regression analysis revealed that the most significant negative predictors for cognitive status as measured by the MMSE and MoCA scores for men and women were age and CCI.

Conclusion. Women scheduled for CABG, having the worst clinical and demographic indicators, are comparable with men in cognitive status using the MMSE score. The MoCA score shows sex differences in naming, abstraction, and verbal fluency domains and revealed a higher percentage of severe cognitive disorders (up to 50%) compared to the MMSE score (7-9%). In male and female candidates for CABG, age and comorbidities are negatively associated with cognitive status.

Keywords: sex characteristics, cognitive status, MMSE and MoCA scores, coronary artery bypass grafting.

Relationships and Activities: none.

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Currently, the leading reason of cognitive decline in patients with cardiovascular diseases (CVD) is not considered to be the processes of natural aging and a number of socio-demographic factors, including a low educational level, but CVD itself, which, together with the above factors and the neurodegeneration processes, can lead to complete cognitive degradation [1, 2]. It was noted that in patients with CVD, atrophic processes in the brain are uneven. First of all, changes are observed in the prefrontal cortex, while here a drop in cerebral blood flow is also observed [3]. A characteristic feature of cognitive deficits in CVD is a decrease in executive control, action planning, and working memory [3, 4]. It takes on crucial significance for the cohort of patients requiring surgical myocardial revascularization due to the fact that already existing cognitive deficits can progress in the postoperative period. This, in turn, can negatively affect the operation results and the quality of life, making it difficult to rehabilitate patients. Therefore, it is important to assess the cognitive status of patients even before intervention.

Recent studies have confirmed the presence of gender differences in the clinical course of coronary artery disease and adherence to therapy [5]. The gender imbalance among candidates for coronary surgery at the age of 45-70 years is also described [6, 7]. The specific gender differences in cognitive functions were found in healthy individuals, as well as in patients with a cardiovascular profile [1, 8, 9].

Therefore, it is believed that the gender differences play an important role in pathological changes in cognitive functions associated with CVD. According to the literature data, cognitive decline in normal and vascular aging begins earlier in men [2]. In case of vascular form of pathological aging, this process occurs more intensively than in relatively healthy elderly people. The study of verbal fluency test indicators revealed a greater depletion of this ability in men at the end of the 3-minute test at a young age and an reverse trend in the older age group, possibly due to the stronger influence of CVD at a relatively young age on cognitive functions. Similar changes in cognitive functions have been described in patients with hypertension [10]. There is an opinion that the vascular factor does not qualitatively change the nature of age factor influence, but, as a rule, shifts the same patterns as in healthy people to a lower cognitive level [1].

A fairly large number of neuropsychological scales are currently used to assess cognitive status [11, 12]. However, the Mini-mental state examination (MMSE) scale is the most commonly used tool with high validity, verified by many studies [11, 13, 14]. The MMSE tests abilities such as orientation, attention, short- and long-term memory, language and ability to perform simple written and oral tasks [15]. Another tool is the Montreal Cognitive Assessment Scale, or the Montreal Cognitive Assessment Scale (MoCA), which assess cognitive abilities such as concentration, counting, orientation, memory, language, as well as visual-spatial skills, executive functions, and abstract thinking that are not studied under the MMSE scale [16]. It was found that MoCA has an advantage in detecting pre-dement cognitive impairment, especially mild cognitive impairment (MCI), compared to MMSE [17-19]. A possible explanation for MoCA superiority is that the subtests of this scale are more difficult to perform than similar MMSE subtests. Consequently, MoCA may be more sensitive to detect milder cognitive impairments [20]. Comparing the results of two most commonly used MMSE and MoCA scales can provide additional data on general state of cognitive status of such a complex patient category as candidates for coronary surgery, as well as about its gender characteristics. Due to the fact that the structure of MMSE and MoCA screening scales is slightly different, the gender factor can make corrections to the effectiveness of these two scales, which is of significant methodological importance.

Thus, taking all the foregoing into account, the goal of this work was to study the gender characteristics of cognitive functions in a cohort of patients requiring coronary artery bypass graft (CABG), when comparing the results of two cognitive screening scales — MMSE and MoCA.

Material and methods

Patients. The prospective cohort study involved 272 people (74 of them women), aged 41 to 82 years, who were admitted to the Federal State Budgetary Scientific Institution of the Research Institute of Complex Problems of CVD. The study was conducted in accordance with the Helsinki Declaration of 1964, and was approved by the Ethics Committee of the Institute. The patient enrollment was carried out after signing a voluntary informed consent. The enrollment criteria were as follows: planned CABG, age 40 and older, ability to adequately complete the tasks included in MMSE and MoCA.

All patients underwent a standard preoperative examination, including clinical and laboratory, electrophysiological and ultrasound methods of examination. Based on the obtained clinical and anamnestic data, the Charlson comorbidity index was calculated according to the standard method [21]. It is a point system for assessing the age and presence of certain concomitant diseases, such as diabetes mellitus, chronic obstructive pulmonary

Table 1

Clinical and anamnestic characteristics of male and female patients proposed for CABG

Indicator	Men (n=198)	Women (n=74)	p
Age, years, M±SD	63,2±7,56	66,3±7,02	0,002
Education level, n (%) secondary and dual, higher education	 158 (80) 40 (20)	 54 (73) 20 (27)	0,28
Body mass index, M±SD	28,5±4,06	30,7±3,75	0,0001
Charlson comorbidity index	3,6±1,10	4,0±1,25	0,008
Left ventricular ejection fraction	56,4±11,72	61,1±9,54	0,002
FC of angina pectoris, n (%) 0-I II III	 60 (30) 107 (54) 31 (16)	 11 (15) 47 (63,5) 16 (21,5)	0,03
CHF (NYHA FC), n (%) 0-I II III	 59 (30) 126 (63,5) 13 (6,5)	 15 (20) 51 (69) 8 (11)	0,19
Post-infarction cardiosclerosis, n (%)	125 (63)	38 (51)	0,07
Type 2 diabetes mellitus, n (%)	40 (20)	26 (35)	0,01
Carotid artery stenosis, n (%) no <50% >50%	 90 (46) 60 (30) 48 (24)	 35 (47) 25 (34) 14 (19)	0,63
Anamnesis of acute disorders of cerebral circulation, n (%)	17 (9)	4 (5)	0,38

Abbreviations: FC — functional class, CHF — chronic heart failure.

Table 2

Indicators of individual subtests of the MMSE scale in the groups of men and women planned for CABG

Subtest	Men (n=198)	Women (n=74)	p
Time knowledge	4,9±0,27	5,0±0,16	0,14
Location knowledge	5,0±0,19	4,9±0,28	0,33
Perception (remember and repeat 3 words)	3,00±0,00	3,0±0,23	0,10
Concentration and counting (consecutive subtraction by 7)	4,3±1,18	4,4±1,18	0,65
Memory	2,1±0,87	1,9±0,79	0,24
Speech: "Show the pen and watch, ask — how does is called?"	1,99±0,07	1,97±0,16	0,12
Speech: "There are no ifs, and or buts about it" — repeat the sentence	0,3±0,51	0,4±0,48	0,51
Speech: Executing a 3-step command	2,97±0,15	3,0±0,00	0,17
Reading: Close your eyes	1,0±0,00	0,99±0,11	0,10
Reading: Write a sentence	0,97±0,17	0,97±0,16	0,88
Reading: Draw a picture	0,4±0,49	0,4±0,49	0,91

diseases, peripheral vascular disease, systemic connective tissue diseases, cerebral circulatory disorders, oncopathology, immunodeficiency, etc.

Neuropsychological study. The cognitive function state assessment was performed using screening neuropsychological scales-MMSE and MoCA. According to the MMSE scale (from 0 to 30), the sum of points equal to or greater than 28 indicates a normal state of cognitive functions, 27-24 points — MCI syndrome, <24 points — severe cognitive impairment (dementia). According to the MoCA scale (also from 0 to 30), a score above 26 points indicates no cognitive impairment, a score of 24-26 points indicates MCI, and a score below 24 points indicates severe cognitive impairment.

Statistical analysis. All types of statistical analysis of the obtained data were performed according to the program STATISTICA 10 (StatSoft, Inc.,

Table 3

Indicators of individual subtests of the MoCA scale in the groups of men and women proposed for CABG

Subtest	Men (n=198)	Women (n=4)	p
Drawing a polyline	0,53±0,50	0,46±0,50	0,31
Copy (cube)	0,44±0,49	0,49±0,50	0,55
Drawing a clock	2,41±0,81	2,21±0,92	0,09
Naming objects	2,98±0,12	2,87±0,44	0,002
Naming of numbers, in direct order	0,84±0,36	0,86±0,35	0,72
Naming of numbers in reverse order	0,83±0,38	0,81±0,40	0,68
Tapping test	0,80±0,44	0,75±0,44	0,40
Sequential subtraction by 7	2,75±0,60	2,69±0,68	0,49
Repetition of sentences	1,15±0,66	1,19±0,64	0,60
Verbal fluency	0,39±0,49	0,53±0,50	0,04
Abstract thinking	1,49±0,65	1,24±0,68	0,005
Delayed recall	1,96±1,47	2,22±1,46	0,19
Orientation	5,93±0,33	5,93±0,31	0,97

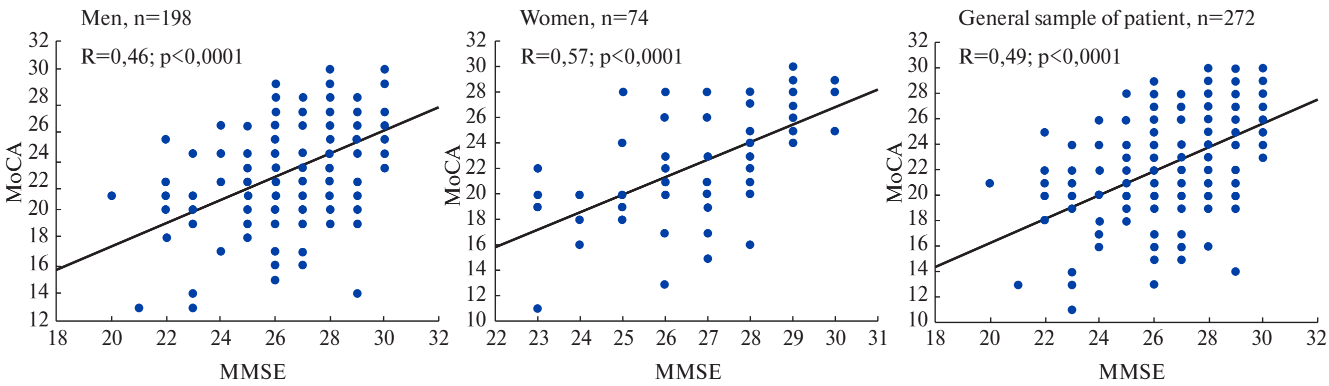

Figure 1. The results of correlation analysis between the MMSE and MoCA scores in the general sample of patients and separately for the groups of male and female patients proposed for CABG.

USA). The distribution normality for quantitative clinical and anamnestic indicators and indicators of cognitive status was assessed using the Kolmogorov-Smirnov test, most of the data had a normal or close to normal data distribution. Consequently, the comparison of indicators was carried out using the t-test for independent samples. "P<0,05" was considered statistically significant. The data is presented as averages and standard deviation.

Results

The clinical and anamnestic characteristics of the examined patients are given in Table 1. It is worth noting that the male patients had a younger age at the time of examination, a lower body mass index and a lower ejection fraction. There was a close to statistically significant trend towards a greater number of men who had a history of myocardial infarction. At the same time, women in 85% of cases had II-III functional class of angina pectoris, while in men such indicators were observed in 70% of patients. There were no statistically significant differences between men and women in the functional class of heart failure according to NYHA, as well as in the number of moderate and severe carotid artery stenoses, the number of people with a history of acute cerebral circulatory disorders. Women were more likely to have type 2 diabetes. Accordingly, the Charlson comorbidity index in women was statistically significantly higher than in men. The samples of men and women were comparable in educational status: the majority of the examined had secondary or specialized secondary education (80% and 73%, respectively).

