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Influence of 5-hydroxymethyluracil on the dynamics of angiogenic growth factors in the perioperative period of surgical myocardial revascularization: results of a randomized trial

Oleinik B. A.[1], Plechev V. V.[1], Evdakov V. A.[2], Izhbuldin R. I.[1], Zagidullin N. Sh.[1]

Aim. To evaluate the effect of 5-hydroxymethyluracil on the dynamics of angiogenic growth factors in the perioperative period of surgical myocardial revascularization.

Material and methods. This prospective, randomized, single-center study included two following groups: experimental group — 25 patients in the perioperative period of coronary artery bypass grafting (5 days before and 14 days after surgery) receiving 5-hydroxymethyluracil (at a dose of 500 mg 3 times a day) in addition to standard therapy; control group — 25 patients receiving standard therapy. The groups were comparable in terms of sex, age, main clinical and functional characteristics and features of surgical intervention. In patients, quantitative indicators of angiogenic growth factors in peripheral blood taken 5 days before and 14 days after surgery were studied by enzyme immunoassay: human vascular endothelial growth factor A (VEGF-A), human hepatocyte growth factor (hHGF), insulin-like factor growth 1 (IGF-1) and basic fibroblast growth factor (bFGF).

Results. In the experimental group of patients, while taking 5-hydroxymethyluracil, there was a significant increase in the peripheral blood concentration of following growth factors compared with the control group: VEGF-A by 26,90% (p=0,0246), IGF-1 by 44,89% (p=0,0011), bFGF by 60,0% (p=0,0006). The hHGF concentration also turned out to be higher by 19,90%, but did not reach the level of statistical significance (p=0,2836).

Conclusion. The use of 5-hydroxymethyluracil, a representative of pyrimidines, in the perioperative period of surgical myocardial revascularization leads to a significant increase in peripheral blood of such angiogenic growth factors as VEGF-A, IGF-1, and bFGF.

Keywords: coronary artery disease, coronary artery bypass grafting, angiogenesis, growth factors, pyrimidines.

Relationships and Activities: none.

[1]Bashkir State Medical University, Ufa; [2]Central Research Institute for Organization and Informatics, Ufa, Russia.

Oleinik B. A.* ORCID: 0000-0002-4144-3946, Plechev V. V. ORCID: 0000-0002-6716-4048, Evdakov V. A. ORCID: 0000-0002-5836-4427, Izhbuldin R. I. ORCID: 0000-0001-6216-2935, Zagidullin N. Sh. ORCID: 0000-0003-2386-6707.

*Corresponding author: bogdan-ufa@mail.ru

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Key messages

- Coronary artery bypass grafting (CABG) is the treatment of choice for multivessel coronary artery disease.
- The clinical effect of the surgery is achieved not only by bypass, but also by collateral circulation, and by the release of factors with angiogenic properties.
- The study of pharmacological substances capable of stimulating angiogenesis process in CABG is of significant research and practical interest in terms of improving the surgery results.
- Pyrimidine representative 5-hydroxymethyluracil in the perioperative period of CABG leads to a significant increase in peripheral blood of angiogenic growth factors: vascular endothelial growth factor A, insulin-like growth factor 1, and basic fibroblast growth factor.

Coronary artery bypass grafting (CABG) is a method of surgical myocardial revascularization that can significantly increase the survival of patients with multivessel coronary artery disease (CAD) [1]. According to modern studies, this result is achieved not only due to improved myocardial blood supply due to bypass creation, but also due to collateral circulation, which can provide blood flow in the event of plaque rupture and bypass artery thrombosis [2]. The biological basis for collateral circulation is arteriogenesis and angiogenesis, and the main trigger for the growth and development of new blood vessels is myocardial ischemia. Thus, arteriogenesis and angiogenesis can be considered fundamental for survival in CAD [3, 4]. However, a number of studies have shown that myocardial revascularization with CABG can cause an independent angiogenic response [5]. Based on this, Gutterman DD, et al. [6] recently put forward a hypothesis, according to which CABG improves the myocardial ischemic environment, establishing "atherostasis" via endogenous release of factors with vasodilatory, anti-inflammatory, antithrombotic, and angiogenic abilities.

In this regard, of considerable scientific and practical interest is the revelation of mechanisms affecting the microcirculation development during surgical myocardial revascularization operations, as well as the search for pharmacological substances that can stimulate the process of angiogenesis and arteriogenesis during these operations [7].

The study aim was to evaluate the effect of 5-hydroxymethyluracil (5-hmU) on angiogenic growth factors in the perioperative period of surgical myocardial revascularization.

Material and mehods

This prospective, randomized, single-center study included 50 patients who underwent surgical myocardial revascularization at the Republican Cardiology Center (Ufa). Inclusion criteria were age 40 years and older, elective CABG, CCS class 3-4 exertional angina. The main exclusion criteria were severe valvular dysfunction in the presence of CAD, left ventricular aneurysm, acute period of myocardial infarction (MI), severe left ventricular systolic dysfunction (left ventricular ejection fraction <30%), severe carotid atherosclerosis (>70% stenosis).

Standard treatment included antiplatelet (acetylsalicylic acid, clopidogrel), β-blocker (metoprolol, bisoprolol, carvedilol), angiotensin-converting enzyme inhibitor (enalapril, lisinopril, perindopril), statin (simvastatin, atorvastatin, rosuvastatin) therapy and, if necessary, short and long-acting nitrates (isosorbide dinitrate, isosorbide mononitrate). Patients with concomitant diabetes received adequate glucose-lowering therapy.

Randomization was carried out using the envelope method. Patients of the main group (n=25) received 5-hmU at a dose of 500 mg 3 times a day in addition to standard therapy 5 days before and within 14 days after surgery. The control group also consisted of 25 patients who received standard therapy. The study design is presented in Figure 1. Both investigators and patients were informed about the prescribed treatment.

The groups were comparable in terms of sex, age, disease duration, functional class of angina pectoris and heart failure, the number of affected vessels, clinical and functional parameters and features of surgical intervention (posteriori comparison using the Mann-Whitney test and Fisher's angular transform did not reveal significant differences (p>0,05)) (Table 1).

In all patients initially (before prescribing the drug) and 2 weeks after CABG, the quantitative assessment of the following angiogenesis growth factors was performed by enzyme immunoassay:

1. Human vascular endothelial growth factor A (VEGF-A) — Human VEGF-A BioLISA kit, Bender MedSystems, Austria.

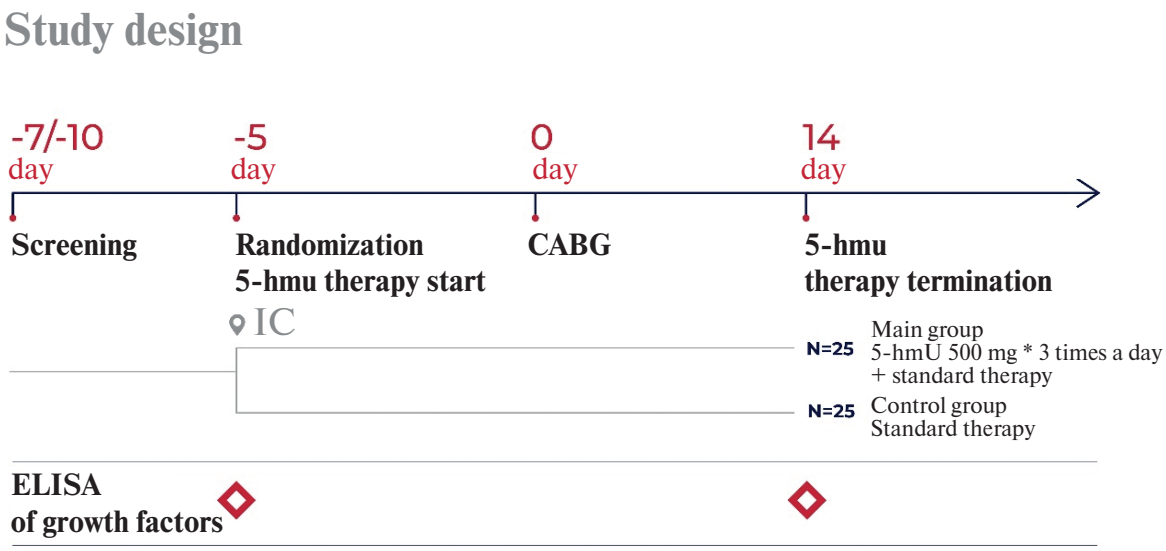

Figure 1. Study design.
Abbreviations: CABG — coronary artery bypass grafting, IC — informed consent, ELISA — enzyme immunoassay, 5-hmU — 5-hydroxymethyluracil.

2. Human hepatocyte growth factor (hHGF) — Human HGF test system, Biosource, Belgium.

3. Insulin-like growth factor 1 (IGF-1) — OCTEIA IGF-1 kit, Immunodiagnostic Systems Holdings Ltd, UK.

4. Human fibroblast growth factor-basic (bFGF) — Human FGF basic Quantikine ELISA kit, R&D Systems, Inc, USA.

The choice of analytes for the study was dictated by experimental studies conducted earlier by our author group on 5-hmU effect on the expression of growth factors in models of chronic and acute myocardial ischemia in rabbits, during which these factors was studied by real-time quantitative reverse transcription polymerase chain reaction [8].

The venous blood sampling with a volume of 10-12 ml in patients was carried out 5 days before CABG and 14 days after in the morning on an empty stomach using a Vacutainer system filled with a stabilizing agent. There were no complications associated with the procedure. The resulting blood samples were incubated for 5-10 min at room temperature, then centrifuged for 20 min at 1500 g and t +40° C. The resulting plasma was placed in 1,5 ml Eppendorf microtubes, after which the samples were frozen and stored in a medical freezer with -18° C.

When choosing control points for assessing angiogenesis biomarkers, we took into account the time of the maximum drug effect on nucleic acid metabolism and protein synthesis, which is in the range between 3 and 7 days [9] and corresponds to the start of administration — 5 days before surgery. The duration of admission (14 days after CABG) is due to the fact that the maturation of primitive blood vessels together with the walls and mesh structures occurs within 2 weeks after ischemic exposure; therefore, this time period is a promising target for therapeutic intervention [10].

Study endpoints. The primary endpoint was the change in the peripheral blood concentration of analyzed growth factors in patients 2 weeks after operation.

5-hmU is a derivative of pyrimidines, is a "minor" base, occurs in significant amounts in transfer RNA and DNA, and has a pronounced immunostimulating effect. In 2002, the use of 5-hmU under the trade name "Immureg" (FSP 42-0415-2777-02) was allowed. According to drug instructions for use, the registered indications for use are infectious and inflammatory diseases (as part of antibiotic therapy): respiratory diseases (pneumonia, chronic obstructive pulmonary disease, lung abscess), chronic pyelonephritis, as well as the prevention of infectious complications during chemotherapy for chronic lymphocytic leukemia.

Prior to inclusion in the study, written informed consent was obtained from each patient. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the local ethics committee at the Bashkir State Medical University.

Statistical processing was carried out using the Statistica 8.0 program. The sample size calculation was based on an expected frequency of primary endpoint (p) of 10%, with a reliability of inference of 95%, t=1,96, and a maximum error of Δ=5%.

Table 1

Demographic, clinical and functional characteristics of the study groups, Me (25%-75%)

Parameter	Main group (n=25)	Control group (n=25)	Statistical significance of differences, p
Main clinical and demographic characteristics			
Mean age, years	50,37 (42,93-66,41)	55,51 (46,84-63,88)	0,63
Male sex, %	92	96	0,60
CCS functional class of stable angina	3,00 (2,51-3,74)	3,34 (2,63-3,72)	0,88
NYHA functional class of HF	2,00 (1,54-2,40)	2,03 (1,66-2,22)	0,41
Disease duration, months	65,36 (55,00-72,08)	59,79 (48,84-69,82)	0,67
Comorbidities			
Old myocardial infarction, %	72	68	0,30
Hypertension, %	60	64	0,29
Diabetes, %	16	20	0,36
Characteristics of coronary system involvement			
Average number of affected arteries	2,62 (2,04-3,00)	2,55 (2,00-2,90)	0,44
Anterior interventricular artery involvement, %	100	100	1,0
Circumflex artery involvement, %	80	84	0,37
Right coronary artery involvement, %	84	80	0,37
Features of surgical intervention			
On-pump operation, %	64	64	1,0
Average duration of operation, min	235,86 (205,65-270,24)	252,00 (210,00-291,24)	0,68
Mean cardiopulmonary bypass time, min	102,18 (81,65-136,00)	111,40 (76,54-128,96)	0,89
Mean aortic cross-clamp time, min	60,76 (52,62-70,44)	55,48 (49,53-68,82)	0,39

Abbreviations: CCS — Canadian Cardiovascular Society, NYHA — New York Heart Association.

Taking into account that, according to Kolmogorov-Smirnov and Shapiro-Wilk test, the distribution was not normal. The nonparametric Mann-Whitney test and Fisher's transformation were used to identify statistical differences between independent samples. Data were presented as median Me and interquartile range (25-75%). Differences were considered significant at $p \leqslant 0,05$.

Results

Statistical analysis showed that the initial values of studied peripheral blood growth factors in the analyzed groups did not have significant differences.

At the next stage, we assessed studied growth factors with (main group) and without (control group) the use of 5-hmU.

VEGF-A in the control group of patients showed a significant increase as follows: the median increased from 204,50 (117,50-297,50) to 420,63 (338,54-563,58) pg/ml — by 105,68% ($p<0,0001$) (Figure 2).

Changes of VEGF-A in the main group of patients after surgical myocardial revascularization with simultaneous administration of 5-hmU was more pronounced as follows: the increase was 184,29% (from 187,50 (101,00-338,54) to 533,05 (435,26-612,03) pg/ml, $p<0,0001$) (Figure 2). At the same time, in the main group, the final level of VEGF-A was significantly higher than in the control group by 26,90% ($p=0,0246$). The result obtained, in our opinion, is associated with a cumulative beneficial effect on the angiogenesis processes of coronary bypass surgery and the use of 5-hmU.

The HGF concentration in the control group was characterized by a downward trend (from 1413,00 (817,50-1912,00) pg/ml in the preoperative period to 1402,00 (937,50-2174,50) pg/ml 2 weeks after CABG ($p=0,4153$)) (Figure 3).

HGF changes in patients of the main group, on the contrary, was positive, but did not reach statistical significance. There was an increase in the median by 6,12% from 1584,00 (1062,00-1965,00) pg/ml in the preoperative period to 1681,00 (1244,50-2179,00) pg/ml ($p=0,2481$) 2 weeks after CABG. At the same time, the differences between the HGF concentration in the control and main groups 14 days after surgical myocardial revascularization also turned out to be insignificant ($p=0,2836$), which indicates a limited beneficial effect of 5-hmU on angiogenesis processes.

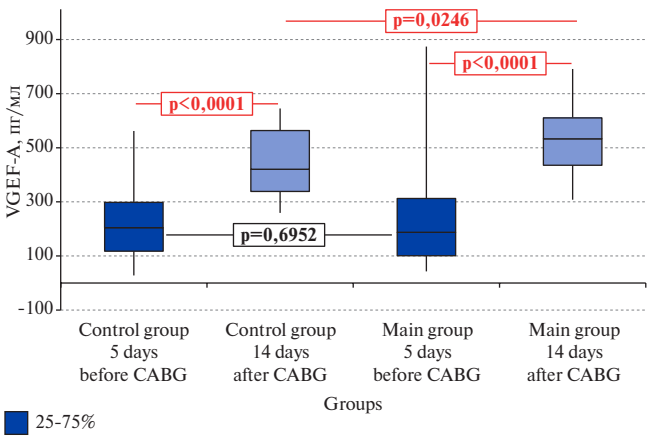

Figure 2. Dynamics of vascular endothelial growth factor A (VEGF-A) blood concentration in patients of the control (n=25) and main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney test).
Abbreviations: CABG — coronary artery bypass grafting, VEGF-A — human vasculoendothelial growth factor A.

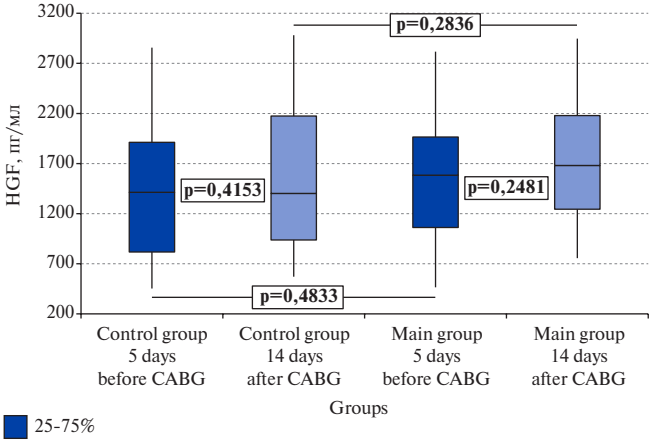

Figure 3. Dynamics of hHGF blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney criterion).
Abbreviations: CABG — coronary artery bypass grafting, hHGF — human hepatocyte growth factor.

Content of IGF-1, in contrast to the two previous analyzed factors, significantly decreased in the control group from 117,50 (88,00-193,00) pg/ml in the preoperative period up to 98,00 (75,00-143,00) pg ml 2 weeks after surgery (by 19,89%, p=0,0177) (Figure 4).

In this regard, interesting data were obtained in patients of the main group, who, instead of decreasing, showed a trend towards an increase in IGF-1 level with 5-hmU use as follows: median increased from 128,50 (75,00-198,00) pg/ml in the preoperative period up to 142,00 (93,00-173,00) pg/ml for 14 days, after CABG, or by 10,5% (p=0,7649). And, most importantly, statistical significance of differences in IGF-1 postoperative levels in the main and control groups of 44,89% (p=0,0011), indicates a clear advantage of 5-hmU in maintaining normoglycemia in the perioperative period.

The bFGF is one of the main regulators of angiogenesis processes. In our studies, it demonstrates a statistically significant increase during CABG in the control group from 3,40 (2,15-6,95) pg/ml to 5,70 (4,65-7,65) pg/ml (p=0,0336), or by 67,64% (Figure 5).

The bFGF level in the main group (against the background of 5-hmU use) showed even more impressive changes than in the control group — from 4,70 (2,70-6,45) pg/ml in the preoperative period to 8,35 (5,30-10,70) pg/ml 14 days after CABG, or by 77,65% (p=0,0006). When comparing the final bFGF levels (14 days after CABG) in the control and main groups, its values were significantly higher in the main group (by 60%, p=0,0006).

Discussion

In connection with the theory of surgical collateralization during CABG formulated in recent years, the study of pyrimidine derivatives as proangiogenic agents is of scientific and clinical interest. This class of drugs has long been used in wide medical practice in various fields due to the wide variety of clinical effects. The effect of pyrimidine derivatives on angiogenesis is also quite well studied in [11, 12], and its effect on angiogenesis is comparable in efficiency with the introduction of VEGF [13].

For 5-hmU, as for all representatives of pyrimidines, there are two proven mechanisms of angiogenic action — antioxidant activity [14] and the ability to accumulate adenosine [15].

The effect of reactive oxygen species on postischemic angiogenesis is associated with local suppression of angiogenic growth factors in the ischemic area. It has been reliably established that reactive oxygen species can inhibit NO directly and through inhibition of endothelial nitric oxide synthase, blocking its effect on the vascular system [16]. Thus, suppression of myocardial oxidative stress by the use of pharmacological substances with antioxidant activity naturally leads to angiogenesis stimulation.

An increase in adenosine content (by disrupting its reuptake) due to the use of pyrimidine nucleotides, as well as the ability to increase the concentration of cyclic adenosine monophosphate, is associated with inhibition of phosphodiesterase enzyme [15]. According to modern data, adenosine activates 4 different subtypes (A1, A2A, A2B, and A3) of receptors, stimulates capillary development in the

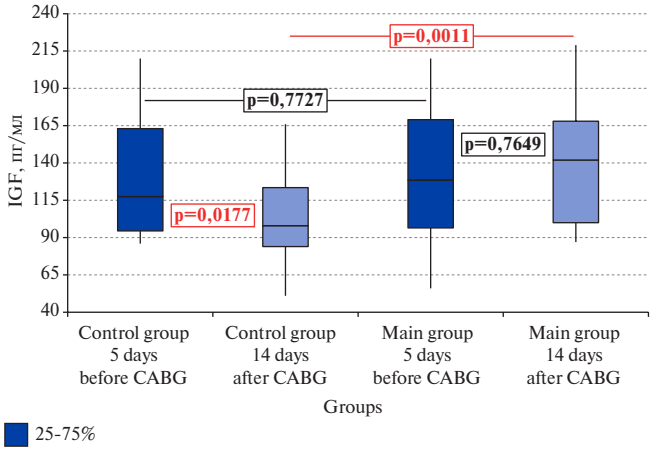

Figure 4. Dynamics of IGF-1 blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney test).
Abbreviations: CABG — coronary artery bypass grafting, hHGF — human hepatocyte growth factor.

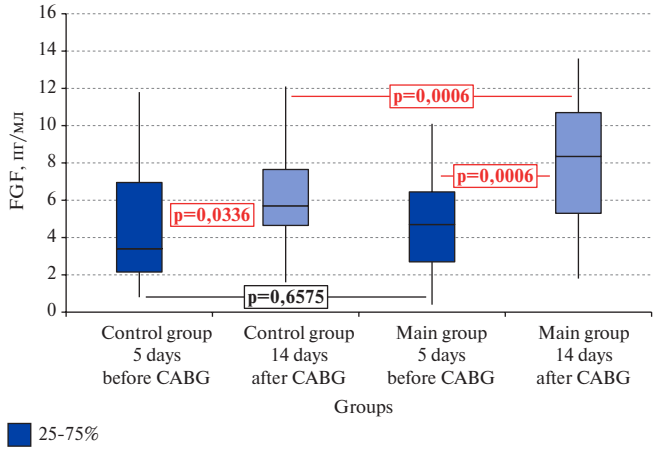

Figure 5. Dynamics of bFGF blood concentration in patients in the Control (n=25) and Main (n=25) groups 5 days before and 14 days after CABG (Me (25%; 75%), p — statistical significance of differences, Mann-Whitney criterion).
Abbreviations: CABG — coronary artery bypass grafting, bFGF — basic human fibroblast growth factor.

ischemic heart, and induces the production of pro-angiogenic factors [17, 18].

The most pronounced concentration changes in the peripheral blood among the growth factors analyzed by us with the 5-hmU use was recorded in VEGF-A, as a key factor in angiogenesis in the myocardial hypoxia [10]. A number of clinical studies have shown that an elevated VEGF-A level promotes the proliferation of vascular endothelial cells, improves vascular permeability, and restores endothelial integrity and vascular function, which is a compensatory mechanism in the development of myocardial ischemia [19, 20]. An analysis of the databases of scientific sources showed that the drug impact on VEGF-A is a promising target for the treatment of cardiovascular diseases. For example, hydroxysafflor yellow improved endothelial progenitor cell function and increased VEGF-A concentration in mice with MI through the HO-1/VEGF-A/SDF-1α signaling cascade, which significantly restored ischemia-induced cardiac dysfunction and improved animal survival [21, 22]. *Pueraria* and *Salvia miltiorrhiza* extracts stimulated angiogenesis by activating the VEGF/VEGFR2 pathway, thereby preserving the myocardium of MI rats [23], and salidroside increased HIF-1α expression and then VEGF levels to inhibit necrosis and apoptosis of cardiomyocytes induced by hypoxia [24].

At the same time, the pronounced changes of pre- and postoperative bFGF values against the background of 5-hmU, which increase was similar to VEGF-A, is noteworthy, which is a natural consequence of the inextricable relationship between FGF-2 and VEGF-A in angiogenesis [25]. The decrease in peripheral blood IGF-1 concentration in control group patients recorded in our study is associated with the activation of catabolic processes after surgical myocardial revascularization, and the depth of this decrease reflects the severity of the surgical injury and, consequently, the catabolism degree after surgery [26]. And, on the contrary, the stabilization of this growth factor in the main group of patients against the background of 5-hmU use is extremely important for maintaining glucose homeostasis in the perioperative period of surgical myocardial revascularization [27].

Previously, the effectiveness of 5-hmU as an angiogenesis stimulator, as well as possible mechanisms of action, were experimentally studied by V. V. Plechev, B. A. Oleinik and R. Yu. Risberg in 2012 on a model of acute MI in rabbits. Thus, in an experiment on 112 male chinchilla rabbits with irreversible myocardial ischemia, the authors demonstrated that 5-hmU contributes to a significant increase in the level of expression of *FGF2* gene by 26%, *HGF* gene by 60%, and *VEGFa* gene by 131% [8], and also leads to an increase in vascular density in the myocardium [28] at the border of ischemic zone, which is generally consistent with this clinical study and, to a certain extent, suggests a similar relationship in patients with CAD against the background of perioperative drug use. At the same time, we realize the need to obtain not indirect, but direct evidence of 5-hmU effectiveness in stimulating angiogenesis processes in the myocardium and take into account the objective difficulties in performing histological studies due to the need for intravital myocardial biopsy.

Therefore, promising tasks of our scientific group will be to conduct modern non-invasive methods imaging, such as single photon emission computed tomography with Tc^{99} [29] and positron emission tomography with angiogenesis radiotracers [30] in patients of this group.

Study limitations. The limitations of this study are the small sample size and short follow-up period.

Conclusion

The use of 5-hydroxymethyluracil, a representative of pyrimidines, in the perioperative period of surgical myocardial revascularization leads to a significant increase in peripheral blood of such angiogenic growth factors as VEGF-A, IGF-1, and bFGF.

Relationships and Activities: none.

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Prevalence of professional burnout among practicing cardiologists in the constituent entities of the Russian Federation

Neplyueva G. A., Solovieva A. E., Krivopolenova S. D., Solovyov A. E., Zaitsev V. V., Zvartau N. E., Konradi A. O., Villevalde S. V.

The burnout syndrome among healthcare professionals is a headline problem in the world, as it leads to poor health of medical workers, affects patient satisfaction with health care and the healthcare system as a whole. At the same time, existing preventive measures can improve the well-being of staff.

Aim. To study the prevalence of professional burnout syndrome among practicing cardiologists in the Russian Federation (RF).

Material and methods. This cross-sectional study was carried out using the method of online anonymous surveying. The inclusion criterion was the current practical activity in the RF. The study involved 452 cardiologists from 8 federal districts (women; n=377, 83,4%), 48,2% of which worked in a hospital. Occupational burnout was assessed using the Maslach Burnout Inventory (MBI) questionnaire in the Russian language adaptation for healthcare workers by N. E. Vodopyanova and E. S. Starchenkova. The score was calculated on three subscales (emotional exhaustion, depersonalization, personal accomplishment), the maximum score for the subscales was 54, 30 and 48, respectively. The personal accomplishment subscale is the opposite as follows: the higher the score, the less the symptom severity. Additionally, demographic parameters, working conditions, the desire to change job and field of activity were taken into account. Regression analysis was used to establish associations of burnout with factors.

Results. The median score of the emotional exhaustion subscale was 29,5 (23,0; 35,0) points, depersonalization — 12,0 (8,0; 16,0) and personal accomplishment — 32,0 (28,0; 37,0). Men had higher depersonalization score than women as follows: 15,0 (10,0; 18,0) vs 11,0 (8,0; 15,0), p=0,001. High degrees of emotional exhaustion and depersonalization (burnout) were found in 235 (52%) cardiologists, while all three symptoms simultaneously — in 132 (29,2%) doctors. There were no symptoms of burnout in 84 (18,6%) cardiologists. A high degree of burnout was associated with a desire to change job (p<0,001).

Conclusion. A high prevalence of professional burnout among practicing cardiologists in the RF was revealed, which, in turn, is associated with the desire to change job or occupation.

Keywords: professional burnout, cardiologists, emotional exhaustion, depersonalization.

Relationships and Activities: none.

Almazov National Medical Research Center, St. Petersburg, Russia.

Neplyueva G. A.* ORCID: 0000-0001-8811-2450, Solovieva A. E. ORCID: 0000-0002-0013-0660, Krivopolenova S. D. ORCID: 0000-0002-9641-0084, Solovyov A. E. ORCID: 0000-0003-2378-9940, Zaitsev V. V. ORCID: 0000-0003-1905-2575, Zvartau N. E. ORCID: 0000-0001-6533-5950, Konradi A. O. ORCID: 0000-0001-8169-7812, Villevalde S. V. ORCID: 0000-0001-7652-2962.

*Corresponding author: neplyueva_ga@almazovcentre.ru

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Key messages

- To determine the prevalence of professional burnout among practicing cardiologists in the Russian Federation, a cross-sectional study was conducted using online anonymous surveying with MBI questionnaire in Russian language adaptation.
- The questionnaire was completed by 452 cardiologists from institutions of different types of incorporation.
- We established that more than 50% of cardiologists have a high emotional exhaustion and depersonalization.
- Identification of severe burnout symptoms is associated with the desire to change job.

Workplace stress can affect the well-being of employees and their productivity. Compared with other fields of activity, the medical environment with its inherent busy working days, lack of time, emotional and mental stress can expose physicians to a greater risk of professional burnout [1]. Burnout has negative health consequences, is associated with depression, suicidal thoughts, and is often combined with smoking and alcohol abuse [2-4].

According to the three-component model by S. Maslach, burnout is a psychological syndrome, including emotional exhaustion, depersonalization, reduction of personal achievements, which develops in connection with prolonged work stress [5]. According to various data, the prevalence of burnout among doctors varies from 10 to 60% [1, 4, 6]. Among the reasons leading to burnout, they note the constantly growing amount of work and the responsibility for the life and health of patients, a large number of contacts with sick people and their relatives, changing working conditions, working with electronic medical documents, the need to spend a lot of time in a close team of specialists, increased requirements for professional competence and dedication, control by management, as well as personal characteristics of specialists [7-9].

Burnout among doctors affects not only their well-being, but also the treatment of patients, interaction with colleagues and the healthcare system as a whole [10]. Survey results show that patients are less satisfied with consultations with physicians experiencing burnout [11]. Some foreign studies have shown a connection between burnout and medical errors [3, 4, 12-14]. Health care systems in such cases suffer financial losses associated with increased staff turnover [15].

Cardiologists are among the professionals who can be particularly stressed due to the high prevalence of severe cardiovascular diseases, the need to make decisions quickly, the increased risk of adverse events and patient death, especially during the coronavirus disease (COVID-19) pandemic. In the US in 2022, 42% of cardiologists experienced burnout[1].

[1] https://www.medscape.com/slideshow/2022-lifestyle-burnout-6014664#2.

In the Russian Federation, there are few studies on the prevalence of burnout among physicians [16-19]. In the largest study among 1668 doctors of various specialties in the Tomsk region, using the Maslach Burnout Inventory (MBI) questionnaire, a high and extremely high professional burnout was detected in 63% of specialists [16]. The prevalence of burnout among Russian cardiologists has not been previously studied.

The study aim was to determine the prevalence of professional burnout syndrome among practicing cardiologists in the Russian Federation.

Material and methods

Study design. Specialists of the Almazov National Medical Research Center planned and conducted a cross-sectional study in the period from November 2021 to March 2022. The main method was an anonymous online survey of doctors, and therefore informed consent was not required. The inclusion criteria were practical activities as a cardiologist in the Russian Federation, in a medical organization of any form of ownership, both at the main place of work and part-time. The questionnaire was published on the websites of the Almazov National Medical Research Center and the Russian Society of Cardiology (RSC). In addition, the questionnaire was additionally sent by e-mail to RSC members.

Sample bias associated with the study design and different responses of physicians in the federal districts is one of the study limitations.

The basis of the developed questionnaire was the MBI questionnaire in Russian-language adaptation by N. E. Vodopyanova and E. S. Starchenkova for medical workers [20]. The questionnaire contains 22 statements about feelings and experiences associated with professional duties. Symptoms of professional burnout were divided into three following subscales: emotional exhaustion (9 statements), depersonalization (5 statements), personal accomplishment reduction (8 statements). Each statement was rated from 0 to 6 points ("never" — 0 points, "very rarely" — 1 point, "rarely" — 2 points, "sometimes" — 3 points, "often" — 4 points, "very often" — 5 points, "always" — 6 points).

Table 1

Assessment of burnout levels

	Burnout degree (number of points)		
Subscale	Low	Moderate	High
Emotional exhaustion	0-15	16-24	⩾25
Depersonalization	0-5	6-10	⩾11
Personal accomplishment reduction	⩾37	31-36	⩽30

Table 2

Characteristics of cardiologists who took part in the study

Parameter	Total, n=452, N (%)	Women, n=377, N (%)	Men, n=75, N (%)	P
Age, years (Me (Q1; Q3))	38 (32; 46)	38 (32; 46)	37 (29; 46)	0,452
Marital status				
Married	295 (65,3)	244 (64,7)	51 (68)	0,586
Single	157 (34,7)	133 (35,3)	24 (32)	
Children				
Yes	307 (67,9)	261 (69,2)	46 (61,3)	0,181
No	145 (32,1)	116 (30,8)	29 (38,7)	
Experience, years (Me, (Q1; Q3)	13 (6; 21)	13 (7; 21)	13 (5; 22)	0,466
Region				
Urban	429 (94,9)	357 (94,7)	72 (96)	0,639
Rural	23 (5,1)	20 (5,3)	3 (4)	
Federal District				
FEFD	4 (0,9)	3 (0,8)	1 (1,3)	0,770
VFD	148 (32,7)	126 (33,4)	22 (29,3)	
NWFD	81 (17,9)	70 (18,6)	11 (14,7)	
NCFD	20 (4,4)	17 (4,5)	3 (4)	
SFD	25 (5,5)	20 (5,3)	5 (6,7)	
UFO	29 (6,4)	26 (6,9)	3 (4)	
CFD	58 (12,8)	45 (11,9)	13 (17,3)	
SFD	87 (19,2)	70 (18,6)	17 (22,7)	
Type of employment				
Full-time	284 (62,8)	234 (62,1)	50 (66,7)	0,628
Full- and part-time	97 (21,5)	84 (22,3)	13 (17,3)	
Only part-time	71 (15,7)	59 (15,6)	12 (16)	
Work status				
Daytime only	270 (59,7)	240 (63,7)	30 (40)	0,001
Daytime and 24-hour	163 (36,1)	122 (32,4)	41 (54,7)	
Only 24-hour	19 (4,2)	15 (4)	4 (5,3)	
Place of work*				
Outpatient clinic	65 (14,4)	59 (15,6)	6 (8)	0,426
Krai/republican/regional/district hospital	99 (21,9)	79 (21)	20 (26,7)	
NMRC	43 (9,5)	38 (10,1)	5 (6,7)	
City hospital	91 (20,1)	72 (19,1)	19 (25,3)	
Private medical organization	29 (6,4)	22 (5,8)	7 (9,3)	
Cardiology dispensary	44 (9,7)	37 (9,8)	7 (9,3)	
Research center	30 (6,6)	27 (7,2)	3 (4)	
University clinic	11 (2,4)	10 (2,7)	1 (1,3)	
Central Regional Hospital	40 (8,8)	33 (8,8)	7 (9,3)	

Table 2. Continuation

Parameter	Total, n=452, N (%)	Women, n=377, N (%)	Men, n=75, N (%)	P
Conditions of care				
Outpatient	218 (48,2)	192 (50,9)	26 (34,7)	0,010
Inpatient	234 (51,8)	185 (49,1)	49 (65,3)	
Want to change jobs	212 (46,9)	173 (45,9)	39 (52)	0,333
Want to change profession	112 (24,8)	90 (23,9)	22 (29,3)	0,317

Note: data are presented as n (%). * — the full-time work where the doctor works in the "cardiology" specialty or, in the absence of such, a part-time job was taken into account.

Abbreviations: FEFD — Far Eastern Federal District, NMRC — National Medical Research Center, VFD — Volga Federal District, NWFD — Northwestern Federal District, NCFD — North Caucasian Federal District, SFD — Siberian Federal District, UFD — Urals Federal District, CFD — Central Federal District, SFD — Southern Federal District.

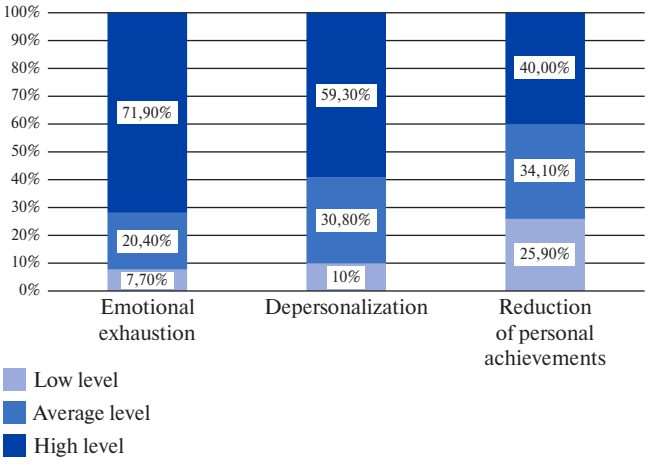

Figure 1. Distribution of burnout signs among cardiologists.

The subscale "personal accomplishment reduction" is reversed, the statement "never" corresponds to 6 points, the statement "always" — 0 points. The scores were summarized for each of the subscales. The maximum score for the subscale "emotional exhaustion" was 54, "depersonalization" — 30, "personal accomplishment reduction" — 48. The level of each burnout symptom was assessed separately and their combinations. The higher the score of the emotional exhaustion and depersonalization subscales and the lower the personal accomplishment reduction scale, the higher the level of burnout. We distinguished low, medium, and high burnout levels for each of the subscales (Table 1) [21].

Burnout syndrome was considered the identification of high rates on emotional exhaustion and depersonalization subscales. The extreme burnout

Table 3

Factors associated with burnout in cardiologists

Parameter	N	Emotional exhaustion	Depersonalization	Personal accomplishment reduction
		Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)
Age, years				
23-30	97	29,0 (24,5; 36,0)	13,0 (9,0; 17,0)	32,0 (28,0; 37,0)
31-40	164	29,5 (23,0; 35,0)	12,0 (8,0; 17,0)	33,0 (28,25; 37,0)
41-50	118	31,0 (23,0; 36,25)	12,0 (8,0; 16,0)	31,0 (28,0; 35,0)
>51	73	29,0 (22,0; 34,5)	11,0 (7,0; 15,0)	32,0 (28,5; 36,5)
P		0,309	0,257	0,498
Sex				
Female	377	30,0 (24,0; 35,0)	11,0 (8,0; 15,0)	32,0 (29,0; 37,0)
Male	755	29,0 (22,0; 36,0)	15,0 (10,0; 18,0)	31,0 (26,0; 36,0)
P		0,765	0,001	0,091
Marital status				
Married	295	30,0 (24,0; 35,0)	12,0 (8,0; 16,0)	32,0 (29,0; 37,0)
Single	157	29,0 (22,0; 36,0)	12,0 (8,5; 16,0)	32,0 (27,5; 36,5)
P		0,636	0,759	0,634

Table 3. Continuation

Parameter	N	Emotional exhaustion	Depersonalization	Personal accomplishment reduction
		Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)
Children				
Yes	307	30,0 (23,0; 35,0)	12,0 (8,0; 16,0)	32,0 (29,0; 37,0)
No	145	29,0 (24,0; 36,0)	12,0 (9,0; 18,0)	32,0 (28,0; 37,0)
p		0,861	0,093	0,706
Experience, years				
1-15	269	29,0 (24,0; 35,0)	12,0 (8,5; 17,0)	32,0 (28,0; 37,0)
16-30	143	31,0 (23,0; 36,0)	12,0 (8,0; 15,0)	31,0 (29,0; 35,0)
>31	40	27,5 (22,0; 31,75)	11,0 (7,0; 14,0)	32,0 (28,25; 39,0)
p		0,071	0,078	0,390
Region				
Urban	429	30,0 (24,0; 35,0)	12,0 (8,0; 16,0)	32,0 (28,5; 37,0)
Rural	23	27,0 (17,0; 35,0)	12,0 (7,0; 15,0)	30,0 (27,0; 35,0)
p		0,204	0,298	0,467
Federal District				
FEFD	4	23,0 (18,8; 28,0)	14,0 (11,0; 14,75)	32,5 (30,0; 39,5)
VFD	148	29,0 (23,0; 34,0)	12,0 (8,0; 16,0)	32,0 (29,0; 36,8)
NWFD	81	28,0 (21,5; 35,0)	11,0 (7,0; 15,5)	32,0 (28,0; 37,5)
NCFD	20	34,0 (26,5; 42,8)	13,5 (9,25; 17,8)	33,0 (28,5; 36,8)
SFD	25	33,0 (27,0; 39,0)	11,0 (8,5; 18,0)	30,0 (26,0; 33,0)
UFO	29	32,0 (27,5; 38,0)	12,0 (10,0; 16,5)	31,0 (28,5; 35,5)
CFD	58	28,0 (21,8; 32,3)	12,0 (8,8; 15,0)	32,0 (29,8; 37,3)
SFD	87	30,0 (25,0; 37,0)	13,0 (9,0; 18,0)	32,0 (27,0; 38,0)
p		0,044	0,296	0,833
Type of employment				
Full-time	284	29,5 (24,0; 35,75)	12,0 (8,0; 16,0)	31,0 (28,0; 36,0)
Full- and part-time	97	29,0 (22,0; 36,0)	12,0 (8,0; 16,0)	34,0 (30,0; 39,0)
Only part-time	71	30,0 (25,0; 34,0)	12,0 (8,0; 16,0)	32,0 (28,0; 39,0)
p		0,943	0,711	0,011
Work status				
Daytime only	270	30,0 (23,0; 35,0)	11,0 (8,0; 15,0)	32,0 (28,75; 37,0)
Daytime and 24-hour	163	30,0 (23,0; 38,0)	13,0 (9,0; 17,0)	33,0 (28,0; 37,0)
Only 24-hour	19	29,0 (26,0; 35,0)	12,0 (11,0; 17,0)	31,0 (27,0; 33,0)
p		0,451	0,011	0,388
Place of work				
Level 3 hospital	112	30,0 (25,0; 36,4)	14,0 (10,0; 18,0)	32,0 (27,0; 37,0)
First contact health organizations	94	30,0 (24,8; 34,3)	12,0 (8,0; 16,0)	32,0 (28,0; 37,0)
CH, CRH	129	29,0 (22,5; 35,0)	12,0 (8,0; 16,0)	32,0 (28,5; 36,5)
Specialized Center	117	29,0 (22,5; 35,0)	10,0 (7,0; 15,0)	33,0 (29,5; 38,0)
P		0,147	0,002	0,644
Conditions of care				
Outpatient	218	29,0 (22,0; 35,0)	11,5 (8,0; 16,0)	32,0 (29,0; 37,0)
Inpatient	234	30,0 (24,0; 37,0)	12,0 (9,0; 16,0)	32,0 (28,0; 36,0)
p		0,169	0,087	0,263
Work load				
Up to 1 rate	234	29,0 (22,0; 35,0)	12,0 (8,0; 16,0)	32,0 (28,0; 35,0)

Table 3. Continuation

Parameter	N	Emotional exhaustion	Depersonalization	Personal accomplishment reduction
		Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)
1,25-1,5 rates	163	30,0 (25,0; 36,0)	12,0 (9,0; 15,0)	32,0 (29,0; 37,0)
>1,5 rates	55	30,0 (24,0; 38,0)	12,0 (8,0; 17,0)	34,0 (29,0; 39,0)
p		0,211	0,958	0,050
Want to change jobs				
Yes	212	34,0 (28,0; 39,0)	14,0 (10,0; 18,0)	30,0 (27,0; 35,0)
No	240	27,0 (21,0; 32,0)	10,0 (7,0; 14,0)	33,0 (30,0; 38,0)
p		<0,001	<0,001	<0,001
Want to change profession				
Yes	112	35,00 (30,00; 41,75)	16,0 (11,0; 19,0)	30,0 (26,0; 35,0)
No	340	28,0 (22,0; 34,0)	11,0 (8,0; 15,0)	32,0 (29,0; 37,0)
p		<0,001	<0,001	<0,001

Abbreviations: CH — city hospital, FEFD — Far Eastern Federal District, NMRC — National Medical Research Center, VFD — Volga Federal District, NWFD — Northwestern Federal District, NCFD — North Caucasian Federal District, SFD — Siberian Federal District, UFD — Urals Federal District, CFD — Central Federal District, SFD — Southern Federal District.

Table 4

Detection rate of symptoms of high burnout among cardiologists depending on a mind to change jobs or profession

High rate	Want to change jobs		Want to change profession	
	Yes, N (%)	No, N (%)	Yes, N (%)	No, N (%)
None of the subscales	18 (8,5)	66 (27,5)	5 (4,5)	79 (23,2)
According to 1 subscale	35 (16,5)	59 (24,6)	14 (12,5)	80 (23,5)
According to 2 subscales	71 (33,5)	71 (29,6)	40 (35,7)	102 (30)
According to 3 subscales	88 (41,5)	44 (18,3)	53 (47,30)	79 (23,2)

Table 5

Univariate regression analysis of the association of a mind to change jobs with burnout symptoms

Predictor	OR	95% CI (OR)	p
Emotional exhaustion score	1,08	1,05-1,11	<0,0001
Depersonalization score	1,08	1,03-1,13	0,0013
Personal accomplishment reduction score	0,97	0,96-1,00	0,026

Abbreviations: CI — confidence interval, OR — odds ratio.

was considered high values for all three subscales.

To study the factors associated with burnout, the questionnaire additionally included data on age, sex, marital status, place and nature of work, length of service, desire to change jobs or profession. Respondents were also asked to rank, from higher to lower significance, the factors affecting job satisfaction (salary, professional support of the team, the level of equipment and the availability of examinations for patients, the management loyalty, the cohort of patients, the prospect of career and professional growth, the degree of daily workload).

Statistical analysis. SPSS 25.0 software was used for statistical processing. Qualitative data are presented as absolute and relative frequencies, while quantitative data are presented as median, first and third quartiles (Me (Q1; Q3)). To compare the frequencies of qualitative features, Pearson's χ^2 test was used. To assess the difference in two or more independent samples, the nonparametric Mann-Whitney and Kruskal-Wallis U tests are used. The null hypothesis of no difference in values between

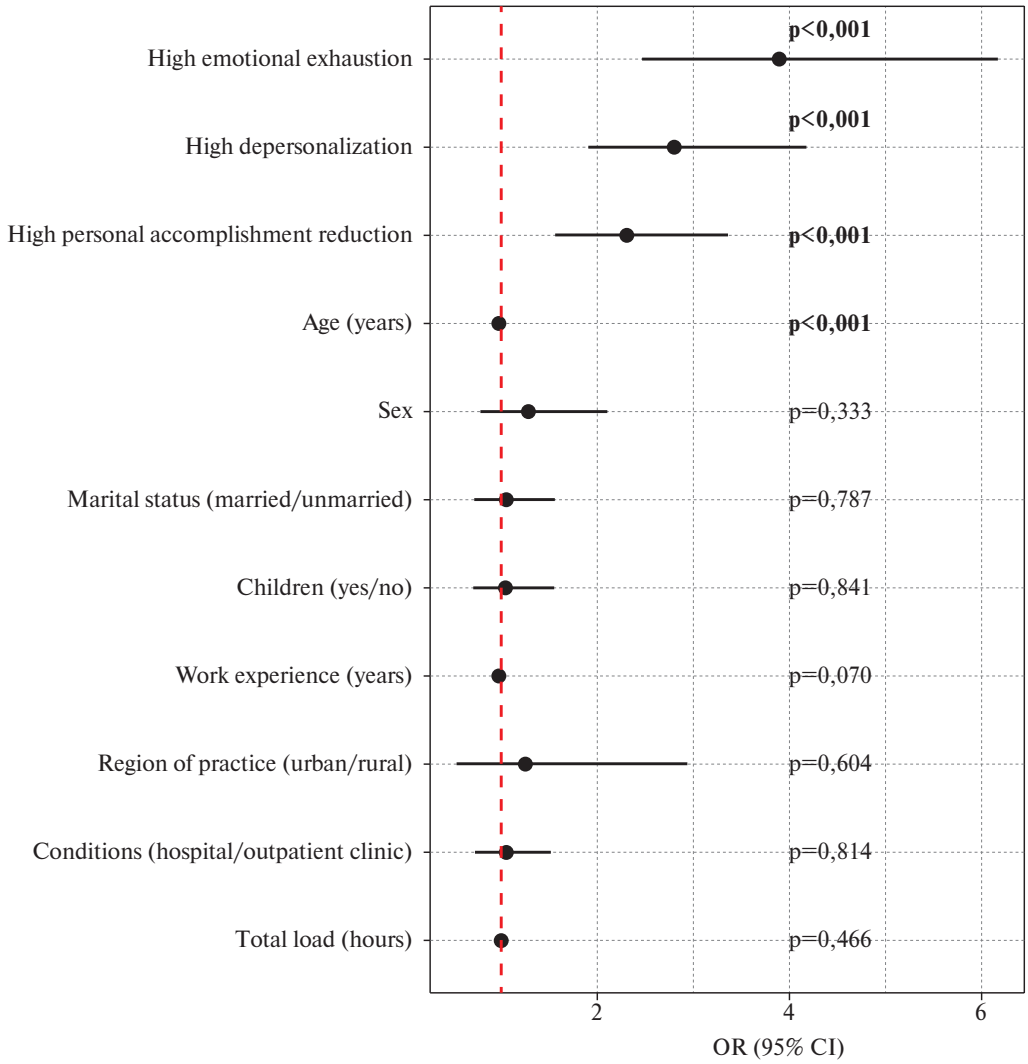

Figure 2. Univariate logistic regression analysis of the association of burnout symptoms and age with a mind to change jobs.
Note: ORs are presented for high burnout symptoms compared to low and moderate, combined in one control group.
Abbreviations: CI — confidence interval, OR — odds ratio.

groups was rejected at p<0,05. Regression analysis was used to identify associations between burnout symptoms and the desire to change jobs or professions. To calculate the odds ratio to change jobs depending on burnout degree, grades 1 and 2 were combined into one group "without burnout", while grade 3 was the burnout factor.

Results

Characteristics of cardiologists participating in the study

The study involved 452 cardiologists from 8 federal districts. The most represented federal district was Privolzhsky. Female cardiologists represented the majority of this sample. The median age of the respondents was 38 years. Most of the respondents were married and had children. The average work experience for all doctors was 14,8 years. Almost all specialists worked in cities. Men more often combined day-time and 24-hour work and worked in a hospital (Table 2).

Prevalence of burnout

When assessing burnout in the entire sample, the average emotional exhaustion score was 29,5 (23,0; 35,0), depersonalization — 12,0 (8,0; 16,0), personal accomplishment reduction — 32,0 (28,0; 37,0). High values on emotional exhaustion subscale were found in 71,9% (n=325) of cardiologists, depersonalization — in 59,3% (n=268), personal accomplishment reduction — in 40% (n=180) respondents (Figure 1). In 81,4% (n=368) cardiologists, from 1 to 3 symptoms of high burnout were detected. Among them, a combination of a high emotional exhaustion and depersonalization (burnout) was revealed

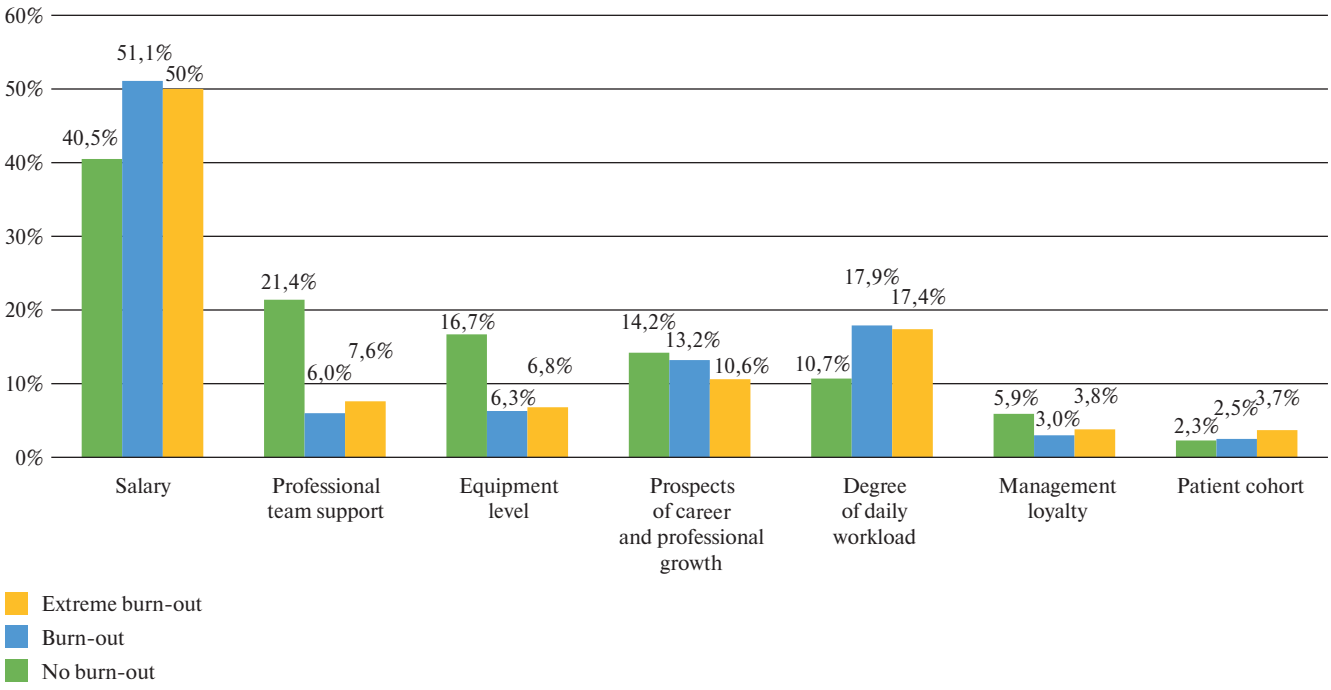

Figure 3. Distribution by significance of factors influencing job satisfaction from the point of view of cardiologists (no burnout — no high values were found on any of the subscales, burnout — a combination of a high emotional exhaustion and depersonalization, extreme burnout — high values on all three subscales).

in 52% (n=235), while all 3 symptoms simultaneously (extreme burnout) — in 29,2% (n=132). No symptoms of burnout were noted in 18,6% (n=84) of physicians.

Analysis of burnout-associated factors

Burnout-associated factors in cardiologists are presented in Table 3. The median depersonalization score is higher for men (p=0,001), as well as for specialists working in level 3 hospitals (p=0,002), combining day-time and 24-hour work (p=0,011).

The study did not reveal significant differences in the prevalence of burnout symptoms depending on marital status, the presence of children, place of residence, location, and conditions for providing care.

Association of burnout with a mind to change jobs or profession

To the question "Do you want to change jobs?" 46,9% of cardiologists answered positively, and to the question "Do you want to change your profession?" — 24,8% of specialists (Table 2).

Groups depending on the mind of doctors to change jobs or professions differed only in the degree of burnout for each of subscales (p<0,001) (Table 3). Among physicians wishing to change jobs or professions, ⩾2 burnout symptoms were more common (Table 4).

Univariate logistic regression analysis revealed a significant relationship between the desire to change jobs, burnout symptoms and age. The likelihood of wanting to change jobs increased with increasing scores on the emotional exhaustion and depersonalization subscales and decreased with increasing scores on personal accomplishment reduction subscale (Table 5).

Higher probability of a mind to change jobs has been established in people with a high emotional exhaustion compared to doctors with a low and moderate score. Similar relationships were observed in the case of a high depersonalization and low personal accomplishment reduction scores in relation to low and moderate degree of these symptoms (Figure 2).

For the desire to change profession, significant associations with burnout symptoms were also found, but the relationship was weak.

Assessment of factors affecting job satisfaction

Factors affecting job satisfaction were also analyzed. For the majority of respondents, the most significant factor was the salary level; for physicians experiencing burnout, to a greater extent. For all doctors, the management loyalty and the cohort of patients were of the least importance. It draws attention to the fact that for cardiologists with burnout symptoms, the next most important factors are the prospect of career growth and workload level, while for cardiologists without burnout it is the professional support of the team and the level of equipment (Figure 3). This may indicate differences in attitudes towards work among doctors with and

without burnout symptoms, associated with their personal characteristics and determining the susceptibility to burnout.

Discussion

This study, with a focus on cardiologists, was conducted in the Russian Federation for the first time, and the data obtained are important for further work in this area. The study revealed a high prevalence of burnout among practicing cardiologists in the Russian Federation (52%).

The average emotional exhaustion scores in our sample were higher than in other studies using the MBI questionnaire: (emotional exhaustion — 29,5 points in this study versus 19 in Kazakhstan and 21,3 in Germany), while the average personal accomplishment reduction score is lower in our sample (32,0 vs 41 and 36,3, respectively) [22, 23]. The results could be influenced by the characteristics of doctors, the increased workload on cardiologists due to the COVID-19 pandemic [24]. According to some reports, the prevalence of burnout among professionals working with COVID-19 patients increased from 20 to 40% at the peak of the pandemic[2,3]. In addition, the recent increase in the prevalence of cardiovascular diseases, demographic shifts towards a population aging are associated with an increased workload on the cardiology service and cardiologists, which can also increase the risk of burnout. The possibility of timely intervention and elimination of this syndrome, improving the health of doctors in order to increase the efficiency of their work and the healthcare system, make any research in this area relevant.

The most common symptom of burnout was emotional exhaustion (72%). Significant differences were found for depersonalization subscale. Higher levels of depersonalization have been found among cardiologists working in level 3 hospitals that combine day-time and 24-hour work. In addition to the hours spent at work, this can be explained by a more severe patient profile, their number, as well as other factors related to the profession. Men's cardiologists had a higher depersonalization score. Similar differences in depersonalization were found among doctors of other specialties [9, 25]. Perhaps this is due to the fact that women are more capable of empathy than men. Not only among doctors, but also in other professions, men are characterized by a high depersonalization and a high assessment of their professional success, while women are more prone to emotional exhaustion [21]. At the same time, a Polish study demonstrated that a high depersonalization is an independent predictor of medical errors [4].

Just like in the study in Germany, we did not find any association between burnout and the presence of a family, place of residence and area of practice, and conditions of care, which is probably due to the sample homogeneity.

This study revealed a relationship between the desire of doctors to change jobs and a high degree of burnout for each of the subscales. These associations have also been demonstrated in studies in Germany and the USA [22, 25]. It is possible that burnout syndrome has been an underestimated factor in employee turnover in the Russian Federation so far, but it can potentially affect the availability of healthcare. Among cardiologists, salary levels were found to be the most important factor in job satisfaction. However, monetary compensation is not a decisive condition in making a decision. This is proved by the identified links between the desire to change jobs and the burnout degree. In another study in the United States, physicians with burnout wanted to change jobs either with a 20% pay increase or a 20% pay cut [25]. Thus, a satisfactory level of wages, together with methods for preventing burnout, can be effective in preventing the outflow of personnel.

Practical application of study results

It is necessary to take into account the revealed relationship between a high degree of burnout and a mind to change jobs, because this may contribute to reduced access to health care. These results are comparable with foreign studies and are important for improving personnel policy. However, larger studies are required, including at the national level, to better assess the prevalence of burnout among cardiologists and develop strategies to combat this problem. One way to prevent high employee turnover could be to include employee burnout surveys during the annual medical check-up, followed by measures to reduce work-related stress levels.

Study limitations. The Russian-language version of the MBI questionnaire and subscale values standardized for the Russian sample were used to identify symptoms of burnout. This technique does not imply a generalized assessment of burnout degree, but only its components and their combinations.

The study limitations are related to the lack of accounting and analysis of the personal characteristics of doctors that affect stress resistance and the development of certain psychological symptoms. The homogeneity and small sample size may have contributed to statistical insignificance for within-

[2] https://www.dicardiology.com/content/burnout-rate-doubles-cardiology-clinicians-amid-covid-19-pandemic.

[3] https://www.healio.com/news/cardiology/20210709/more-than-1-in-3-cardiology-professionals-reported-burnout-during-covid19-pandemic.

sample differences in many dimensions. The number of cardiologists participating in the survey is 3,5% of the total number of specialists in the state healthcare system of the Russian Federation, which limits us in generalizations and requires additional research in this area.

Conclusion

More than half of cardiologists (52%) practicing in the Russian Federation have a high emotional exhaustion and depersonalization, 26% of specialists are characterized by a high degree of all three burnout symptoms (extreme burnout). Higher degrees of depersonalization were associated with male sex, level 3 hospital work, and workload. It has been established that symptoms of high burnout degree are factors that increase the likelihood of a mind to change jobs, which emphasizes the importance of developing measures aimed at reducing the stress associated with professional activities in order to prevent the personnel outflow.

Relationships and Activities: none.

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Sleep-related breathing disorders in patients with heart failure with reduced and mildly reduced ejection fraction: main types and their dependence on heart failure etiology

Krupichka K. S., Agaltsov M. V., Beregovskaya S. A., Myasnikov R. P., Drapkina O. M.

Aim. To identify and study the nature of sleep-related breathing disorders (SBDs) in a cohort of hospitalized patients with heart failure (HF) with reduced and mildly reduced ejection fraction (EF), as well as to clarify the relationship between SBD type, etiology and severity of HF.

Material and methods. The study included 117 patients with HF with reduced and mildly reduced ejection fraction hospitalized at the National Medical Research Center for Therapy and Preventive Medicine from 2019 to 2021. All patients underwent clinical and paraclinical examination, including cardiorespiratory sleep study. Patients were divided into three groups according to the type and severity of SBD: no or mild SBD, predominantly with obstructive sleep apnea (OSA) and predominantly with central sleep apnea (CSA). Severity of SBD and clinical data were compared between these groups.

Results. A total of 5 patients (4,27%) did not have any SBDs, while 47 (40,17%) were diagnosed with CSA, and 65 (55,56%) — OSA of varying severity. The proportions of patients with moderate and severe CSA and OSA differed insignificantly and amounted to 35,9% (n=42) and 44,4% (n=52), respectively. There were following proportions of diseases related to HF: coronary artery disease (41,88%), non-ischemic cardiomyopathy (26,5%), arrhythmogenic cardiomyopathy (15,38%) and other causes (16,24%) (hypertension, myocarditis, heart defects). We found that reduced EF <40%, end-diastolic volume >210 ml, and ventricular ectopy (>300 extrasystoles/day) were associated with CSA, and body mass index >30 kg/m^2 was traditionally associated with OSA.

Conclusion. More than half of HF patients with reduced and mildly reduced EF have SBDs. Decreased LVEF and ventricular ectopic activity are associated with CSA, while increased body mass index is associated with OSA. Consideration of SBD risk factors may improve patient phenotyping for individualized therapy.

Keywords: sleep-related breathing disorders, obstructive sleep apnea, central sleep apnea, heart failure.

Relationships and Activities: none.

National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia.

Krupichka K. S.* ORCID: 0000-0001-8711-7348, Agaltsov M. V. ORCID: 0000-0002-4982-628X, Beregovskaya S. A. ORCID: 0000-0002-0192-186X, Myasnikov R. P. ORCID: 0000-0002-9024-5364, Drapkina O. M. ORCID: 0000-0002-4453-8430.

*Corresponding author:
kristinakrupichka@gmail.com

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Heart failure (HF) is one of the most common causes of cardiovascular morbidity and mortality and is a global health problem affecting people in different countries.

The prevalence of chronic heart failure (CHF) in Russia in the general population is 7%, including with clinical manifestations — 4,5%, increasing in older age groups [1]. Since studies usually only

Table 1
Characteristics of the included patients (M±SD; Me)

Parameter	All patients (n=117)
Age, years	61 (±12,76)
Male sex, n (%)	99 (84,6%)
BMI, kg/m^2	30,99 (±6,46)
BPs/BPd, mm Hg	123,38/75,42 (±18,95/11,23)
CAD, n (%)	49 (42%)
AF (persistent and permanent), n (%)	47 (40,2%)
AF (paroxysmal), n (%)	15 (12,8%)
COPD, n (%)	15 (13%)
ICD, n (%)	22 (19%)
NYHA class III, n (%)	61 (52%)
NYHA classIV, n (%)	5 (4,3%)
CRTD, n (%)	4 (3%)
LVEF, %	34,026 (±9,44)
LVEF <35%, n (%)	62 (53%)
PASP, mm Hg	38,83 (±16,22)
NT-proBNP, pg/ml	2259,3 (±3118,6)
Hemoglobin, g/l	144,6 (±16,2)
Mean HR, bpm	71,5 (±13,8)
ACE inhibitor/ARA, n (%)	60 (51%)
Sacubitril/Valsartan, n (%)	35 (30%)
Beta-blockers, n (%)	90 (80%)
Diuretics, n (%)	77 (66%)

Abbreviations: ARA — angiotensin II receptor antagonists, BPs/BPd — systolic/diastolic blood pressure, ACE — angiotensin-converting enzyme, CAD — coronary heart disease, ICD — implanted cardioverter-defibrillator, BMI — body mass index, LV — left ventricle, PASP — pulmonary artery systolic pressure, HR — heart rate, EF — ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CRTD — cardiac resynchronization therapy defibrillator, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association.

include identified cases of HF, the true prevalence is likely to be higher [2]. Despite therapeutic progress, the mortality rate among patients with CHF remains very high, accounting for 12% per year among patients with severe CHF in the Russian Federation (RF). This necessitates early identification of risk groups prone to sudden death and frequent hospitalizations to prevent serious complications and death.

Breathing-related sleep disorders (BRSDs) have been shown to be one of the factors affecting poor prognosis in HF and are also associated with an increased risk of CHF in patients. The Sleep Heart Health Study, which included 6424 men and women, found that obstructive sleep apnea (OSA) contributed to HF onset, regardless of other known risk factors. Data on the BRSD prevalence in patients with CHF in the RF are limited, which prevents practitioners from understanding the relevance of the problem and the need to treat BRSDs.

It is noteworthy that BRSDs in CHF is much more common than in the general population (more than one third of patients with a stable HF, with an increase in occurrence in decompensated HF [3]). The most common types of BRSD are OSA, central sleep apnea (CSA) (including Cheyne-Stokes respiration (CSR)), and mixed sleep apnea, which combines first two sleep disorders.

The main links in BRSD pathogenesis, such as repeated episodes of hypoxia and reoxygenation, as well as sympathetic activation associated with frequent waking up, contribute to HF progression [2]. The bidirectional pathogenetic relationship between HF and BRSD suggests that BRSD may be a modifiable risk factor in HF and have potential therapeutic value. Attention to the diagnosis and treatment of BRSD in patients with HF can improve outcomes and lead to a clinical stabilization and an increase in the quality of life.

In the present study, we studied the occurrence of different BRSD types in a cohort of patients with HF with reduced and mildly reduced ejection fraction (EF) admitted to the hospital. The relationship between the type of BRSD, etiology and severity of HF was also analyzed.

Material and methods

The study was conducted among patients hospitalized at the National Medical Research Center for Therapy and Preventive Medicine from 2019 to 2021. Patients with NYHA class II-IV HF and mildly reduced or reduced EF were included. The study included 117 patients, predominantly men (84,6%), with a mean age of 61 years (±12,76). The study protocol was approved by the Ethics Committee of the National Medical Research Center for Therapy and Preventive Medicine (protocol № 01-06/20 dated February 4, 2020). All participants signed written informed consent. The exclusion criteria were refusal to participate in the study, class IV angina, acute coronary syndrome, stroke (within 30 days before screening), resynchronization therapy (<3 months before and after screening), implanted left ventricular (LV) assist device/inclusion in heart transplant waiting list.