Neuropsychological indicators. According to the MMSE scale, in the group of men, 46% (92 patients) did not have cognitive impairment, the MCI frequency was 45% (89 patients), and dementia —

Table 4

The main parameters of regression models and predictors of cognitive status according to the MMSE and MoCA scale in patients proposed for CABG

Predictor	Beta	t	p
MMSE			
Men			
$F_{(2,196)}$=4,0; p<0,02; R^2=0,04			
Age	-0,16	-1,49	0,14
Charlson comorbidity index	-0,11	-1,05	0,30
Women			
$F_{(3,70)}$=5,03; p<0,004; R^2=0,18			
Charlson comorbidity index	-0,29	-1,98	0,05
Number of training years	0,18	1,52	0,13
Age	-0,17	-1,11	0,27
MoCA			
Men			
$F_{(2,196)}$=6,27; p<0,0025; R^2=0,07			
Age	-0,28	-3,33	0,001
Number of training years	-0,11	-1,29	0,20
Women			
$F_{(3,70)}$=5,31; p<0,003; R^2=0,20			
Age	-0,33	-2,18	0,03
Number of training years	0,17	1,41	0,16
Charlson comorbidity index	-0,16	-1,05	0,30

9% (17 people). In women, the absence of cognitive deficits was noted in 54% (40 people), in 39% (29 people) — MCI was observed, dementia — in 7% of cases (5 patients). The significance of intergroup differences according to the χ^2 criterion was — F $(_{1;272})$=1,27; p=0,53. Men were 1,36 times more likely to have moderate to severe cognitive disorders than women, but this effect was not statistically significant (odds ratio (OR) =1,35; 95% confidence interval (CI): 0,79-2,32, Z=1,11, p=0,27).

The analysis of individual subtests of the MMSE scale did not reveal statistically significant differences between the groups of men and women (Table 2). Women were slightly more time-oriented, perceived information better, performed a 3-stage command, while men had slightly better delayed reproduction rates, were more successful at naming items, but these differences were only at the trend level.

The indicator study of the MoCA neuropsychological scale revealed that the absence of cognitive impairment was observed in 17% of men (n=34) and 22% of women (n=16). The MCI syndrome was observed in 34% of men (n=67) and 28% of women (n=21), and half of the male (49%, n=97) and (50%, n=37) female participants had severe cognitive impairment. The significance of intergroup differences according to the χ^2 criterion was — F$(_{1;272})$=1,34; p=0,51. As for the MMSE scale, men were 1,33 times more likely to have moderate to severe cognitive disorders than women, but this effect was not statistically significant (OR =1,33; 95% CI: 0,68-2,59, Z=0,841, p=0,40).

A comparison of the performance of the MoCA scale subtests revealed differences between the groups of men and women in terms of "Naming objects", "Abstract thinking" and "Verbal fluency" (Table 3).

It was found that men were more successful at naming objects and had higher rates of abstract thinking, while women had an advantage in the verbal fluency test.

The analysis of correlations between the MMSE and MoCA total score indicators both in the general group of examined patients and separately in the groups of men and women demonstrated statistically significant positive relationships (Figure 1).

As can be seen in the figure, higher MoCA scores corresponded to higher MMSE scores in all the examined groups.

Further, a regression analysis was performed separately for men and women. In some models, the dependent variable was the total score according to the MMSE scale, in others — according to the MoCA scale. Age, learning duration in years, Charlson comorbidity index, body mass index, and left ventricular ejection fraction were considered as independent predictors of cognitive status in all statistical models. The correlation coefficients between the indicators selected as independent predictors were <0,7, which make it possible to state that there is no multicollinearity between them.

For the dependent variables — the total score according to the MMSE and MoCA scales, statistically significant models were obtained (Table 4). However, statistical significance test for the regression equations with the selected predictors demonstrated that the equations are statistically significant in general, but the weighted coefficient of determination (R^2) indicate a low overall quality of the obtained models.

It was found that age and the Charlson comorbidity index were predictors of the cognitive status determined by the MMSE scale in men. Older age and higher values of the comorbidity index were associated with a low level of cognitive function, but the relationship was not statistically significant. In women, the Charlson comorbidity index was also the only statistically significant negative predictor for this method of determining basic cognitive status.

The selected predictors for the cognitive status determined by the MoCA scale had a slightly greater predictive ability. For both men and women, age was a statistically significant negative predictor. Older patients proposed for CABG have poorer cognitive status.

Discussion

As the study results shown, male and female patients who need in CABG, despite the greater clinical severity and older age in women, have the comparable cognitive status. Only certain subtests of the MoCA scale, such as "Naming objects", "Abstract Thinking" and "Verbal Fluency", revealed statistically significant gender differences. Men had higher scores in abstract thinking and semantic memory, while women had an advantage in the verbal fluency test. The data obtained in this study are consistent with previous studies on healthy individuals, where women were more successful in verbal cognitive tests and men-in figurative-spatial and abstract tasks [22, 23]. Thus, the presence of severe CVD does not change the gender profile of intellectual abilities. However, only the use of the MoHS scale allowed to reveal gender differences, which suggests its more pronounced sensitivity to cognitive deficits in men and women.

However, special consideration should be given to the fact that older women with more pronounced comorbidity retain a cognitive level comparable to men. Psychophysiological studies have shown that equal success in performing a number of cognitive tasks by healthy men and women is ensured by different strategies [24-26]. According to one hypothesis, women use the resources of the left and right hemispheres more flexibly in information processing, which leads to better verbal skills, while figurative-spatial information is processed worse in them due to competition with verbal signals in the right hemisphere [22, 27]. The men's advantage in figurative-spatial abilities is associated with a greater specialization of the hemispheres, i.e., the performance of speech functions at the expense of the left hemisphere, and figurative-spatial — right [24, 28]. At the same time, a feature of brain damage in CVD is the predominant left hemisphere involvement in the pathological process [4, 29]. Left-hemisphere strokes were found to be associated with an increased risk of vascular cognitive impairment [4, 30]. It was found that the functional significance of left hemisphere damage is higher compared to damage to the right brain [29]. Taking all the foregoing into account, it can be expected that women's cognitive status is more resistant to factors connected with vascular brain damage, given the smaller hemisphere specialization and the possibility of using right-hemisphere strategies to solve left-hemisphere problems. However, this issue requires additional study.

It is also paying attention that the basic cognitive status determination according to the MoCA scale revealed more cases of severe cognitive disorders (~50% in both men and women) as compared to testing according to the MMSE scale (7-9% in the male and female samples). Given the significant positive correlations between the two scales, it can be expected that the MoCA scale additionally reveals the deficit of those functions that the MMSE scale does not take into account (figurative-spatial, executive functions, abstract thinking). It was previously emphasized that the MoCA scale assess more cognitive domains and contains tasks that are considered more complex by the subjects than similar MMSE tests [31]. The MMSE scale proved itself to be good as a screening tool that is widely used in studies of various brain pathologies [32], but is now increasingly criticized regarding the possibility of detecting cognitive deficits in early stages of brain pathology [33].

The detection in the present study of a high percentage of severe cognitive impairment (~50%) in both men and women may be of crucial significance for patients undergoing direct myocardial revascularization, and in the postoperative period may be associated with the progression of cognitive deficits, a violation of the normal course of the CABG recovery period in this category of patients with coronary artery disease. Therefore, in preparation for surgery and in the postoperative CABG period, these patients need additional preventive and rehabilitative services, as well as possible changes in the surgical tactics of patient management.

At the same time, in this specific sample of patients-candidates for cardiac surgery, it was confirmed that age and comorbid diseases are the most significant clinical and demographic factors connected with lower cognitive status in both men and women, and the cognitive reserve, indirectly measured by the length of training years, resists the deterioration of intellectual abilities. It has been demonstrated that a high level of cognitive reserve is a protective factor, creating opportunities for "successful" mental aging [34].

Understanding gender characteristics when examining the cognitive functions of cardiac surgery patients is important for many reasons. First, vascular cognitive impairment is a very common and progressive condition with time or perioperative risk factors. Secondly, since gender differences in cognitive functions in healthy individuals are in existence, it is possible to assume their preservation during the CVD development, and their study will reveal what has a protective effect for people of different sexes or makes them vulnerable. This will contribute to the development of new therapeutic and rehabilitative approaches. Third, vascular cognitive disorders develop inseparably and in parallel with the aging process in conditions of reduced levels of sex hormones. How reduced endocrine function of the gonads affects the brains of men and women, as well as how the use of hormone replacement therapy changes the brain vulnerability to the development of vascular cognitive deficits, are relevant issues, and obtaining strong evidence in this field will have serious clinical consequences for future personalized medicine.

Conclusion

Female patients, candidates for CABG, with worse clinical and demographic indicators, including a higher Charlson comorbidity index and older age, have a comparable cognitive status with men when assessed according to the MMSE scale. However, the assessment of basic cognitive status using the MoCA scale showed gender differences in the subtests "Naming objects", "Abstract thinking" and "Verbal fluency". Using the MoCA scale, up to 50% of severe cognitive disorders are detected in male and female patients, which is significantly higher than the MMSE score (7-9%), which allows to give it preference for assessing the cognitive status of this category of cardiac surgery patients. Age and comorbid diseases are the most significant clinical and demographic factors connected with lower cognitive status in both men and women, and a high level of education is a protective factor.

Relationships and Activities: none.

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Profile of a patient with non-ST segment elevation myocardial infarction in actual clinical practice

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Aim. To describe profile of a modern portrait with non-ST-segment elevation myocardial infarction (non-STEMI) through a comprehensive analysis of the Emergency Cardiology Unit (ECU) practice, which discharge a function of a regional vascular centre.

Material and methods. To describe the non-STEMI trends of the last decade, we analysed the annual reports on ECU work. The main analysis included patients with a documented non-STEMI treated in 2019 (n=221). We used information from the department database. A Microsoft Excel software was used to create the database. The base has been filled in by the ECU head in real time since 2009. Statistical data processing was performed using the Statistica 10,0 software package. The methods of descriptive statistics and Yates-corrected chi-square test were used.

Results. The following clinical and demographic trends of the last decade were revealed: an increase in the number of patients with non-STEMI, proportion of male patients, mean age of patients, proportion of patients with MI with non-obstructive coronary artery disease; no decrease in in-hospital mortality, despite the introduction of modern guidelines, pharmacological and invasive treatment of non-STEMI. In 2019, the proportion of male patients and patients 75 years and older was 62,4% and 32%, respectively. The mean age of patients was 64,6±13,0 years. Clopidogrel was the predominant $P2Y_{12}$ receptor blockers (56,1%). A total of 176 patients (79,6%) underwent the invasive procedures. Endovascular myocardial revascularization was performed in 97 patients (43,9%), while in the group over 75 years old — in 16 (7%) patients. The leading causes for absence of myocardial revascularization were chronic kidney disease (4,6%), severe coronary artery disease (6,3%), "borderline" (50-60%) coronary artery stenosis. The overall in-hospital mortality rate was 9,0%, while in the group of patients over 75 years old — 19,7%. Mortality rates did not differ in patients with and without myocardial revascularization (p=0,2). However, the incidence of pulmonary oedema was higher in the conservative treatment group (p=0,04).

Conclusion. Treatment of patients 75 years and older remains the main barrier in management of patients with non-STEMI. We observe the treatment-risk paradox, which consists in choosing a less aggressive treatment strategy in the group of the most high-risk patients. Other relevant aspects in the management of non-STEMI patients are the selection of a method for myocardial revascularization in multivessel coronary artery disease, assessment of the hemodynamic significance of coronary artery stenosis, and patients with non-obstructive coronary artery disease.

Keywords: acute coronary syndrome, myocardial infarction, register.

Relationships and Activities. The work was carried out within the exploratory research № 0421-2020-0018 "Development of technologies for personalized diagnosis, risk stratification and treatment of acute and chronic types of coronary artery disease and its risk factors."

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Reducing mortality from cardiovascular diseases (CVD) is one of the priority goals of the national project "Health Care", approved in 2018. To achieve this goal, the federal project "Fight against CVD" was developed, according to which the expected reduction in mortality from CVD by 2024 should be 25%. The leading position among the reasons of death is occupied by myocardial infarction (MI). Thus, in 2017, the hospital mortality rate from MI in the Russian Federation was 13,2% [1]. In the European Union, by 2015, this figure was 6,8% [2]. Non-ST segment elevation MI (NSTEMI) remains one of the most common causes of emergency hospitalizations [3-5]. Researchers have observed trends for an increase in the proportion of patients with NSTEMI in the structure of acute coronary syndrome (ACS), an increase in long-term mortality and recurrent ischemic events in patients with NSTEMI compared to patients with ST-segment elevation, a sharp slowdown in the rate of decline in hospital mortality in NSTEMI, despite the increasing introduction of percutaneous coronary intervention (PCI) [3, 6].

To this day, approaches to the management of patients with ST-segment elevation MI have clear algorithms, which makes it easier to work with this category of patients [7]. While approaches to the aggressive treatment of patients with NSTEMI vary from immediate PCI to the possibility of planned intervention [8]. This is largely due to the heterogeneity of patients with NSTEMI, which makes it necessary to conduct a strict risk stratification and follow a patient-oriented approach in work. The area of the Russian Federation is an additional factor that affects the care delivery to patients with NSTEMI, namely, routing, accumulation of local experience in each region, and slower pace of recommendation implementation in clinical practice. Thus, each department that delivers care to patients with ACS is faced with the issue on what needs to be done to reduce mortality rate in this group of patients.