All patients underwent standard clinical and paraclinical examination including history collection, physical examination, laboratory tests (complete blood count, biochemical blood profile, N-terminal pro-brain natriuretic peptide (NT-proBNP)), echocardiography, Holter monitoring, and a 6-minute walk test. Clinical information collected for analysis included age, sex, anthropometry, blood pressure,

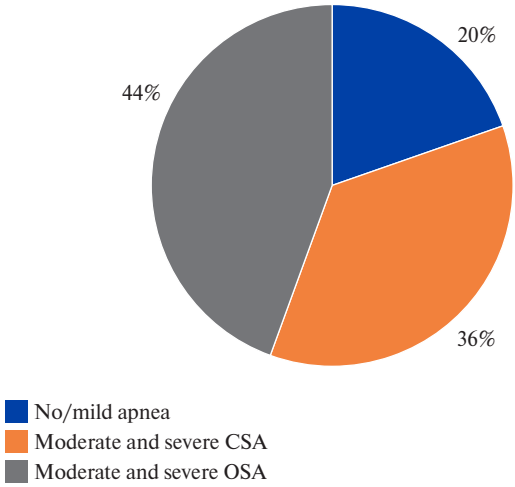

Figure 1. Distribution of groups depending on the type of BRSD and apnea severity.
Abbreviations: OSA — obstructive sleep apnea, CSA — central sleep apnea.

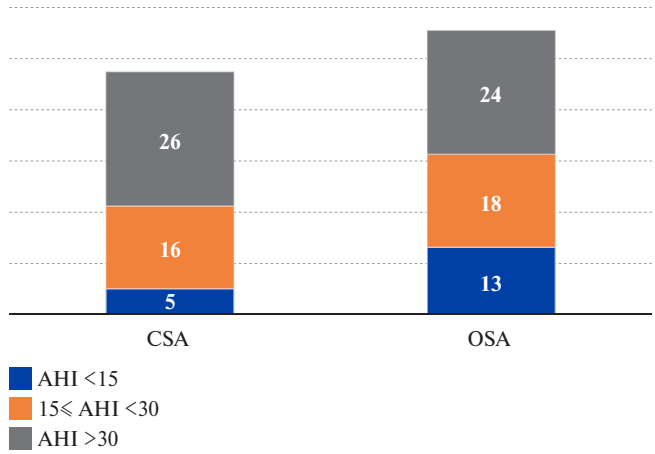

Figure 2. Severity of BRSD (N=112).
Abbreviations: AHI — apnea-hypopnea index, OSA — obstructive sleep apnea, CSA — central sleep apnea.

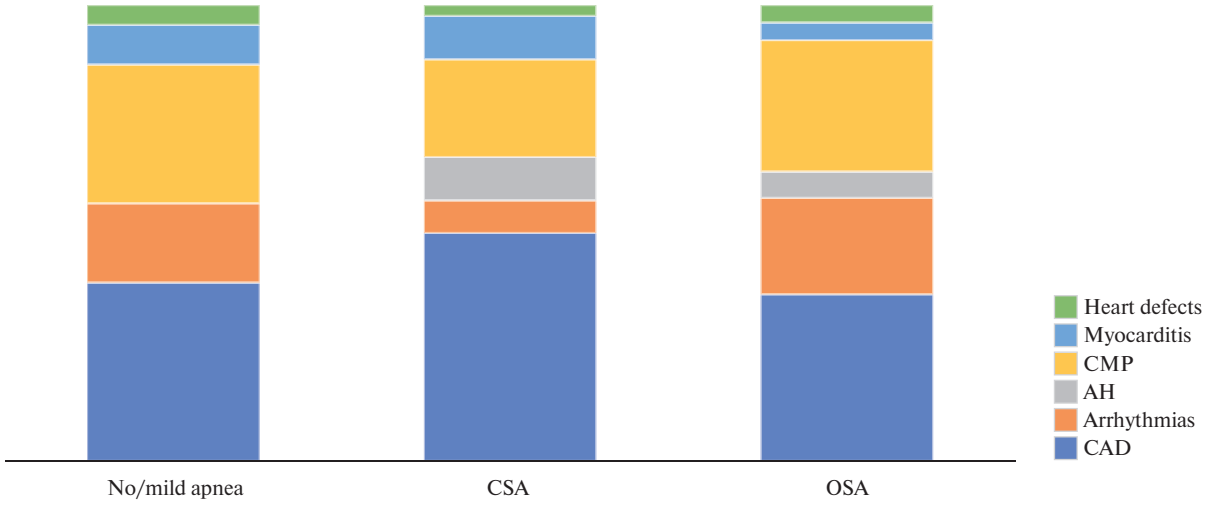

Figure 3. Etiology of HF in patients.
Abbreviations: AH — hypertension, CAD — coronary heart disease, CMP — cardiomyopathy, OSA — obstructive sleep apnea, CSA — central sleep apnea.

Epworth Sleepiness Scale, comorbidity profile, medications taken. All patients were prescribed standard therapy in accordance with national and international guidelines for HF treatment.

In order to identify BRSD, cardiorespiratory monitoring (CRM) was performed, manufactured by Meditek, Russia. During the study, the following indicators were recorded: respiratory tract airflow, chest and abdominal breathing efforts, arterial oxygen saturation, heart rate. The analysis was performed automatically using standard software and then corrected manually by a sleep medicine specialist. BRSD were determined in accordance with the criteria of the American Academy of Sleep Medicine [4]. Sleep apnea was defined as an airflow decrease by ⩾90% for at least 10 s, hypopnea — a decrease in airflow by ⩾30% for at least 10 s, accompanied by oxygen desaturation for at least 3%. CSA was diagnosed in the cessation of airflow without respiratory effort, while OSA was defined in the collapse of upper airways and sustained respiratory efforts. The criterion for CSA or OSA diagnosis in a patient was one or another type of apnea in more than 50% of all respiratory events. The severity of BRSD was defined as the number of events per hour of sleep (Apnea/Hypopnea Index (AHI)) as follows: 5-14 events per hour — mild, 15-30 events per hour — moderate, and >30 events per hour — severe.

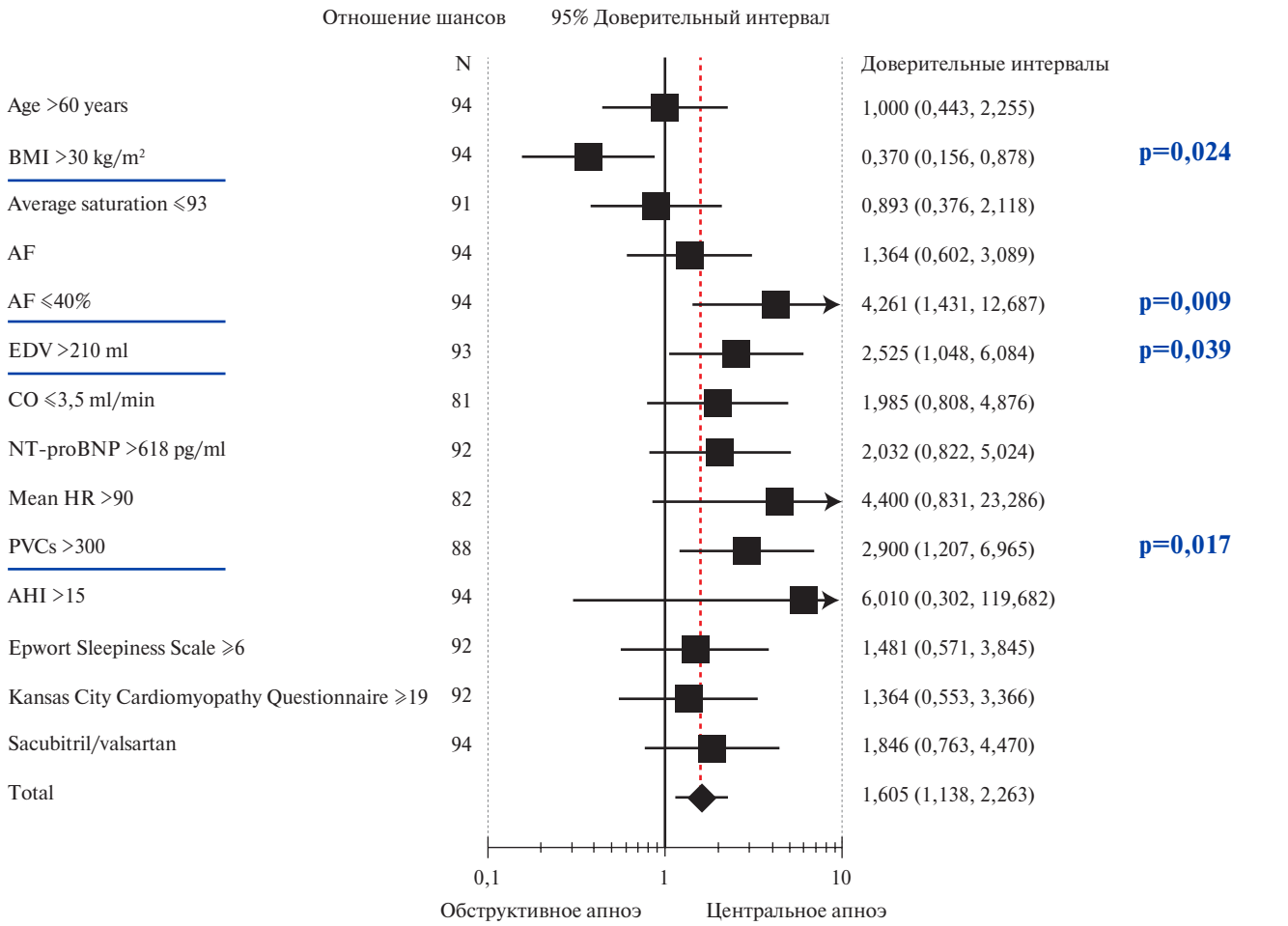

Figure 4. Clinical and laboratory parameters associated with BRSD in patients with HF.
Abbreviations: PVC — premature ventricular contraction, AHI — apnea-hypopnea index, BMI — body mass index, EDV — end-diastolic volume, KCCQ — Kansas City Cardiomyopathy Questionnaire, LV — left ventricle, CO — cardiac output, HR — heart rate, EF — ejection fraction, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, NT-proBNP — (a cut-off value of 618 pg/ml was taken based on statistical analysis — 25 quartile for CSA).

The statistical program Statistica (version 25.0) was used to analyze the obtained data. (StatSoft Inc). Results are presented as means (M) and standard deviations (SD) or median (Me, quartile (Q) 25 — quartile 75) for quantitive variables and absolute values and percentages for categorical variables. Scores were compared using the Mann-Whitney U-test. The analysis of qualitative variables and contingency tables were performed using the Pearson chi-square test. Results were considered significant at $p<0,05$.

Results

The general characteristics of included patients are presented in Table 1. Out of 117 patients, men predominated (n=99 (84,6%)). The mean age of included patients (Me, Q25-Q75) was 61 years (50-69). Patients had early-stage obesity (M±SD, 31±6,5). The mean LVEF (M±SD) was 34,026±9,44%. More than half of the patients (53%) had an LVEF <35%. The largest proportion of patients had NYHA class III HF (52,14%). There were 4,3% of patients with severe heart failure (NYHA class IV).

Atrial fibrillation was present in 53% (n=62) of patients, while permanent or persistent atrial fibrillation — in 40,2% of patients (n=47).

In 19% of patients, a cardioverter-defibrillator was implanted, and in 3% — a cardiac resynchronization therapy defibrillator was implanted. A total of 80% (n=90) of patients received baseline HF therapy, while 30% of the total number of patients (n=35) received angiotensin II receptor antagonists in combination with a neprilysin inhibitor (sacubitril/valsartan).

According to CRM, only 5 patients (4,27%) did not register any BRSD. Forty-seven (40,17%) were diagnosed with CSA, and 65 people (55,56%) — with OSA. The proportions of patients with moderate

and severe CSA and OSA differed insignificantly and amounted to 35,9% (n=42) and 44,4% (n=52) respectively (Figure 1).

Based on CRM, patients were divided into 3 groups: without BRSD (group I), predominant OSA (group II), and predominant CSA (group III) (Figure 1). In patients with CSA and OSA, moderate and severe sleep apnea predominated, as evidenced by AHI (Figure 2).

Among HF causes, the largest proportion in all three groups was coronary artery disease (CAD) (41,88% of the total), non-ischemic cardiomyopathy (26,5%), arrhythmogenic cardiomyopathy (15,38%) and other causes (16,24%), which included hypertension, myocarditis, heart defects (Figure 3). A large proportion in all three groups were patients with CAD. Arrhythmogenic cardiomyopathy (predominantly atrial fibrillation) was the only cause of HF, which showed a tendency to differ between groups, which is widely represented in the group of patients with OSA compared with patients with CSA (p=0,057).

Pearson chi-square test was used to evaluate the significance of various associations of the main severity parameters of HF with CSA and OSA (Figure 4). It was found that reduced EF <40%, end-diastolic volume (EDV) >210 ml and ventricular ectopy count (>300/day) were associated with CSA, while body mass index >30 kg/m^2 was traditionally associated with OSA.

Discussion

The data obtained in our study confirm the results of a few previous studies devoted to BRSD prevalence in patients with HF. Registered BRSD rates in patients with systolic HF remain high. This applies to both OSA and CSA with CSR. The registry by Schla HF with 6876 patients with stable HF with reduced EF [5] found that almost half of the patients in this registry had moderate and severe CSR. Two large epidemiological studies of populations with HF that assessed the prevalence of apnea were published in 1999 [6] and 2007 [7]. In the first study, among 450 patients with HF, patients with OSA and CSA-CSR with AHI ⩾10 eps/hour accounted for 38% and 33%, respectively. In a 2007 study, among 700 patients with HF (LVEF <40%) and AHI ⩾15 eps/hour, 36% had OSA and 40% — CSA-CSR. It is obvious that the use of different AHI thresholds for diagnosing BRSD determines the difference in its prevalence. It is worth noting that the study by Oldenburg O, et al. included patients with lower EF (<40%), which may explain the prevalence of CSA [7]. However, different threshold values for BRSD severity do not significantly affect the high incidence of BRSD among HF patients with reduced EF. In a very recent study by Wang T, et al., the prevalence of BRSD in patients with HF remains at the level obtained in previous studies [8]. Our data on BRSD representation among HF patients complement the existing literature and are among the first in the Russian Federation [9, 10], showing that previously recorded prevalence rates are most likely not outdated and dependent on HF therapy.

For example, in the study by Yumino D, et al. despite the widespread use of beta-blockers and spironolactone in the treatment of HF, the prevalence of BRSD remains high [11]. At the same time, the ENTRESTO-SAS study demonstrates the high efficacy of therapy with an angiotensin II receptor antagonist in combination with a neprilysin inhibitor (sacubitril/valsartan) (for 3 months) on the severity of CSA and gives hope for a possible effect of this therapy on CSA severity [12].

The proportion of patients with OSA in our study exceeds that in similar studies [6]. Inconsistencies in most cases can be explained by the difference in the studied populations (patients of different HF classes), as well as the methodology used to diagnose BRSD (polysomnography against CRM).

In our work, we have demonstrated the relationship between ventricular ectopic activity and CSA. According to the data obtained, it was more often observed in the CSA group, which may be due to the relationship between ventricular arrhythmias and significant myocardial dysfunction in HF [13].

It is interesting to analyze the hypotheses about the relationship between HF etiology and the type and severity of BRSD. In our study, the leading cause of HF in patients with both OSA and CSA was CAD. The data obtained are consistent with the previously identified wide prevalence of BRSD in patients with ischemic HF [14, 15]. A decrease in systolic function as a result of cardiomyocyte necrosis leads to edema and its subsequent participation in the development of both OSA and CSA.

In most large studies, a significant relationship between HF etiology and BRSD type has not been identified [5, 7, 16]. In a recent 2022 study according to Wang T, et al. [8] the prevalence of BRSD was relatively low in patients with arrhythmogenic HF. On the contrary, our results revealed a trend towards a significant relationship between arrhythmogenic HF and OSA. Probably, the discrepancies are due to the methodology of patient selection and the interventions performed in the hospital. In other earlier works, the prevalence of BRSD in arrhythmic HF was not reported [5, 7, 16].

Several previous studies have shown that the severity of HF is closely related to the prevalence and severity of BRSD and, in particular, CSA, and the development and severity of CSA, in turn,

reflect the severity of cardiac dysfunction. CSA is often associated with elevated brain natriuretic peptide levels, low LVEF, and the prevalence of CSA increases with increasing severity of HF [6, 17, 18].

The results of our study demonstrated that the presence of CSA is associated with worse structural and functional cardiac parameters, as assessed by echocardiography. Patients with CSA had more severe systolic (lower LVEF) LV dysfunction and enlarged chambers (EDV >210 ml). The study by Sin DD, et al. [6] also found lower LVEF in patients with CSA than those with OSA. Oldenburg O, et al. also found lower LVEF in patients with CSA, but the difference was not significant [7]. However, it should be noted that not all researchers have observed an association between CSA and the severity of LV dysfunction. Schulz R, et al. [16] found no difference in LVEF among patients with CSA compared with patients with OSA or without BRSD. Carmona-Bernali C, et al. [19] also did not confirm significant differences in echocardiographic parameters (LVEF, LV EDV). In our study, there were no significant differences in the EF value between the groups of patients with OSA and without BRSD, which once again confirms the hypothesis of more severe cardiac dysfunction in patients with CSA.

We failed to identify a significant association with NT-proBNP level and the type of BRSD, which can be explained by the small sample size and the obviously higher level of NT-proBNP in patients with atrial fibrillation [20], whose representation in the OSA group was high.

Research limitations. Limitations are related to the methodology for BRSD diagnosis. CRM was used to establish the diagnosis. Thus, the entire recording time was evaluated, not just the sleep time, which could lead to an underestimation of BRSD severity.

Conclusion

In this work, one of the first attempts in the Russian Federation was made to assess the representation of various BRSD types in patients with HF with mildly reduced and reduced EF. BRSD has been shown to remain widespread in HF patients despite advances in HF treatment. In our study, more than half of patients with HF with reduced and mildly reduced EF had severe OSA or CSA. We evaluated the relationship of OSA and CSA with clinical and paraclinical characteristics of HF. Decreased LVEF and ventricular ectopic activity are associated with CSA, while an increase in body mass index is associated with OSA. This once again emphasizes the importance of diagnosing BRSD in patients with HF, as well as further sleep studies. It is also necessary to evaluate the treatment of different types of sleep apnea, which we plan to evaluate in our next publication. Algorithms for managing patients with a combination of BRSD and HF should be developed.

Relationships and Activities: none.

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Surgical treatment of cardiac echinococcosis: a case report

Chernov I. I.[1], Kozmin D. Yu.[1], Demetskaya V. V.[1], Magomedov G. M.[1], Enginoev S. T.[1,2]

Echinococcosis refers is a chronic disease caused by tapeworms of the order *Cyclophyllidea*. Echinococcal cysts increase in size slowly and are often asymptomatic, and the symptoms of cardiac echinococcosis are nonspecific, which in turn can make diagnosis difficult. Early diagnosis and surgical treatment of this disease is crucial to prevent severe complications. Considering that the heart is affected extremely rarely, we want to demonstrate the successful surgical treatment.

Keywords: echinococcus, infection, pericarditis, cyst, heart masses.

Relationships and Activities: none.

[1]Federal Center for Cardiovascular Surgery, Astrakhan; [2]Astrakhan State Medical University, Astrakhan, Russia.

Chernov I. I. ORCID: 0000-0002-9924-5125, Kozmin D. Yu. ORCID: 0000-0002-6999-9671, Demetskaya V. V. ORCID: 0000-0003-1506-179X, Magomedov G. M. ORCID: 0000-0002-1278-9278, Enginoev S. T.* ORCID: 0000-0002-8376-3104.

*Corresponding author:
Soslan.Enginoev@gmail.com

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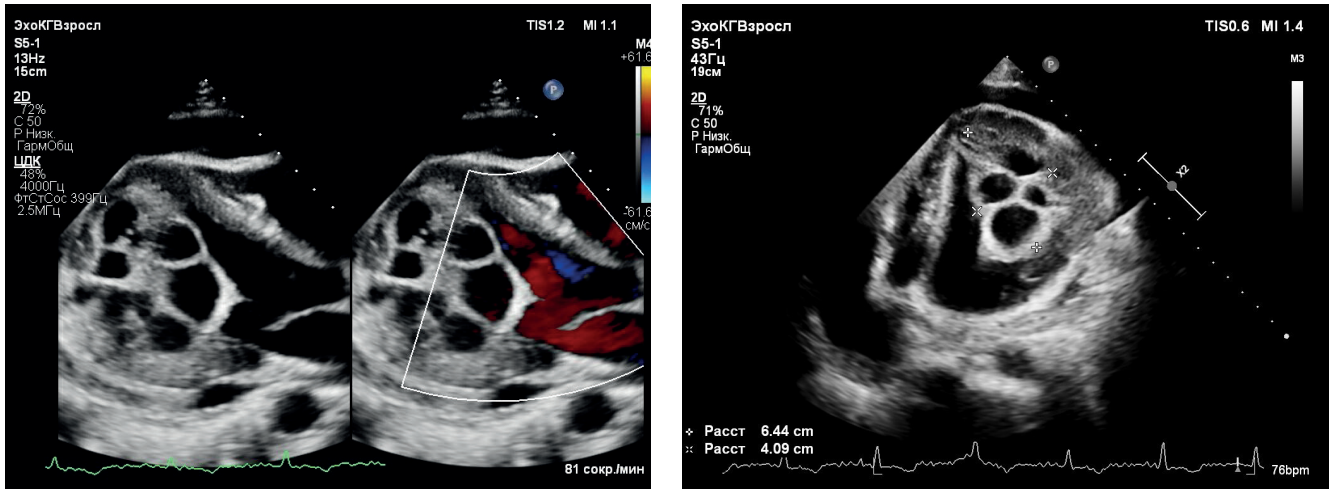
Key messages

- Cardiac echinococcosis is rare (0,5-2%). Cardiac echinococcal cysts are slow growing and nonspecific. The location of cysts determines the symptoms.
- The most serious complications of cardiac echinococcosis are ruptured pericardial cyst with the development of tamponade and anaphylactoid reaction.
- The case clearly reflects the need for an integrated diagnostic approach in verification.

Echinococcosis is an endemic parasitic disease in which the dog, sheep, wolf, jackal, fox, lynx, as a rule, are the definitive hosts [1]. Echinococcosis refers to chronic diseases caused by damage to human organs and tissues by the tapeworm of the order *Cyclophyllidea echinococcus*. Humans become infected from food and water contaminated with animal feces [1]. An echinococcus embryo, passing through the intestinal venous system, can enter the liver, and then the systemic circulation, after which it can enter any organ [1]. Although an echinococcal cyst can affect any organ, the liver is most commonly affected (60%). The second most commonly affected organ is the lungs (20-30%), while heart and brain damage is extremely rare, in 0,5-2% and 2% of cases, respectively [2, 3].

We present a case of surgical treatment of cardiac hydatid cyst.



A **B**

Figure 1. Transthoracic echocardiography. **A** — parasternal view. A multi-chamber formation is visualized in the LV cavity, 6,44×4,1 cm in size, area — 37 cm^2. **B** — four-chamber view, the length and width of the formation are indicated.

Case report

A 22-year-old man was hospitalized in the cardiac surgery department № 3 (September 12, 2022) with complaints of left chest pain, upper abdomen without any connection with physical activity, shortness of breath with minimal physical activity and periodically at rest.

Historical information: he considers himself ill for about 2 weeks, when the above complaints appeared. In this connection, he was examined at the local clinic, where an echinococcal cyst in the left ventricle (LV) was suspected. The patient underwent chest and abdominal computed tomography (CT) — no mass was detected, while pleural, pericardial and abdominal effusion was revealed. With a diagnosis of LV mass, the patient was referred for hospitalization at the Federal Center for Cardiovascular Surgery (Astrakhan). Heredity is not burdened. The patient denies bad habits.

Preliminary diagnosis at admission: LV mass (parasitic LV cyst (echinococcosis)) with a rupture into the pericardial cavity.

NYHA class III heart failure (IIB). ICD-10: I50.0

Physical examination was of moderate severity. The patient was adequate and had normal consciousness. Normosthenic type, satisfactorily nourished. The skin is of normal color, moderate moisture. Peripheral lymph nodes are not enlarged. The chest is symmetrical, painless. Lung percussion and auscultation were without abnormalities. No visual alterations of heart region. On auscultation: muffled heart sounds, normal rhythm, no heart murmurs. The pulse is of satisfactory filling, without deficit. There is no noise of neck arteries. Pulsation in the peripheral arteries of the feet is preserved. The tongue is moist and clean. The abdomen is soft, moderately painful on upper palpation, more on the right. There were no symptoms of peritoneal irritation. The liver percussion protrudes from under the edge of the costal arch +1 cm. The spleen is not palpated. The kidneys are not palpable. Tapping on the lower back painless on both sides. There was no peripheral edema. Blood oxygen saturation was 98%.

At admission, complete blood count noted eosinophilic leukocytosis (leukocyte count — 12,27, eosinophils — 48,4%). Biochemical test revealed alanine aminotransferase of 67,2 (reference values 0-41), creatinine of 128 mmol/l (reference values 60-105 mmol/l), C-reactive protein of 25,77 (reference values 0-6). According to common urine test, proteinuria of 0,18 g/l was detected.

According to transthoracic echocardiography (September 7, 2022) (Figure 1 A, B), there were following LV characteristics: LV end-diastolic volume — 64 ml; LV end-systolic volume — 14 ml; Simpson's LV ejection fraction — 77%; right ventricle (RV): basal section — 3,15 cm; left atrium (LA) — 2,9 cm; LA volume — 40 ml. Cardiac chambers were not dilated. Global myocardial contractility was normal. There was no impairment of local contractility. A multi-chamber mass was located in the LV cavity, occupying most of the LV cavity, attached and tightly connected, probably infiltrating the lateral LV wall, 6,45×4,1 cm in size (area — 37 cm^2). LV diastolic function was normal. The RV systolic function was not impaired. Pulmonary artery systolic pressure — 35 mm Hg. Separation of pericardial layers behind the free RV wall was 1,6 cm, behind the LV posterior wall — 0,7 cm, behind the LV lateral wall — 1,7-1,8

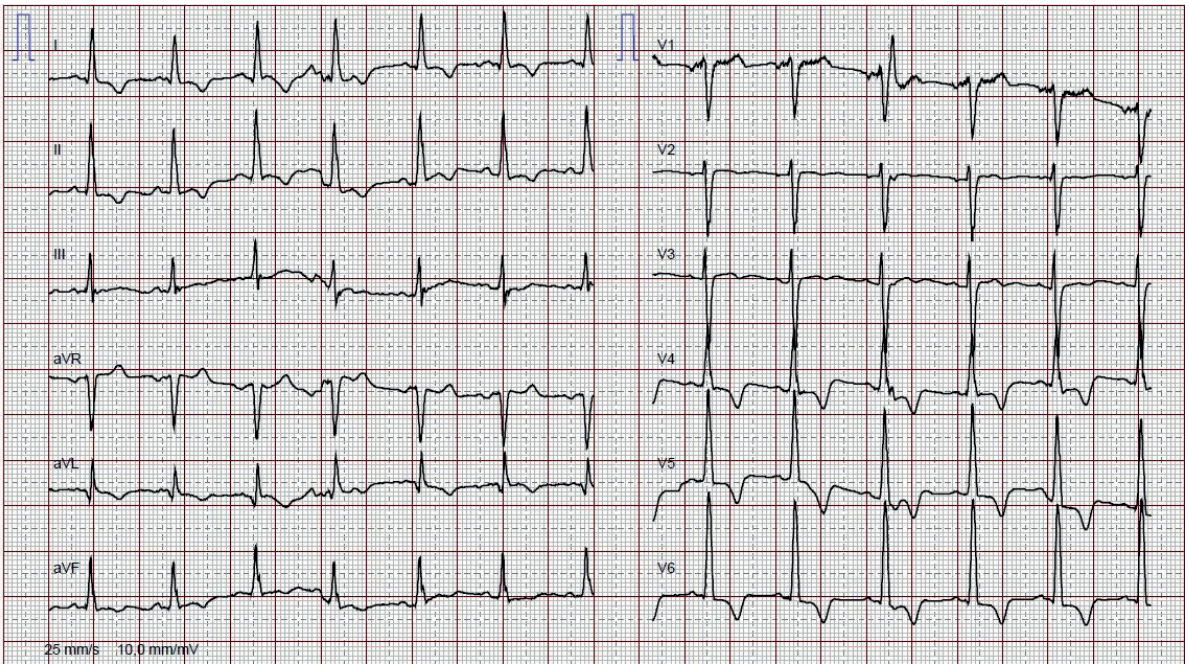


Figure 2. Electrocardiography.

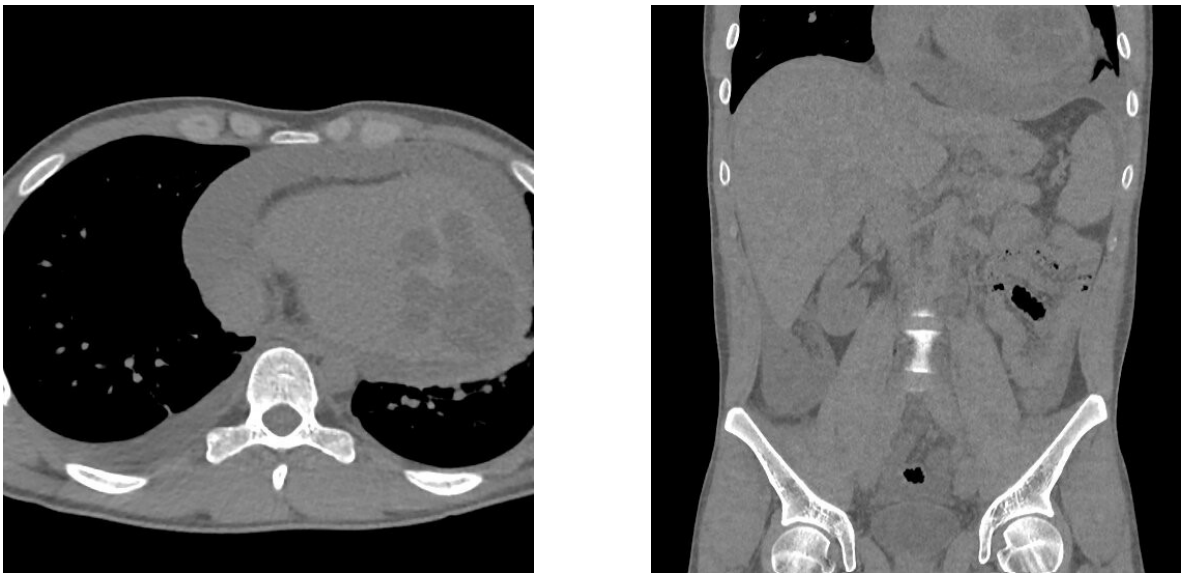


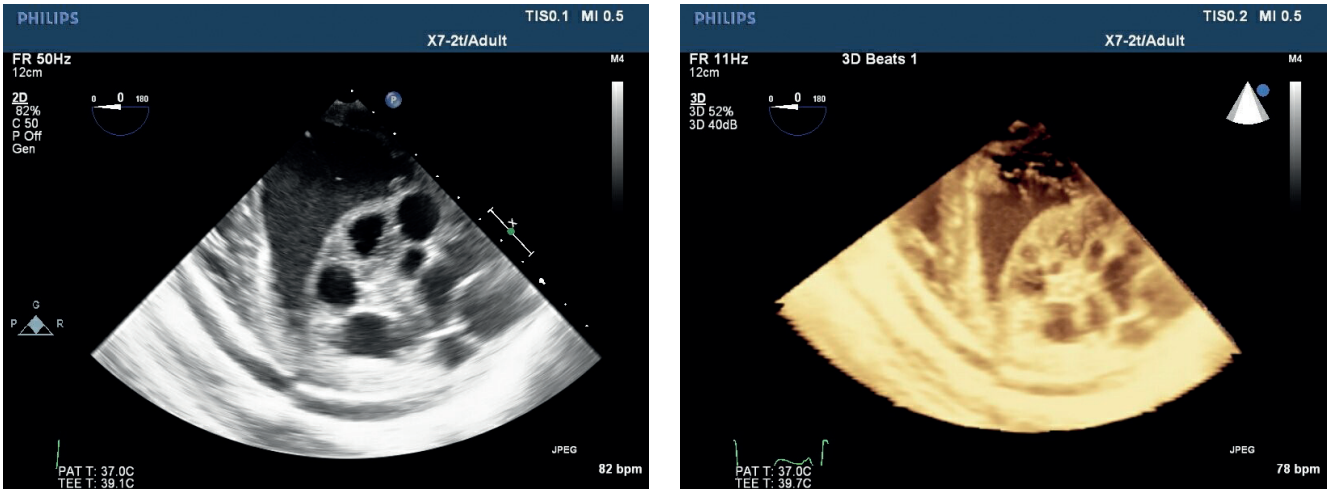
Figure 3. Cardiac CT.

cm, behind the vascular bundle — 0,9 cm, behind the left ventricular apex — 0,6-0,7 cm, behind the right atrium (RA) — 2 cm. The RV wall was with moderate collapse. Fluid was located in the left lateral recess and small pelvis. The pleural fluid was 5,5 cm on the left, 5,6 cm on the right.

According to electrocardiography (September 7, 2022) (Figure 2), sinus rhythm was noted with a heart rate of 80 bpm. The cardiac electrical axis was horizontal. LV systolic overload signs were revealed.

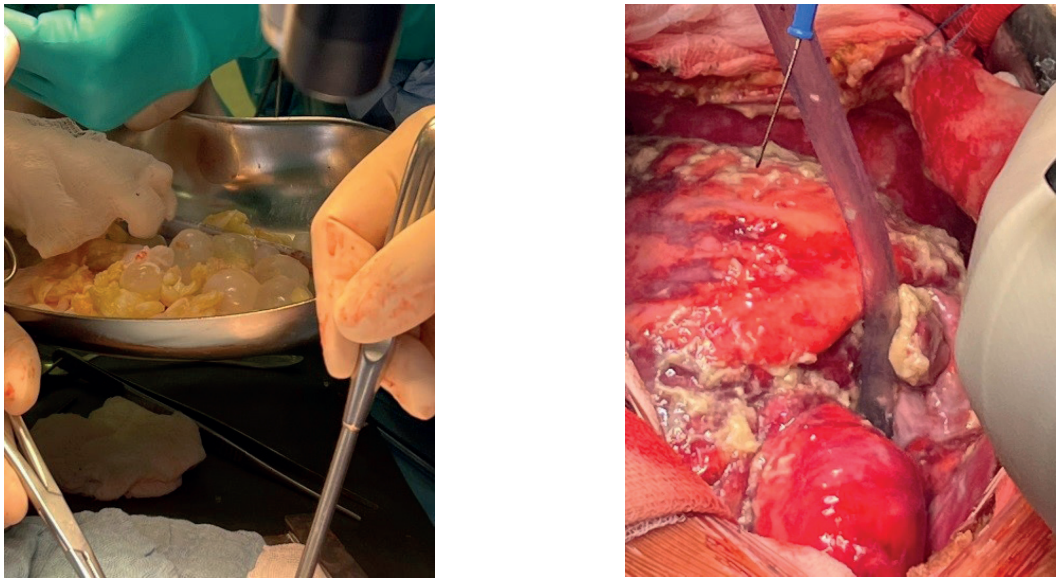
The patient underwent a chest CT (September 7, 2022). Circular fluid accumulation in the pericardial cavity was without collapse signs: 1,8 cm behind the RA, 1,6 cm behind the RV, 1,6 cm to the LV side; the approximate volume was 652 ml. The LV cavity had hypodense multi-chamber cystic formation 7,4×5,6 cm — echinococcus? (Figure 3)

On the back pleural wall there was a small amount of fluid — 1,5 cm thick on the right, 1,2 cm on the left.



A **B**

Figure 4. Intraoperative transesophageal echocardiography. **A** — LV cavity, **B** — 3D echocardiography.



A **B**

Figure 5. Intraoperative view. **A** — echinococcal cysts; **B** — inflammation in the pericardial cavity.

In order to rule out ischemic foci and mass in the brain, the patient underwent a cerebral CT (January 11, 2022) — no mass lesions were detected. Ischemic changes and intracerebral hemorrhages were not detected.

Intraoperative transesophageal echocardiography (Figure 4 A, B) (January 13, 2022) showed that a multi-chamber formation was located in the LV cavity, occupying most of the LV cavity, infiltrating the LV lateral wall with an area of 40 cm^2.

Cardiac access was through a median sternotomy. In the pericardial cavity, there was an inflammatory adhesive process, cloudy yellowish effusion with flakes. The pericardium was thickened up to 4 mm. Cardiolysis. Exploration revealed infiltrate in the area of LV lateral with a wall defect of up to 1,5×1 cm with serous-fibrinous fluid and single balls with transparent contents. A rupture of the echinococcal cyst into the pericardial cavity was revealed (Figure 5 A, B). The pericardial cavity was treated with a hypertonic NaCl solution. The cyst wall of LV lateral wall was additionally dissected. The echinococcal cyst contains many daughter cysts of a grayish color with a transparent content ranging in size from 3 mm to 2 cm. The contents of the cyst and fragments of the chitinous membrane were removed. The residual cavity in LV wall with dimensions of 6×4×3 cm was treated with germicides (hypertonic solution of sodium chloride and 85% solution of glycerol, exposure). It was not connected with the LV cavity and was sutured.

The early postoperative period was uneventful. On the 8th day, the patient was discharged home with a following clinical diagnosis:

Main: LV formation (echinococcal cyst) with a rupture into the pericardial cavity dated September 1, 2022. AHF dated September 1, 2022. ICD-10: D15.1.

Complications: stage IIB NYHA class III chronic heart failure, predominantly right-sided, decompensation.

Operation: removal of a cardiac echinococcal cyst dated September 12, 2022.

The patient was recommended to receive Nemazol 400 mg × 2 times a day for a month, then a break of 2 weeks, then according to the scheme (4 courses in total with breaks of 2 weeks each) + Torasemide 5 mg in the morning (long-term) + Spironolactone 50 mg in the morning (long-term) + Carvedilol 3,13 mg × 2 times a day (constantly) + Omeprazole 20 mg (1 month) + Acetylsalicylic acid 100 mg in the afternoon (constantly).

Discussion

Cardiac echinococcosis was first described by Williams in 1836. In 1846, Griesinger reported 15 autopsy cases. The first successful surgical intervention was performed by Long in 1932. The first successful on-pump operation for cardiac echinococcosis was reported [4, 5]. The most common location of echinococcal cysts is the liver (in 50-70% of cases), lungs (5-30%), muscles (5%), bones (3%), kidneys (2%), spleen (1%) and brain (1%). Cardiac echinococcosis is rare (0,5-2%) [4-6].

Echinococcal cysts increase in size slowly and are often asymptomatic [7, 8], and the symptoms of cardiac echinococcosis are nonspecific, which, in turn, can make diagnosis difficult [9]. Symptoms will vary depending on cyst location. Coronary blood flow is the main route by which parasite larvae reach the heart [10]. Due to the rich coronary blood supply, the LV in 55-60% of cases is the focus of cardiac echinococcosis, while RV — in 10-15% of cases, pericardium — in 7%, pulmonary artery — in 6-7%, LA — in 6-8%, RA — in 3-4%, and interventricular septum — in 4% [2, 6, 10, 11]. Thus, the most frequent localization is the LV free wall, as in our case [7, 12]. In general, surgical excision of cysts is the preferred method of treatment [7, 8]. There are several complications associated with echinococcal cysts, among which the most serious is acute rupture of the cyst into the systemic circulation [7, 8, 12]. In addition, a life-threatening anaphylactoid reaction may occur [8].

Early diagnosis of this condition is critical to prevent these complications. Chest x-ray usually show a normal cardiothoracic ratio or cardiomegaly [13]. Electrocardiographic findings vary depending on cyst location. Echocardiography is simple and useful in the diagnosis of cardiac echinococcosis [13]. CT and magnetic resonance imaging (MRI) provide additional information such as the size and anatomical relationship of the cysts [2, 6, 14]. Serological tests can be false negative in 10-20% of patients with hepatic echinococcal cysts, in 40% with pulmonary cysts, and in 50% with cardiac cysts, this is most likely due to an insufficient immune response [5, 6, 15]. However, enzyme immunoassay is one of the most specific serological tests that can be used, and a positive result for echinococcus antibodies confirms the diagnosis.

The main method of treatment of such patients is a combined approach, which consists in surgical resection of intracardiac echinococcosis with washing of the remaining cavity with hypertonic saline and simultaneous therapy with albendazole. During surgery, care must be taken to avoid rough manipulation of the heart, and to fix the surgical field with gauze soaked in saline to minimize local spread [3, 16-18].

Conclusion

Although cardiac echinococcosis can be fatal, it is rare and often asymptomatic in its early stages. Therefore, clinical suspicion is important for a correct diagnosis. Echocardiography, CT and MRI are useful in the diagnosis and localization of cardiac echinococcosis. Combined surgical resection of intracardiac echinococcosis, lavage of the remaining cavity with hypertonic saline, and simultaneous therapy with albendazole is the main treatment for such patients.

Relationships and Activities: none.

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Red flags to diagnose infiltrative cardiomyopathies

Reznik E. V.[1,2], Nguyen T. L.[1], Ustyuzhanin D. V.[3], Semyachkina A. N.[1], Shkolnikova M. A.[1]

Infiltrative cardiomyopathies are a group of diseases characterized by the deposition of abnormal substances in heart tissues, which leads to thickening of the walls or dilation of chambers with a secondary decrease in wall thickness and the development of diastolic, less often systolic, ventricular dysfunction. Most often, these are progressive diseases that, in the absence of adequate therapy, have an unfavorable prognosis. Clinical manifestations of infiltrative cardiac diseases are variable, which often leads to diagnostic difficulties and errors. In most cases, specific laboratory and morphological tests are required to confirm or clarify the diagnosis. Early diagnosis is critical to initiating therapy and improving patient prognosis. This article provides characteristic signs and symptoms, the so-called "red flags", making it possible to suspect infiltrative cardiomyopathies, diagnose them at an early stage and start life-saving therapy.

Keywords: infiltrative heart diseases, infiltrative cardiomyopathies, red flags, diagnostic keys, amyloidosis, sarcoidosis, hemochromatosis, Fabry disease, mucopolysaccharidosis, Danon disease, Pompe disease, heart failure, arrhythmia.

Relationships and Activities: none.

[1]Pirogov Russian National Research Medical University, Moscow; [2]City Clinical Hospital № 31, Moscow; [3]E. I. Chazov National Medical Research Center of Cardiology, Moscow, Russia.

Reznik E. V.* ORCID: 0000-0001-7479-418X, Nguyen T. L. ORCID: 0000-0002-8856-4542, Ustyuzhanin D. V. ORCID: 0000-0002-0402-3977, Semyachkina A. N. ORCID: 0000-0002-4026-3791, Shkolnikova M. A. ORCID: 0000-0001-7115-0186.

*Corresponding author:
elenaresnik@gmail.com

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Infiltrative cardiomyopathy (ICM) is a group of diseases characterized by the deposition of abnormal substances in the heart tissue, causing diastolic, less often systolic, dysfunction of the ventricle(s). Physiological and morphological characteristics of ICM are variable, which quite often leads to diagnostic and therapeutic errors.

The aim of this review was to analyze current studies on the clinical course of ICM, to identify symptoms and signs characteristic of ICM for the timely diagnosis of the disease — their "red flags" and "diagnostic keys".

Material and methods

We systematically searched the PubMed database for the following keywords: "infiltrative heart diseases", "infiltrative cardiomyopathies", "red flags", "keys for diagnosis", "amyloidosis", "sarcoidosis", "hemochromatosis", "Fabry disease", "mucopolysaccharidosis", "Danon's disease", "Pompe's disease", "oxalosis" and in the eLIBRARY.RU database for the corresponding Russian keywords for the period from January 1, 2012 to June 1, 2022. Based on the results of the search, 242 following literature sources were analyzed: consensus docu-

ments, meta-analyses, literature reviews, articles, case reports.

The review provides information on the definition, classification of ICM, their clinical manifestations, diagnostic methods, "diagnostic keys" and the examination algorithm.

Classification

The term ICMappeared in connection with modern ideas about the etiology, pathophysiology of diastolic dysfunction and restrictive cardiomyopathy (RCM) — the development of myocardial fibrosis or infiltration by certain substances or cellular elements. In 1997, Kushwaha SS, et al. proposed a classification of RCM, where ICM includes 5 diseases: amyloidosis, sarcoidosis, Gaucher disease, Hurler disease, fatty infiltration [1]. Subsequently, Moiseev VS, Braunwald E, Sewald JB, Madan N suggested some definitions and expanded the list of diseases in the ICM group [2-5] (Table 1). Currently, ICM includes cardiac amyloidosis, cardiac sarcoidosis, hemochromatosis, Fabry disease (FD), ANCA-associated vasculitis, Danon disease, Friedreich ataxia, mucopolysaccharidosis, cardiac oxalosis, etc.

Over the past decades, several revisions to ICM definitions have been proposed, but a single classification still does not exist. The MOGE(S) classification system, published in 2013, reflecting information about morphofunctional features, affected organs and tissues, genetic mutations, acquired causes, inspired us to the idea of ICM classification, which was named after the first letters of the parameters underlying the classification, MORAL-STAGE (Table 2).

As a simpler tool for clinical practice, we a staging system for ICM from 3 stages can be proposed (Figure 1):

Stage 1 — the stage of infiltration, the accumulation of foreign substances in the heart begins, which can be detected microscopically. Patients are mostly asymptomatic, and the standard clinical and imaging evaluation does not reveal any pathology. There may be an increase in specific biomarkers.

Stage 2 — the stage of structural and functional cardiac changes. Changes are revealed during echocardiography, magnetic resonance imaging (MRI), DPD-scintigraphy. In addition, the infiltrative process can be indirectly detected by pathologically elevated levels of high-sensitivity troponin T (hs-TnT). Clinically, this can be manifested by unexplained chronic fatigue, decreased physical activity. Symptoms and signs of heart failure (HF), as a rule, are not yet present.

Stage 3 — HF. It is characterized by pronounced structural changes, including fibrosis from local to diffuse. With echocardiography, structural and functional cardiac anomalies are more pronounced.

Table 1

Different classifications of ICM

Authors	Year	Diseases classified as ICM											
		Amyloidosis	Sarcoidosis	Hemochromatosis	Fabry disease	Gaucher disease	Mucopolysaccharidosis	Glycogen storage diseases	Cardiac oxalosis	Friedreich's ataxia	ANCA-associated vasculitis	Endomyocardial diseases, radiation injury	Radiation injury	Metastasis	Fat infiltration
Kushwala SS, et al. [1]	1997	+	+	-	-	+	+ (Hurler syndrome)	-	-	-	-	-	-	-	+
Моисеев В.С. [5]	2011	+	+	+	-	-	-	+	-	-	-	-	-	-	-
Braunwald E, et al. [4]	2001	+	+	+	+	+	-	+	-	-	-	-	-	-	-
Sewald JB, et al. [2]	2010	+	+	+	+	-	+	+ (Danon disease)	+	+	+ (Wegener's granulomatosis)	-	-	-	-
Madan N, et al. [3]	2020	+	+	+	+	-	+	+ (Danon disease)	+	+	+ (Wegener's granulomatosis)	+	+	+	-

Abbreviation: ICM — infiltrative cardiomyopathy.

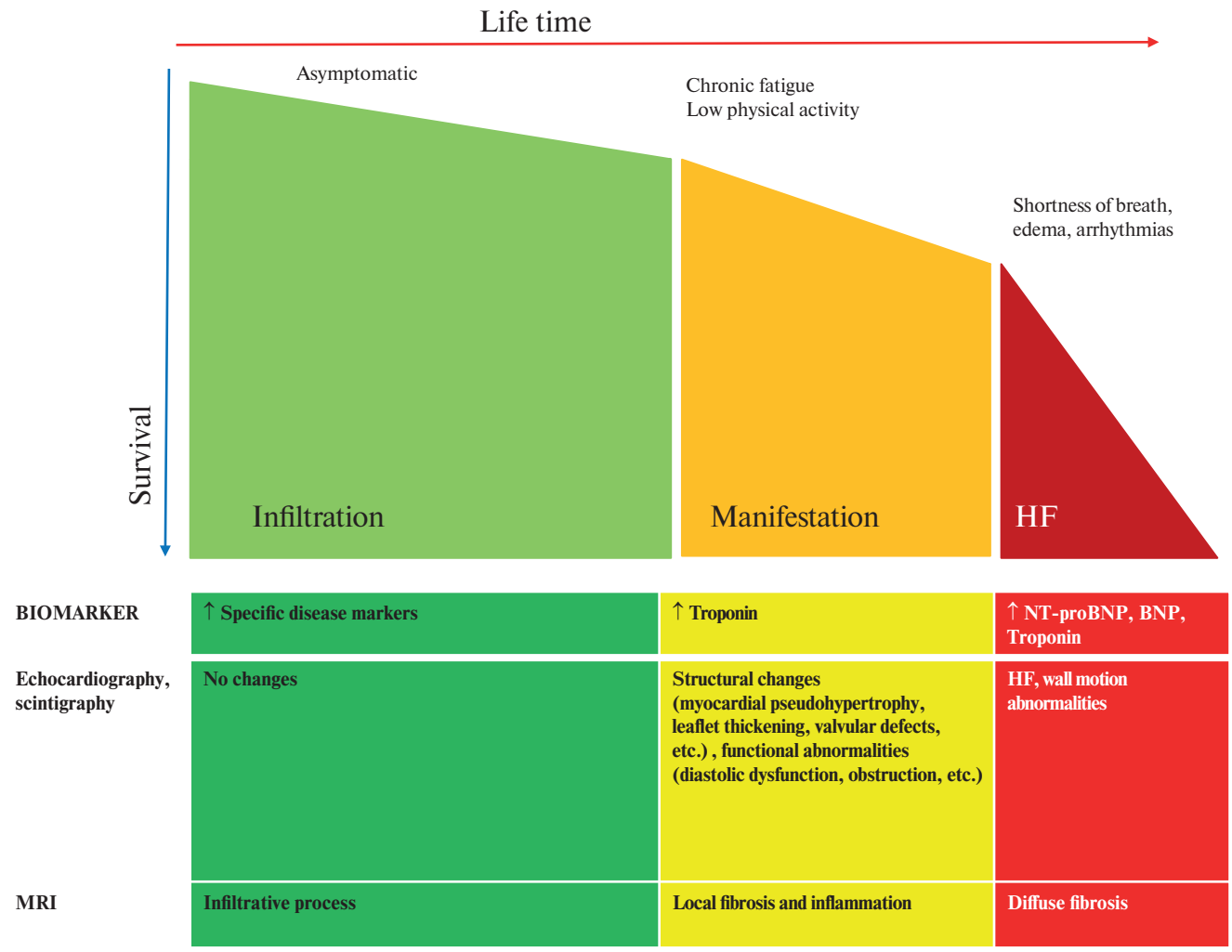

Figure 1. Staging of ICM.
Abbreviations: MRI — magnetic resonance imaging, HF — heart failure, BNP — brain natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide.

Increased levels of hs-TnT, the N-terminal pro-brain natriuretic peptide (NT-proBNP), brain natriuretic peptide. Clinically, shortness of breath, edema, weakness, fatigue, and arrhythmias are detected.

Understanding and identifying the 3 stages of cardiac involvement in ICM patients is important for treatment, the effectiveness of which is related to the stage of therapy initiation.

Clinical signs

ICM in young people (<30 years) is largely due to genetic abnormalities, while in the elderly (>65 years), amyloidosis, iron overload, and sarcoidosis are more common causes [2].

ICM in general are part of a systemic pathology whose phenotypic expression in other organs usually precedes cardiac manifestations. The role of the cardiologist is to look for heart disease in a patient who already has a diagnosis. In some cases, heart damage is a characteristic sign (Friedreich's ataxia, transthyretin amyloidosis (ATTR-amyloidosis), mucopolysaccharidosis), while the probability of correct diagnosis depends on the qualification and clinical alertness of the cardiologist in relation to ICM (Figure 2).

Carpal tunnel syndrome, especially bilateral, occurs in about half of patients with amyloidosis and often precedes cardiac manifestations by several years. It and proximal biceps tendon rupture, leading to Popeye sign, are "red flags" of amyloidosis [6]. Carpal tunnel syndrome can occur not only in amyloidosis, but also in mucopolysaccharidosis. Such signs of amyloidosis, as well as macroglossia or periorbital purpura, are highly specific but poorly sensitive and should not be used to exclude the disease (Figure 3).

Ocular impairments are not uncommon in patients with ICM. In FD, *cornea verticillata*, lens

Table 2

MORAL-STAGE classification

Designation	Characteristics	Letter code
M (Morpho-functional phenotype)	Morphofunctional signs or external clinical manifestations	D — dilated cardiomyopathy, H — hypertrophic cardiomyopathy, R — restrictive cardiomyopathy, E — early stage without clear phenotype, E(D) — early diagnosis of dilated cardiomyopathy, E(H) — early diagnosis of hypertrophic cardiomyopathy, NS — non-specific variant, 0 — without cardiac involvement, NA — not available.
O (Organ/system invovement)	What organs/systems are affected	H — heart (LV — left ventricle, RV — right ventricle, RLV — right and left ventricles), A — hearing organs, C — cutaneum, E — eyes, G — gastrointestinal tract, K — kidneys, Li — liver, Lu — lungs, M — skeletal muscles, N — nervous system, S — skeleton, 0 — without organ and system damage.
R (RIsk of cardiac death)	Cardiovascular risk	SCD — 5-year risk of sudden cardiac death according to the HCM risk SCD score (%), HF — 3-year risk of mortality for HF patients according to the MAGGIC score (%).
A (Age of onset, time on treatment)	Onset age and duration of pathogenetic therapy	2 digits: first — onset age (years), second — duration of pathogenetic therapy (years).
L (localization of pathological process)	Location of the pathological process outside or inside the cell	O — pathological process outside cells, I — pathological process inside cells, OI — pathological process outside and inside cells.
S (Stage)	ICM and heart failure stages with NYHA functional class	ICM stage (1-3). Heart failure stage (I-III). NYHA functional class (I-IV).
T (Treatment)	Treatment	0 — not treated, S — symptomatic therapy (treatment of HF, arrhythmias), P — pathogenetic therapy.
A (Type of arrhthmias, conduction disturbance	Arrhythmias, conduction disorders	0 — no arrhythmia, AF — atrial fibrillation, VT — ventricular tachycardia, AF+VT — atrial fibrillation and ventricular tachycardia, VF — ventricular fibrillation, AVRT — atrioventricular reciprocating tachycardia, LBBB — left bundle branch block.
G (Genetic)	Inheritance type	AD — autosomal dominant, AR — autosomal recessive, XL–X-linked, M — maternal line, 0 — no data, S — sporadic, N — non-hereditary, U — unknown.
E (Etiology)	Etiology	G — genetic, A — amyloidosis (AA — AA-amyloidosis, AL — AL-amyloidosis), S — sarcoidosis, H — hemochromatosis, U — unknown etiology, non-hereditary amyloidosis, H-T — secondary hemochromatosis in thalassemia, O — oxalosis, W — Wilson-Konovalov disease.

Abbreviations: ICM — infiltrative cardiomyopathy, HF — heart failure, NYHA — New York Heart Association.

opacity (Fabry cataract), increased tortuosity of the vessels of the conjunctiva and retina are observed [7]. Such signs usually do not impair vision, but correlate well with disease severity and genotype [8]. In contrast to FD, ocular lesions in mucopolysaccharidosis, including retinal pigment degeneration, retinal angiospasm, corneal clouding, edema, optic nerve atrophy, and glaucoma, can lead to significant visual impairment [9].

Skeletal muscle weakness indicative of a primary neuromuscular disorder (Friedreich ataxia, storage disease) usually precedes cardiac involvement and dominates the clinical picture, but sometimes skeletal myopathy is subtle and early symptoms or signs of disease may be due to cardiomyopathy (for example, in Danon disease) [10, 11].

If patients have symptoms such as fatigue, pain in the right hypochondrium, arthralgia, chondrocalcinosis, skin pigmentation, liver enlargement, especially the presence of cirrhosis, HF events, or diabetes, hemochromatosis should be suspected [12].

Electrocardiography

Electrocardiography (ECG) in ICM car reveal low QRS voltage, which is associated with the accumulation of non-conductive substances in the myocardium (glycosaminoglycans, amyloid, iron) and, possibly, also with myocardial edema [9, 13]. Low QRS voltage is a warning sign of the disease, often preceded by significant left ventricular (LV) hypertrophy; however, in hemochromatosis and amyloidosis, it manifests itself in late stages [14, 15]. There is usually a characteristic discrepancy between the limb leads and the precordial leads, with low voltage in the limb leads and normal or high voltage in the precordial leads. This discrepancy is not seen in low voltage QRS conditions such as pericardial or pleural effusion, obesity, emphysema, pneumothorax, or myxedema. The prevalence of low QRS

Figure 2. Red flags for ICM diagnosis.
Note: cardiac and systemic red flags with an increasing likelihood of ICM from internal (cardiac symptoms) to external circles (specific symptoms). Popeye sign: prominence above the elbow, with simultaneous concavity near the shoulder due to proximal biceps tendon rupture. Cherry-on-top or apical sparing: intact apical regions with high strain values, located in the central part and colored red against the background of low strain of the middle and basal regions in cardiac amyloidosis. Limb- precordial voltage dissociation: voltage mismatch between the limb leads and precordial leads, with low voltage in the limb leads while normal or sometimes high voltage in the precordial leads.
Abbreviations: AV block — atrioventricular block, LBBB — left bundle branch block, RBBB — right bundle branch block, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, DCM — dilated cardiomyopathy, VT — ventricular tachycardia, ICM — infiltrative cardiomyopathy, MRI — magnetic resonance imaging, SVT — supraventricular tachycardia, GFR — glomerular filtration rate, TIA — transient ischemic attack, AF — atrial fibrillation, CHF — chronic heart failure, ECG — electrocardiography, BNP — brain natriuretic peptide, GAA — acid alpha-glucosidase, GAG — glycosaminoglycan, Glc4 — glucose tetrasaccharide, LGE — late gadolinium enhancement, Lyso-Gb3 — globotriaosylsphingosine, NT-proBNP — N-terminal pro-brain natriuretic peptide.

voltage in AL amyloidosis ranged from 27% to 84% depending on its criterion. Notably, the absence of a low-voltage ECG pattern does not rule out ICM. The discrepancy between QRS voltage and LV mass measured on echocardiography may be even greater than QRS voltage alone [16].

In ICM, in addition to myocardial pseudohypertrophy, true hypertrophy also occurs (FD, Danon

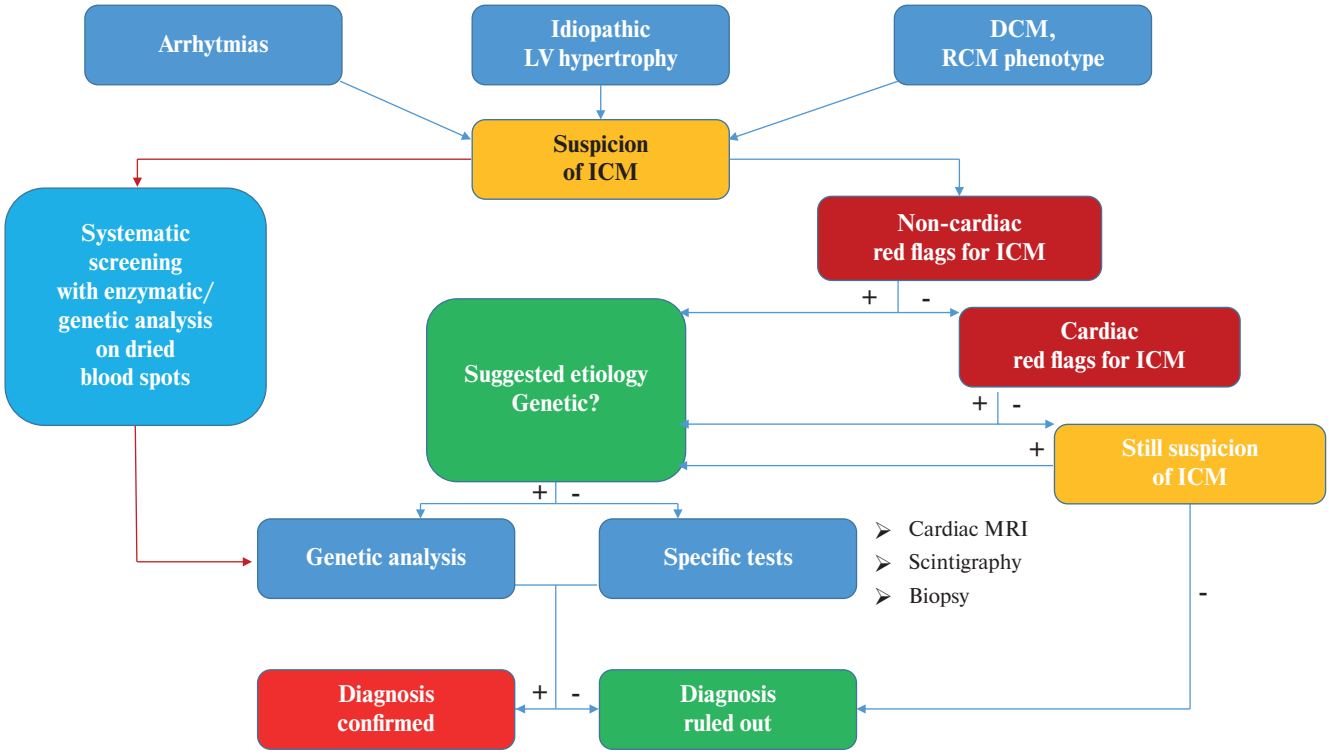

Figure 3. Proposed scheme-algorithm for ICM diagnosis.
Abbreviations: DCM — dilated cardiomyopathy, ICM — infiltrative cardiomyopathy, LV — left ventricle, MRI — magnetic resonance imaging, RCM — restrictive cardiomyopathy.

disease, partially ATTR-amyloidosis). In the second group, there is a sharp increase in the QRS amplitude with impaired repolarization (usually at a young age, even in childhood) [17].

For FD, short PR interval is often the first (and sometimes the only) sign of heart damage due to a decrease in P wave duration [18]. Wolff-Parkinson-White syndrome in the presence of LV hypertrophy is a screening criterion for Danon disease [10] and Pompe disease [19] diagnosis, while it is rare in hypertrophic cardiomyopathy (HCM).

Conduction disorders are common in patients with coronary artery disease [16]. In patients with LV hypertrophy, a QTc prolongation >440 ms with a simultaneous Sokolow-Lyon index <1,5 mV has a sensitivity of 85% and a specificity of 100% for the detection of cardiac amyloidosis, and a QTc <440 ms in combination with a PQ interval minus P-wave duration in lead II <40 ms had 100% sensitivity and 99% specificity for FD [17]. Patients with cardiac oxalosis usually develop complete atrioventricular block and ventricular conduction disorders [20]. In cardiac sarcoidosis, conduction disturbances were detected in 75% of patients [21].

Other ECG features reported in patients with ICM include abnormal P wave morphology and duration, a pseudoinfarct pattern with QS complexes in the anterior leads, and an unusual QRS axis [6]. Atrial fibrillation is also quite common in patients with ICM: in our retrospective study, 44% of patients with amyloidosis had some form of atrial fibrillation [14].

Holter ECG monitoring

Patients with ICM often have symptoms such as dizziness, fainting, and palpitations, for which Holter ECG monitoring (HM ECG) is indicated. In addition, HM ECG can be a useful tool for the differential diagnosis of LV hypertrophy etiology. In a study by Yamada S, et al. severe disorders of heart rate variability and turbulence have been shown in cardiac AL-amyloidosis. The standard deviation of all R-R intervals, the standard deviation of the 5-minute mean R-R intervals, and the turbulence slope were significantly lower in cardiac amyloidosis compared with HCM (P<0,001, respectively) [22].

According to Azevedo O, et al., myocardial hypertrophy with the presence of bifascicular block and areas of contrast enhancement in the delayed phase on MRI in the basal segment of LV inferolateral wall are characteristic signs of FD, and their absence makes it possible to exclude this diagnosis in a patient with an accuracy of 95,8% [23].

Presence of ventricular ectopic beats of 100 or more in HM ECG with a sensitivity of 67% and

Table 3

Revised 2012 Mayo staging system of AL-amyloidosis

Thresholds for risk factors	Stage		Death hazard ratio (95% CI)*
Troponin: Cardiac troponin T ⩾0,025 μg/l *or* High-sensitivity cardiac troponin T ⩾40 ng/l BNP: NT-proBNP ⩾1800 ng/l *or* BNP ⩾400 ng/l dFLC ⩾18 mg/dl	I stage	No risk factors	Reference
	II stage	1 risk factor	1,7 (1,2-2,3)
	III stage	2 risk factors	4,1 (3,1-5,5)
	IV stage	3 risk factors	6,3 (4,8-8,3)

Note: * — hazard ratios presented reflect the use of cardiac troponin T and NT-proBNP.

Abbreviations: BNP — brain natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide, dFLC — difference between involved and uninvolved free light chains.

a specificity of 80% identifies cardiac involvement in patients with systemic sarcoidosis [24].

Laboratory data

Cardiac biomarkers

Troponin T and NT-proBNP are included in the diagnostic criteria for heart damage in ICM [2, 25]. The normal range of their values almost excludes cardiac involvement, while an elevated level may indicate involvement of the heart, but is not specific for ICM, and should be interpreted in accordance with cardiac imaging data [25].

NT-proBNP and troponins are elevated in ICM patients due to an infiltrative process in the myocardium or direct toxic effects of abnormal substances on cardiomyocytes. In one study among patients with cardiac AL amyloidosis, NT-proBNP levels were never below the 97,5 percentile for normal individuals, indicating 100% sensitivity; moreover, the NT-proBNP threshold of 1285 ng/L was 92% accurate for detecting cardiac involvement [26]. NT-proBNP can serve as an early indicator of LV diastolic dysfunction in patients with iron overload and FD [15, 23]. Since an increase in NT-proBNP predicts the development of HF in amyloidosis, hemochromatosis, FD, and other ICM, routine determination of NT-proBNP during the observation of patients at high risk of ICM is recommended [15].

An increase in plasma level of hs-TnT is observed in most patients with ICM [27], including in patients without overt cardiac involvement, and represents a "red flag" for the disease. Moreover, hs-TnT is associated with HF severity, LV systolic dysfunction, and wall thickness in patients with ICM [27]. Hs-TnT is a useful marker for assessing the activity of cardiac sarcoidosis: sensitivity and specificity were 87,5% and 75,0%, respectively [28]. Interestingly, troponin is elevated in patients with ATTR cardiomyopathy, usually to a lesser extent than in AL cardiomyopathy, despite a greater increase in wall thickness and deterioration in LV systolic function [29].

In addition to NT-proBNP and troponin, several measures of myocardial injury and cardiac function have been proposed as biomarkers, but they lack sensitivity and specificity for detecting ICM, or there is insufficient evidence for their diagnostic value.

To assess the severity of heart damage in AL-amyloidosis, the already mentioned Mayo classification based on troponin T, NT-proBNP and the difference between free kappa and lambda light chains is of primary importance (Table 3) [6]. The most recent proposed system for staging cardiac ATTR amyloidosis uses NT-proBNP (>3000 pg/ml) and glomerular filtration rate (<45 ml/min) [30]. Staging in both systems is defined such that stage 1 has none of the criteria, stage 2 has 1 of the 2 criteria, and stage 3 has both criteria.

Amyloidosis

There are 36 types of amyloidosis, of which special attention will be paid to those in which heart involvement is frequently observed.

Unlike AL amyloidosis, no plasma or urine biomarkers are currently available to diagnose ATTR amyloidosis. There are newer serological assays for the endogenous transthyretin-retinol-binding protein ligand, which may serve as a tested biomarker in the future [31]. Separate studies have shown the predictive value of transthyretin as a serum marker for wild-type ATTR amyloidosis. A low serum transthyretin level at the time of diagnosis is prognostically unfavorable [6].

If AL-amyloidosis is suspected, additional laboratory tests are needed. First, electrophoresis is performed with the determination of the M-gradient and immunofixation electrophoresis of blood serum and urine, followed by a quantitative determination of free kappa and lambda light chains in blood serum, as well as the calculation of their ratio and

difference. A kappa-lambda ratio <0,26 indicates monoclonal lambda gammopathy, and a kappa-lambda ratio >1,65 indicates monoclonal kappa gammopathy [32]. In addition, 24-hour urine should be quantified for albumin and protein excretion. Proteinuria >500 mg per day indicates severe kidney damage.