Analysis of departments operation and register studies are the tools that provide a detailed description of patients in one or another region, assess the implementation of clinical recommendations and disease outcomes, identify existing barriers, develop new prospects and medical technologies, and promote the exchange of best practices between medical institutions. The aim of this work was to describe a modern portrait of a patient with NSTEMI by conducting a comprehensive analysis of the routine practice of the Chest-Pain Unit (CPU), which serves as a regional vascular center. The CPU operation analysis was faced with the following objectives: 1) to study the clinical and demographic NSTEMI trends and trends of invasive strategy for the treatment of patients with NSTEMI; 2) to describe anamnestic, demographic, and clinical characteristics of patients; 3) to assess the treatment of patients from the time of admission until discharge from the hospital; 4) to assess the reasons why myocardial revascularization was not performed in the acute period of the disease; 5) to assess in-hospital complications and outcomes of the disease; 6) identify barriers to the health care delivery.

Material and methods

CPU is a part of the regional vascular center and provides assistance to patients with MI living in the territory of Tomsk and Tomsk region.

To describe the clinical and demographic NSTEMI trends and trends in the introduction of an invasive therapeutic strategy of patients with NSTEMI in the last decade, we analyzed data from the annual reports on CPU operation.

The main analysis included patients with confirmed NSTEMI [9] who were under medical treatment in CPU in 2019 (n=221). We used data from the unit's database that reflects the main anamnestic and clinical characteristics of patients. To create a database, the Microsoft Excel table processor is used. The database has been maintained in the unit since 2009. The head of the unit is responsible for entering data in real time. All patients being under medical treatment in the unit sign their consent to receive inpatient medical care and consent to the personal data processing. No cases of consent withdrawal by means of a corresponding written document have been registered.

The main operating parameters of the unit are given in Table 1.

The statistical data processing was performed using the software package Statistica 10.0. The comparison of discrete values was carried out using the χ^2-criterion adjusted for Yates continuity. The data are presented as absolute and relative frequencies, mean and standard deviation (M±SD), or median and interquartile range (Me (Q1; Q3)). The differences were considered statistically significant at p<0,05.

Results

We found an increasing trend in the number of patients with NSTEMI (Figure 1). Among the demographic indicators, we noted a tendency to increase in the proportion of men and increase in the average age of patients (Figure 2, 3). Patients with NSTEMI invariably represent a heterogeneous group of patients with a severe disease course, as indirectly indicated by the high risk of hospital mortality according to the GRACE scale (Figure 4). There is a tendency to increase in patients with NSTEMI and the absence of obstructive coronary artery damage (MINOCA) (Figure 5). Another observation is the persistence of hospital mortality rates in NSTEMI, despite the active introduction of an invasive management strategy for this group of patients and an increase in the frequency of endovascular myocardium revascularization (Figure 6).

The further analysis group consisted of 221 patients with NSTEMI who were under medical treatment in 2019. The proportion of male patients was 62,4%. The average age of the patients was 64,6±13,0 years. The proportion of patients aged 65 years and older was 29,9%, 75 years and older — 32%. The main clinical and anamnestic characteristics of patients, data on the coronary bed anatomy, complications and outcomes of the disease are shown in Table 2.

Data on drug treatment of patients with NSTEMI are shown in Table 3.

Invasive strategy (coronary angiography and/or endovascular myocardium revascularization) as a primary strategy (Table 4) for the care of patients with NSTEMI was used in 176 patients, which was 79,6%. Endovascular revascularization

Table 1

Basic parameters of the CPU operation

Value	Description
Mode of operation	7/24
Standards for providing assistance applied in the unit	ESC recommendations for management of patients with ACS, standard of specialized medical care for MI of the Ministry of Health of the Russian Federation
Number of residents served by the branch	786763
Area of the territory served by the branch	10818 km^2
Number of patients with MI for 1 month	100
Presence of cardiological ICU	Yes
Ability to detect highly sensitive troponin 24 hours a day	Yes
Ability to perform echocardiography 24 hours a day	Yes
Ability to perform PCI 24 hours a day	Yes
Possibility of IABC conduction	Yes
Possibility of ECMO conduction	No
Possibility of substitutive renal therapy	No
Availability of emergency cardiac surgery	No

Abbreviations: ICU — intensive care unit, IABC — intra-aortic balloon counterpulsation, MI — myocardial infarction, ACS — acute coronary syndrome, PCI — percutaneous coronary intervention, ECMO — extracorporeal membrane oxygenation.

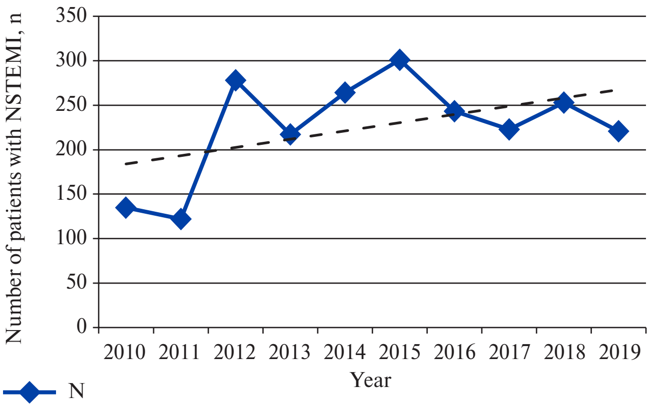

Figure 1. Dynamics of the number of patients with NSTEMI.
Abbreviation: NSTEMI — non-ST-segment elevation myocardial infarction.

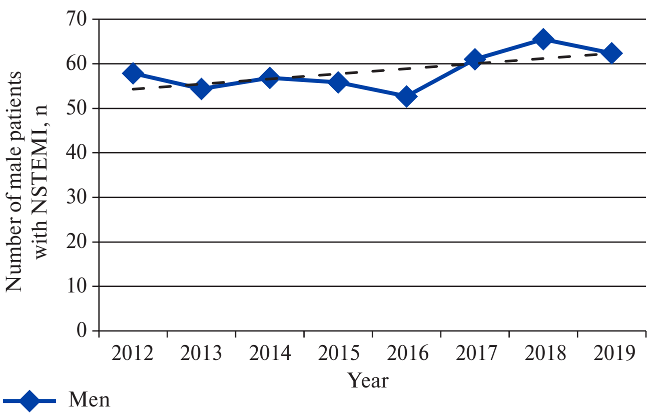

Figure 2. Dynamics of the number of male patients with NSTEMI.
Abbreviation: NSTEMI — non-ST-segment elevation myocardial infarction.

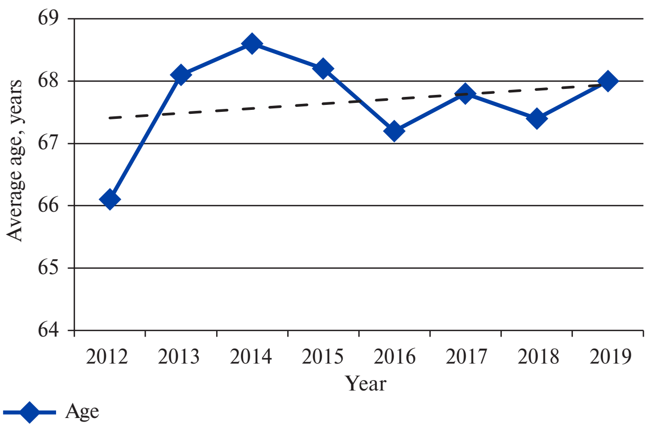

Figure 3. Dynamics of the average age of patients with NSTEMI.

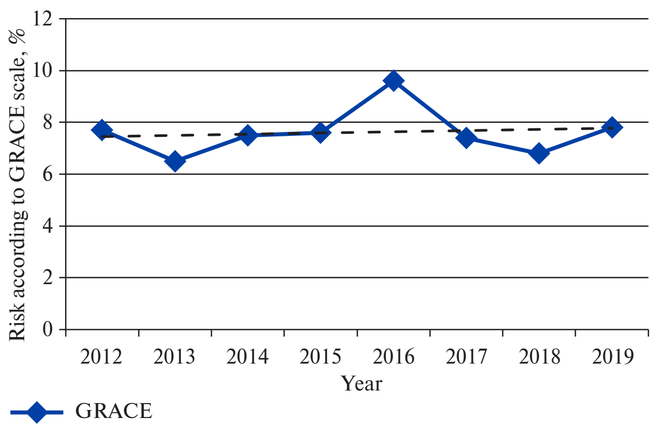

Figure 4. Dynamics of the average risk value according to the GRACE scale.

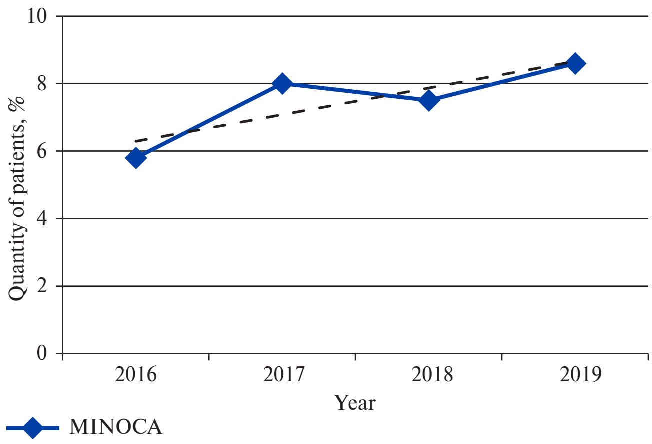

Figure 5. Proportion of patients with MINOCA.
Abbreviation: MINOCA — myocardial infarction without obstructive coronary atherosclerosis.

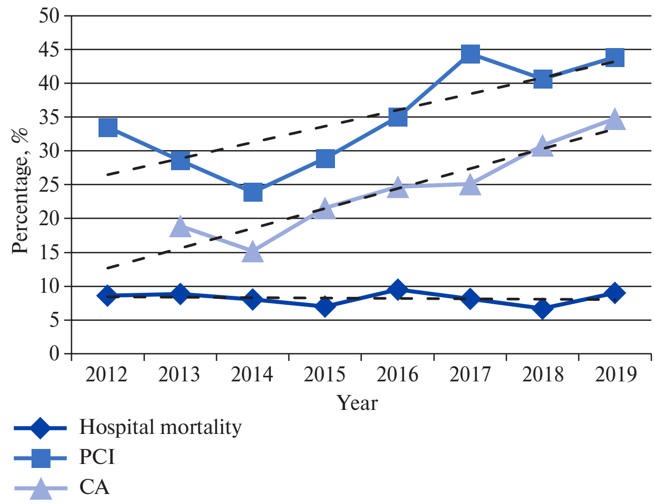

Figure 6. Proportion of patients with NSTEMI who underwent an invasive strategy and dynamics of hospital mortality rates.
Abbreviations: CA — coronary angiography, PCI — percutaneous coronary intervention.

Table 2

Clinical and anamnestic characteristics, coronary bed state, complications and outcomes of the disease in patients with NSTEMI

Indicator	Parameter
Number of patients, n	221 (100%)
Age, years	68±13,0
Male sex, n	138 (62,4%)
Number of patients admitted from onset of MI symptoms to hospitalization, n:	
Within 24 hours Within 72 hours Later than 72 hours Time could not be assessed	121 (54,6%) 44 (19,9%) 40 (18,1%) 16 (7,4%)
Time from the of MI symptoms to hospitalization in patients admitted in the first 24 hours, min	276 (150; 543)
Anamnesis of MI, n	100 (45,2%)
Hemoglobin at admission, g/l	135 (120; 149)
Glomerular filtration rate at admission (according to the Cockcroft-Gault formula), ml/min	61 (43; 80)
Left ventricular ejection fraction, %	57 (46; 63)
Hospital mortality risk according to the GRACE scale at admission, %	7,8±13,2
Hemorrhagic complication risk according to the CRUSADE scale at admission, %	10,7±7,2

Table 2. Continued

Indicator	Parameter
MINOCA, n	19 (8,6%)
MI localization:	
Anterior MI, n	123 (55,7%)
Posterior MI, n	48 (21,7%)
Anterior-posterior MI, n	28 (12,7%)
IM of unspecified localization, n	22 (9,9%)
Risk factors for coronary artery disease:	
Hypertension disease, n	216 (97,7%)
Dyslipidemia, n	172 (77,8%)
Smoking at the time of admission or in anamnesis, n	103 (47,9%)
Obesity, n	72 (33,0%)
Diabetes mellitus, n	60 (27,0%)
Impaired glucose tolerance, n	15 (6,8%)
Coronary bed anatomy (coronary arteries with stenoses >50%):	
Single-vessel disease, n	29 (13,1%)
Two-vessel disease, n	36 (16,9%)
Three-vessel disease, n	100 (45,2%)
MI complications:	
Cardiogenic shock, n	21 (9,5%)
<65 years (n=84)	1 (1,2%)
65-74 years (n=66)	5 (7,6%)
⩾75 years (n=71)	15 (21,1%)
Pulmonary edema, n	40 (18%)
<65 years (n=84)	8 (9,5%)
65-74 years (n=66)	9 (13,6%)
⩾75 years (n=71)	23 (32,4%)
Somatogenic delirium, n	12 (5,4%)
Cardiogenic shock + pulmonary edema, n	15 (6,8%)
Pulmonary edema + somatogenic delirium, n	4 (1,8%)
Cardiogenic shock + pulmonary edema + somatogenic delirium, n	1 (0,45%)
Left ventricular aneurysm, n	4 (1,8%)
Relapse in the hospital, n	7 (3,2%)
NYHA class at release:	
I, n	52 (23,5%)
II, n	76 (34,4%)
III, n	61 (27,6%)
IV, n	7 (3,2%)
Hospital mortality rate:	
Total, n	20 (9%)
<65 years (n=84)	1 (1,2%)
65-74 years (n=66)	5 (7,6%)
⩾75 years (n=71)	14 (19,7%)
Cause of death, n=20 (100%):	
Cardiogenic shock, n	16 (80%)
Cerebral edema, n	2 (10%)
Multiple organ failure, n	2 (10%)

Note: data is presented as absolute and relative values, M±SD, Me (Q1; Q3).
Abbreviations: MI — myocardial infarction, MINOCA — myocardial infarction without obstructive coronary atherosclerosis.

of the myocardium was performed in 97 patients, which was 43,9%. In the group of patients over 75 years of age, endovascular revascularization was performed in 16 patients, which was only 7% of all patients or 16,5% of patients who underwent revascularization. The conservative treatment strategy as the primary care strategy was chosen for 45 (20,4%) patients.

Further, Table 5 shows the reasons why endovascular myocardium revascularization was not performed.

Data on complications of infarction and mortality during myocardial revascularization in acuity and in its absence are shown in Table 6.

Discussion

Patients with NSTEMI still represent a heterogeneous group of patients with a severe disease course. An important aspect is the presence of a large number of elderly patients [10]. In the clinical and anamnestic characteristics of patients, attention is drawn to the preservation of wide prevalence of modifiable risk factors and presence of previous MI. In addition, the relevant indicator is the increasing number of patients with MINOCA. A section on the management of this category of patients has already been included in recommendations of the European Society of Cardiology on patient management with ACS without persistent ST-segment elevation 2020 (hereinafter — the recommendations 2020) [11]. The recommendations emphasize the need for comprehensive multimodal diagnosis and personalized approach to the treatment and follow-up of patients with MINOCA both in the short and long term [11, 12].

A good side in the medical treatment of NSTEMI is the widespread use of dual antiplatelet therapy, beta-blockers, statins, angiotensin-converting enzyme inhibitors and sartans, low-molecular-weight heparins. These indicators hold out the corresponding indicators of the countries of Europe and North America [3, 5, 6]. However, with regard to antiplatelet therapy, the predominant $P2Y_{12}$ receptor inhibitor is clopidogrel, which does not comply with the current recommendations for the NSTEMI treatment. Today, taking into account the increase in PCI frequency, the data of the ISAR-REACT 5 study and the recommendations 2020 pose a new challenge for the wider introduction of prasugrel into the practice of treating patients with NSTEMI [11, 13].

Table 3

Drug therapy of patients with NSTEMI

Medication	Number of patients and %
Acetylsalicylic acid	205 (92,8%)
$P2Y_{12}$	218 (98,6%)
Clopidogrel	124 (56,1%)
Aspirin+clopidogrel	111 (50,2%)
Ticagrelor	81 (36,6%)
Aspirin+ticagrelor	81 (36,6%)
Prasugrel	13 (5,9%)
Aspirin+prasugrel	13 (5,9%)
Dual antiplatelet therapy	205 (92,8%)
IIb/IIIa blockers	7 (3,2%)
Low molecular weight heparin	162 (73,3%)
Beta-blockers	190 (86,0%)
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	189 (85,5%)
Statins	208 (94,1%)

Table 4

Primary therapeutic strategy for patients with NSTEMI and its outcomes

Indicator	Parameter		
I. Invasive therapeutic strategy	176 (79,6%)		
	Coronary angiography and/or endovascular myocardium revascularization	Endovascular revascularization of the myocardium	Coronary angiography and/or endovascular myocardium revascularization
	176 (79,6%)	97 (43,9%)	79 (35,7%)
— Urgent invasive therapeutic strategy (<2 h)	21 (9,5%)	16 (7,2%)	5 (2,3%)
— Early invasive therapeutic strategy (<24 h)	108 (48,9%)	56 (25,4%)	52 (23,5%)
— Invasive (<72 h)	20 (9,0%)	10 (4,5%)	10 (4,5%)
— Planned invasive (>72 h)	22 (9,9%)	12 (5,4%)	10 (4,5%)
— Time frame assessment was not possible	5 (2,3%)	3 (1,4%)	2 (0,9%)
II. Conservative strategy	45 (20,4%)		

Table 5

Therapeutic strategy after coronary angiography and the reasons why endovascular myocardium revascularization was not conducted

Indicator	Parameter
I. Myocardial revascularization	97 (43,9%)
II. Conservative strategy, on grounds of:	124 (56,1%)
1. Three-vessel disease of coronary bed, including:	52 (23,5%)
— Surgical revascularization is recommended for 1-3 months.	16 (7,2%)
— Surgical revascularization is doubtful (patients aged 75 years and older)	14 (6,3%)
— Conducting surgical revascularization for index MI within 21 days is recommended	9 (4,1%)
— Presence of coronary artery stenosis of 50-60%	4 (1,8%)
— Presence of indications for repeated surgical myocardium revascularization	2 (0,9%)
— Reason for the selected strategy could not be determined	7 (3,2%)
2. MINOCA	19 (8,6%)
3. Single- or two-vessel disease of coronary bed in presence of coronary artery stenosis of 50-60%	16 (7,2%)
4. Chronic kidney disease	11 (5,0%)
<65 years (n=84)	0
65-74 years (n=66)	1 (0,45%)
⩾75 years (n=71)	10 (4,6%)
5. Anemia	6 (2,7%)
6. Combination of chronic kidney disease and anemia	1 (0,45%)
7. Fragility	7 (3,2%)
8. Refusal of coronary angiography	5 (2,3%)
9. Severity of condition	3 (1,3%)
10. Acute cerebrovascular accident at the time of admission	1 (0,45%)
11. Technical limitations — patient's weight	1 (0,45%)
12. The reasons could not be assessed	2 (0,9%)

Note: data is presented as n (%).
Abbreviations: MI — myocardial infarction, MINOCA — myocardial infarction without obstructive coronary atherosclerosis.

Table 6

MI complications and mortality depending on the performance/non-performance of myocardial revascularization in disease acute period, n=221

Indicator	Patients who underwent myocardial revascularization in disease acute period, n=97	Patients who did not undergo myocardial revascularization in disease acute period, n=124	P-value
Cardiogenic shock	8 (3,6%)	13 (5,9%)	0,5
Pulmonary edema	12 (5,4%)	28 (12,7%)	0,04
Psychosis	5 (2,3%)	7 (3,2%)	0,8
LV aneurysm	1 (0,45%)	3 (1,3%)	0,8
Relapse in the hospital	3 (1,3%)	4 (1,8%)	0,9
NYHA class:			
I	31 (14,0%)	21 (9,5%)	0,02
II	36 (16,3%)	40 (18,1%)	0,1
III	19 (8,6%)	40 (18,1%)	0,02
IV	3 (1,3%)	4 (1,8%)	0,9
Mortality	6 (2,7%)	14 (6,3%)	0,2

Note: data is presented as n (%).
Abbreviation: LV — left ventricle.

The trend that characterizes the frequency of choosing an aggressive treatment of patients with NSTEMI in CPU, on the one hand, indicates a positive trend — a high proportion of patients who underwent PCI, compared with the data of the Russian RECORD-3 register, but on the other hand — a slower introduction of high-tech medical care in Russia compared to the indicators of European registers [3, 6, 14]. The issue on revascularization of elderly patients remains open. Thus, in CPU, in group of patients 75 years and older, revascularization was carried out only in 7% of all patients or in 16,5% of patients who underwent revascularization, despite the fact that elderly patients belong to the most high-risk category of patients, which is confirmed by the frequency of acute left ventricular failure and high mortality observed in this group. This occurrence called the "risk-treatment paradox" is typical not only for Russia, but also for most highly developed countries [15]. Among the reasons why myocardial revascularization was not performed in elderly patients, attention is drawn to prevalence of chronic kidney disease and presence of multivessel damage to the coronary bed. Treatment of elderly patients is certainly a difficult task. Nevertheless, risk stratification is the basis for choosing a patient management strategy. Moreover, according to the recommendations 2020, diagnostic and therapeutic algorithms for the management of elderly patients do not differ from those of a younger category of patients [11].

An important follow-up, characteristic for the world clinical practice, is the preservation of hospital mortality rates in patients with NSTEMI, despite the active introduction of invasive strategy and an increase in the frequency of endovascular myocardium revascularization. At the same time, a positive aspect is a decrease in the frequency of manifestations of heart failure in patients who underwent revascularization during the acute disease period. The remaining mortality rates are largely due to the problem of treating a group of patients 75 years and older. It is also important to say that our analysis does not take into account the PCI methodology impact, namely the selected access, catheter and stent.

Revascularization of patients with multivessel coronary artery disease and management of patients with so-called "frontier" stenosis of the coronary arteries remains other topical issues.

Conclusion

A comprehensive analysis of the unit's work allowed to obtain a modern clinical portrait of a patient with NSTEMI. Clinical and demographic trends include an increase in the number of patients with NSTEMI, the proportion of male patients, and the average age of patients. Patients with NSTEMI are a heterogeneous group of patients with a severe disease course. At the same time, despite the active introduction of medical and MI invasive treatment, the mortality rates among patients with NSTEMI remain high. In the most frequent cases, patients 75 years and older have restrictions on myocardial revascularization. The main limitations are the presence of chronic kidney disease and multivessel disease of the coronary bed. It is in this category of patients that we observe the frequent development of acute heart failure and the highest mortality rates.

The data standardization and the analysis of unit's work made it possible to clearly identify the aspects of providing assistance for patients with NSTEMI that require changes and contribute to high mortality rates. The analysis data allowed to identify trends, assess own results from the point of view of world practices, focus on the main barriers, and finally form directions for overcoming them. One of the main directions is to provide assistance to patients with NSTEMI 75 years and older, which primarily require strict risk stratification and a patient-oriented approach. Other areas include issues of myocardial revascularization in multivessel coronary damage, development of emergency cardiac surgery, assessment of hemodynamic significance of coronary artery stenosis, multimodal heart imaging in patients with MINOCA. The relevance of these areas is also emphasized by the new recommendations of the European Society of Cardiology 2020.

Thus, the analysis of our own practice is an integral part of the CPU operation: tool for assessing the implementation of existing recommendations, point of transition to new recommendations, stage in the development of approaches to overcome local and world-level barriers that prevent mortality reduction in NSTEMI.

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Predictive value of growth differentiation factor-15 in patients with myocardial infarction

Sabirzyanova A. A., Galyavich A. S., Baleeva L. V., Galeeva Z. M.

Aim. To evaluate the prognostic value of growth differentiation factor-15 (GDF-15) in patients with acute myocardial infarction (MI).

Material and methods. The study included 118 patients under the age of 70 with ST- and non-ST segment elevation myocardial infarction, who, in addition to routine examination, were tested for GDF-15 by enzyme-linked immunosorbent assay in the first 48 hours from the onset. The statistical significance of the differences in quantitative indicators was assessed by the Student's t-test for a normal distribution and by the nonparametric U Mann-Whitney test for a non-normal distribution, while in qualitative indicators — by Pearson's chi-squared test. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used as an indicator of strength of relationship between quantitative indicators.

Results. The average GDF-15 level in patients with MI was 2,25±1,0 ng/ml. For 6 months of follow-up, 15,25% of patients were rehospitalized for unstable angina or recurrent myocardial infarction. The GDF-15 level in 82,6% of cases was in the third and fourth quartiles (≥2,07 ng/ml). All patients with recurrent MI had GDF-15 levels in the upper quartile (≥2,73 ng/ml). Patients with GDF-15 levels in the upper quartile had a significantly higher risk of rehospitalization (hazard ratio, 3,3 (95% CI, 1,65-6,76), $p<0,05$) compared with patients with GDF-15 levels in other quartiles. The potential for the combined use of GDF-15 and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels to assess the risk of readmission has been evaluated. Patients who had both GDF-15 and NT-proBNP levels in the upper quartiles (GDF-15 >2,73 ng/ml, NT-proBNP >1418 pg/ml) had 4,8 times higher risk of rehospitalizations for unstable angina or recurrent myocardial infarction.