Fabry disease

Detection of insufficient activity of α-galactosidase in blood plasma or leukocytes is the method of choice for laboratory diagnosis of FD in men [8]. On the contrary, in girls and adult women, enzyme activity may be within the normal range, so they need genotyping (detection of a *GLA* gene mutation) [8]. According to recent results, plasma globotriaosylsphingosine with a cut-off value of 2,7 ng/mL can serve as a useful and reliable biomarker to improve the diagnosis of FD in heterozygous women, as well as for therapeutic evaluation and monitoring [8].

Hemochromatosis

If the transferrin saturation is ⩾45% and/or the serum ferritin level is >200 μg/l in women or 300 μg/l in men, then a genetic study is necessary to determine the HFE genotype [2]. In homozygotes (C288Y/C288Y), the diagnosis of hereditary hemochromatosis was confirmed. In C288Y/H63D heterozygotes, other C288Y heterozygotes, or non-C288Y heterozygotes, careful exclusion of other hepatic or hematologic diseases should be considered [2]. Serum ferritin and its iron saturation ratio is also an easy way to monitor therapy.

Danon disease

Laboratory diagnostic tools include detection of normal acid maltase activity, vacuolization in skeletal and/or endomyocardial biopsy, LAMP-2 deficiency in various tissues, including leukocytes, and detection of a *LAMP-2* gene mutation. In Danon disease, there is an increase in following cardiomyocyte damage indicators: troponin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase [33]. *LAMP-2* is commonly included in genetic panels used to test unclassified cardiomyopathies, and gene testing is currently the most common and least invasive method used to diagnose Danon disease.

Oxalosis

Oxaluria must be confirmed by two urine samples. Primary hyperoxaluria is characterized by urinary oxalate excretion in most cases >0,7 mmol/1,73 m^2 per day, and in some cases may exceed 2,0 mmol/1,73 m^2 per day in contrast to normal urinary excretion, which is usually <0,45 mmol/1,73 m^2 per day [34].

As the glomerular filtration rate decreases, urinary oxalate excretion decreases and its estimate may be inaccurate. Plasma oxalate levels should be measured. The final diagnosis of primary hyperoxaluria is established using genetic studies [34].

Mucopolysaccharidosis

Mucopolysaccharidoses include 13 different conditions caused by a deficiency of specific enzymes in the glycosaminoglycan degradation pathway. Enzyme tests are usually performed on the blood. Identification of variants in the specific genes that encode each enzyme associated with mucopolysaccharidosis is useful for diagnosis confirmation, carrier detection, prenatal diagnosis, and phenotype prediction [9]. There is a growing trend to conduct genotype-based studies at the start of the survey, with the pathogenicity of identified genetic variants to be confirmed by measurement of enzyme activity and/or identification and/or quantification of glycosaminoglycan classes [9].

Echocardiography

The most common echocardiographic features seen in ICM are biatrial enlargement, symmetrical ventricular hypertrophy with small or normal LV size, pericardial effusion. Although asymmetric interventricular septal (IVS) hypertrophy, normal wall thickness, and ventricular dilatation may also occur. AL-amyloidosis is characterized by a rapid increase in heart wall thickness over several months, while the indexed stroke volume is usually greatly reduced against the background of HF with preserved ejection fraction (EF) [13].

The endocardial "binary" sign, first discovered and described by Pieroni, et al., in the form of a hyperechoic endocardium and a hypoechoic subendocardial space, can be a "red flag" of FD, although its specificity and sensitivity are not high [35]. Absolute papillary muscle area and the ratio of papillary muscle size to LV circumference have been proposed as an echocardiographic marker for FD [23].

In sarcoidosis, cardiac dilatation, LV systolic dysfunction, impaired local myocardial contractility without coronary artery involvement, focal intracardiac inclusions caused by granulomas, and pericardial effusion can be detected [36]. Wall aneurysm may develop with retraction of an area of fibrosis, especially in patients treated with corticosteroids.

The myocardium in ICM usually has a heterogeneous structure, may acquire a granular shiny pattern in cardiac amyloidosis, or contain inclusions of high echo intensity indicating granulomatous inflammation in cardiac sarcoidosis, as well as an inhomogeneous echo-dense signal, most noticeable in papillary muscles, in primary hyperoxaluria [2, 3]. The deposition of non-conductive substances in the myocardium explains the discrepancy between QRS voltage and LV hypertrophy severity, as described above.

Doppler ultrasound usually reveals mild valvular dysfunction, leaflet thickening, while more often the mitral and aortic valves are affected with the appearance of insufficiency and/or stenosis [13, 37]. Diastolic function is often significantly impaired. At the initial stages, there is an impaired relaxation, possibly progression to a restrictive pattern. With cardiac oxalosis, there is a rapid deterioration in diastolic function with an increase in filling pressure and a restrictive pattern [20]. In cardiac amyloidosis, the peak early diastolic velocity (e') decreases in the earliest stages of the disease and further decreases as the disease progresses [6].

The technique for assessing myocardial strain makes it possible to detect impaired ventricular longitudinal contraction before a decrease in EF and HF development. A LVEF strain coefficient was proposed with a threshold value of 4,1, which makes it possible to distinguish cardiac amyloidosis from HCM or normal with an accuracy of 91% [38]. Usually there is a severe impairment of the basal longitudinal strain with a relative preservation of apical strain [39]. This apical preservation has both high sensitivity and specificity for diagnosing cardiac amyloidosis [6]. Studies by Serra W, et al. proved that visualization of the strain rate makes it possible to differentiate sarcomeric HCM from cardiomyopathy in FD and cardiac amyloidosis [18]. Değirmenci H, et al., using strain assessment, showed that the detection of left atrial and ventricular myocardial strain may indicate subclinical LV dysfunction and subclinical electrophysiological cardiac changes in patients with respiratory sarcoidosis [40].

Left atrial function is very often impaired in ICM [40]. In cardiac amyloidosis, the prevalence of left atrial thrombosis is very high, even among patients with sinus rhythm [13].

Cardiac MRI

Cardiac MRI is the gold standard method for quantifying the cardiac size and volume, myocardial thickness, and determining ventricular EF. In delayed contrast-enhanced cardiac MRI, myocardial contrasting occurs both due to fibrosis, and due to impaired kinetics of the contrast agent and its delay in the intercellular space, where the accumulation of pathological proteins or other substances occurs in most ICMs. Amyloidosis is characterized by diffuse subendocardial accumulation with damage to all LV walls, which can be combined with early darkening of the blood pool due to rapid washout of contrast from the blood into the interstitial space, which is enlarged due to amyloid deposition. A typical contrast pattern is a red flag for the diagnosis of amyloidosis, which appears before a significant increase in myocardial mass develops [13]. Notably, atypical patterns of contrast agent accumulation (focal, diffuse transmural, or patchy) do not completely rule out cardiac amyloidosis.

In hemochromatosis, MRI can quantify the iron content in the heart, liver, and spleen by reducing the signal in T2 and T2* modes [41]. In sarcoidosis, it is possible to visualize sarcoid granulomas and assess the activity of inflammation by edema on T2-weighted images [42].

The absence of areas of delayed enhancement in IVS in male patients with suspected HCM is an indication for genetic screening for Danon disease [43]. In female patients with HCM, Danon disease should be suspected if inhomogeneous subendocardial enhancement without coronary involvement is detected [43]. The classical location of contrast enhancement in FD is the inferolateral wall in the basal segment, where fibrosis is detected in 50% of patients at a late disease stage [23].

T1 mapping without contrast agent injection can potentially distinguish HCM from ICM. Myocardial T1 values gradually increase in various pathological conditions from diffuse fibrosis, scar tissue to abnormal substances [6]. An increase in T1 values is observed before LV myocardial thickening or an increase in blood biomarkers and is a red flag for cardiac amyloidosis. For MRI machines with a field strength of 1,5 T, threshold values of native T1-mapping were determined (T1 <1036 ms to exclude cardiac amyloidosis with a negative predictive value of 98%; T1 >1164 ms to confirm cardiac amyloidosis with a positive predictive value of 98%), which allowed develop a diagnostic algorithm that involves the administration of a contrast agent only to patients with intermediate T1 values [44].

Areas with low T1 values represent sphingolipid deposition in FD associated with an increase in extracellular volume, but are not seen in cardiac amyloidosis. Karur GR, et al. confirmed that the IVS T1 value of 1220 ms can be used as a cutoff point for differentiating FD from HCM with a sensitivity of 97% and a specificity of 93% [45].

The T2-mapping technique can detect edema (an important element of AL-cardiomyopathy), inflammation, and can be used to detect active cardiac sarcoidosis [42], identify an increased risk of ventricular arrhythmias, and assess the adequacy of therapy [46].

Scintigraphy and positron emission tomography

Myocardial scintigraphy with phosphate-labeled complexes is the method of choice for diagnosing cardiac ATTR amyloidosis, among which ^{99m}Tc-pyrophosphate (PYP) is the most widely used in Russia. Intense retention of phosphate-labeled complexes is mostly pathognomonic for ATTR amyloidosis, and the absence of uptake usually excludes this diagnosis [47].

To determine the severity of cardiac damage, the Perugini scale was proposed: degree 0 — no cardiac uptake; grade 1 — cardiac uptake which is less intense than the bone signal; grade 2 — cardiac uptake with intensity similar or greater than bone signal; grade 3 — cardiac uptake with much attenuated or absent bone signal [47]. This system was included in the algorithm for non-biopsy diagnosis of cardiac ATTP amyloidosis in suspected cardiac amyloidosis based on a combination of clinical signs, biohumoral and/or imaging data. When the Perugini grade is 2 or 3 and no monoclonal protein is found, the diagnosis of cardiac ATTR amyloidosis is confirmed. When a monoclonal protein or Perugini grade 1 is detected, histological confirmation and amyloid typing are suggested. Finally, when the Perugini degree is 0, ATTR-cardiomyopathy is unlikely [47]. There is a quantitative scale for differentiating cardiac AL and ATTR amyloidosis, based on the calculation of the ratio of cardiac uptake to that in the contralateral side. The value of this indicator >1,5 showed a sensitivity of 97% and a specificity of 100% for the detection of cardiac ATTR amyloidosis [48].

For other ICMs, more advanced nuclear imaging techniques, including combined positron emission tomography and MRI, can examine the role of inflammation along with assessment of angina and coronary blood flow and identify early signs of cardiac involvement. Numerous studies have demonstrated the presence of abnormal perfusion on both single photon emission computed tomography and positron emission tomography in the absence of epicardial coronary artery disease, suggesting microvascular dysfunction [49].

Conclusion

The diagnosis of ICM is challenging due to phenotypic heterogeneity, multiple organ involvement, lack of a single non-invasive diagnostic tool, and limited awareness in the medical community. Interaction between experts from different fields is often required. Recent studies have challenged the dogma of ICM as a rare, incurable disease and have redefined the epidemiology and therapeutic possibilities of these conditions. Absence or delay in diagnosis of ICM can have a major impact on outcome, as potentially life-saving treatment may not be initiated or recommended at the stage of irreversible change. For timely identification, physicians potentially facing ICM should pay attention to its "red flags" that require specific diagnosis.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Omega-3 polyunsaturated fatty acids in the prevention of postoperative atrial fibrillation in open heart surgery: a systematic review and meta-analysis

Rubanenko O. A., Rubanenko A. O., Davydkin I. L.

Aim. To evaluate the literature data on the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) in the prevention of postoperative atrial fibrillation (POAF) in elective cardiac surgery, including on- or off-pump coronary artery bypass grafting and/or valve replacement and/or repair.

Material and methods. The search for studies was carried out using the PubMed database and Google Scholar from 2005 to January 31, 2022. From the initially identified search results, 19 articles were analyzed. The design of articles corresponded to randomized clinical trials. Omega-3 PUFAs was selected as an interventional effect. The studies were to include, as an end point, the assessment of new POAF cases in the early period after open heart surgery.

Results. The meta-analysis included 15 studies with 3980 patients, of which 1992 (50,0%) patients took omega-3 PUFAs. POAF occurred in 587 (29,5%) patients receiving omega-3 PUFAs and 679 (34,2%) patients on standard therapy (hazard ratio, 0,8, 0,68-0,93, p=0,004). There is a variation in effect size for POAF patients in the presented randomized clinical trials relative to the axis of the central trend and heterogeneity of studies with a significant number of patients included (I^2=51%, p=0,01).

Conclusion. Our systematic review and meta-analysis showed the effectiveness of omega-3 PUFAs in the prevention of POAF during open heart surgery.

Keywords: omega-3 polyunsaturated fatty acids, atrial fibrillation, cardiac surgery.

Relationships and Activities: none.

Samara State Medical University, Samara, Russia.

Rubanenko O. A.* ORCID: 0000-0001-9351-6177, Rubanenko A. O. ORCID: 0000-0002-3996-4689, Davydkin I. L. ORCID: 0000-0002-4318-4247.

*Corresponding author: olesya.rubanenko@gmail.com

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Omega-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), decrease the risk of cardiovascular events by reducing the incidence of supraventricular and ventricular arrhythmias [1]. Analysis of the cellular and molecular mechanisms of omega-3 PUFA action is relevant for the prevention of arrhythmias.

The use of omega-3 PUFAs to prevent new episodes of atrial fibrillation (AF) in the early postoperative period of open-heart surgery is controversial. The first studies demonstrated the effectiveness of prescribing omega-3 PUFAs in the short-term perioperative period of coronary artery bypass grafting (CABG) [2, 3]. More recent studies have shown opposite results, showing that omega-3 PUFAs do not lead to an additional reduction in the risk of postoperative AF (POAF) [4, 5]. Thus, conflicting data on the antiarrhythmic effect of omega-3 PUFAs in patients undergoing cardiac surgery in terms of the prevention of POAF raises questions. Systematic review and meta-analysis will determine the effectiveness of omega-3 PUFAs in the short term to prevent new cases of AF in cardiac surgery.

The aim of this review was to evaluate literature data on the efficacy of omega-3 PUFAs in the prevention of POAF during elective cardiac surgery, including on- or off-pump CABG and/or heart valve repair/replacement.

Material and methods

Search for publications and selection of studies. The search for information was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [8] in the PubMed and Google Scholar database and included research search using search queries, keywords (including MeSH) and logical operators. Poster presentations, dissertations, symposiums, case reports, books, meta-analyses, systematic reviews, review articles, letters to readers, recommendations, animal studies were not used according to the search goal. English and Russian were established as the main language of literature.

Keywords in the PubMed database: (omega-3 polyunsaturated fatty acids) AND (postoperative atrial fibrillation) AND (coronary artery bypass graft) AND (cardiac surgery). To search the Google Scholar database, we used the query: omega-3 polyunsaturated fatty acids AND postoperative atrial fibrillation AND coronary artery bypass graft AND cardiac surgery.

The PICO (population, intervention, comparator, outcome) model was used to search for studies. The last search was carried out on January 31, 2022. The systematic review included randomized controlled trials (RCTs) where the initial data were adequately presented — study design, clinical characteristics of patients, type of intervention, control and comparison group. Cardiac surgical interventions such as on- and off-pump CABG, and/or heart valve repair/replacement were taken into account. Omega-3 PUFAs, prescribed in the perioperative period for the prevention of POAF, was chosen as an interventional effect. The studies were to include as an endpoint an assessment of POAF risk by electrocardiographic monitoring or recording.

Risk of bias. The risk of bias for individual studies included in the systematic review was assessed using The Cochrane Collaboration's tool for assessing risk of bias. The overall risk of bias was assessed in 6 domains: random sequence generation; allocation concealment; blinding of patients and personnel; blinding of outcome assessment; incomplete outcome data and selective reporting [12, 13].

Statistical analysis. Statistical processing was performed using Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020). The meta-analysis was carried out according to the random effects model, using the inverse dispersion method. The results of meta-analysis were presented as a forest plot. Statistical heterogeneity was assessed using Pearson's chi-square test and heterogeneity index (I^2>40%, p<0,10). Meta-analysis of the absolute values in the study and control groups was performed according to the data on absolute values, taking into account the number of subjects in the compared groups. We assessed the efficacy of omega-3 PUFAs in addition to standard therapy compared with standard therapy using odds ratios (OR) with 95% confidence intervals (CI).

Results

Data extraction and synthesis. Primary screening using the search queries described above yielded 23 PubMed publications and 924 results using the Google Scholar database. Of the 947 results found, 44 posts were duplicated, so only non-duplicate search results were left.

The study did not include symposiums, case reports and case series, books, meta-analyzes, systematic reviews, reviews, letters to readers, guidelines, animal studies. After analyzing the titles and their abstracts, 122 publications contained full-text articles. Evaluation of full-text copies resulted in the exclusion of 102 publications due to lack of specified data or submission of sub-analysis. Thus, the initially identified search results, the summary quantitative data of 19 articles (2,0%) were processed using statistical analysis (Figure 1). Subsequently, a detailed analysis of each article was carried out with an assessment of the study design, which allowed the selection of RCTs. English and Russian have been set as the language limit.

The analysis of each presented study took into account information on the number of patients in each group, type of cardiac surgery, blinding, incidence of POAF, placebo, duration of omega-3 PUFA therapy, methods for verifying POAF, and follow-up duration.

Characteristics of the included RCTs. The main characteristics of RCTs meeting the inclusion criteria are presented in Table 1.

Assessement of bias risks. The risks of bias in the included RCTs were assessed in accordance with the Cochrane Collaboration questionnaire (Tables 2, 3). It should be noted that most RCTs were open-label. This could affect performance and detection bias. Ten studies did not note the results of randomization sequence generation, while concealment of the randomization sequence was not specified in 11 studies, and was absent in 3 studies (selection bias). Two studies did not specify, and 1 study did not specify outcome biases (attrition bias). Sixteen studies were not specified and 2 studies lacked information on the presentation of study results (selective reporting).

An evaluation of the included RCTs showed that 4 studies, due to the high risk of bias, could not be used for meta-analysis, as a result of which they were excluded [18-21]. For the remaining studies, design, methodology, and patient characteristics were con-

Table 1

Characteristics of the included studies

Author, year	Type of surgery	Blinding	N (treatment/ control)	Control group	Dose of omega-3 PUFAs	Duration of administration	Criteria for AF	Duration of monitoring	Duration of follow-up
Calo, 2005 [2]	Off-pump CABG (n=19 (23,7%) patients), on-pump	Open-label	160 (79/81)	Standard therapy	Omega-3 PUFA 2 g/day (EPA:DHA = 1:2)	24-36 hours after surgery and until discharge	AF >5 min or requiring intervention	Continuous ECG monitoring for 4-5 days, then daily ECG recording until discharge	4 weeks after discharge
Heidt, 2009 [3]	On-pump CABG	Double-blind	102 (52/50)	Soybean oil 100 mg/kg per day	Fish oil 100 mg/kg per day (EPA:DHA = 0,9:1)	Continuous infusion started before surgery and continued until transfer to the ICU	AF >15 min	Continuous ECG monitoring in the ICU, then daily ECG	Until discharge
Saravanan, 2010 [4]	On-pump CABG	Double-blind	103 (52/51)	Olive oil 2 g/day	Omega-3 PUFAs 2 g/ day (EPA:DHA = 1,2:1)	At least 5 days before surgery and continued until discharge	AF ⩾30 sec	Continuous ECG monitoring for 5 days, then daily ECG recording	During inpatient treatment
Heidarsdottir, 2010 [6]	Off-pump CABG (n=20 (11,9%) patients), on-pump CABG (n=103 (61,3%) patients), heart valve repair/replacement (n=45 (26,8%) patients)	Double-blind	168 (83/85)	Olive oil 2 g/day	EPA 1,24 g/ day, DHA 1 g/ day.	5-7 days before surgery and until discharge or 2 weeks after surgery	AF >5 min	Continuous ECG monitoring in the ICU	During inpatient treatment (<14 days)
Sorice, 2011 [7]	Off-pump CABG (n=93 (46,3%) patients), on-pump CABG (n=108 (53,7%) patients)	Not indicated	201 (96/105)	Standard therapy	Omega-3 PUFAs 2 g/ day (EPA:DHA = 1:2)	5 days before surgery and until discharge	AF >5 min or requiring intervention due to hemodynamic instability	Continuous ECG monitoring for 4 days after surgery, and then daily ECG recording or in case of complaints	In the hospital
Farquharson, 2011 [8]	On-pump CABG (n=122 (62,9%) patients), combination of CABG and heart valve repair/ replacement (n=72 (37,1%) patients)	Double-blind	194 (97/97)	Sunflower oil 15 ml/ day	Omega-3 PUFAs 15 ml/ day (2,7 g EPA and 1,9 g DPC)	3 weeks before surgery	AF >10 min or requiring intervention	Continuous ECG monitoring for 72 hours, then daily ECG recording	In the hospital

Table 1. Continuation

Author, year	Type of surgery	Blinding	N (treatment/ control)	Control group	Dose of omega-3 PUFAs	Duration of administration	Criteria for AF	Duration of monitoring	Duration of follow-up
Sandesara, 2012 [9]	Off-pump CABG (n=61 (25,1%) patients), on-pump CABG (n=154 (63,4%) patients), combination of CABG and heart valve replacement (n=28 (11,5%) patients)	Double-blind	243 (120/123)	Corn oil 2 g/day	Omega-3 PUFAs 4 g/day (EPA:DHA = 1,24:1)	Up to 16 days	AF or atrial flutter requiring intervention	Continuous ECG monitoring and ECG recording	14 days
Mozaffarian, 2012 [10]	Off-pump CABG (n=460 (30,3%) patients), valve replacement (n=785 (51,8%) patients), radiofrequency ablation (12 (0,8%) patients). Not specified (259 (17,1%) patients)	Double-blind	1516 (758/758)	Olive oil 2 g/day	Omega-3 PUFAs 1 g/day (EPA:DHA = 1,24:1)	3-5 days before surgery and at least 10 days after surgery	AF ⩾30 sec	Continuous ECG monitoring for 5 days and daily ECG recording or when arrhythmia occurs	In the hospital
Veljović, 2013 [11]	On-pump CABG	Not indicated	40 (20/20)	Standard therapy	Omega-3 PUFAs 100 ml	4 days before surgery 100 ml omega-3 PUFAs at a rate of 25 ml/h	AF >5 min	ECG recording every 6 hours for the first 24 hours for 48 hours	In the hospital
Stanger, 2014 [12]	On-pump CABG (n=24 (61,5%) patients), CABG and valve replacement (n=15 (20,0%) patients)	Double-blind	39 (19/20)	Standard therapy	Omega-3 PUFAs 0,5 ml/kg/body weight before surgery, 50 ml after surgery	3 infusions (42 hours and 18 hours before surgery and 42 hours after surgery)	According to ECG	ECG recording every day	3 days
Wilbring, 2014 [13]	On-pump CABG	Not indicated	198 (99/99)	Standard therapy	Omega-3 PUFAs 2 g/day (EPA:DHA = 1,24:1)	5 days before surgery and until discharge	According to ECG	Continuous ECG monitoring until discharge	In the hospital
Lomivorotov, 2014 [14]	On-pump CABG	Double-blind	39 (18/21)	Standard therapy	Omega-3 PUFAs 200 mg/kg/day	200 mg/kg/day, within 24 hours before induction of anesthesia followed by 100 mg/kg/day after surgery from days 2 to 7	AF >30 sec within 10 days after surgery	Continuous ECG monitoring	2 years

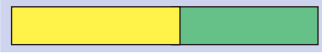
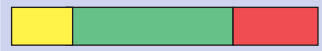
Table 1. Continuation

Author, year	Type of surgery	Blinding	N (treatment/ control)	Control group	Dose of omega-3 PUFAs	Duration of administration	Criteria for AF	Duration of monitoring	Duration of follow-up
Feguri, 2017 [15]	On-pump CABG	Double-blind	28 (14/14)	Standard therapy	Omega-3 PUFA 0,2 mcg/kg	4-hour intraoperative infusion	ECG recording	ECG recording	In the hospital
Joss, 2017 [16]	On-pump CABG (n=373 (66,7%) patients), CABG and/ or valve replacement (n=186 (33,3%) patients)	Double-blind	561 (284/275)	Mineral oil 2 g/day	Omega-3 PUFAs 2 g/ day (EPA:DHA = 3:2)	5 days before surgery and after surgery for 4 weeks	AF >5 min or requiring intervention due to hemodynamic instability	Telemonitoring or ECG recording	Within 4 weeks after surgery
Farahani, 2017 [17]	Off-pump CABG (n=29 (7,2%) patients), on-pump CABG (n=372 (92,8%) patients)	Double-blind	401 (202/199)	Olive oil 2 g/ day	Omega-3 PUFAs 2 g/day (EPA:DHA = 1,5:12)	5 days before surgery and until discharge	AF >5 min	Continuous ECG monitoring until discharge	In the hospital
Belan, 2014 [18]	On-pump CABG	Open-label	120 (60/60)	Standard therapy	Omega-3 PUFAs 2 g/day (EPA:DHA = 1,2:1)	5 days before surgery and after surgery for 3 months	ECG recording	Continuous ECG monitoring in the ICU, then daily ECG recording until discharge and in case of complaints	In the hospital
Kolesnikov, 2015 [19]	On-pump CABG	Open-label	73 (33/40)	Standard therapy	Intravenous infusion of omega-3 PUFA emulsion at a dose of 100 ml per day	Once in the first 5-7 days after the operation	AF >30 sec within 7-10 days after surgery	ECG recording	In the hospital
Panov, 2008 [20]	CABG (not specified)	Open-label	189 (94/95)	Standard therapy	Omega-3 PUFA at a dose of 2 g/day	7±4 days before CABG, and early after surgery (24-36 h) and continued for 14 days	ECG recording	Continuous ECG monitoring in the ICU, then daily ECG recording until discharge and in case of complaints	In the hospital
Rubanenko, 2017 [21]	On- and off-pump CABG	Open-label	102 (51/51)	Standard therapy	Omega-3 PUFAs before surgery at a dose of 2 g/day and at a dose of 1 g/day after operation	On average, 5 days before surgery and within 3 weeks after operation	ECG recording	Continuous ECG monitoring in the ICU, then daily ECG recording until discharge	In the hospital

Abbreviations: DHA — docosahexaenoic acid, CABG — coronary artery bypass grafting, ICU — intensive care unit, PUFAs — polyunsaturated fatty acids, AF — atrial fibrillation, ECG — electrocardiogram, EPA — eicosapentaenoic acid.

Table 2

Assessment of the risks of bias in the included RCTs. The authors' judgments about each element of the risk of bias in percent for all included RCTs are presented

Random sequence generation	Selection bias	
Allocation concealment	Selection bias	
Blinding of patients and personnel	Performance bias	
Blinding of outcome assessment	Detection bias	
Incomplete outcome data	Attrition bias	
Selective reporting	Reporting bias	

— low risk — uncertain risk — high risk

Table 3

Summary assessment of the bias risk. An overview of the authors' judgments about each element of the bias risk for each included RCT is presented

	Random sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Calo, 2005	+	?	−	?	+	?
Heidt, 2009	?	?	+	?	+	?
Saravanan, 2010	+	?	+	+	+	?
Heidarsdottir, 2010	?	?	+	?	+	?
Sorice, 2011	?	?	?	?	+	+
Farquharson, 2011	+	+	+	+	+	?
Sandesara, 2012	?	?	+	+	+	?
Mozaffarian, 2012	+	+	+	?	+	?
Veljović, 2013	?	?	?	?	?	?
Stanger, 2014	+	?	+	?	+	−
Wilbring, 2014	?	?	?	?	+	?
Lomivorotov, 2014	+	+	+	?	−	−
Feguri, 2017	+	?	+	+	+	?
Joss, 2017	+	+	+	?	+	?
Farahani, 2017	+	+	+	?	?	?
Panov, 2008	?	−	−	−	+	?
Belan, 2014	?	−	−	−	+	?
Kolesnikov, 2015	?	−	−	−	+	?
Rubanenko, 2017	?	?	−	−	+	?

— low risk — uncertain risk — high risk

sistent with the aim of this study. The results of the meta-analysis are presented in Figure 2.

Assessment of the risk of publication bias. Figure 3 shows a funnel plot. Noteworthy is the scatter in the size of effects for patients with POAF in the presented RCTs relative to central tendency axis. Some asymmetry of the funnel plot is noted with a considerable number of studies included in the analysis.

Ultimately, the meta-analysis included 15 studies with 3980 patients, of which 1992 (50,0%) patients were taking omega-3 PUFAs. POAF occurred in 587 patients on omega-3 PUFAs and 679 patients on standard therapy (hazard ratio, 0,8, 0,68-0,93, p=0,004; I^2=51%, p=0,01).

Discussion

Data from our systematic review and meta-analysis demonstrated a favorable effect of omega-3 PUFAs in the prevention of POAF during open heart surgery. Our results are consistent with previous information from the literature [22]. An important difference of our systematic review is the inclusion of Russian papers [18-21]. On the other hand, domestic publications on the study of omega-3 PUFA effect on the prevention of POAF showed a high risk of bias, which was the reason for not including these sources in the meta-analysis.

The effectiveness of the use of omega-3 PUFAs is due to the anti-inflammatory, antioxidant effect, which determines the incidence of this arrhythmia [20, 21]. It was shown that patients with POAF during surgery had higher malondialdehyde levels in the atrial tissues compared with patients without arrhythmia (4,47 μmol/mg vs 3,85 μmol/mg protein, p<0,01). There was a strong direct correlation both in the placebo and treatment group between the level of malondialdehyde in atrial tissues and in the blood. Among patients receiving omega-3 PUFAs, the concentration of C-reactive protein was 35,4% less, while leukocytosis was 32,5% higher compared with the control group. This study demonstrated that a strategy of prescribing omega-3 PUFAs with vitamins C and E not only reduced the occurrence of arrhythmia, but also reduced the oxidative stress. This short-term, safe treatment has improved the outcomes of patients undergoing on-pump cardiac surgery [23].

Wang H, et al. (2018), Wilbring M, et al. (2014) on the effectiveness of omega-3 PUFAs in the prevention of POAF is inconsistent with the data of Gu J, et al. (2016), Stanger O, et al. (2014) [12, 13, 22, 24]. For example, elevated serum and atrial concentrations of omega-3 PUFAs, EPA, or DHA have not been associated with a reduction in AF [25] or inflammation [26] in some studies.

Domestic publications also demonstrate the favorable effect of omega-3 PUFAs in reducing the risk of POAF, which, according to our results, leads to a decrease in the severity of hemodynamic disorders and the length of stay in the hospital [18-21]. In addition, a study by Rubanenko OA, et al. (2017) showed that patients taking omega-3 PUFAs have a lower concentration of interleukin-6 in the postoperative period, as an inflammation factor, myeloperoxidase and superoxide dismutase, as markers of oxidative stress, which confirms the additional effects of the drug [21].

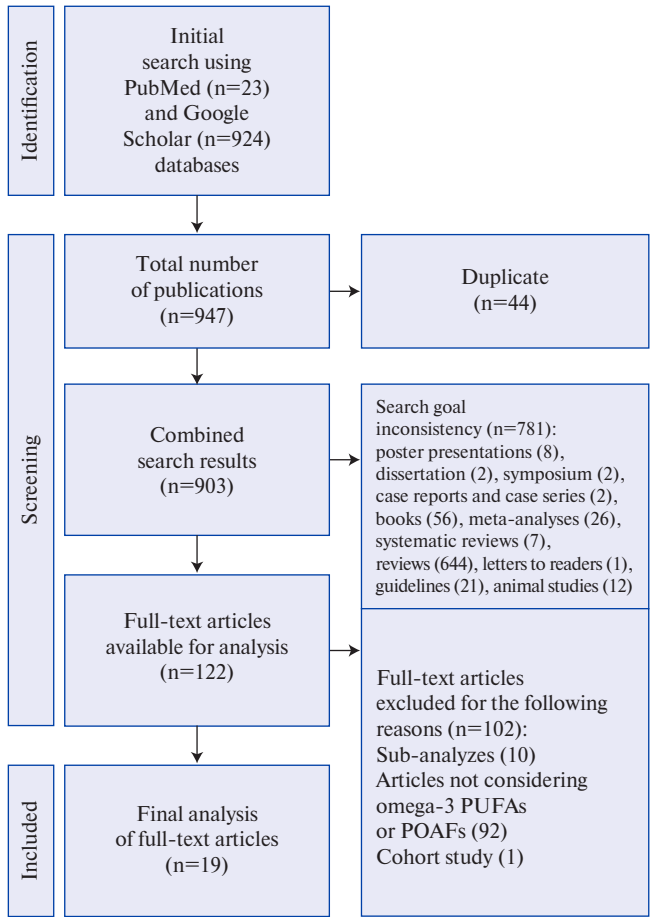


Figure 1. Publication selection algorithm.
Abbreviations: PUFAs — polyunsaturated fatty acids, POAF — postoperative atrial fibrillation.

Omega-3 index test can characterize the individual response to the drug and contribute to a better understanding of the pharmacokinetics and pharmacodynamics of PUFAs. Considering the results of the Garg PK, et al. (2021), showing a U-shaped relationship between the concentration of PUFAs and AF, the prevention of arrhythmia will depend on personal targeted incorporation of omega-3 acids into cell membranes [27].