Conclusion. In patients with MI, the determination of the GDF-15 level has prognostic value and may serve as an additional marker of the risk of recurrent cardiovascular events.

Keywords: growth differentiation factor-15, GDF-15, myocardial infarction; cardiovascular events.

Relationships and Activities: none.

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Myocardial infarction (MI) holds one of the leading positions in the hospital mortality structure in patients with a therapeutic profile. In this regard, the search for new markers for a more accurate assessment of patient prognosis continues. Growth differentiation factor-15 (GDF-15) may be a candidate for this role. GDF-15 — one of the proteins of the transforming growth factor-β superfamily. Proteins of this family are involved in the processes of development, differentiation and repair of tissues of various organs. GDF-15 expression is normally found in the placenta and prostate. It was found that GDF-15 can be expressed under the influence of various stress factors, including hypoxia, inflammation, or acute tissue damage, including cardiac muscle [1].

There are not many studies on GDF-15 in patients with MI today. According to the available data, GDF-15 levels are elevated and are independently associated with mortality in patients with MI with both ST-segment elevation (STEMI) and non-ST-segment elevation (NSTEMI) on an electrocardiogram (ECG) [2-4].

Material and methods

The study included 118 patients with STEMI or NSTEMI on ECG. The enrollment criteria were: acute stage of MI, age of patients up to 70 years, signed patient's voluntary informed consent to participate in the study. The exclusion criteria were: age over 70 years; refusal to sign an informed consent to participate in the study; acute inflammatory disease and/or exacerbation of chronic inflammatory disease of any etiology and localization within 6 months before hospitalization; chronic obstructive pulmonary disease; connective tissue diseases; type 1 or type 2 diabetes mellitus; acute cerebrovascular accident or transient ischemic attack in less than 6 months prior to enrollment; any cardiac arrhythmias and conduction disorders requiring medication, including atrial fibrillation, grade II or III atrioventricular blockades, bradycardia ⩽50 beats/min, sinoatrial nodal block; heart failure of class II and higher according to Killip; heart failure with Simpson ejection fraction of <40% according to echocardiography (EchoCG); increased blood creatinine levels >160 mmol/l; increased levels of blood transaminases 3 times or more from upper limit of norm; pregnancy and lactation; alcoholism; drug addiction; cancer in anamnesis of any localization.

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The protocol of this study was approved by the Local Ethics Committee. All participants received written, voluntary, informed consent to participate in the study prior to the enrollment.

All enrolled patients underwent routine examination: general blood analysis; biochemical blood assay, including determination of creatinine, urea, potassium, sodium, lipid profile; blood levels of highly sensitive troponin and NT-pro-brain natriuretic peptide (NT-pro-BNP), glomerular filtration rate by MDRD formula; ECG; daily monitoring of ECG; EchoCG.

In each patient, the GDF-15 level was determined by enzyme immunoassay. Venous blood was collected in the first 48 hours from the beginning of MI clinical picture. After collection, the blood samples were centrifuged and frozen at a temperature of -70° C. The enzyme immunoassay was performed using ELISA Kit for Growth Differentiation factor 15 reagents (Cloud-Clone Corp., USA). The detection range was 0,156-10,0 ng/ml, the sensitivity was 0,065 ng/ml.

The obtained data analysis was carried out according to 110 parameters, including clinical, laboratory and instrumental indicators.

The patients' clinical state was assessed by a survey after 1, 3 and 6 months after their discharge from hospital.

Statistical processing of the obtained data was carried out with the help of computational program STATISTICA v10.0. Quantitative indicators were assessed for compliance with the normal distribution using the Kolmogorov-Smirnov test. The description of quantitative indicators that had a normal distribution was presented in the form of arithmetic averages (M) and standard deviations (σ) in the form of M±σ. Quantitative indicators whose distribution was different from the normal one were described using the values of median (Me) and lower and upper quartiles (Q1-Q3). The statistical significance of differences in quantitative values were assessed by Student's t-test for normal distribution and by non-parametric U Mann-Whitney test for a distribution other than normal. For qualitative indicators, the Pearson criterion χ^2 was applied. The Pearson and Spearman correlation coefficients were applied as an indicator of relationship tightness between quantitative indicators. The results were considered statistically significant at the value of $p<0,05$.

Results

Of the 118 enrolled patients, 82,2% were men. The average age of the enrolled patients was 57,3±8,7 years. In the anamnesis, 65,3% of patients had hypertension disease, and 12,7% of patients had post-infarction cardiosclerosis.

The average GDF-15 level in the acute stage of MI was 2,25±1,0 ng/ml. The patients' division into

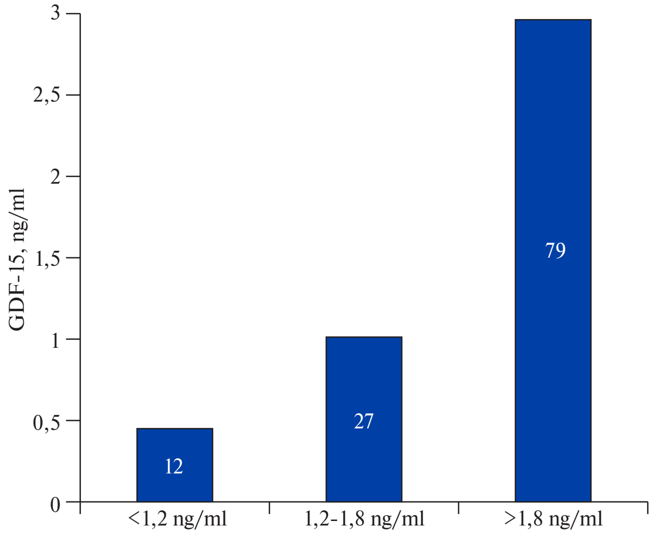

Figure 1. GDF-15 levels in acute stage of MI.
Abbreviation: GDF-15 — growth differentiation factor-15.

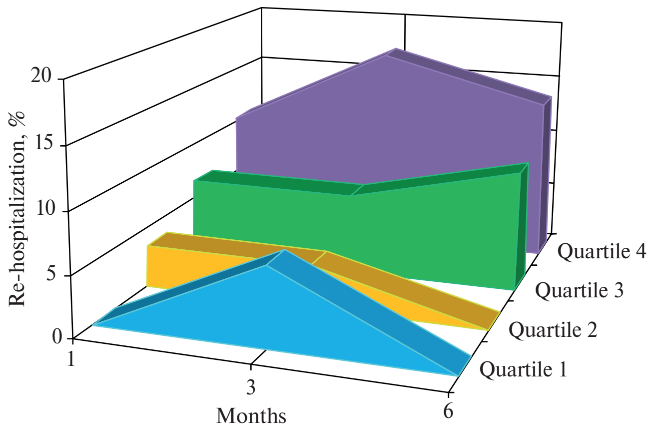

Figure 2. Re-hospitalizations due to unstable angina or recurrent MI in the time section, depending on GDF-15 levels (quartile division).

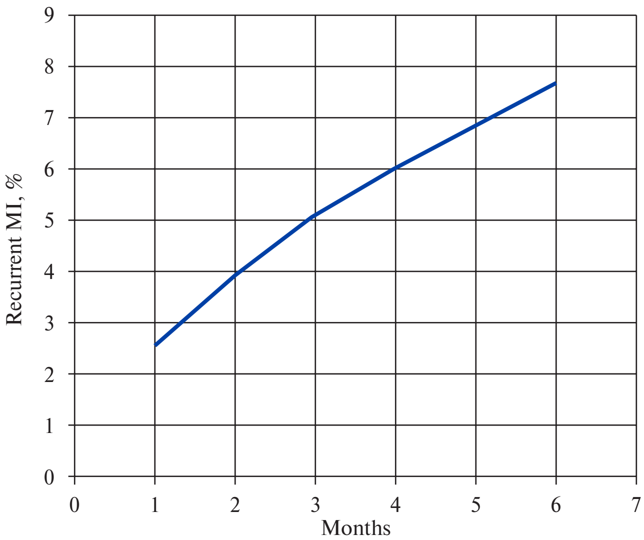

Figure 3. Dependence curve of recurrent MI on time in patients with GDF-15 in the upper quartile (>2,73 ng/ml).

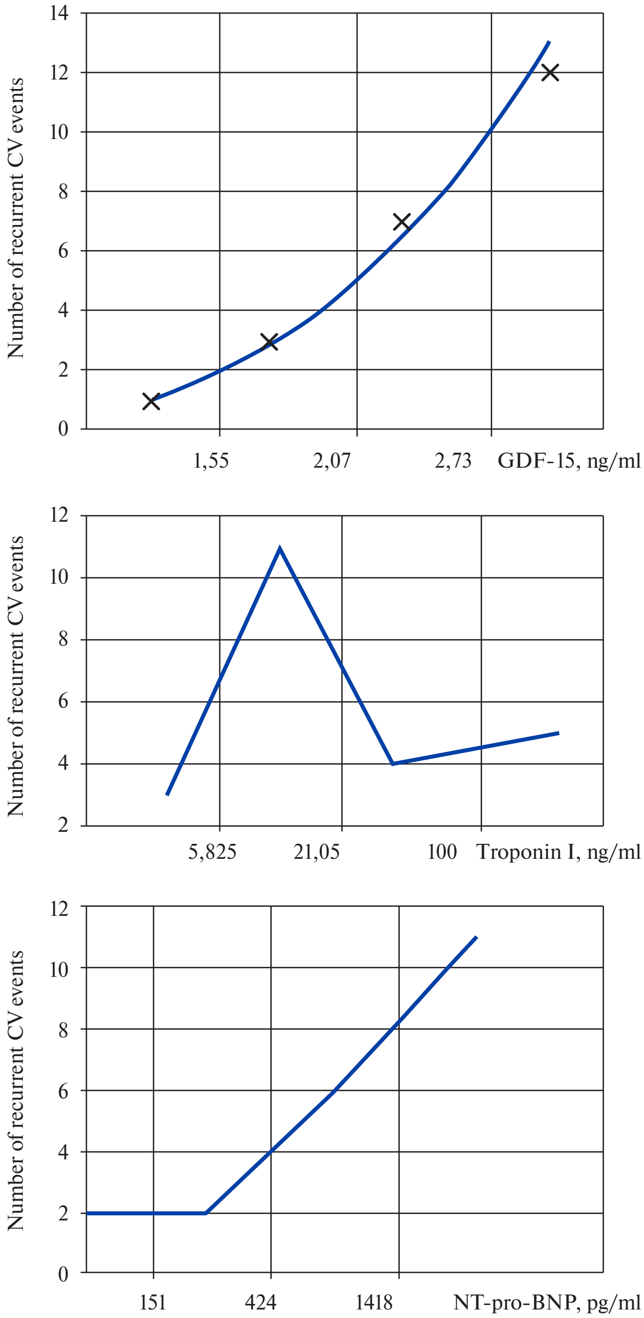

Figure 4. Simultaneous graphs of the dependence of repeated cardiovascular events (hospitalization due to unstable angina and recurrent MI) on the biomarker levels in blood plasma.
Abbreviations: CV — cardiovascular, GDF-15 — growth differentiation factor-15, NT-pro-BNP — NT-pro-brain natriuretic peptide.

groups according to the reference values of GDF-15 <1,2 ng/ml, 1,2-1,8 ng/ml and >1,8 ng/ml was carried out in accordance with the literature data [4]. In 79 patients (66.9%), GDF-15 levels were significantly increased (>1,8 ng/ml), in 27 patients (22,9%) — moderately increased (1,2-1,8 ng/ml), and in 12 (10,2%) — slightly increased (<1,2 ng/ml). The GDF-15 levels by group are shown in Figure 1.

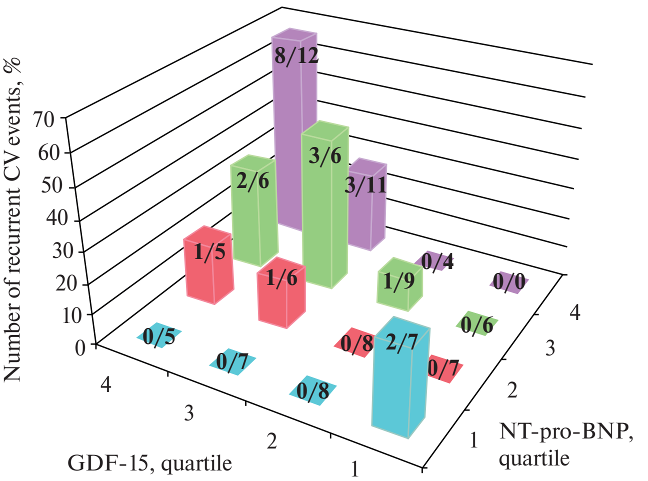

Figure 5. Hospitalization due to unstable angina and recurrent MI in 6 months, depending on the baseline levels of GDF-15 and NT-pro-BNP (quartile division).
Abbreviations: CV — cardiovascular, GDF-15 — growth differentiation factor-15, NT-pro-BNP — NT-pro-brain natriuretic peptide.