In 2018, a meta-analysis was conducted, where out of 269 identified articles, 14 studies were included involving 3570 patients [28]. PUFAs reduced the incidence of POAF (OR, 0,84 (95% CI 0,73-0,98), p=0,03). Subgroup sensitivity analysis found that omega-3 PUFAs were effective in preventing POAF for an EPA/DHA ratio <1 (OR, 0,51 (95% CI 0,36-0,73), p=0,0003), but not in an EPA/DHA ratio >1 or an unknown ratio. In addition, efficacy in reducing POAF was evident when placebo was standard

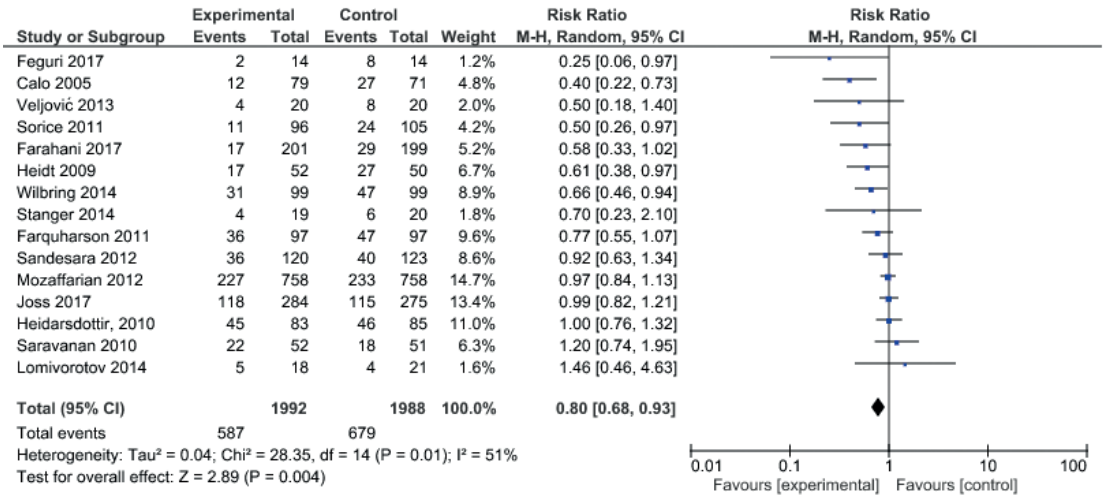


Figure 2. Random effects model comparing omega-3 PUFAs and standard therapy.
Note: the squares show the weighted effect size for each specific study (the square size corresponds to the weight of the studies); the bars show 95% CI; the diamond shows the weighted average of the POAF relative risk. Below in the experimental group is interpreted as a favorable sign.
Abbreviations: CI — confidence interval, POAF — postoperative atrial fibrillation.

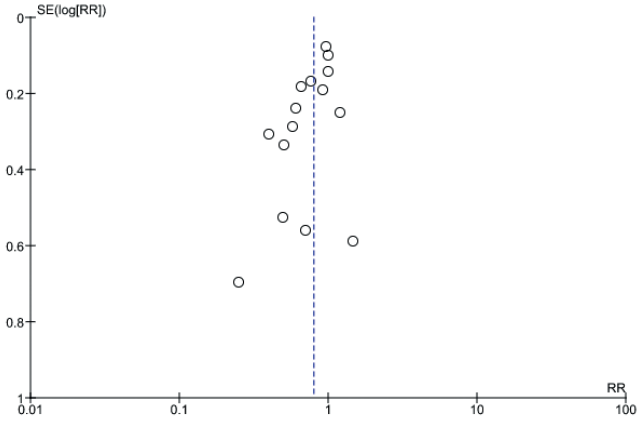


Figure 3. Risk of publication bias (funnel plot) of POAF prevention assessment with standard therapy and omega-3 PUFAs.
Note: vertical line represents the weighted average of the POAF risk ratio. This line reflects how much the experimental group is better (or worse) than the control group.
The funnel is formed because the accuracy of the effect estimate increases as the sample size increases. Therefore, smaller studies will form a wide bottom of the funnel (large variation in effect estimates cause small studies to be far from the weighted mean RR) and large studies will form a narrow top (greater accuracy in effect estimates, so that the results of such studies will not diverge far from weighted mean RR).
Abbreviations: POAF — postoperative atrial fibrillation, SE — standard error, RR — relative risk.

therapy versus placebo with fish oil inclusion (OR, 0,59 (95% CI 0,44-0,80), p=0,0005). Noteworthy that PUFAs reduced POAF after CABG (OR, 0,68 (95% CI 0,47-0,97), p=0,03), but not after other cardiac surgeries.

Thus, the results of our meta-analysis demonstrate the effectiveness of omega-3 PUFAs in reducing the risk of POAF during open heart surgery, including CABG and valvular replacement/repair. However, the analysis of Russian publications demonstrates the shortcomings in the collection and presentation of information on the subject of a systematic review, which may increase the risk of bias. Further prospects for omega-3 PUFA use dictate the need to determine the contingent of patients with coronary artery disease who are prescribed this drug in the perioperative period, mainly undergoing CABG, with an assessment of the omega-3 index as an indicator reflecting the content of omega-3 acids in the membrane of myocardial cells, factors of inflammation, oxidative stress, myocardial damage and dysfunction. This will make it possible to single out the group with the highest efficiency in prescribing omega-3 PUFAs.

Study limitations. This study has a number of limitations, many of which are related to design, in particular, the inclusion of patients undergoing off- or on-pump CABG and/or heart valve repair/replacement, the exclusion of cohort studies, and the presented heterogeneity of data from RCTs.

Conclusion

Our systematic review and meta-analysis showed the effectiveness of omega-3 PUFAs in patients with coronary artery disease in the prevention of POAF during off- or on-pump CABG and/or heart valve repair/replacement.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Impact of assessment of fractional flow reserve and instantaneous wave-free ratio on clinical outcomes of percutaneous coronary intervention: a systematic review, meta-analysis and meta-regression analysis

Golukhova E.Z., Petrosyan K.V., Abrosimov A.V., Bulaeva N.I., Goncharova E.S., Berdibekov B.Sh.

Aim. To conduct a systematic review and meta-analysis to compare clinical outcomes in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) using conventional coronary angiography (CAG) or fractional flow reserve (FFR)-guided PCI. In addition, FFR-guided PCI and PCI guided with instantaneous wave-free ratio (iFR) were compared.

Material and methods. PubMed, Google Scholar databases were searched for studies comparing clinical outcomes in patients with CAD undergoing CAG-guided or FFR/iFR-guided PCI. Dichotomous data analysis was presented as odds ratio (OR) with 95% confidence interval (CI). Adjusted hazard ratio (HR) values from studies with similar evaluation criteria were pooled for meta-analysis.

Results. Six randomized controlled trials (RCTs) from 184 publications were selected for this systematic review and meta-analysis. A total of 2193 patients (mean age, 64,2 years, mean follow-up, 28,0 months) were included. Analysis of RCTs showed that CAG-guided and FFR-guided PCI did not have a significant difference in the incidence of major adverse cardiovascular events (MACE) (OR: 0,78; 95% CI: 0,61-1,00; p=0,05; I^2=0%), all-cause death (OR: 0,86; 95% CI: 0,51-1,44; p=0,57; I^2=0%) or emergency revascularization (OR: 0,69, 95% CI: 0,46-1,04, p=0,08, I^2=0%). However, FFR-guided PCI was associated with a reduced risk of subsequent MI compared with CAG-guided PCI (OR: 0,70; 95% CI: 0,50-0,99; p=0,04; I^2=0%). In addition to the results of previous RCTs, we conducted a meta-analysis of 3 observational studies. In total, the CAG-guided and FFR-guided PCI groups included 165012 and 11450 patients, respectively. A meta-analysis showed that FFR-guided PCI was associated with a reduced risk of all-cause mortality (HR: 0,74; 95% CI: 0,63-0,87; P=0,0003) and MI (HR: 0,75; 95% CI: 0,61-0,94; p=0,01). In addition, there was no significant difference between iFR- and FFR-guided PCI in terms of MACE (OR: 0,97; 95% CI: 0,76-1,23; p=0,81), all-cause mortality (OR: 0,66; 95% CI: 0,40-1,10; p=0,11), MI (OR: 0,83; 95% CI: 0,56-1,24; p=0,37) or emergency repeated revascularization (OR: 1,16; 95% CI: 0,85-1,58; p=0,34).

Conclusion. FFR-guided PCI is associated with a reduced risk of all-cause mortality and subsequent MI compared with CAG-guided PCI. At the same time, the iFR-guided PCI is not inferior to the FFR-guided method in terms of MACE rate.

Keywords: percutaneous coronary intervention, coronary angiography, fractional flow reserve, instantaneous wave-free ratio.

Relationships and Activities: none.

A.N. Bakulev National Medical Research Center for Cardiovascular Surgery, Moscow, Russia.

Golukhova E.Z. ORCID: 0000-0002-6252-0322, Petrosyan K.V. ORCID: 0000-0002-3370-0295, Abrosimov A.V. ORCID: 0000-0001-5907-9508, Bulaeva N.I. ORCID: 0000-0002-5091-0518, Goncharova E.S. ORCID: 0000-0003-0038-5193, Berdibekov B.Sh.* ORCID: 0000-0001-7717-4971.

*Corresponding author:
b.berdibekov@yahoo.com

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Key messages

- Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) versus angiography-guided PCI is associated with a reduced risk of all-cause mortality and myocardial infarction.
- PCI guided with instantaneous wave-free ratio is not inferior to FFR-guided method in terms of the rate of major adverse cardiovascular events.

Fractional flow reserve (FFR) is currently the gold standard for determining the functional significance of borderline coronary artery (CA) stenosis [1]. At the moment, the FFR ⩽0,8 is defined as a cut-off point of the hemodynamic significance of narrowing and is reflected in current guidelines for myocardial revascularization [2, 3]. However, as shown in studies, there is a frequent discrepancy between the angiographic and hemodynamic severity of coronary stenoses. Thus, according to the FAME randomized controlled trial (RCT), only 35% of stenoses of 50-70% (visual estimation) were hemodynamically significant [4]. In the visual assessment subgroup, ~20% of stenosis cases of 71-90% was not significant. Only in the case of a visual assessment of stenosis as >90%, sufficient agreement was achieved with hemodynamic severity (~96%). According to study results, myocardial revascularization by FFR-guided percutaneous coronary intervention (PCI) in addition to angiography, compared with visual assessment of CA narrowing, significantly reduced the composite endpoint rate, which included death, non-fatal myocardial infarction (MI), and repeated revascularization within 1-year follow-up. However, no significant differences were found for individual components of the primary endpoint in the form of mortality, non-fatal MI, and repeated myocardial revascularization [4]. In addition, in most subsequent small RCTs and a few observational studies, the strategy of FFR-guided PCI in addition to angiography has not demonstrated a prognosis advantage over visual assessment by coronary angiography (CAG). Notably, most of these studies had single center design with small sample sizes and few events.

Istantaneous wave-free ratio (iFR) is a recently developed method for determining the functional significance of stenosis, which does not require the administration of agents that cause hyperemia, in particular adenosine, and also has a number of advantages compared to FFR [1]. Although there are some differences between FFR and iFR in the results, according to two multicenter RCTs iFR-SWEDEHEART and DEFINE-FLAIR [5, 6], there is no significant difference in main endpoints depending on the method of stenosis assessment.

In the light of the above data, we conducted a systematic review and meta-analysis of studies where myocardial revascularization by PCI was performed under the guidance of FFR in addition to angiography compared with CAG-guided PCI, as well as a comparison of two methods of hemodynamic severity assessment (FFR and iFR).

Material and methods

Search for publications and selection of studies. The information retrieval algorithm was developed in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [7] in the PubMed database (Medline), Google Scholar. The last data search for inclusion in this analysis was conducted on October 15, 2022. We used the following keywords to search PubMed (Medline) databases: ((percutaneous coronary intervention) OR (PCI) OR (coronary revascularization)) AND ((coronary angiography)) AND ((ffr) OR (fractional flow reserve)) AND ((ifr) OR (instantaneous free-wave ratio) OR (wave-free ratio)). The following query was used to search the Google Scholar database: percutaneous coronary intervention, PCI, coronary angiography, ffr, fractional flow reserve, ifr, instantaneous free-wave ratio, wave-free ratio. To select eligible studies for inclusion in this systematic review and meta-analysis, two authors independently reviewed abstracts and full-text reports for inclusion criteria.

Inclusion/exclusion criteria. There were following inclusion criteria for primary studies in a systematic review followed by meta-analysis: studies with access to full texts; all participants were adults (18 years of age or older); studies with adequately presented baseline data, in particular on the incidence of endpoints. The systematic review includes both RCTs and observational studies, including registries that compared the strategy of myocardial revascularization by PCI method according to FFR/iFR data with the strategy of myocardial revascularization based on CAG data. The lower threshold for follow-up period for patients was set to 12 months. Articles in languages other than English, case reports, preclinical studies, reviews, and expert opinions were excluded from the meta-analysis.

Assessment of methodological quality. The assessment of bias risk was carried out in accordance with the Cochrane criteria for assessing the metho-

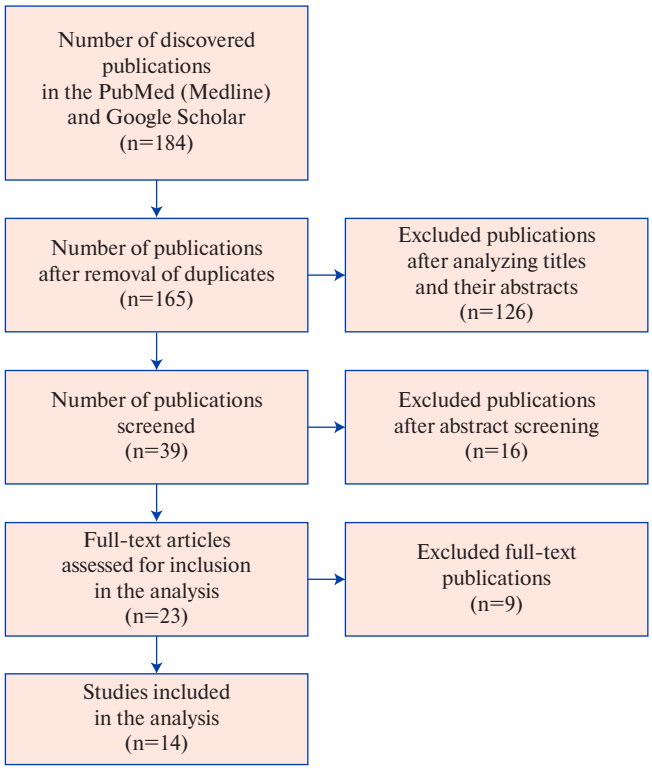


Figure 1. Flowchart for the selection of studies included in the review.

dological quality of RCTs (RoB 2 tool). In the case of observational studies, assessment was carried out according to the Newcastle-Ottawa Quality Assessment Form for Cohort Studies [8]. All inconsistencies were eliminated by discussion by the authors.

Statistical analysis. Statistical data processing was performed using Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) and Comprehensive Meta-Analysis 3.0 (Biostat, NJ). The main results are presented as a forest plot. Testing for the statistical heterogeneity was carried out using a Q-test based on χ^2, as well as the heterogeneity index I^2. Interpretation of the assessment of statistical heterogeneity, according to the I^2 index, was carried out according the Cochrane guidelines, according to which I^2 of 0-40% corresponds to insignificant heterogeneity; 30-60% — moderate heterogeneity; 50-90% — significant heterogeneity; 75-100% — high heterogeneity. Dichotomous data were analyzed using the Mantel-Haenszel test and presented as an odds ratio (OR) with a 95% confidence interval (CI). The random effects model was adopted at $P<0,1$ in the χ^2 test and $I^2>40\%$, the fixed effect model at $P\geqslant 0,1$ in the χ^2 test and $I^2\leqslant 40\%$. As initial values for the survival meta-analysis, the values of the adjusted (obtained for the multivariate model, adjusted) hazard ratio (HR) was used. In this case, the meta-analysis was carried out according to the random effects model, using the inverse dispersion method. The effect was considered significant at $p<0,05$. The possible presence of bias associated with the predominant publication of positive study results was analyzed using a funnel plot. Publication bias was also assessed using the Egger test.

Results

Literature search results. Keyword search in the PubMed (Medline), Google Scholar database revealed 184 publications. The number of publications after the removal of duplicates was 165. After analyzing the titles and their abstracts, 39 publications corresponded to the goal. 23 publications passed full-text screening. Thus, 14 studies were finally included in our review, while the selection process for relevant studies is shown in Figure 1.

General characteristics of studies

The total number of patients in RCTs [4, 9-13] included in this analysis was 2193. The mean age of patients was 64,2 years. The mean follow-up period was 28 months. In three observational retrospective studies [14-16], the total number of patients was 2313. Given that observational studies are subject to the influence of confounders, these retrospective studies were excluded. However, we analyzed the results of recent large registries [17-19] regarding the impact on the prognosis of a revascularization strategy with an assessment of FFR in addition to angiography. The total number of patients in these registries was 176462. Data on study design, baseline patient characteristics are summarized in Tables 1 and 2.

Comparative analysis of FFR-guided revascularization in comparison with CAG-guided strategy according to RCT data

All of the included 6 RCTs [4, 9-13] reported on the incidence of major adverse cardiac events (MACE). The total number of patients was 2193. The average follow-up duration was 28 months. During the follow-up period, the endpoint in the form of MACE was 306 cases (13,9%). A meta-analysis showed a trend towards a lower incidence of MACE in the group of patients with FFR-guided PCI compared with CAG-guided strategy (OR: 0,78; 95% CI: 0,61-1,00; p=0,05) (Figure 2). For the individual components of MACE, data on all-cause death were reported in five studies for a total of 1964 patients in these studies. The meta-analysis showed no significant difference between groups in the incidence of all-cause death (OR: 0,86; 95% CI: 0,51-1,44; p=0,57) (Figure 2). In four studies reported data on the incidence of myocardial infarction, the

total number of patients was 1895 (follow-up period, 12 months). In each of the above studies, no significant difference was found between the incidence of MI depending on the strategy of myocardial revascularization (FFR-PCI and CAG-PCI). However, their combined analysis revealed a lower incidence of myocardial infarction in the group of patients with FFR-guided PCI compared with CAG-guided strategy, and these differences were significant (OR: 0,70; 95% CI: 0,50-0,99; p=0,04) (Figure 2). Data on non-elective revascularization were presented only in two studies with the total number of 1325 patients (follow-up period, 12 months). There was no significant difference between the groups in the frequency of repeated myocardial revascularization (OR: 0,69; 95% CI: 0,46-1,04; p=0,08) (Figure 2). It is noteworthy that statistically insignificant result was obtained for homogeneity as follows: p>0,1; and heterogeneity index I^2=0%, suggesting low heterogeneity among the studies included in this analysis.

Risk of bias in included studies

The funnel plot for MACE showed some right-sided asymmetry, which indicates a publication bias (Figure 3). This conclusion was confirmed by the quantitative results of the Egger test: t=1,93; p=0,06. With respect to all-cause mortality and MI,

Table 1

General characteristics of studies included in the systematic review

First author	Year	Design	Patients	Duration, months	Inclusion criteria	Exclusion criteria
FFR vs CAG						
Tonino [4]	2009	РКИ	509/496	12	CAD (>50% stenosis in at least two large epicardial coronary arteries) that required revascularization based on angiographic and clinical findings	Recent STEMI (<5 days); NSTE-ACS with peak creatinine kinase levels >1000 U/L; CABG in history; cardiogenic shock; extremely tortuous or calcified CAs; life expectancy <2 years; pregnancy
Puymirat [14]	2012	Retrospective	222/495	60	Stable or unstable angina with small coronary vessels (diameter <3 mm)	Patients with PCI and vessel diameter ⩾3 mm; shunt stenting; STEMI or NSTEMI
Chen [9]	2015	РКИ	160/160	12	Silent myocardial ischemia, stable or unstable angina with coronary artery bifurcation lesion (stenosis ⩾50% in both the main vessel and the lateral branch, each with a reference diameter of ⩾2,5 to ⩽4,5 mm)	MI within 1 month; LVEF <30%; CABG in history; distal lesion of LCA trifurcation with non-recanalized chronic total occlusion; coronary artery calcification, requiring rotational atherectomy; elective surgery requiring interruption of antiplatelet therapy 6 months after PCI; GFR <40 ml/min/1,73 m^2; platelet count <10×10^9/l; liver dysfunction; pregnancy; life expectancy <1 year; no informed consent
Layland [10]	2015	РКИ	176/174	12	Patients with a clinical diagnosis of recent NSTEMI and at least one risk factor who were eligible for randomization if emergency invasive treatment was planned within 72 hours of an episode of myocardial ischemia or if there was recurrent ischemic symptoms within 5 days	Ischemia symptoms without therapy, hemodynamic instability, STEMI, intolerance to antiplatelet agents, expected duration <1 year
Park [11]	2015	РКИ	114/115	60	Intermediate coronary stenosis	Angiographically significant LCA lesion; cardiogenic shock; CKD; life expectancy <2 years; degree 2-3 AV block; contraindications for adenosine

Table 1. Continuation

First author	Year	Design	Patients	Duration, months	Inclusion criteria	Exclusion criteria
De Backer [15]	2016	PSM	695/695	48	Coronary stenosis <50% or >89%	Previous CABG; life expectancy <1 year; unstable hemodynamics
Zhang [12]	2016	РКИ	110/110	12	NSTEMI over 65 of age	Cardiogenic shock or hemodynamic instability; intolerance to antiplatelet agents; technical impossibility for PCI; excessively tortuous or calcified CAs; life expectancy <1 year
Huang [16]	2017	Retrospective	101/105	14	Intermediate coronary stenosis	–
Quintella [13]	2019	РКИ	34/35	60	Patients aged 21 years and older with stable multivessel disease or on day 7 after ACS, with at least one moderate stenosis (>60%) without significant LV dysfunction and with urgent intensive care for ischemia were divided into two groups	–
Parikh [17]	2020	Observational Study (Register)	2967/15022	12	Angiographically intermediate stenoses (visually defined as 40% to 69% stenosis)	Patients with coronary artery stenoses ⩾70%, including chronic total occlusion and/or ACS
Völz [18]	2020	Observational Study (Register)	3367/20493	56	Stable angina	History of CABG
Hong [19]	2022	Observational Study (Register)	5116/129497	36	Stable angina	Acute MI, including STEMI or NSTEMI, history of CABG
iFR vs FFR						
Davies [5]	2017	РКИ	1147/1179	12	Intermediate coronary stenosis	Tandem stenosis prior to CABG, severe LCA stenosis, total coronary occlusion, restenosis, hemodynamic instability, contraindications to adenosine administration, highly calcified or tortuous vessels, severe comorbidities with a poor prognosis, pregnancy, severe valvular heart disease, recent STEMI
Götberg [6]	2017	РКИ	1012/1007	12	Stable or unstable angina, NSTEMI	Previous CABG; life expectancy <1 year; unstable hemodynamics

Abbreviations: ACS — acute coronary syndrome, AV — atrioventricular, CABG — coronary artery bypass grafting, CA — coronary artery, CAD — coronary artery disease, CAG — coronary angiography, CKD — chronic kidney disease, FFR — fractional flow reserve, GFR — glomerular filtration rate, EF — ejection fraction, iFR — instantaneous wave-free ratio, MI — myocardial infarction, STEMI — non-ST segment myocardial infarction, LV — left ventricle, LCA — left coronary artery, NSTE-ACS — non-ST elevation acute coronary syndrome, PCI — percutaneous coronary intervention, RCT — randomized clinical trial, STEMI — ST segment myocardial infarction.

funnel plots did not reveal significant asymmetry (Figure 3). When evaluating the Egger test for MI, an insignificant result was obtained: t=0,52; p=0,33. However, the Egger test for the all-cause mortality revealed a significant result: t=3,70; p=0,02.

Meta-regression analysis

Meta-regression analysis did not reveal any evidence of modification of the effect of non-ST elevation acute coronary syndrome (NSTE-ACS) rate in the included studies on MI, MACE, all-cause mortality (Q=0,09,

Table 2

General characteristics of patients included in the systematic review

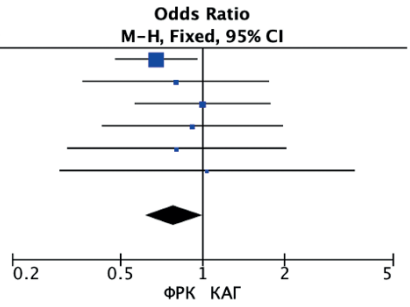
Author, year	Methodl	Patients	Age±SD	BMI (kg/m^2)	Men (%)	HTN (%)	Diabetes (%)	Old myocardial infarction (%)	Multivessel CAD (%)	NSTE-ACS
Tonino, et al. 2009 [4]	FFR	509	64,6±10,3	–	384 (75,4)	312 (61,3)	123 (24,2)	187 (36,7)	509 (100)	150 (29,4)
	CA	496	64,2±10,2	–	360 (72,6)	327 (65,9)	125 (25,2)	180 (36,3)	496 (100)	178 (35,9)
Puymirat, et al. 2012 [14]	FFR	222	71,6±9,8	26,6±4,3	129 (58)	130 (59)	58 (26)	–	38 (17)	23 (10)
	CA	495	71,7±10,6	27,0±4,4	336 (68)	323 (65)	163 (33)	–	46 (9)	103 (21)
Chen, et al. 2015 [9]	FFR	160	65,2±9,6	–	121 (75,6)	116 (72,5)	48 (30,0)	12 (7,5)	112 (69,8)	98 (61,7)
	CA	160	65,4±9,2	–	116 (72,5)	106 (68,3)	43 (26,9)	19 (11,9)	110 (68,8)	99 (61,9)
Layland, et al. 2015 [10]	FFR	176	62,3±11,0	–	133 (75,6)	78 (44,3)	26 (14,8)	22 (12,5)	51 (29,0)	176 (100)
	CA	174	61,6±11,1	–	127 (73,0)	81 (46,6)	26 (14,9)	24 (13,8)	55 (31,6)	174 (100)
Park, et al. 2015 [11]	FFR	114	62±10	–	83 (72,8)	73 (64)	30 (26)	22 (19)	72 (63)	58 (51)
	CA	115	63±10	–	87 (75,7)	65 (57)	39 (34)	20 (17)	66 (57)	55 (48)
De Backer, et al. 2016 [15]	FFR	695	64,6±10,5	28,3±10,6	511 (73,5)	465 (66,9)	179 (25,8)	238 (34,2)	199 (28,7)	–
	CA	695	64,7±10,3	27,7±7,9	507 (72,9)	477 (68,6)	164 (23,6)	237 (34,1)	202 (29,1)	–
Zhang, et al. 2016 [12]	FFR	110	70±3,7	–	75 (68,2)	81 (73,6)	40 (36,4)	24 (21,8)	–	110 (100)
	CA	110	70±3,4	–	78 (70,9)	83 (75,5)	36 (32,7)	23 (20,9)	–	110 (100)
Huang, et al. 2017 [16]	FFR	101	66±9	–	74 (73)	76 (75)	35 (35)	15 (15)	73 (72)	–
	CA	105	61±11	–	82 (78)	72 (69)	39 (37)	23 (22)	72 (69)	–
Quintella, et al. 2019 [13]	FFR	34	62,7±8,4	–	25 (73,5)	25 (73,5)	12 (35,3)	8 (23,5)	34 (100)	14 (57,1)
	CA	35	59,5±9,4	–	22 (62,8)	26 (74,3)	12 (34,3)	7 (20,0)	35 (100)	13 (42,8)
Parikh, et al. 2020 [17]	FFR	2967	65,7±9,6	30,9±6,0	2624 (77,9)	2561 (76,1)	755 (22,4)	1053 (31,3)	1984 (66,8)	0 (0)
	CA	15022	67,0±9,8	30,6±6,3	15421 (75,4)	15285 (74,6)	4500 (21,9)	5694 (27,8)	9715 (64,7)	0 (0)
Völz, et al. 2020 [18]	FFR	3367	65±8,4	–	2866 (96,6)	2631 (88,7)	1294 (43,6)	686 (23,1)	1,589 (47,7)	0 (0)
	CA	20493	66±8,9	–	14615 (97,3)	13431 (89,4)	6731 (44,8)	3284 (21,9)	8,824 (43,2)	0 (0)
Hong, et al. 2022 [19]	FFR	5116	65,7±10,0	–	3557 (69,5)	3745 (73,2)	2643 (51,7)	–	–	1887 (36,9)
	CA	129497	66,9±10,3	–	85144 (65,7)	92735 (71,6)	63666 (49,2)	–	–	63302 (48,9)
Davies, et al. 2017 [5]	iFR	1250	65,2±10,6	–	929 (74,3)	884 (70,7)	376 (30,1)	376 (30,1)	519 (41,5)	186 (15,0)
	FFR	1242	65,5±10,8	–	962 (77,5)	873 (70,3)	382 (30,8)	358 (28,8)	505 (40,7)	184 (14,7)
Götberg, et al. 2017 [6]	iFR	1007	67,4±9,2	27,6±4,3	766 (75,2)	710 (69,7)	213 (20,9)	335 (32,9)	368 (36,1)	387 (38,4)
	FFR	1012	67,6±9,6	27,6±4,3	756 (74,2)	730 (71,6)	232 (22,8)	337 (33,1)	364 (35,7)	386 (37,9)

Abbreviations: HTN — hypertension, BMI — body mass index, CA — coronary angiography, iFR — instantaneous wave-free ratio, NSTE-ACS — non-ST elevation acute coronary syndrome, FFR — fractional flow reserve, PCI — percutaneous coronary intervention.

Major adverse cardiac events (MACE)

Study or Subgroup	ФРК Events	ФРК Total	КАГ Events	КАГ Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Tonino et al.	67	509	91	496	54.5%	0.67 [0.48, 0.95]	2009
Park et al.	13	114	16	115	9.6%	0.80 [0.36, 1.74]	2015
Chen et al.	29	160	29	160	16.2%	1.00 [0.57, 1.77]	2015
Layland et al.	14	176	15	174	9.5%	0.92 [0.43, 1.96]	2015
Zhang et al.	9	110	11	110	6.9%	0.80 [0.32, 2.02]	2016
Quintella et al.	6	34	6	35	3.3%	1.04 [0.30, 3.60]	2019
Total (95% CI)		**1103**		**1090**	**100.0%**	**0.78 [0.61, 1.00]**	
Total events	138		168				

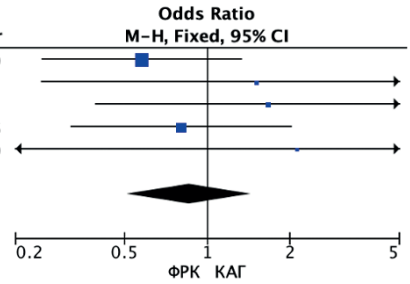
Heterogeneity: $Chi^2 = 1.80$, df = 5 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 1.97 (P = 0.05)



All-cause mortality

Study or Subgroup	ФРК Events	ФРК Total	КАГ Events	КАГ Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Tonino et al.	9	509	15	496	48.4%	0.58 [0.25, 1.33]	2009
Chen et al.	3	160	2	160	6.4%	1.51 [0.25, 9.16]	2015
Layland et al.	5	176	3	174	9.5%	1.67 [0.39, 7.08]	2015
Zhang et al.	9	110	11	110	32.7%	0.80 [0.32, 2.02]	2016
Quintella et al.	2	34	1	35	3.0%	2.13 [0.18, 24.59]	2019
Total (95% CI)		**989**		**975**	**100.0%**	**0.86 [0.51, 1.44]**	
Total events	28		32				

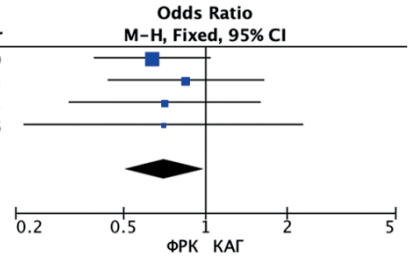
Heterogeneity: $Chi^2 = 2.60$, df = 4 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 0.57 (P = 0.57)



Myocardial infarction

Study or Subgroup	ФРК Events	ФРК Total	КАГ Events	КАГ Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Tonino et al.	29	509	43	496	50.5%	0.64 [0.39, 1.04]	2009
Chen et al.	19	160	22	160	23.9%	0.85 [0.44, 1.63]	2015
Layland et al.	11	176	15	174	17.4%	0.71 [0.32, 1.59]	2015
Zhang et al.	5	110	7	110	8.2%	0.70 [0.22, 2.28]	2016
Total (95% CI)		**955**		**940**	**100.0%**	**0.70 [0.50, 0.99]**	
Total events	64		87				

Heterogeneity: $Chi^2 = 0.46$, df = 3 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = 2.04 (P = 0.04)



Emergency repeat revascularization

Study or Subgroup	ФРК Events	ФРК Total	КАГ Events	КАГ Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Tonino et al.	33	509	47	496	81.1%	0.66 [0.42, 1.05]	2009
Chen et al.	9	160	11	160	18.9%	0.81 [0.33, 2.00]	2015
Total (95% CI)		**669**		**656**	**100.0%**	**0.69 [0.46, 1.04]**	
Total events	42		58				

Heterogeneity: $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 1.76 (P = 0.08)

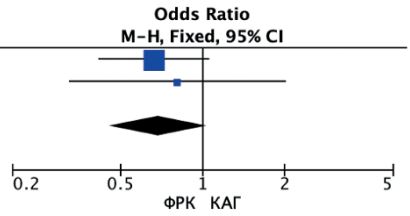


Figure 2. Forest plot of OR for endpoints depending on FFR-PCI in comparison with CA-PCI.
Abbreviations: CA — coronary angiography, FFR — fractional flow reserve.

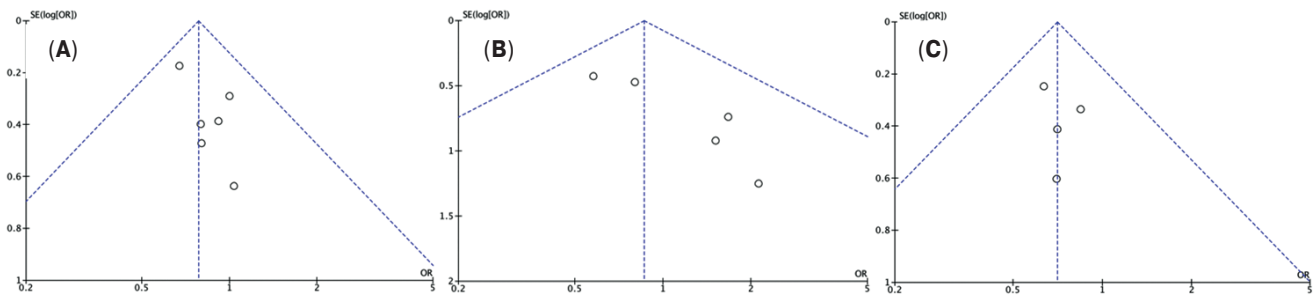


Figure 3. Funnel plot: (**A**) MACE; (**B**) all-cause mortality; (**C**) MI.