As a result of subgroups analysis, differences in the GDF-15 level between men and women (2,26±1,02 ng/ml vs 2,22±0,99 ng/ml, p=0,84), as well as depending on the patients' age were not detected. Association of GDF-15 levels with the presence of hypertension, post-infarction cardiosclerosis, body mass index, smoking history, as well as with the levels of total cholesterol and low-density lipoprotein cholesterol in patients was not detected.

The GDF-15 level was higher in patients with STEMI on ECG compared to patients with NSTEMI (2,36±1,02 ng/ml vs 1,99±0,96 ng/ml, p<0,05), and it was also higher in patients with hypo- or akinesis zones according to EchoCG data (2,35±1,05 ng/ml vs 1,85±0,70 ng/ml, p<0,05) and in patients without left ventricular hypertrophy according to EchoCG data (2,51±1,09 ng/ml vs 2,10±0,94 ng/ml, p<0,05).

All revealed correlations of GDF-15 levels with laboratory and tool parameters were of moderate or weak order: with NT-pro-BNP level (r=0,36, p=0,0001), with the number of white blood cells (r=0,32, p=0,0003), with troponin I levels (r=0,21, p=0,02) and urea (r=0,20, p=0,04), with the Simpson left ventricular ejection fraction (r=-0,32, p=0,0003) and thickness of interventricular septum according to EchoCG data (r=-0,26, p=0,004).

For further analysis of the obtained results, the GDF-15 levels were divided into quartiles: quartile 1 — <1,55 ng/ml, quartile 2 — 1,55-2,07 ng/ml, quartile 3 — 2,07-2,73 ng/ml, quartile 4 — >2,73 ng/ml.

During 6 months of follow-up, 15,25% of patients had repeated hospitalizations for unstable angina or recurrent MI (23 cases). During the first month of follow-up, there were 6 hospitalizations (1 of them due to recurrent MI); for 3 months — 10 re-hospitalizations (2 of them due to recurrent MI); for 6 months of follow-up — 7 hospitalizations (3 of them due to recurrent MI).

The GDF-15 level in 82,6% of cases of repeated hospitalizations was in the upper (third and fourth) quartiles. Figure 2 demonstrates a graph of repeated hospitalizations due to unstable angina or recurrent MI, depending on the GDF-15 levels.

In all patients with recurrent MI, the GDF-15 level was in the upper quartile (>2,73 ng/ml). This relationship with MI in patients with GDF-15 levels in the upper quartile was close to linear (Figure 3).

We compared the effects of baseline levels of cardiac troponin I, NT-pro-BNP and GDF-15 on re-hospitalizations. For this purpose, the levels of troponin I and NT-pro-BNP were divided into the quartiles. For troponin I: quartile 1 — <5,82 ng/ml, quartile 2 — 5,82-21,05 ng/ml, quartile 3 — 21,05-100 ng/ml, quartile 4 — >100 ng/ml, For NT-pro-BNP: quartile 1 — <151,0 pg/ml, quartile 2 — 151,0-424,0 pg/ml, quartile 3 — 424,0-1418,0 pg/ml, quartile 4 — >1418,0 pg/ml.

Patients with GDF-15 levels in the upper quartile had a higher risk of re-hospitalization for unstable angina and recurrent MI (risk ratio (HR) 3,3 (95% confidence interval (CI) 1,65-6,76), p<0,05) compared to patients with GDF-15 levels in other quartiles. In 20,6% of patients whose GDF-15 level was in the upper quartile, recurrent MI was recorded during 6 months of follow-up. The high NT-pro-BNP levels were also associated with a significant increase in the hospitalization risk due to unstable angina and recurrent MI (RR 6,2 (95% CI 1,21-32,08), p<0,05). The significant association of cardiac troponin I levels with recurrent cardiovascular events was not detected. Figure 4 demonstrates the graphs of repeated cardiovascular event dependence (hospitalization due to unstable angina and recurrent MI) on levels of biomarkers in blood plasma over the follow-up period of 6 months.

We assessed the possibility of combining GDF-15 and NT-pro-BNP levels to assess the risk of repeated hospitalizations for unstable angina and recurrent MI. Patients with GDF-15 and NT-pro-BNP levels in the upper quartiles (GDF-15 2,73 ng/ml, NT-pro-BNP 1418 pg/ml) had 4,8 times higher risk of re-hospitalization compared to patients with both of these biomarkers in the lower quartiles (RR 4,8 (95% CI 2,55-9,27), p<0,05). 66,6% of patients with GDF-15 and NT-pro-BNP levels in the upper quartiles within 6 months were re-hospitalized. Figure 5 demonstrates a graph of hospitalizations due to unstable angina and recurrent MI over the follow-up period of 6 months, depending on baseline levels of GDF-15 and NT-pro-BNP.

Discussion

A number of studies have identified relationships between GDF-15 levels and other cardiac markers. In the PROVE IT TIMI-22 study, patients with MI showed a moderate correlation of GDF-15 levels with NT-pro-BNP and C-reactive protein r=0,24, (p<0,001 for each indicator) [5]. In our study, a moderate correlation was detected between the levels of GDF-15 and NT-pro-BNP (r=0,36, p=0,0001), and a weaker relationship between the levels of GDF-15 and troponin I (r=0,21, p=0,02). The absence of a correlation between the levels of GDF-15 and cardiac troponin in the study [5] can be explained by the fact that blood sampling followed by determination of GDF-15 concentration was carried out during 3-5 days from the development of MI clinical picture, while the enrollment of patients with subsequent blood sampling was carried out earlier — within 48 hours from MI onset. It is understood that GDF-15 levels do not change significantly over 4 months after MI [5]. The GDF-15 levels of do not show the typical dynamics in the form of an increase followed by a drop in blood concentration, unlike cardiac troponins. Such changes in laboratory parameters over time can explain the presence or absence of relationships between the GDF-15 and troponin levels in different studies.

In the GUSTO-IV study, two-thirds of patients with NSTEMI had GDF-15 levels >1,2 ng/ml [4]. In our study, 89,8% of patients had GDF-15 level >1,2 ng/ml, It should be noted that our study included patients with both STEMI on ECG and NSTEMI, and GDF-15 levels were higher in patients with STEMI (2,36±1,02 vs 1,99±0,96, p<0,05).

The results of studying the GDF-15 levels as a prognostic marker in patients with MI were presented in several studies. In the GUSTO-IV study, it was noted that in patients with GDF-15 levels >1,8 ng/ml, the mortality rate for 1 year was 14,1%. It was concluded that the GDF-15 levels are associated with mortality rate in patients with NSTEMI [4].

In our study, it was not possible to assess the relationship of GDF-15 with the mortality rate of patients with MI, because during the follow-up period of 6 months, no deaths were reported. At the same time, patients with GDF-15 levels in the upper quartile had a higher risk of re-hospitalization for unstable angina and recurrent MI (RR 3,3 (95% CI 1,65-6,76), p<0,05) compared to patients with GDF-15 levels in the lower three quartiles.

In the PROVE IT TIMI-22 study, the elevated GDF-15 levels were also associated with a significantly higher risk of death or recurrent MI (5,5% vs 12,6%; RR 2,40 (95% CI 1,88-3,06); p<0,001) [5].

In our study, the high NT-pro-BNP level was associated with an increased risk of hospitalization due to unstable angina and recurrent MI, and also showed a significant association with the occurrence of recurrent MI (RR 6,2 (95% CI 1,21-32,08), p<0,05). The combined use of the two biomarkers in our study was more pronounced: patients whose GDF-15 and NT-pro-BNP levels were in the upper quartiles had a 4.8 times higher risk of re-hospitalization due to unstable angina and recurrent MI.

It is acknowledged that the GDF-15 level reflects integral information on cell oxygenation, inflammatory response, and cardiac dysfunction [6]. In addition, there is evidence that the GDF-15 and NT-pro-BNP levels are associated with the level of soluble angiotensin converting enzyme of type 2 and cause a high risk of mortality [7]. There are also facts confirming the direct effect of GDF-15 on the processes of inflammation, hypertrophy and fibrosis leading to heart failure [1].

Based on the above-described pathological processes in the heart and the results obtained by us, it can be assumed that the GDF-15 level determination can be included in the multi-marker risk stratification scales for patients with MI along with the NT-pro-BNP level. One of the previous studies showed the possibility of GDF-15 integration into risk scales for patients with MI, namely, the inclusion of GDF-15 in the GRACE scale increased the prognostic value of the scale in patients with NSTEMI [8].

Study limitations: small sample of patients, small number of repeated cardiovascular events, including the absence of fatal outcomes for 6 months of follow-up.

Conclusion

1. In patients with MI, the elevated GDF-15 level reflects a high risk of re-hospitalizations due to unstable angina and recurrent MI within 6 months.

2. The GDF-15 level has a prognostic value and can serve as an additional marker of the risk of repeated cardiovascular events.

Relationships and Activities: none.

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Lungs volume status and oxygen transport in patients with coronary artery disease with various types of comorbidity before and after coronary artery bypass grafting

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Aim. Assessment of lung volume status and oxygen transport system in patients with coronary artery disease (CAD) with different clinical types of comorbidity before and after coronary artery bypass grafting (CABG).

Material and methods. The observational controlled study included 66 patients with CAD with a median age of 67 years (95% confidence interval [59; 74]), admitted to the Far Eastern Federal University Hospital for elective CABG. Depending on the prevalence of clinical manifestations of comorbidities, CAD patients were ranked into 3 groups of comorbidity: cardiovascular, respiratory and metabolic. The first of them was represented by a combination of CAD and peripheral artery disease, the second — CAD and chronic obstructive pulmonary disease (COPD), the third — CAD and metabolic syndrome. All patients underwent isolated CABG under cardiopulmonary bypass (CPB). Volume and hemodynamic monitoring was carried out by transpulmonary thermodilution using the Pulsion PiCCO Plus (Germany) technology and the following indices: cardiac function index (CFI), extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI). Pulmonary blood volume and oxygen transport indices were determined: oxygen delivery (DO_2I) and consumption (VO_2I) indices, oxygen-utilization coefficient, and pulmonary shunt fraction (Qs/Qt). The study was carried out in three stages: before the onset of CABG, after its completion and one day after CABG.

Results. The analysis of volume and hemodynamic monitoring data demonstrated the heterogeneity of their changes during CABG and one day after with different comorbidity profile. A more noticeable inhibition of the circulatory component of oxygen transport was revealed in patients with COPD, which was illustrated by the lowest CFI (3,2-3,4 ml/min) in relation to other groups of patients. The imbalance of cardio-respiratory interactions in this cohort after withdrawal from cardiopulmonary bypass was manifested by lower DO_2I and VO_2I and a maximum increase in Qs/Qt, exceeding 1,6 times the comparison groups. The respiratory and metabolic comorbidity of CAD was characterized by a significantly larger volume of extravascular lung water due to the higher permeability of the pulmonary vessels, which was documented by EVLW values, which exceeded the upper reference limit by 1,8-2 times and an increase in PVPI. In patients with cardiovascular comorbidity, lung volume violation was less noticeable.

Conclusion. A comprehensive analysis of lung volume status and oxygen transport makes it possible to more accurately assess the functional status of patients with CAD, to increase the effectiveness of risk stratification and toprevent possible complications during CABG and in the early postoperative period.

Keywords: coronary artery disease, comorbidity, oxygen transport, lung volume status, coronary artery bypass grafting.

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Coronary artery disease (CAD) is one of the main reasons of population disablement and mortality in most countries of the world. In the Russian Federation, the death rate from CAD is 322 cases per 100 thousand population, including the death rate from myocardial infarction, which reaches >40 cases per 100 thousand population per year [1]. Coronary artery bypass grafting (CABG) is one of the leading surgical technologies for blood flow recovery. Currently, our country performs ~24,5 surgical interventions per 100 thousand population per year, which is significantly lower than in a number of European countries (Germany, Poland), where the level of this indicator is ~50 surgical interventions per 100 thousand population [2]. It is emphasized that the increase in cardiac surgical activity should be provided with an increase in the requirements on quality of patient selection. This is especially important in CAD combination with some variants of comorbid pathology, which limits the CABG effectiveness due to increasing likelihood of postoperative complications and mortality. The most "aggressive" factors of surgical stress during CABG include artificial circulation (AC), during which functional and metabolic disorders develop due to tissue hypoperfusion, oxygen debt formation, accumulation of under-oxidized metabolic products in cells [3]. CABG with the use of AC affects simultaneously all components of the oxygen transport system: respiratory, circulatory, hemic, tissue [4]. The most important role in formation of oxygen deficiency in the tissues during CABG and in the early postoperative period belongs to respiratory component, which is due to a violation of oxygenating lung function associated with the background of alveolar tissue reperfusion and increased intrapulmonary blood bypass. The pathophysiological consequences of reperfusion processes are associated with extravascular fluid accumulation in the lungs due to an increase in the microvascular leakage and an increasing probability of acute lung damage. The presence of certain types of comorbid pathology in patients with CAD significantly worsens the initial status of hemocirculation and may be an additional risk factor for reperfusion disorders [5]. With that in mind, the performance of CABG with AC in patients of this category should be provided with more thorough volumetric and hemodynamic monitoring. One of its technologies includes transpulmonary thermodilution (TPTD), which allows a comprehensive assessment of pre- and after loading on the myocardium, its contractility, degree of pulmonary blood volume and pulmonary vessel permeability [6]. TPTD in combination with modern technical capabilities of blood gases test allows to most accurately determine the current status of the system-forming factors of oxygen transport: its delivery (DO_2), consumption (VO_2), utilization coefficient (O_2ER), fraction of pulmonary blood bypass (Qs/Qt). The use of this approach allows to timely diagnose and correct disorders of pulmonary hemodynamics and oxygen supply of tissues, which is especially important for patients with high-risk CAD associated with severe comorbidity [7].

The study's goal was to assess the pulmonary blood volume and the oxygen transport system in patients with CAD with different clinical comorbidity variants before and after CABG.

Material and methods

The observational controlled clinical study enrolled 66 patients with CAD (40 men and 26 women) aged 53 to 77 years with a median (Me) of 67 years and a 95% confidence interval (CI) [59; 74] who were admitted to the clinic of the Far Eastern Federal University for planned CABG in 2018-2019. Patients with a complicated course of postoperative period requiring long-term inotropic support and prolonged artificial lung ventilation were excluded from the study. The study protocols were approved by the local ethics committee of the School of Biomedicine of the Far Eastern Federal University and complied with the Helsinki Declaration of the World Association "Ethical Conduct of Scientific Medical Studies with Human Participation". Informed consent for the study was obtained from each patient. All patients underwent isolated CABG under AC conditions. Depending on clinical manifestation predominance of coexisting diseases, patients with CAD were ranked into 3 comorbidity groups: cardiovascular, respiratory, and metabolic. The first group included 24 patients with a combination of CAD and multifocal atherosclerosis (chronic lower limb ischemia and atherosclerotic narrowing of the carotid arteries ⩾50%). The second group consisted of 20 patients with chronic obstructive pulmonary disease (COPD) of the II-III degree without recrudescence. The third group was represented by 22 patients with CAD with cardiometabolic syndrome (CMS). Among the latter studied group, the body mass index was in the range of 31-34 kg/m^2, which shown first degree obesity. Patients of all groups were diagnosed with NYHA-class II-III chronic heart failure and controlled grade II-III arterial hypertension with a very high risk [8]. All patients before CABG received standard therapy for CAD, chronic heart failure and arterial hypertension, including nitrates, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium antagonists, fixed combinations with diuretics. In the preoperative period, loop diuretics

Table 1

Clinical and anamnestic characteristics of patients with CAD with various comorbidity variants

Indicators	CAD+PAT (n=24)	CAD+COPD (n=20)	CAD+CMS (n=22)	P-value
Age, years	62,3 [57; 64]	68,5 [61; 70]	66,7 [58; 69]	P_{1-2}=0,04; P_{1-3}=0,062; P_{2-3}=0,34
Men, n (%)	18 (75)	14 (70)	13 (59)	P_{1-2}=0,058; P_{1-3}=0,03; P_{2-3}=0,086
BMI, kg/m^2	25,7 [24,8; 27,3]	26,8 [25,4; 30,2]	32,6 [31,4; 33,8]	P_{1-2}=0,21; P_{1-3}=0,024; P_{2-3}=0,032
Anamnesis of MI, n (%)	8 (33,3)	6 (30)	5 (22,7)	P_{1-2}=0,42; P_{1-3}=0,035; P_{2-3}=0,14
AF, n (%)	2 (8,3)	3 (15)	3 (13,6)	P_{1-2}=0,15; P_{1-3}=0,48; P_{2-3}=0,76
Type 2 DM, n (%)	3 (12,5)	5 (25)	19 (86,4)	P_{1-2}=0,24; P_{1-3}<0,0001; P_{2-3}<0,0001
LV EF, (%)	64,5 [58; 65]	56,3 [54; 62]	61,3 [55; 66]	P_{1-2}=0,028; P_{1-3}=0,37; P_{2-3}=0,036
LV EF 30-50%, n (%)	2 (8,3)	5 (25)	3 (13,6)	P_{1-2}=0,026; P_{1-3}=0,15; P_{2-3}=0,04
GFR, ml/min/1,73 m^2	72,4 [67; 82]	64,5 [62; 74]	68,4 [63; 78]	P_{1-2}=0,017; P_{1-3}=0,065; P_{2-3}=0,38
AC duration, min.	89,8 [82,6; 97,7]	88,5 [84,3; 91,8]	90,3 [76,4; 101,3]	P_{1-2}=0,56; P_{1-3}=0,74; P_{2-3}=0,62

Note: $P_{1, 2, 3}$ — significance of differences between the experimental groups.

Abbreviations: CAD — coronary artery disease, AC — artificial circulation, MI — myocardial infarction, BMI — body mass index, CMS — cardiometabolic syndrome, PAT — lesions of peripheral arterial territory, DM — diabetes mellitus, GFR — glomerular filtration rate, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease.

(torasemide) were used in 10 (15,2%) patients with clinical signs of congestion in the large circulatory system. The preoperative clinical and anamnestic status of patients with CAD of various groups and the duration of AC are presented in Table 1.

Blood volume and hemodynamic parameters were recorded by the TPTD method using the Dreger Delta XL monitor and the Pulse PiCCO Plus module (Germany) after catheterization of the brachial artery with the PV2015L20 equipment. The duration of its stay in the arterial bed was no more than 3 days. The arterial line flushing was carried out with boluses of 0,9% NaCl solution with 1 U/ml heparin. During calibration, three consecutive thermal dilutions were performed. The study of blood volume, cardiac pumping function and the calculation of oxygen transport parameters were performed at three stages of the study: immediately after tracheal intubation and beginning of artificial ventilation (phase I); after AC completion and heparin inactivation (phase II); 24 hours after surgery (phase III). Recorded the following parameters: extravascular lung water index (EVLW) and global end diastolic volume (GEDV), cardiac function index (CFI) = cardiac index (CI)/GEDV. The pulmonary blood volume (PBV) was calculated as the difference between GEDV and VSVL. The pulmonary vascular permeability index (PVPI) was determined by the EVLW/PBV ratio [9]. To calculate the oxygen transport parameters, the gas composition of arterial and mixed venous blood was determined using the Radiometer ABL — 800 gas analyzer (Denmark). The following parameters were recorded: PaO_2 — partial oxygen tension in arterial blood; SvO_2 — saturation of mixed venous blood taken from right atrium; $ctvO_2$ — oxygen concentration in mixed venous blood, $ctaO_2$ — oxygen concentration in arterial blood; DO_2I — oxygen delivery index $=(CI\times ctaO_2)$; VO_2I — oxygen consumption index $=CI\times(ctaO_2\text{-}ctvO_2)$. O_2ER was calculated by the ratio $(VO_2/DO_2)\times 100\%$, and pulmonary blood bypass (Qs/Qt) — by the formula:

$$Qs/Qt=(CcO_2\text{-}ctaO_2)/(CcO_2\text{-}ctvO_2),$$

where CcO_2 — oxygen concentration in alveolo-capillary blood [6]. The latter was found by the formula:

$$CcO_2=[(ctaO_2)\times(1{,}33)\times(SaO_2)]+[(RAO_2)\times(0{,}00314)],$$

where 1,33 — Hufner coefficient and 0,00314 — free dissolved oxygen in blood plasma.

Statistical data processing was performed using the software STATISTICA 10 (StatSoft, Inc., USA) and Excel (Microsoft Office 2018) in Windows 10 operating system. The hypothesis testing for normality of continuous character distribution in the analyzed groups was carried out using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. The data analysis was performed using descriptive statistics: Me and their 95% CI. Paired intergroup differences were assessed using the nonparametric Mann-Whitney U-test. The differences were considered statistically significant at $p<0{,}05$.

Results

The study results showed that before the surgical intervention, all patients with CAD, regardless of the comorbidity clinical form, had systolic-diastolic myocardial dysfunction, as evidenced by a high level of GEDV (960-1120 ml) and low value of CFI (3,2-3,8 ml). After the departure from the AC and 24 hours after the surgical intervention in patients of all groups, GEDV decreased, but did not reach the upper

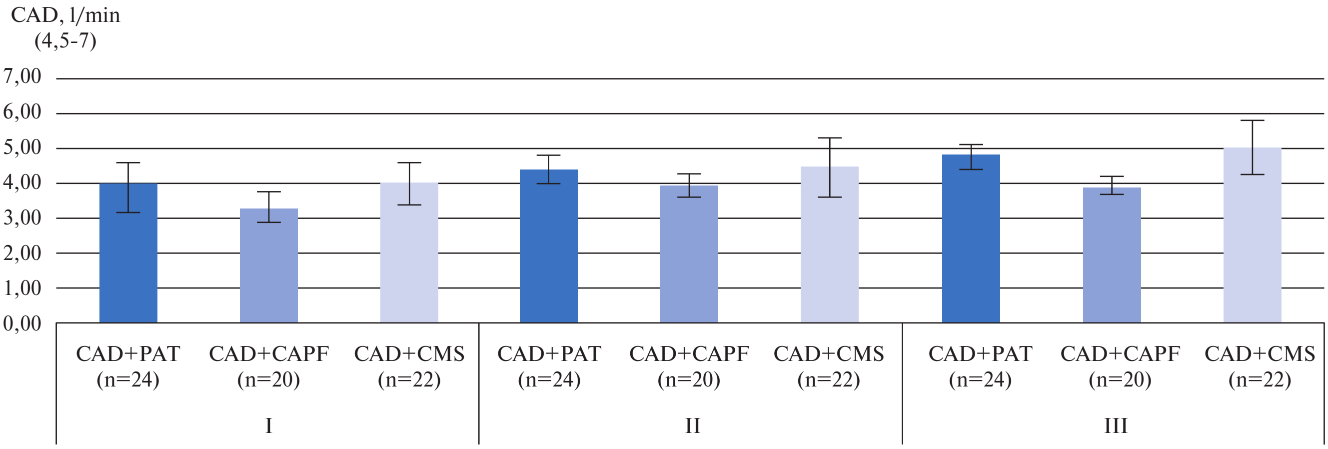

Figure 1. Dynamics of CFI changes at the research stages.
Note: the standard range of this indicator is shown in brackets.
Abbreviations: CAD — coronary artery disease, CFI — cardiac function index, CMS — cardiometabolic syndrome, PAT — lesion of peripheral arterial territory, COPD — chronic obstructive pulmonary disease.

limit of the reference range (800 ml). The dynamics of changes in CFI indicated an improvement in pumping ability of the heart within a day after CABG in patients with CAD with cardiovascular and metabolic comorbidity. In its respiratory variant, this indicator had a minimum value (3,4 l/min, with a norm of 4,5-7 l/min), which testified a more pronounced violation of cardiodynamics in this category of patients (Figure 1). In patients of all groups at the first stage of the study, the level of EVLW exceeded the standard values, but was highest among patients with respiratory and metabolic forms of comorbidity (Table 2). After AC completion, this indicator did not change significantly, and it significantly decreased after CABG, but did not reach the reference values. In patients with a combination of CAD and CMS, the EVLW level at the III stage of the study was higher than in those examined with other comorbidity variants, which may be due to the influence of excessive intraabdominal pressure on pulmonary hemodynamics [10]. PBV before surgery in the combination of CAD and COPD was significantly lower than in patients of other groups. After the departure from AC, all the patients showed a tendency to decrease its level, which persisted in the early postoperative period. Before surgical treatment, the PVPI level in all patients did not exceed the threshold value, but with a combination of CAD and COPD, it was higher than in patients of other groups. At the second stage of the study, the PVPI level in patients with CAD with respiratory and metabolic comorbidity significantly increased, which could indicate an increasing risk of acute lung injury. After 24 hours after CABG, a positive dynamics of changes in this parameter in all groups of subjects was noted.