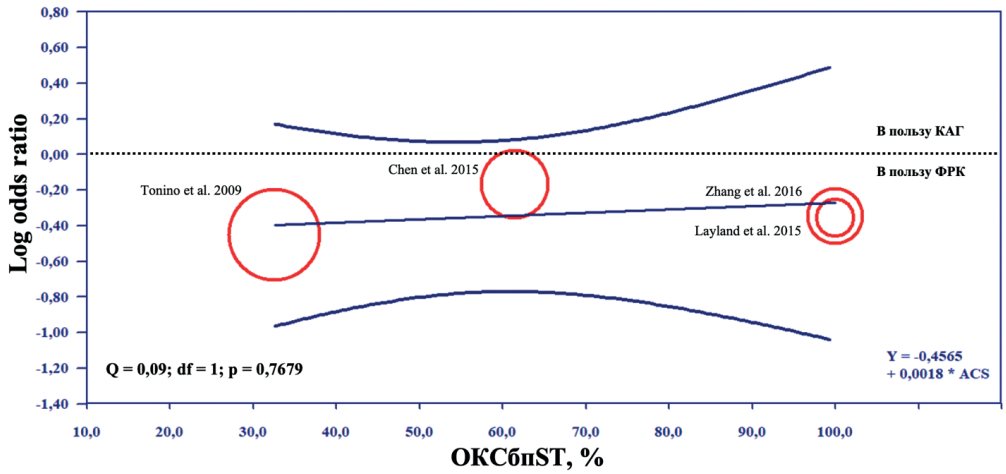


Figure 4. Random effects meta-regression analysis: association between the proportion of NSTE-ACS in the included studies with MI after myocardial revascularization.
Note: negative log OR indicate benefits of FFR. The circle size corresponds to the inverse variance of log OR and is related to the weight of individual study. Curved lines represent 95% CI.
Abbreviations: CI — confidence interval, MI — myocardial infarction, CA — coronary angiography, NSTE-ACS — non-ST elevation acute coronary syndrome, FFR — fractional flow reserve.

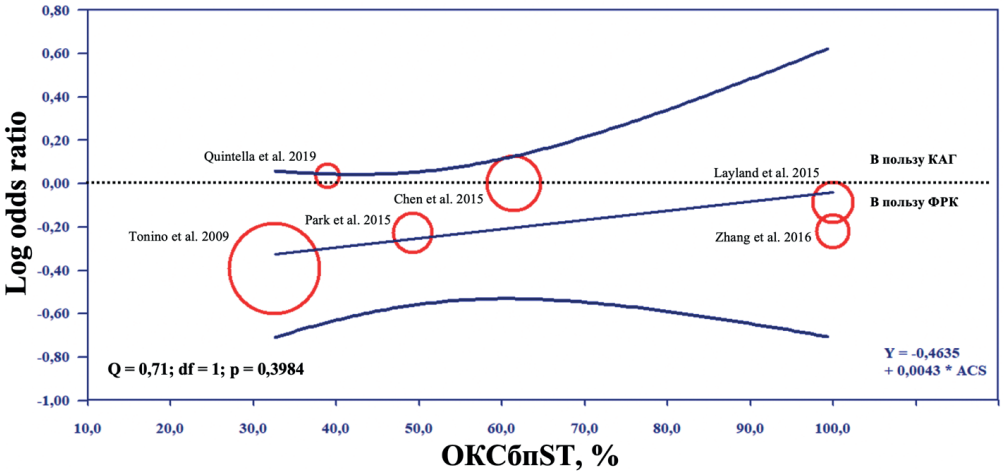


Figure 5. Random effects meta-regression analysis: association between the proportion of NSTE-ACS in the included studies with MACE after myocardial revascularization.
Note: negative log OR indicate benefits of FFR. The circle size corresponds to the inverse variance of log OR and is related to the weight of individual study. Curved lines represent 95% CI.
Abbreviations: CI — confidence interval, CA — coronary angiography, NSTE-ACS — non-ST elevation acute coronary syndrome, FFR — fractional flow reserve, MACE — major adverse cardiac events.

p=0,77; Q=0,71, p=0,40; and Q=0,52, p=0,47, respectively). Diagrams of meta-regression analysis of MI and MACE PRs depending on NSTE-ACS incidence are presented in Figures 4 and 5, respectively.

Analysis of FFR-guided PCI compared with CAG-guided strategy according to large registries

As already noted, three large registries have recently been conducted [17-19], in which the total number of patients in the group of patients with FFR-guided myocardial was 11450, while in the CAG group consisted of 165012 participants.

In contrast to the above RCTs, in these registries, the total number of patients included and the endpoint incidence made it possible to define all-cause mortality as the main primary endpoint. In addition, a study by Völz S, et al. [18] presented data on the risk of restenosis or stent thrombosis depending on myocardial revascularization strategy. In a study by Parikh RV, et al. [17], in addition to data on the risk of all-cause mortality, MI, repeated myocardial revascularization, and a composite point including the above events were presented. Finally, recently

Table 3

Main endpoints of studies included in the systematic review

Author, year	Method	Patients	All-cause mortality (%)	MI (%)	Emergency repeat revascularization (%)	MACE (%)
Tonino, et al. 2009 [4]	FFR	509	9 (1,8)	29 (5,7)	33 (6,5)	67 (13,2)
	CA	496	15 (3,0)	43 (8,7)	47 (9,5)	91 (18,3)
Puymirat, et al. 2012 [14]	FFR	222	3 (1,4)	NR	10 (4,5)	13 (5,9)
	CA	479	13 (2,7)	NR	59 (12,3)	90 (18,8)
Chen, et al. 2015 [9]	FFR	160	3 (1,9)	19 (11,9)	9 (5,6)	29 (18,1)
	CA	160	2 (1,3)	22 (13,8)	11 (6,9)	29 (18,1)
Layland, et al. 2015 [10]	FFR	176	5 (2,8)	11 (6,2)	–	14 (8,0)
	CA	174	3 (1,7)	15 (8,6)	–	15 (8,6)
Park, et al. 2015 [11]	FFR	114	–	–	–	13 (11,4)
	CA	115	–	–	–	16 (13,9)
De Backer, et al. 2016 [15]	FFR	695	110 (15,8)	217 (31,2)	254 (36,5)	255 (36,7)
	CA	695	191 (27,5)	210 (30,2)	231 (33,2)	236 (34,0)
Zhang, et al. 2016 [12]	FFR	110	9 (8,2)	5 (4,5)	–	9 (8,2)
	CA	110	11 (10,0)	7 (6,4)	–	11 (10,0)
Huang, et al. 2017 [16]	FFR	101	1 (1)	0 (0)	–	3 (3)
	CA	105	0 (0)	1 (1)	–	6 (6)
Quintella, et al. 2019 [13]	FFR	34	2 (5,8)	–	–	6 (17,6)
	CA	35	1 (2,8)	–	–	6 (17,1)
Parikh, et al. 2020 [17]	FFR	2967	82 (2,8)	19 (0,64)	112 (3,8)	203 (6,8)
	CA	15022	890 (5,9)	111 (0,79)	510 (3,4)	1403 (9,3)
Völz, et al. 2020 [18]	FFR	3367	275 (8,2)	–	–	–
	CA	20493	2916 (14,2)	–	–	–
Hong, et al. 2022 [19]	FFR	5116	205 (5,8)	64 (1,6)	586 (15,7)	–
	CA	129497	7532 (7,7)	2115 (2,2)	15147 (15,2)	–
Davies, et al. 2017 [5]	iFR	1148	22 (1,9)	31 (2,7)	46 (4,0)	78 (6,8)
	FFR	1182	13 (1,1)	28 (2,4)	63 (5,3)	83 (7,0)
Götberg, et al. 2017 [6]	iFR	1012	15 (1,5)	22 (2,2)	47 (4,6)	68 (6,7)
	FFR	1007	12 (1,2)	17 (1,7)	46 (4,6)	61 (6,1)

Abbreviations: MI — myocardial infarction, CA — coronary angiography, iFR — instantaneous wave-free ratio, FFR — fractional flow reserve, PCI — percutaneous coronary intervention, MACE — major adverse cardiac events.

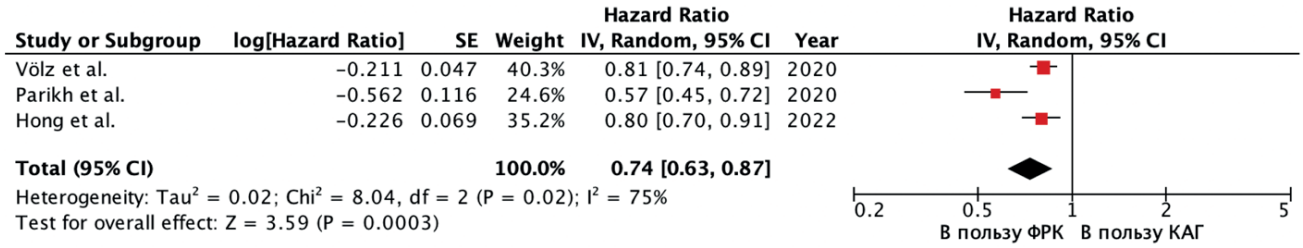
published registry by Hong D, et al. [19] presented data on the risk of MI, non-elective myocardial revascularization, and the combination of MI and mortality depending on myocardial revascularization strategy (Table 3).

The above studies presented HR data from multivariate Cox regression analysis (Table 4). These HR values by study endpoint were further pooled in a meta-analysis. A meta-analysis showed that FFR-guided PCI was associated with a significantly lower risk of all-cause death (HR: 0,74; 95% CI: 0,63-0,87; p=0,0003) compared with CAG-guided strategy (Figure 6). When evaluating the Egger test, a statistically insignificant result was obtained (t=2,33; p=0,129).

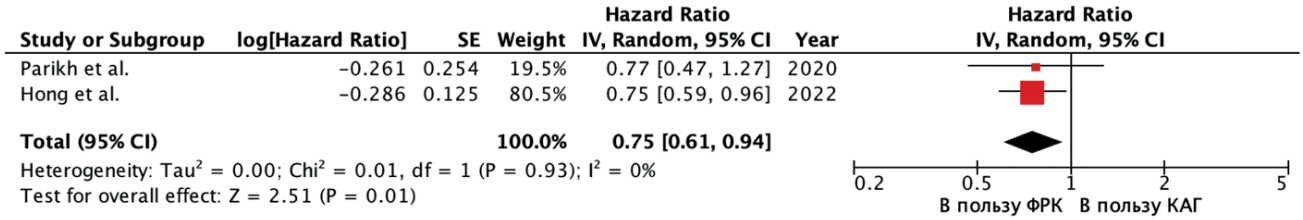
However, the first two registries SCAAR and VA failed to show concrete results that could contribute to the reduction of mortality in a FFR-based approach [17, 18]. MI, as a key outcome that could affect mortality, was not studied in the SCAAR registry [18], and did not differ depending on FFR use in the VA registry [17] (0,64% vs 0,79% for FFR-PCI and CAG-PCI, respectively; HR: 0,77; 95% CI: 0,47-1,27; p=0,31). Only in the recent largest registry, Hong D, et al. managed to demonstrate a significantly lower risk of MI with FFR-PCI (HR: 0,75; 95% CI: 0,59-0,96; p=0,02) compared with CAG-PCI [19].

A meta-analysis of two recent studies [17, 19] showed that a FFR-guided approach to myocardial

All-cause death



Myocardial infarction



Repeated myocardial revascularization

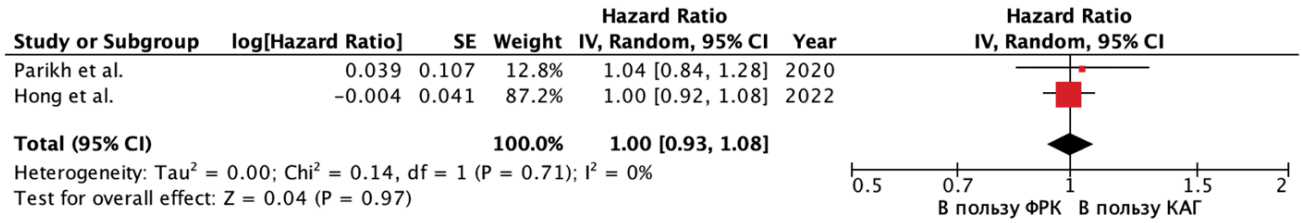


Figure 6. Forest plot of clinical outcomes after FFR-guided PCI according to registers.
Abbreviations: CA — coronary angiography, FFR — fractional flow reserve.

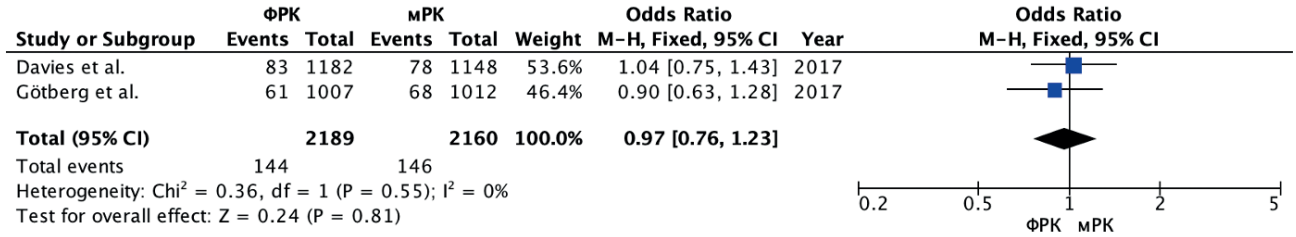
Table 4

OR according to multivariate Cox regression

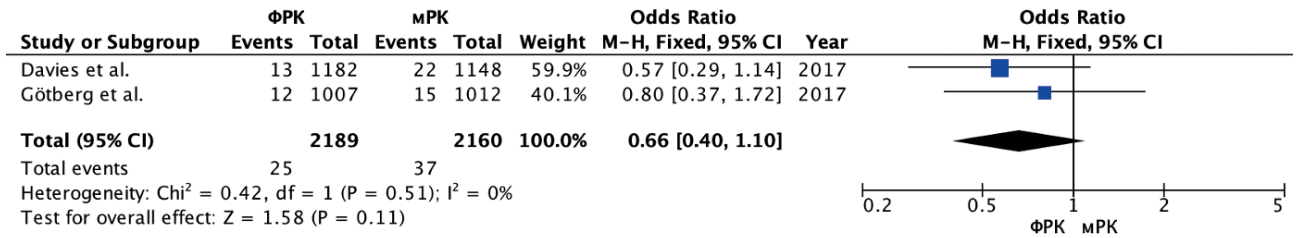
Study	End point	HR	95% CI	p	Log OP	SE
Völz, et al. 2020 [18]	All-cause mortality	0,81	0,73-0,89	<0,001	-0,211	0,047
	Restenosis or stent thrombosis	0,74	0,57-0,96	0,022	–	–
	Stent restenosis	0,71	0,54-0,94	0,016	–	–
	Stent thrombosis	0,98	0,45-2,14	0,958	–	–
Parikh, et al. 2020 [17]	All-cause death	0,57	0,45-0,71	<0,0001	-0,562	0,116
	MI	0,77	0,47-1,27	0,31	-0,261	0,254
	Repeated myocardial revascularization	1,04	0,84-1,28	0,74	0,039	0,107
	Composite point: all-cause mortality, MI, repeat myocardial revascularization	0,80	0,69-0,93	0,004	-0,223	0,076
	Stroke	0,68	0,38-1,21	0,19	–	–
Hong, et al. 2022 [19]	All-cause death	0,798	0,698-0,913	0,001	-0,226	0,069
	MI	0,751	0,587-0,959	0,022	-0,286	0,125
	Emergency repeated myocardial revascularization	0,996	0,918-1,080	0,922	-0,004	0,041
	Death or spontaneous MI	0,773	0,685-0,872	<0,001	-0,257	0,062

Abbreviations: CI — confidence interval, MI — myocardial infarction, HR — hazard ratio.

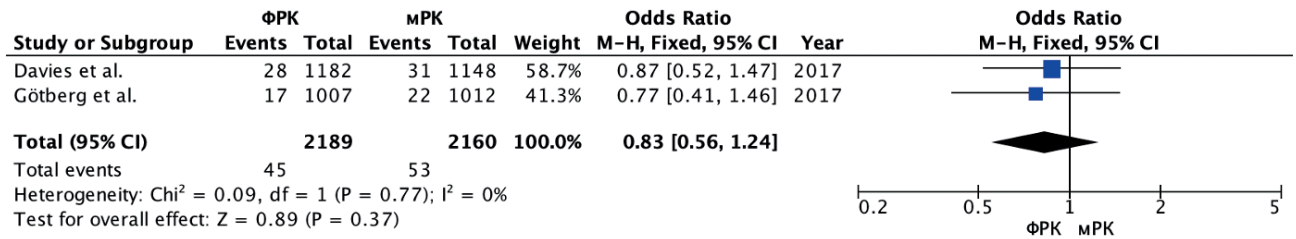
Major adverse cardiac events (MACE)



All-cause mortality



Myocardial infarction



Emergency repeat revascularization

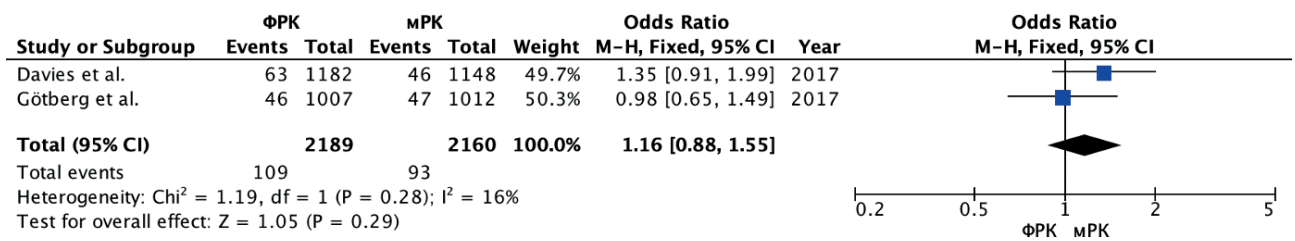


Figure 7. Forest plot of clinical outcomes within 12 months after FFR- and iFR-guided PCI.
Abbreviations: iFR — instantaneous wave-free ratio, FFR — fractional flow reserve.

revascularization was associated with a significantly lower risk of MI (HR: 0,75; 95% CI: 0,61-0,94; p=0,01) (Figure 6). When assessing the homogeneity of studies, an insignificant result was obtained: p=0,93; and heterogeneity index I^2=0%. At the same time, there was no significant association between the risk of recurrent myocardial revascularization depending on FFR-PCI or CAG-PCI (HR: 1,00; 95% CI: 0,93-1,08; p=0,97) (Figure 6).

Analysis of iFR-strategy myocardial revascularization compared with FFR-guided strategy

The DEFINE-FLAIR [5] and iFR-SWEDE-HEART [6] randomized trials compared the iFR- and PCI-guided myocardial revascularization in terms of adverse outcomes over 12 months. The primary endpoint in the studies was the composite endpoint (MACE), which included all-cause mortality, non-fatal MI, and non-elective myocardial

revascularization 12 months after the procedure. The primary secondary endpoints were the frequency of each component of the primary endpoint over 12 months after PCI. Meta-analysis showed no significant difference between groups in the incidence of the combined endpoint (MACE) (OR: 0,97; 95% CI: 0,76-1,23; p=0,81). There was also no significant difference between groups in the incidence of each component of the primary endpoint, namely the development of all-cause mortality (OR: 0,66; 95% CI: 0,40-1,10; p=0,11), MI (OR: 0,83; 95% CI: 0,56-1,24; p=0,37) and non-elective myocardial revascularization (OR: 1,16; 95% CI: 0,88-1,55; p=0,29) (Figure 7).

Thus, according to two large randomized trials, the iFR-guided myocardial revascularization demonstrated a similar clinical result compared to the FFR-guided strategy in patients with chronic and NSTE-ACS within 12-month follow-up period.

Discussion

In our study, a pooled RCT analysis of patients with FFR-guided PCI, in addition to angiography, revealed significantly lower incidence of MI compared with single CAG. In addition, MACE and repeat myocardial revascularization also tended to have lower event rates in the FFR-PCI group (p<0,1).

Over the past few years, a number of meta-analyses have been published, but they have shown conflicting results. For example, Verardi R, et al. analyzed in 2018 conducted a network meta-analysis to evaluate the effectiveness and safety of FFR and iFR strategies compared to CAG. The authors showed that after 12 months MACE and all-cause mortality rates did not differ between groups. At the same time, in patients with stable coronary artery disease (CAD), both FFR and iFR reduced the risk of subsequent MI compared with CAG [20].

A meta-analysis by Baumann S, et al. published in 2019 found no significant differences for the main endpoints: MACE (OR: 0,78; 95% CI: 0,59-1,04; I^2=73%), all-cause mortality (OR: 0,74; 95% CI: 0,46-1,18; I^2=74%), MI (OR: 0,93; 95% CI: 0,81-1,07; I^2=0%) and non-elective revascularization (OR: 0,71; 95% CI: 0,41-1,23; I^2=79%) [21]. However, this meta-analysis also included three small retrospective observational studies, which most likely resulted in high heterogeneity (I^2>70%) and indicated the need for careful interpretation of the pooled OR estimates for all studies.

In our study, we performed a meta-analysis of individual RCTs, while excluding retrospective studies from the pooled analysis in order to exclude the influence of confounders and reduce study heterogeneity. So, when assessing the homogeneity of studies in relation to all four endpoints, we obtained an insignificant result (p>0,1) and heterogeneity index I^2 of 0%, suggesting low heterogeneity among the studies included in the analysis.

In a systematic review and meta-analysis published in December 2022 [22], the authors found no differences in all-cause mortality, MI, or non-elective myocardial revascularization. However, the number of patients undergoing elective revascularization with PCI with coronary artery stenting or coronary artery bypass grafting was significantly lower with the FFR-guided strategy compared with the CAG-guided strategy (p<0,001). In addition, it should be noted that, in the case of PCI with coronary stenting, the average number of implanted stents was significantly lower also when using the FFR-guided revascularization strategy (weighted mean difference -0,45 (95% CI -0,70 to -0,20), p=0,004). However, eight RCTs were included in this analysis, of which two studies performed myocardial revascularization exclusively by coronary artery bypass grafting [23, 24]. In addition, two RCTs were included in patients with ST-segment elevation ACS and multivessel CAD who underwent successful PCI of an infarct-related artery and who underwent total myocardial revascularization guided by FFR or CAG [22, 25]. Perhaps the above factors are responsible for the differences between the results of this meta-analysis and our study. Recall that our meta-analysis included patients with stable CAD or NSTE-ACS who underwent myocardial revascularization exclusively or to a greater extent by PCI with coronary stenting.

Another distinguishing feature of our study was the meta-regression analysis performed, since the RCTs included patients with NSTE-ACS along with patients with stable CAD, and the frequency of inclusion of these patients in the studies varied. The analysis did not reveal any evidence of an effect modification of NSTE-ACS incidence in the included studies on the development of MI, MACE, or all-cause mortality.

RCTs are still the "gold standard" in the hierarchy of evidence-based medicine research. However, they are characterized by strict inclusion and exclusion criteria, which, on the one hand, allows minimizing the risk of the influence of uncontrolled factors on the RCT results, and, on the other hand, limits the application of obtained results to entire population. This is due to the fact that entire groups of patients that are present in clinical practice do not pass the strict inclusion and exclusion criteria for RCTs [26]. Healthcare registries complement the information obtained in RCTs, provide objective data on the efficacy and safety of therapy in patients who were not included in RCTs according to exclusion criteria.

As noted, over the past few years, large registries have been published on the impact on prognosis and cost-effectiveness of a revascularization strategy with FFR in addition to angiography. We performed the first meta-analysis based on the above registries and showed that a FFR-guided myocardial revascularization was associated with a significantly lower risk of all-cause death. When analyzing the factors that could contribute to a reduction in mortality with a FFR-guided approach, we found that this approach is associated with a significantly lower risk of MI. At the same time, there was no significant association between the risk of repeated myocardial revascularization depending on FFR-PCI or CAG-PCI.

Finally, another aspect of our meta-analysis was to assess the difference between iFR- and FFR-guided PCI. In 2017, the results of two multicenter RCTs iFR-SWEDEHEART and DEFINE-FLAIR [5, 6] were published, according to which no significant difference was found in relation to the main endpoints depending on the method selected. Our meta-analysis also demonstrated that there was no significant difference between groups in the incidence of the composite endpoint, MACE, and in the incidence of each component of the primary endpoint, namely all-cause death, MI, and non-elective myocardial revascularization. Thus, according to two large randomized trials, iFR-guided myocardial revascularization showed a FFR strategy for 12 months. Nevertheless, the question of the effectiveness and safety of this strategy in the long-term period (>12 months) remained unclear. However, more recently, the JAAC published the results of a 5-year follow-up of patients from the iFR-SWEDEHEART study [27]. The authors showed that the frequency of the primary composite endpoint at 5 years did not differ significantly between the groups and was 21,5% in the iFR group and 19,9% in the FFR group (HR: 1,09; 95% CI: 0,90 -1,33). All-cause death (9,4% vs 7,9%; HR: 1,20; 95% CI: 0,89-1,62), non-fatal MI (5,7% vs 5,8%; HR: 1,00; 95% CI: 0,70-1,44) and non-elective myocardial revascularization (11,6% vs 11,3%; HR: 1,02; 95% CI: 0,79-1,32) also did not differ between the two groups.

Study limitations. First, a small number of studies were included in our systematic review and meta-analysis. Secondly, the inclusion and exclusion criteria in the studies in most cases differed. In particular, the incidence of NSTE-ACS and the number of coronary lesions in the studies were different. In addition, registries as a variant of observational studies are also susceptible to confounders and selection bias.

Conclusion

This systematic review and meta-analysis based on RCTs showed that a FFR-guided PCI in patients with CAD is associated with a reduced risk of MI compared with single CAG strategy. In addition, real-world data from large registries have shown that a FFR-based approach to PCI is associated with a reduction in the mortality risk, and this is primarily based on a reduction in the MI risk. The iFR-guided myocardial revascularization strategy demonstrated a similar clinical outcome compared to the FFR-guided strategy.

The results of our analysis support the current clinical guidelines that FFR/iFR should be used to assess the functional significance of borderline coronary stenosis in order to make decision about the need for myocardial revascularization.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Determinants of prognosis and management of patients with pulmonary hypertension due to left heart disease: a systematic review

Lyapina I. N.[1], Teplova Yu. E.[1], Martynyuk T. V.[2]

Patients with pulmonary hypertension (PH) associated with left heart disease usually have a complex comorbidity status and a postcapillary component of PH. The presence and identification of a combined post-/precapillary PH in a cohort of patients with left heart disease is reflected in the more pronounced structural and functional right ventricular changes due to higher pulmonary vascular resistance. Patients with combined post-/precapillary PH have reduced exercise tolerance and PH phenotype similar to pulmonary arterial hypertension. Detection of combined PH is critical as it may influence the prognosis and management of patients. This review presents modern prognosis markers for patients with PH due to left heart disease, which can be used in clinical practice. The results of randomized clinical trials and pilot studies on the expansion of treatment options in group 2 patients, including the use of PAH-specific agents, were analyzed. The prospects for the treatment of this cohort of patients are discussed.

Keywords: pulmonary hypertension due to left heart disease, combined post-/precapillary pulmonary hypertension, prognostic markers, treatment prospects.

Relationships and Activities: none.

[1]Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo; [2]E. I. Chazov National Medical Research Center of Cardiology, Moscow, Russia.

Lyapina I. N.* ORCID: 0000-0002-4649-5921, Teplova Yu. E. ORCID: 0000-0001-7549-8075, Martynyuk T. V. ORCID: none.

*Corresponding author:
zaviirina@mail.ru

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Key messages

- We presented modern prognosis markers for patients with pulmonary hypertension due to left heart disease, based on right ventricular structural and functional parameters, hemodynamic and functional characteristics, respiratory function data, blood biomarkers that can potentially be used in clinical practice.
- An analysis of the results of pilot and randomized studies on the evaluation of efficacy and safety of PAH-specific agents for patients with pulmonary hypertension due to left heart disease was demonstrated.

A common cause of increased pulmonary pressure is the development of post-capillary pulmonary hypertension (PH) against the background of left heart pathology, mainly acquired, which is >80% of all etiological factors for PH [1-3].

According to the national guidelines of the Eurasian Association of Cardiology, PH with left heart disease has following characteristics: mean pulmonary artery (PA) pressure ⩾25 mm Hg and PA wedge pressure (PAWP) ⩾15 mm Hg according to right heart catheterization (RHC) [1, 2]. At the same time, in the updated guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), released in August 2022, the threshold value of the mean PA pressure (MPAP), as one of the hemodynamic criteria for PH, was reduced from 25 mm Hg to >20 mm Hg [3].

It is not possible to accurately determine the prevalence of PH in the population. According to some data, the incidence of PH in the world is 1% of the population and among people over 65 years of age increases to 10% [4].

According to transthoracic echocardiography, 60% of patients with systolic and 83% of patients with diastolic left ventricular (LV) dysfunction have signs of PH with a level of estimated PA systolic pressure (ePASP) >35 mm Hg [5]. The prevalence of PH among patients with heart failure (HF) with reduced ejection fraction (HFrEF) varies within 40-75%, while among patients with HF with preserved EF (HFpEF) within 36-83% patients [6].

There are two hemodynamic variants of PH in the presence of left heart pathology, which are presented as isolated postcapillary PH (pulmonary vascular resistance (PVR) ⩽3 Wood units and diastolic pressure gradient (DPG) <7 mm Hg [1, 2], according to the updated ESC/ERS guidelines — PVR ⩽2 Woods units [3]) and mixed post-/precapillary PH (PVR >3 Woods units and DPG ⩾7 mm Hg [1, 2], according to the updated ESC/ERS guidelines — PVR >2 Wood units).

Identification of a mixed PH in DPG ⩾7 mm Hg observed in 22,6% of patients with HFpEF and in 18,8% of patients with HFpEF [7].

In mixed post-/precapillary PH, a chronic increase in left atrial pressure in patients with left heart pathology induces a more pronounced pulmonary system remodeling with an increase in PVR and subsequent development of right ventricular (RV) dysfunction, which is practically not typical for isolated postcapillary PH [8 , 9]. That is why patients with a combined post-/precapillary component of PH are characterized by a more pronounced exercise intolerance and PH phenotype similar to pulmonary arterial hypertension (PAH) [10, 11].

The presence and identification of a precapillary component in addition to postcapillary PH is critical, as it may affect the prognosis and principles of patient management [9, 12-14].

The aim of this review is to study the main markers of the prognosis of mortality, worsening of HF and rehospitalizations in patients with PH due to left heart diseases, as well as the role of specific therapy in the treatment of this cohort of patients.

Methodological approaches

The information retrieval algorithm was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) in the PubMed database (132 articles) and included the search for studies using search queries, keywords and logical operators. According to the search goal, abstracts, minutes of meetings, books, case reports and case series were not used. English has been set as the language limit. Two authors independently examined the titles and abstracts of publications for compliance with the inclusion criteria, while the disagreements were resolved through negotiations or with a third author. Primarily, studies were filtered by checking titles and/or abstracts, excluding reviews, duplicate publications, and case reports. The second stage was the selection of studies after reading the full text. The studies were included if they have the following parameters: 1) samples of adult patients with PH associated with left heart pathology (with post-capillary PH or mixed post-/pre-capillary PH) with a description of the clinical and paraclinical characteristics of patients, data on the prognosis and outcomes of the disease; 2) studies demonstrating the changes over time in patients with group 2 PH against the background of interventional or PAH-specific treatment.

The following key words in the PubMed database were used: ((pulmonary hypertension) and (left heart disease)) or (pulmonary hypertension associated with left heart disease) or (postcapillary pulmonary hypertension) or (combined precapillary and postcapillary pulmonary hypertension) or ((heart failure preserved/reduced ejection fraction) and (pulmonary hypertension)).

The last search was carried out on September 28, 2022.

Inclusion/exclusion criteria. The systematic review included only studies with a full description of clinical and paraclinical data, the changes and outcomes of the disease course. The review did not include studies on the effect of PAH-specific therapy alone in patients with acquired heart disease before/after surgery. Animal studies, reviews, case reports and case series were also excluded. The number of patients included in the studies and the established

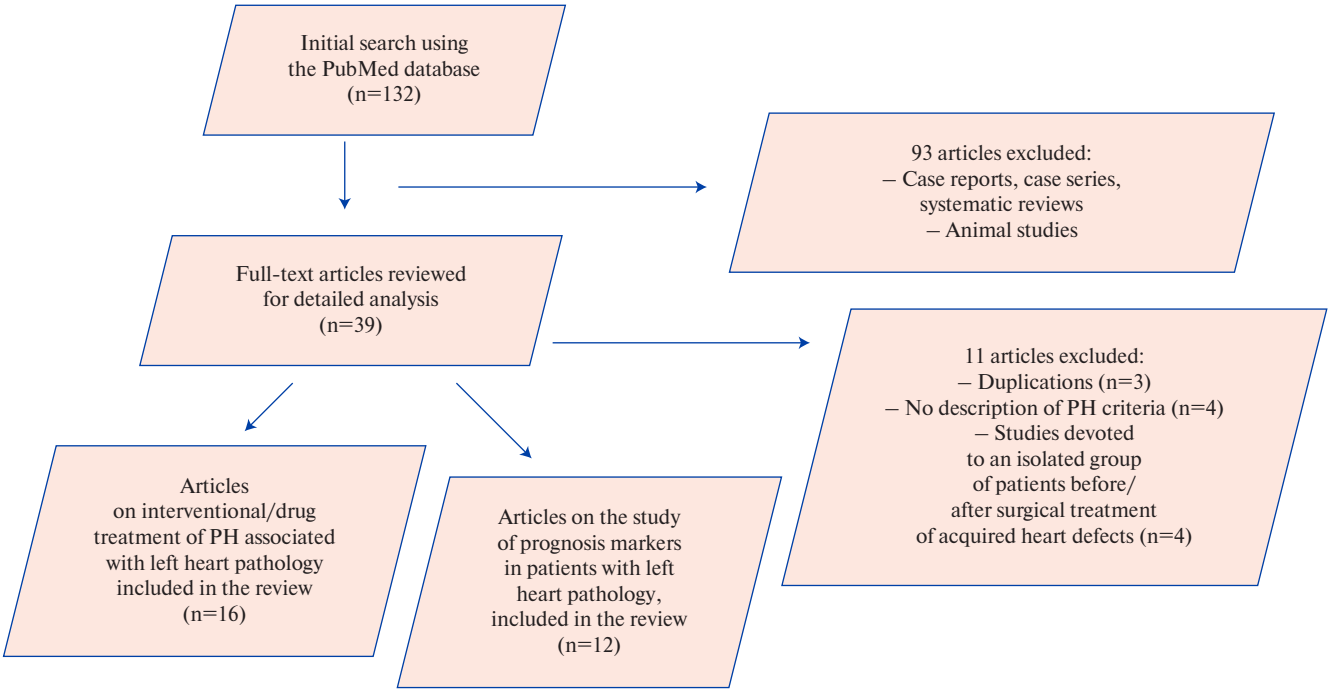

Figure 1. Algorithm for selecting publications for systematic review.
Abbreviation: PH — pulmonary hypertension.

diagnosis of PH by a non-invasive investigation (i.e., using echocardiography) were not the determining factors for selection.