In a comprehensive assessment of oxygen transport parameters, it was found that before surgical treatment, all patients had an increase in fraction of the pulmonary bypass, especially noticeable in the combination of CAD and COPD. At the second stage of the study, Qs/Qt in patients with respiratory comorbidity reached the maximum values and exceeded the upper limit of the reference level by 2,6 times. The venous admixture index in other comorbidity variants did not differ from each other and was 1,5-1,6 times higher than the standard values. After 24 hours after myocardial revascularization, the pulmonary bypass fraction was normalized in all the study groups. The dynamic pattern in the PaO_2 index indicated that in patients with CAD with respiratory comorbidity at all stages of follow-up, its level was lower than in the experimental groups. These differences may be due to the initial limit of ventilation and blood oxygenation in COPD as a result of remodeling of conductive and respiratory parts of the respiratory system, which reduces the lung volume and the pulmonary ventilation effectiveness. The SvO_2 index during the study was within the limits of physiological norm (70-80%) and did not depend on clinical variant of comorbidity. This can be explained by the fact that the SvO_2 level in hypothermia significantly increases, decreases by the end of warming and almost normalizes after AC switch off, which was confirmed by the results of our study. When assessing the oxygen delivery to the tissues over time, it was noted that the DO_2 level before CABG in patients with respiratory comorbidity was lower than in other variants. In this group, the minimum values of the DO_2 index were fixed after the departure from AC, and a day after CABG, this tendency continued.

Table 2

Indicators of pulmonary blood volume and oxygen transport in patients with CAD with various comorbidity variants (Me, 95% CI)

Indicators and their standard values	Stages of research									P-value
	I			II			III			
	CAD PAT (n=24)	CAD COPD (n=20)	CAD CMS (n=22)	CAD PAT (n=24)	CAD COPD (n=20)	CAD CMS (n=22)	CAD PAT (n=24)	CAD COPD (n=20)	CAD CMS (n=22)	
PBV, ml (170-200)	$437,94^{1}$ [395,75; 480,14]	$395,33^{2}$ [369,74; 420,92]	$487,1^{3}$ [398,93; 574,62]	$392,47^{4}$ [359,34; 425,6]	356^{5} [307,1; 444,9]	$370,8^{6}$ [315,11; 426,67]	$396,82^{7}$ [350,1; 443,7]	$350,83^{8}$ [313,1; 389,1]	$361,78^{9}$ [293,65; 429,91]	P_{1-4}=0,002; P_{1-7}=0,035; P_{2-5}=0,84; P_{2-8}=0,13; P_{3-6}=0,015; P_{3-9}=0,32
EVLW, ml/kg (3-7)	10^{1} [8,4; 11,6]	$13,6^{2}$ [12,2; 15,1]	$14,2^{3}$ [13,1; 15,4]	$11,2^{4}$ [9,1; 13,25]	$14,3^{5}$ [12,1; 17,1]	$13,07^{6}$ [11,8; 14,3]	$7,88^{7}$ [7,16; 8,6]	10^{8} [9,1; 11]	12^{9} [10,2; 13,8]	P_{1-4}=0,15; P_{1-7}=0,068; P_{2-5}=0,08; P_{2-8}=0,044; P_{3-6}=0,37; P_{3-9}=0,027
PVPI, c.u. (1-3)	$1,57^{1}$ [1,32; 1,82]	$2,22^{2}$ [1,94; 2,5]	$1,71^{3}$ [1,35; 2,1]	$1,66^{4}$ [1,45; 1,87]	$2,49^{5}$ [2,22; 2,7]	$2,52^{6}$ [2,32; 2,72]	$1,64^{7}$ [1,4; 1,8]	$1,8^{8}$ [1,7; 2]	$1,84^{9}$ [1,7; 2,0]	P_{1-4}=0,08; P_{1-7}=0,036; P_{2-5}=0,03; P_{2-8}=0,018; P_{3-6}=0,032; P_{3-9}=0,13
Qs/Qt, (4-10%)	14^{1} [10; 18]	16^{2} [9; 25]	13^{3} [8; 18]	15^{4} [19; 22]	26^{5} [15; 37]	16^{6} [10; 23]	7^{7} [3; 10]	8^{8} [5; 12]	6^{9} [3; 9]	P_{1-4}=0,08; P_{1-7}=0,032; P_{2-5}=0,018; P_{2-8}=0,015; P_{3-6}=0,034; P_{3-9}=0,0016
DO_2I, (420-720 ml/min/m^2)	$551,3^{1}$ [480,68; 622,08]	$511,47^{2}$ [463,46; 558,23]	$629,21^{3}$ [508,15; 750,27]	$450,1^{4}$ [408,43; 490,97]	$416,2^{5}$ [381,12; 450,21]	$456,62^{6}$ [380,4; 532,82]	$519,22^{7}$ [471,9; 566,5]	$449,58^{8}$ [329,93; 569,24]	$548,2^{9}$ [451,11; 638,37]	P_{1-4}=0,004; P_{1-7}=0,51; P_{2-5}=0,015; P_{2-8}=0,083; P_{3-6}=0,034; P_{3-9}=0,042
VO_2I, (200-250 ml/min/m^2)	$177,37^{1}$ [135,3; 219,4]	$149,12^{2}$ [38,1; 260,13]	$192,45^{3}$ [118,1; 266,8]	$107,07^{4}$ [86,5; 127,6]	$92,37^{5}$ [19,56; 65,19]	$141,45^{6}$ [117,2; 165,7]	$131,8^{7}$ [103,85; 159,83]	$120,33^{8}$ [66,25; 174,4]	$171,52^{9}$ [107,28; 235,76]	P_{1-4}=0,015; P_{1-7}=0,14; P_{2-5}=0,026; P_{2-8}=0,91; P_{3-6}=0,11; P_{3-9}=0,43
O_2ER, (20-30%)	$0,32^{1}$ [0,26; 0,38]	$0,31^{2}$ [0,19; 0,43]	$0,3^{3}$ [0,23; 0,37]	$0,24^{4}$ [0,2; 0,28]	$0,22^{5}$ [0,19; 0,23]	$0,32^{6}$ [0,26; 0,38]	$0,25^{7}$ [0,21; 0,29]	$0,22^{8}$ [0,19; 0,25]	$0,31^{9}$ [0,22; 0,39]	P_{1-4}=0,053; P_{1-7}=0,06; P_{2-5}=0,002; P_{2-8}=0,034; P_{3-6}=0,3; P_{3-9}=0,47

Note: P_{1-9} — reliability of differences in indicators between stages of the study. The standard values are shown in brackets.

Abbreviations: PAT — lesions of peripheral arterial territories, EVLW — index of extravascular water of the lungs, PBV — pulmonary blood volume, PVPI — pulmonary vascular permeability index, Qs/Qt — fraction of veno-arterial blood bypass, DO_2 — index of oxygen delivery, VO_2 — oxygen consumption index; O_2ER — oxygen utilization coefficient.

The dynamic pattern analysis on the VO_2I oxygen delivery showed that its level did not reach the lower limit of physiological norm in the entire cohort of subjects at any point of measurement. The most significant decrease in this indicator (by 2.2 times) was recorded in patients with cardio-respiratory comorbidity after departure from AC and a day after CABG. The O_2ER oxygen utilization index due to the optimal ratio of calculated components (VO_2 and DO_2) at all stages of observation did not go beyond the standard values (20-30%). When departure from AC and 24 hours after it, the level of this indicator in patients with CAD with CMS was significantly higher than in other comorbidity variants, which can be explained by a higher need for energy supply and the intensity of intracellular metabolism in overweight individuals.

Discussion

The main purpose of monitoring physiological functions in cardiac surgery is to obtain timely data on the current status of regional and systemic blood circulation, tissue oxygen demand and its actual delivery. It is shown, for example, that in CABG, the SvO_2 value at the level of 60% or less increases the risk of intrahospital mortality by 5,4% and is more often accompanied by intra- and postoperative complications [11]. The need for careful monitoring of the hemocirculation parameters and other factors of oxygen transport increases significantly with the CAD comorbidity, which initially reduces the functional reserves of these systems. In our study, the use of TPTD technology with the calculation of individual indicators of hemodynamics, lungs volume status and oxygen transport allowed to verify the phenotypic features of blood circulation and oxygen supply of tissues in different variants of CAD comorbidity during CABG and in the immediate postoperative period.

The study's results showed that the preoperative clinical and anamnestic status of patients with CAD with certain forms of comorbidity had certain differences (Table 1). Thus, in its respiratory variant, the ejection fraction level was significantly lower than in the comparison groups, which indicated a more noticeable limit of systolic function in this category of patients. A more pronounced violation of the heart contractile function in the combination of CAD and COPD was also indicated by the indicators of CFI and GEDV, which are referred to the "gold standards" for assessing its contractile potential, which allow to detail the circulatory-volume status of patients [12]. The prevalence of right ventricular failure in patients with COPD was indicated by the PBV level, which was significantly lower than in other comorbidity variants. The obtained results demonstrate a more expressed limit of the circulatory link functions in the oxygen transport system in this category of patients.

The EVLW and PVPI indicator analysis allowed to differentially assess the lungs volume status, depending on the clinical forms of comorbid pathology. Thus, the maximum values of EVLW and PVPI were recorded among patients with CAD with respiratory and metabolic comorbidity. An increase in blood volume level indicators in patients with COPD is associated with increased permeability of the capillary bed as a result of pathological modifications of the lung tissue due to emphysematous-pneumosclerosis processes, chronic systemic inflammation, pulmonary hypertension and disorders of the mechanisms of intercellular space drainage [12]. The main pathogenetic factors of extravascular fluid accumulation in the lungs by combination of CAD and CMS may include excessive intra-abdominal pressure, a decrease in functional activity of the diaphragm with a limit of lung volumes and microatelectasis of basal lung segments, an imbalance in synthesis of adipokines with a predominance of their vasoconstrictor pool [13]. According to the literature data, the main reason for the ventilation violation in CABG under AC conditions is an increase in the pulmonary bypass fraction [9]. In the present study, in all patients with CAD before surgical treatment and after departure from AC, the venoarterial bypass fraction was higher than the standard values and reached the maximum level in respiratory comorbidity, which was associated with violation of ventilation-perfusion relations as a result of subclinical pulmonary edema and was confirmed by the EVLW indicator. The increase in venous impurity in patients with COPD is associated with an expressed endothelial dysfunction of the pulmonary vessels, which leads to violation of regulation of their tone and prevents the effective implementation of the Euler-Liljestrand reflex, which leads to the preservation of blood flow in unventilated alveoli [5]. After departure from AC, the increase in venous admixture may also be due to peripheral bypass in the microcirculatory bed of the large circulatory circle with limited oxygen extraction, which in our study was confirmed by a low level of O_2ER. 24 h after surgery veno-arterial bypass fraction in patients of all groups were significantly reduced due to involvement in the process of respiration unventilated alveoli and limit the amount of extravascular fluid in the lungs, which illustrated by the EVLW dynamics. Despite the presence of chronic heart failure in all patients, the O_2 oxygen delivery index before the start of CABG did not exceed the reference values, and the level of its consumption was moderately reduced. This may be due to the pharmacological effects of combinations of opiate drugs, halogenated inhaled anesthetics and neuromuscular blocking agents that reduce the need for energy supply. At the second stage of the study, patients with respiratory comorbidity showed the most noticeable decrease in oxygen consumption, which persisted 24 hours after CABG, which is associated with a higher risk of hypoxic tissue damage and multiple organ failure.

The limitations of this study include a relatively small number of observations, which requires the analyzed sample expansion, taking into account the features of initial clinical and functional status of patients, intraoperative factors and the use of multivariate analysis methods for data processing.

Conclusion

The study's results indicate the heterogeneity of changes in the circulatory-volume status and oxygen transport in patients with CAD with various comorbidity variants. A more noticeable inhibition of the circulatory component of oxygen transport occurs in patients with COPD due to a pronounced decrease in contractile function of the myocardium. The imbalance of cardiorespiratory interactions in this cohort of patients was illustrated by lower parameters of oxygen delivery and consumption compared to patients without pulmonary pathology. Respiratory comorbidity of CAD was also manifested by the maximum increase in intrapulmonary blood bypass, which worsens the oxygen supply of tissues. Violations of the lungs volume status as a result of increased permeability of the pulmonary capillaries and accumulation of extravascular fluid were more often recorded in respiratory and metabolic comorbidity. A comprehensive analysis of the lungs volume status and oxygen transport in comparison with the "nosological" portrait of comorbid pathology of patients with CAD makes it possible to increase the effectiveness of risk stratification and prevention of possible complications during CABG and in the early postoperative period.

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