In the primary selection using the above search queries, 132 publications (PubMed) were obtained (Figure 1).

For each study investigating the safety and efficacy of interventional/PAH-specific therapy for the treatment of PH patients with left heart disease, the following data were recorded: first author and/or study title, study population, number of patients included, age, sex, type of left heart pathology and LVEF value, characteristics of PH and the method of its determination, intervention method/drug and duration of therapy, endpoints, achievement of study endpoints. Any disagreements were resolved through discussion.

In total, after the removal of duplicate articles, reviews, and case reports, 31 studies remained on the interventional and/or drug treatment of patients with PH associated with left heart pathology. Two independent researchers reviewed the full-text versions of the remaining publications. After discussion and the involvement of a third expert, an analysis of 16 articles included in this systematic review was carried out. After selection, we also analyzed 12 original studies on prognostic markers in patients with left heart disease and PH (Figure 1).

Determinants of prognosis in patients with PH due to left heart disease

The main prognosis markers in patients with PH and left heart pathology are shown in Figure 2.

RV function as a predictor of prognosis (according to transthoracic echocardiography)

RV function is one of the main determinants of the status and prognosis of patients with PH.

Over a median (Me) of 2 years, the survival rate of patients with HFpEF and RV dysfunction was 56% compared with patients without RV dysfunction (93%) [15]. It demonstrated that RV dysfunction in HFpEF is more typical for male patients with concomitant atrial fibrillation, renal dysfunction and coronary pathology [15].

A number of works describe the contribution of RV systolic function to the prognosis of HFpEF patients [15, 16]. Results of a meta-analysis by Gorter TM, et al. demonstrated that a 5 mm decrease in RV systolic function as measured by transthoracic echocardiography (tricuspid annular plane systolic excursion (TAPSE)) was associated with a 38% increased risk of hospitalization for heart failure (95% confidence interval (CI), 1,21-1,58; p<0,0001) (n=919) and a 26% risk of death (95% CI, 1,16-1,38; p<0,0001) (n=1156) in patients with HFpEF. The TAPSE value, indicative of RV dysfunction, is <17 mm [16].

In a study by Melenovsky V, et al. the presence of RV dysfunction in the form of a decrease in the right ventricular fractional area change (RVFAC) <35% in patients with HFpEF was associated with a 2,2-fold increase in the risk of all-cause death after adjusting for ePASP according to transthoracic echocardiography (95% CI, 1,4-3,5; p=0,001). The lower limit of normal RVFAC is 35% [15].

Data from a meta-analysis by Gorter TM, et al. indicate an increased risk of hospitalization for HF by 9% (95% CI, 1,00-1,19; p=0,07) (n=869) and an increased risk of death by 16% with a decrease in RVFAC by 5% in patients with HFpEF (95% CI, 1,08-1,24; p<0,0001) (n=965) [16].

Such an indicator as the RV-PA coupling, estimated as the ratio of TAPSE to ePASP according to echocardiography, has been studied in a number of studies in patients with HF [17, 18]. This indicator is presented as a powerful predictor of survival in patients with heart failure. TAPSE/ePASP <0,35 mm/mm Hg was associated with a tenfold increase in the death risk in patients with HF (odds ratio (OR), 10,3 (95% CI, 5,4-19,8; p<0,05) [17]. After 4 years of follow-up, patients with HFpEF with a TAPSE/ePASP <0,35 mm/mm Hg had the survival rate of 62%, while at a level of 0,35 to 0,50 mm/mm Hg — 88,4%, and at a level >0,65 mm/mm Hg — 100% [18].

Parameters of cardiac magnetic resonance imaging as predictors of prognosis

Cardiac magnetic resonance imaging (MRI) makes it possible to assess structural changes in the heart, verifying the existing left heart pathology, both the cause of PH and the severity of structural and functional RV changes. Cardiac MRI may also be useful in verifying the phenotype of mixed post-/precapillary PH. Thus, according to cardiac MRI, end-systolic interventricular septal angle (the angle between the ventricles and the middle septal part) correlates with the level of DPG (r=0,74; p<0,001) and PVR (r=0,63; p<0,001). Interventricular septal angle according to cardiac MRI, equal to 160°, is a diagnostic threshold for identifying patients with mixed post-/precapillary PH (with a DPG level of 7 mm Hg and above) with a sensitivity of 67% and a specificity of 93%. According to univariate analysis using Cox proportional hazards regression, a systolic ventricular septal angle of 160° or more can predict all-cause mortality over 2 years (OR, 1,615 (95% CI, 1,253-2,082; p<0,001) [19].

Hemodynamic predictors according to the RHC

PAWP is the main hemodynamic indicator in patients with PH and left heart pathology, reflecting the involvement of venous pulmonary system and isolated postcapillary component of PH (PAWP ⩾15 mm Hg; PVR ⩽3 Wood units) or the addition of combined remodeling as venous, and the arterial pulmonary system with the formation of mixed post-/precapillary PH (PAWP ⩾15 mm Hg; PVR >3 Wood units).

A retrospective analysis of data from 2587 patients with PH and HFpEF at Me follow-up of patients for 1383 days showed that transpulmonary pressure gradient ⩾12 mm Hg, PVR ⩾3 Wood units and DPG ⩾7 mm Hg were predictors of mortality and readmissions for decompensated heart failure. Thus, the risk of death/rehospitalization due to decompensated HF increased by 1,41 times at the level of the transpulmonary pressure gradient ⩾12 mm Hg, (95% CI 1,27-1,56; p<0,001), 1,54 times with PVR ⩾3 Woods units (95% CI, 1,39-1,72; p<0,001) and 1,44 times at the level of DPG ⩾7 mm Hg (95% CI 1,25-1,66; p<0,001), respectively [7].

Right atrial pressure is a component that reflects the volume status of patients with HFpEF, the increase of which is directly related to accession and right ventricular HF.

Measurement of the RV cardiac index for PH patients with left heart pathology with an invasive study is also important for understanding the severity of RV dysfunction, which is a direct mirror of the functional status and prognosis of patients with PH.

Functional status parameters as prognosis determinants

The pathophysiological mechanisms of exercise intolerance in HF are multifactorial and include both impaired cardiac and pulmonary reserves and reduced perfusion and/or peripheral and respiratory skeletal muscle function.

The study demonstrated that a 6-min walk test (6MWT) distance <300 m is an independent predictor of cardiovascular death in patients with NYHA class II-III HFrEF; however, attention is focused on the importance of assessing 6MWT changes over time [20].

The generally accepted gold standard for determining the physical condition of patients with HF is cardiopulmonary exercise test (CPET), which noninvasively assesses the mechanisms that limit physical performance. For patients with both HFpEF and HFrEF during CPET, the value of peak oxygen uptake (VO_2peak) >20 ml/kg/min, ventilatory carbon dioxide equivalent (VE/VCO_2 slope) <30, end-tidal carbon dioxide tension ($PETCO_2$) at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET are associated with the best prognosis in HF patients over 4 years with ⩾90% freedom from adverse events. With a value of VO_2peak of 16-20 ml/kg/min, VE/VCO_2 slope of 30-35,9, $PETCO_2$ at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET, within 1-4 years, freedom from adverse events in patients with heart failure was

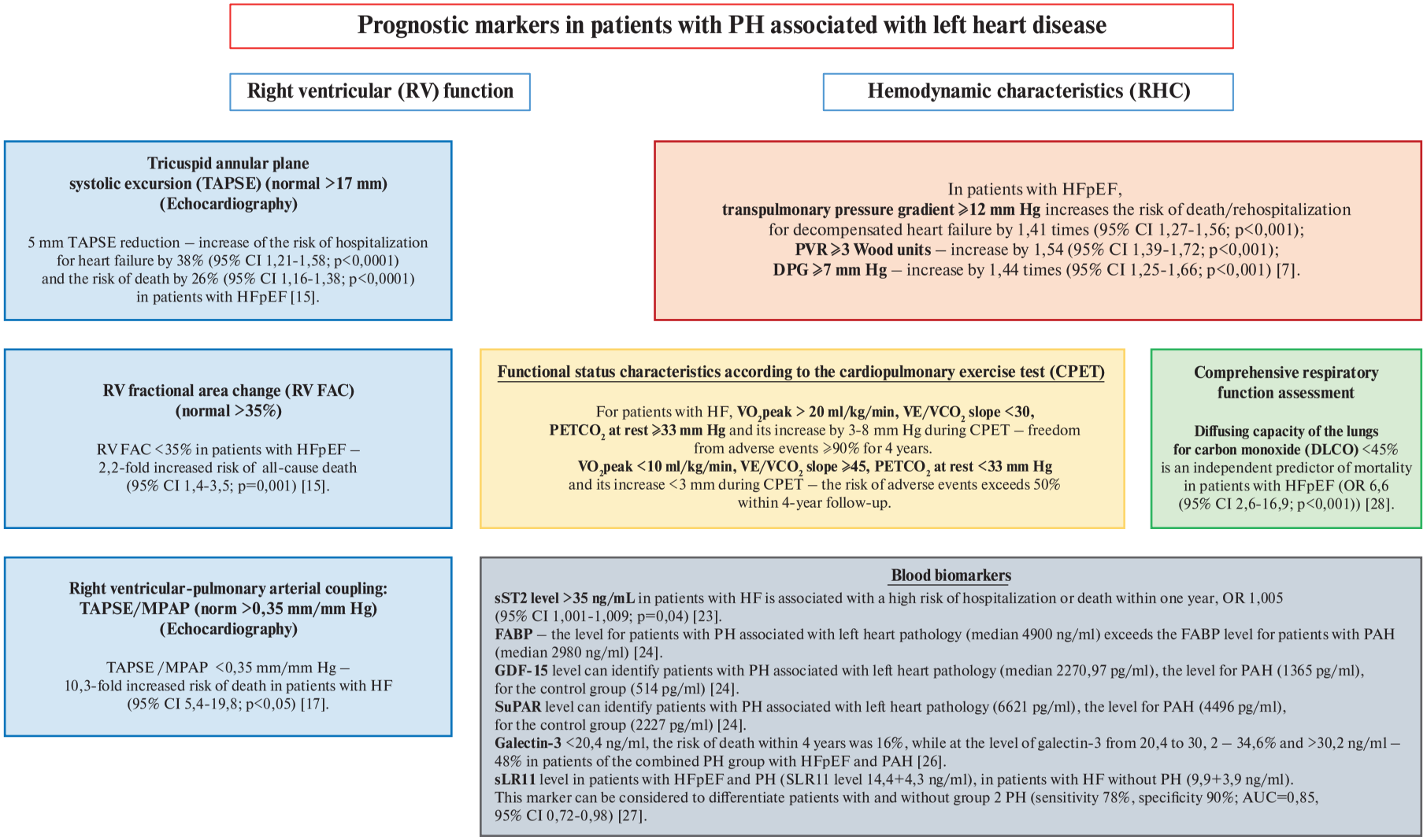

Figure 2. Prognostic markers in patients with PH associated with left heart disease.
Abbreviations: FABP — fatty acid binding protein, DPG — diastolic pressure gradient, CI — confidence interval, CPET — cardiopulmonary exercise testing, RHC — right heart catheterization, PAH — pulmonary arterial hypertension, PH — pulmonary hypertension, PVR — pulmonary vascular resistance, OR — odds ratio, RV — right ventricle, ePAP — estimated pulmonary artery pressure, HF — heart failure, HFpEF — heart failure with preserved ejection fraction, RV FAC RV — right ventricular fractional area change, GDF-15 — growth differentiation factor-15, sLR11 — soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats, sST2 — soluble growth stimulation expressed gene 2, suPAR — soluble urokinase plasminogen activator receptor, $PETCO_2$ — end-expiratory carbon dioxide partial pressure, TAPSE — tricuspid annular plane systolic excursion, VE/VCO_2 slope — ventilatory carbon dioxide equivalent, VO_2peak — peak oxygen uptake.

⩾75%. VO_2peak of 10-15,9 ml/kg/min, VE/VCO_2 slope 36-44,9, $PETCO_2$ at rest ⩾33 mm Hg and its increase by 3-8 mm Hg during CPET in patients with HF is associated with freedom from adverse events ⩾50% during the period of 1-4 years of follow-up. Patients with HF and VO_2peak <10 ml/kg/min, VE/VCO_2 slope ⩾45, $PETCO_2$ at rest <33 mm Hg have a more unfavorable prognosis and its increase by less than 3 mm during CPET, while the risk of adverse events in these patients exceeds 50% during 1-4 years of follow-up [21].

Blood biomarkers as determinants of prognosis

Biomarkers of HF, cardiac remodeling and myocardial stress

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are universal markers for diagnosing and predicting the outcomes of a number of cardiovascular pathologies. It is known that an increase in NT-proBNP directly correlates with RV HF manifestations and the risk of death in patients with PH.

For example, for patients with PAH, there are three strata that divide these patients into low/medium/high risk of mortality during the year, taking into account a comprehensive assessment of criteria that also includes the BNP/NT-proBNP level. Levels of BNP <50 ng/L and/or NT-proBNP <300 ng/L correspond to a low risk of death within a year. BNP in the range of 50-300 ng/L and/or NT-proBNP in the range of 300-1400 ng/L, according to national guidelines, correspond to an intermediate risk of death [1]. The updated ESC guidelines changed the range of these markers for intermediate risk: BNP within 50-800 ng/l and/or NT-proBNP within 300-1100 ng/l [3]. BNP levels >300 ng/L and/or NT-proBNP >1400 ng/L, according to national guidelines [1], and BNP >800 ng/L and/or NT-proBNP >1100 ng/L, according to European guidelines for diagnosis and treatment of PH, corresponds to high risk.

At the same time, the level of these markers distinguishes between chronic (BNP ⩾35 pg/ml and NT-proBNP ⩾125 pg/ml) (adjusted for atrial fibrillation)) or acute HF (BNP ⩾100 pg/ml and NT-proBNP ⩾300 pg/ml) [22]. However, there is no established range of BNP and NT-proBNP levels as part of the risk stratification of disease progression and mortality specifically for patients with group 2 PH. Interpretation of NT-proBNP level in any cardiovascular disease should be carried out in conjunction with the clinical status, taking into account comorbidities.

In addition to the natriuretic peptide family, another promising biomarker in PH patients is soluble growth stimulation expressed gene 2 (sST2). sST2 is a biomarker that is expressed in mechanically deformed cardiac fibroblasts and cardiomyocytes and plays a role in remodeling and fibrosis in HF. An increase in sST2 and NT-proBNP in patients with PH is caused by dysfunction and an increase in RV filling pressure, more pronounced myocardial tension, followed by RV dilatation, which determines the severity and prognosis of patients with PH. An sST2 >35 ng/mL in patients with HF is associated with a higher risk of adverse events, defined as hospitalization or death within one year, compared with subjects with an sST2 level below this value [23].

Another promising marker for verification of PH type and its severity is the heart-type fatty acid-binding protein, which is expressed in the cytosol of cardiomyocytes, being a marker of cardiomyocyte damage. In PH patients, fatty acid-binding protein was studied by Mirna M, et al. Its higher level (as an indicator of early myocardial ischemia among all PH types) was found in patients with PH associated with left heart pathology (group 2) and in the group of PH (Me, 4900 ng/ml) associated with lung pathology (group 3), while in patients with PAH its level was 16 times lower (Me, 2980 ng/ml) [24].

Markers of inflammation

There is growing evidence that inflammatory processes play an important role in pulmonary vascular remodeling in patients with PH. However, the inflammatory component may also reflect a response caused by ischemia and increased sympathetic activity due to reduced cardiac output in patients with PH.

Below are relatively new and not widely known markers for patients with group 2 PH.

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor beta superfamily. GDF-15 is exposed in various cell types in response to tissue injury, ischemia, or stress. GDF-15 is an inflammatory marker but is also involved in the regulation of cell repair and growth [25]. Detection of a higher GDF-15 level in patients with PH on the background of left heart pathology (group 2 PH) (Me, 2270,97 pg/ml for group 2 PH vs 1365 pg/ml for patients with PAH vs 514 pg/ml for the group control) may be due to pronounced myocardial remodeling and cardiomyocyte death, because the study also included patients with HFrEF against the background of ischemic cardiomyopathy as a cause of group 2 PH [24].

In a study by Mirna M, et al. patients with PH in group 2 also showed a more pronounced increase in the level of soluble urokinase plasminogen activator receptor (suPAR) (6621 pg/ml for group 2 LH vs 4496 pg/ml for patients with PAH vs 2227 pg/ml for the control group). It is a marker of inflammation and organ damage, which is also involved in the process of myocardial remodeling [24].

Another promising marker for PH patients is galectin-3, which is a beta-galactoside-binding lectin expressed in inflammatory cells (macrophages, neutrophils, eosinophils, and mast cells) and endothelial cells in response to tissue injury. Galectin-3 is considered to be a mediator of inflammation and fibrosis, and its activity leads to increased adverse cardiac remodeling. In a study by Mazurek JA, et al. the correlation of the level of this marker with the mortality of patients with PH of various origins was demonstrated. This study included patients (n=37) with PAH and group 2 PH on the background of HFpEF. Me levels of galectin-3 for patients with PAH were 22,33 ng/ml and 28,94 ng/ml for patients with PH group 2 (p=0,07). The results of this study demonstrated the relationship of galectin-3 level with 4-year mortality of patients in the combined group of PAH and group 2 PH, which was 16% with a level of galectin-3 at <20,4 ng/ml, 34,6% from 20,4 to 30,2 and 48% at >30,2 ng/mL [26]. However, this marker has not been studied in isolation for patients with PH against the background of left heart pathology.

Soluble low-density lipoprotein receptor with 11 ligand-binding repeats (sLR11), a marker of smooth muscle cell proliferation and endothelial dysfunction, has demonstrated its role in the severity of patients with group 2 PH. The single-center pilot study included 34 patients with HFpEF and mitral regurgitation. Of these, in 10 patients with PH, the level of sLR11 was significantly higher (14,4±4,3 ng/ml) than in patients without PH (9,9±3,9 ng/ml), p=0,002. Adverse events after 5 years in patients with elevated levels of this marker were represented by 5 hospitalizations (25%) and 2 deaths (10%), while no adverse events were observed in patients with normal levels of sLR11. The authors suggested that this marker can be considered to differentiate patients with and without PH (sensitivity 78%, specificity 90%; AUC=0,85, 95% CI 0,72-0,98), to determine the severity of mitral regurgitation and PH [27]. The main limitations of this marker may be the presence of concomitant coronary artery disease (CAD)/unstable angina, because sLR11 is also used to predict CAD course.

Comprehensive assessment of respiratory function

A marker of prognosis for patients with PH and left heart pathology is also the indicator of the diffusing capacity of the lungs for carbon monoxide (DLCO), which demonstrates the ability of the lungs to transport gas through the alveolar-capillary barrier. Changes in pulmonary capillaries and postcapillary venules can cause functional changes in the lungs, in particular DLCO disturbance. The presence of concomitant chronic obstructive pulmonary disease, a combination of emphysema and pulmonary fibrosis may also be additional reasons for a decrease in DLCO in patients with left heart pathology; however, mechanical disruption of breathing and volume may be absent, as well as the dependence of impaired diffusing capacity of the lungs on PH severity [28].

The study by Hooper MM, et al. included 52 patients with HFpEF with a decrease in DLCO <45% of the predicted value and 56 patients with HFpEF with a DLCO level ⩾45% of the predicted value. The presence of a pronounced decrease in DLCO <45% most often characterized male patients (OR 2,71 (95% CI 1,05-6,88; p=0,039)) with history of smoking (OR 5,01 (95% CI 1,91-13,1; p<0,001)). A DLCO value <45% is an independent predictor of mortality for patients with HFpEF (OR 6,6 (95% CI 2,6-16,9; p<0,001)). The 3-year survival rate of patients with HFpEF and DLCO <45% is 3 times lower than that of patients with DLCO ⩾45% (36,5% vs 87,8%, respectively; p<0,001) [28]. Therefore, pulmonary function test and the assessment of the diffusing capacity of the lungs in group 2 PH helps to diagnose lung pathology and assess its severity, which is necessary to understand its contribution to the severity and origin of PH.

Treatment prospects

In accordance with the current 2022 European guidelines for the diagnosis and treatment of PH, as well as the 2020 guidelines of the Ministry of Health of Russia, the treatment of patients with PH and left heart pathology is aimed at eliminating structural and functional left heart disorders as the main cause of group 2 PH (valve pathology, LV diastolic/systolic dysfunction, LV outflow obstruction, etc.), as well as drug therapy approved for patients with HFrEF and HFpEF [1, 3, 22, 29].

Over the past decade, the search for new ways to treat patients with HF and PH has continued, with the testing of both new drugs and interventional interventions (Table 1).

Interventional treatment

The CHAMPION study analyzing the long-term safety and clinical efficacy of a Wireless Pulmonary Artery Pressure Monitoring System — CardioMEMS Heart Sensor) of implantation of pulmonary artery pressure monitoring system during RHC in patients with HF and LVEF ⩾40% (n=550) during the observation period of 17,6 months stability of clinical status was achieved with a 50% reduction in hospital admissions for heart failure. It is the daily assessment of the hemodynamics of the pulmonary circulation with dynamic control of pressure in the pulmonary artery and the selection of the necessary doses of diuretic therapy, the use of vasodilators in some cases, which made it possible to stabilize the volume status of patients [30].

Table 1

Results of studies on the effect and safety of interventional and drug treatment (PAH-specific therapy) for patients with PH associated with left heart disease

Study	Study population	Studied device/drug	Endpoints	Result
Interventional methods				
CHAMPION [30]	550 patients with HF: 119 of them with LVEF ⩾40% (mean value 50,6%) (of which 66 patients with LV EF ⩾50%); 430 patients with LVEF <40% (mean 23,3%). Patients with LVEF ⩾40% in the treatment group (n=62) had MPAP of 26 mm Hg, PAWP of 14 mm Hg; in the control group, MPAP of 24 mm Hg, PAWP of 13,5 mm Hg (n=57) according to RHC. For patients with LVEF <40% Me, MPAP was 29 mm Hg, PAWP — 19 mm Hg according to RHC.	Implantation of a PAP monitoring system during RHC was performed in all 550 patients: the "treatment group" with daily monitoring of pressure curves included following patients: n=62 with heart failure with LVEF ⩾40% (of which n=35 with LVEF ⩾50%) and 208 patients with LVEF <40%. The "control group" with no control of pressure curves included following patients: n=57 LV EF ⩾40% (of which n=31 with LVEF ⩾50%) and 222 patients with LV EF <40%.	The primary endpoint was hospitalization for HF.	After 6 months, patients with HF with LVEF ⩾40% of the "treatment group" (n=62) were 46% less likely to be hospitalized for HF compared with patients in the control group (n=57), OR 0,54 (95% CI 0,38-0,70; p<0,0001) (11 hospitalizations in the treatment group/19 hospitalizations in the control group). After 6 months, patients with LVEF <40% in the "treatment group" (n=208) were 24% less likely to be hospitalized for heart failure (n=222), OR 0,76 (95% CI 0,61-0,91; p=0,008) (73 hospitalizations in the treatment group/101 hospitalizations in the control group). After 17,6 months, in HF patients with LVEF ⩾40%, hospitalization rates in the treatment group were 50% lower than in the control group, OR 0,50 (95% CI 0,35-0,70; p<0,0001) (29 hospitalizations in the treatment group/59 in the control group). After 17,6 months in patients with heart failure with an LVEF <40%, the rate of hospitalizations in the treatment group was 26% less than in the control group, OR 0,74 (95% CI 0,63-0,89; p=0,001) (153 hospitalizations in treatment group/220 in the control group).
REDUCE-LAP-HF [31]	Patients (n=64) with NYHA class II-IV HF with LVEF >40% with a mean age of 69 years with a mean PAWP of 17 mm Hg and MPAP of 25 mm Hg according to the RHC and without severe right ventricular HF events (central venous pressure <14 mm Hg and TAPSE >1,4 cm).	Through venous access, implantation of a device that creates an interatrial shunt (n=64).	Primary endpoints: periprocedural safety of the intervention and safety in the form of an assessment of cerebrovascular and cardiovascular events 6 and 12 months after the implantation. Secondary endpoints: hospitalization for heart failure within 1 year, as well as changes in echocardiography and hemodynamic parameters, functional status, quality of life.	Within 6 months no patient had perioperative or serious adverse cardiac or cerebrovascular events, including death, stroke, myocardial infarction, pulmonary or systemic embolism, or the need for cardiac surgery for device-related complications. 17 hospitalizations due to HF during the year. One-year survival was 95% (within one year 3 deaths: pneumonia and kidney failure; stroke; cause unknown). Dynamics of the functional status: 6MWTD a year later increased from 331±90 m to 363±93 m; (p=0,001). Significant improvement in quality of life. Improvement in TAPSE from 2,0±0,4 cm to 2,2±0,4 cm after one year (p<0,05). An increase in RV CO from 5,2 to 6,7 l/min a year later (p<0,05) and a decrease in the PAWP/MRAP gradient from 10 to 7 mm Hg.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
PADN-5 [35]	Patients with mixed post-/precapillary PH (n=98) without PAH-specific therapy, 61,2% — patients with HFrEF and 38,8% — patients with HFpEF with MPAP ⩾25 mm Hg, PAWP >15 mm Hg and PVR >3,0 Wood units.	LA denervation group (n=48) and sildenafil + PA denervation simulation group (n=50).	The primary endpoint was an increase in 6MWTD within 6-month follow-up. The secondary endpoint was change in PVR. The primary safety endpoint was pulmonary embolism.	After 6 months, the mean increase in 6MWTD was 83 m in the denervation group and 15 m in the 66 m sildenafil group (95% CI: 38,2-98,8 m; p<0,001). Against the background of denervation, the PVR level was significantly lower (4,2±1,5 Wood units) than in the sildenafil group (6,1±2,9 Wood units; p=0,001). The denervation group experienced less clinical deterioration (16,7%) compared to the sildenafil group (40%), p=0,014. At the end of the study, there were 7 all-cause deaths and 2 cases of pulmonary embolism.
Pharmacotherapy				
FIRST [36]	Patients with HFrEF (n=471) with median age of 65 years with LVEF <25% and NYAH class III-IV HF, PAWP ⩾15 mm Hg, cardiac index ⩽2,2 l/min, median systemic vascular resistance of 20,76 Wood units, median MPAP in the epoprostenol group of 38 mm Hg/in the placebo group of 40 mm Hg according to RHC.	Epoprostenol (n=237) or standard medical therapy for HF (n=234).	Primary: death; a serious event such as the need for mechanical ventilation, inotropic drugs, or mechanical circulatory support. Secondary: 6MWTD, quality of life, dynamics of clinical status after 3 months.	There was a significant increase in cardiac index, a decrease in PAWP and PVR in the group of epoprostenol therapy at a dose of Me 4,0 ng/kg/min. Early termination of the study due to increased mortality from acute HF in the epoprostenol group.
Lewis GD, et al. [37]	HFrEF (n=34) with a median age of 54 years for the sildenafil group and 62 years for the placebo group. LVEF <40% and NYHA class II-IV HF, MPAP >25 mm Hg with an average PVR >4 Wood units according to the RHC data.	Sildenafil 25-75 mg 3 times/day (n=17) or placebo (n=17) for 12 weeks.	Primary: VO_2peak. Secondary: DT6MH, PVR.	In the sildenafil treatment group, the level of VO_2peak, 6MWTD increased, and PVR decreased.
Guazzi M, et al. [38]	HFrEF (n=32) with mean age for sildenafil group 66 years/placebo group 68 years, with LV EF <45%, MPAP of 25-35 mm Hg according to RHC, median PVR of 4,5 Wood units.	Sildenafil 50 mg 3 times/day (n=16) or placebo (n=16) for 1 year.	Cardiopulmonary test parameters after 6 and 12 months. Pulmonary circulation hemodynamics after 6 and 12 months.	In the treatment group, a significant increase in VO_2peak and a decrease in ventilation carbon dioxide equivalent. Significant decrease in PAWP and PVR, increase in CO in the treatment group.
SilHF [39]	HFrEF (n=69) with median age of 68 years, median LVEF of 29%, ePASP ⩾40 mm Hg according to echocardiography (Me 45 mm Hg). Without assessing the parameters of right heart catheterization.	Sildenafil up to 40 mg 3 times/day (n=45) or placebo (n=24) or 24 weeks.	Primary endpoints: improvement in the patient's clinical status and dynamics of 6MWTD after 24 weeks.	Against the background of sildenafil, no significant dynamics of the clinical picture, quality of life and 6MWTD were revealed.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
Guazzi M, et al. [40]	HFpEF with mixed post-/precapillary PH (n=44) with a mean age of 72,5 years and LVEF >50%, NYHA class II-IV HAF with MPAP >40 mm Hg, mean PAWP 22 mm Hg, mean PVR 3,88 Wood units for the sildenafil group and 3,27 Wood units for the placebo group according to transthoracic echocardiography.	Sildenafil 50 mg 3 times/day (n=22) or placebo (n=22) for 52 weeks.	Primary: hemodynamics of the pulmonary circulation, RV function (TAPSE). Secondary: quality of life.	Significant reduction in MRAP, MPAP, PAWP, and PVR; improvement of RV function, CO and quality of life.
Hoendermis ES, et al. [41]	HFpEF with isolated postcapillary PH (n=52), age 74±10 years. LV EF ⩾45%, MPAP >25 mm Hg, PAWP >15 mm Hg, median PVR 4 Wood units (PVR >3 Wood units in 45% of the included patients) according to RHC.	Sildenafil 20 mg 3 times/day (n=26) or placebo (n=26) for 12 weeks.	Dynamics of MPAP, PAWP, SV, VO_2peak.	Significant dynamics was not revealed.
RELAX trial [42]	HFpEF (n=216) with median age of 69 years, median LVEF of 60% and ePASP of 41 mm Hg according to echocardiography (without assessing RHC parameters).	Sildenafil (n=113) 20 mg 3 times/day within 12 weeks with an increase in dose to 60 mg 3 times/day within 12 weeks or placebo (n=103).	Primary endpoint: Change in VO_2peak within 24-week treatment. Secondary endpoints: 6MWTD and comprehensive assessment of clinical status (time to death/to cardiovascular or cardiorenal hospitalization/change in quality of life of participants without cardiovascular or cardiorenal hospitalization after 24 weeks).	There were no significant changes in clinical status and quality of life. Deterioration of renal function in the sildenafil group.
Kramer T, et al. [43]	Chronic HFpEF and mixed post-/precapillary PH (n=40). The mean age of patients was 73 years. Median MPAP of 46,2 mm Hg, median PAWP of 21,2 mm Hg, median DPG of 5,5+7,2 mm Hg, median PVR of 6,2±3,0 Wood units.	Sildenafil 20 mg 3 times/day >1 year	Changes of 6MWTD, NT-proBNP level, RV function according to two-dimensional echocardiography, hospitalization rate due to heart failure.	An increase in 6MWTD, a decrease in the level of NT-proBNP, an improvement in RV function in the form of an increase in TAPSE; reduction in the frequency of hospitalizations for heart failure.

Table 1. Continuation

Study	Study population	Studied device/drug	Endpoints	Result
Belyavskiy E, et al. [44]	HFpEF, patients with mixed post-/precapillary PH prevailed (n=50) with ePASP of 40 mm Hg according to echocardiography (without assessing RHC parameters).	Sildenafil (n=30) 25 mg 3 times/day within 3 months with a further increase in dose to 50 mg 3 times/day within 3 months or placebo (n=20).	Changes of the functional status and RV function.	Increased 6MWTD, decreased PASP, RV and LV filling pressure, LV hypertrophy; improvement in RV function, LV diastolic function, and NYHA class of HF.
LEPHT [45]	HFrEF (n=201) Me age 58,1 years. LV EF <40% with NYHA class II-IV and MPAP ⩾25 mm Hg according to RHC. Mean PVR for the placebo group, riociguat 0,5 mg, 1 mg and 2 mg 3 times/day were 3,81 Wood units, 3,43 Wood units, 2,78, and 3,64 Wood units, respectively.	Riociguat in 4 parallel groups at a dose of 0,5, 1 or 2 mg 3 times/day (n=132) or placebo (n=69) for 16 weeks.	Primary endpoints: MPAP changes. Secondary endpoints: hemodynamic parameters.	The primary endpoint was not reached: there were no significant differences in MPAP changes in the riociguat 2,0 mg group compared to the placebo group. However, in the riociguat 2 mg treatment group, there was a significant increase in cardiac index and a decrease in PVR compared with placebo.
BADDHY [48]	HFpEF (n=20); mean age of 68,1 for the bosentan group/67,4 years for the placebo group. LVEF ⩾50%, MPAP >25 mm Hg, PAWP >15 mm Hg according to the RHC; RV dysfunction according to echocardiography. The value of PVR is not specified.	Bosentan 125 mg daily during the first month with an increase in dose after up to 250 mg per day (n=9) or placebo (n=11) for 12 weeks.	Changes of 6MWTD, MPAP and RA pressure according to echocardiography.	Acute HF in 3 patients in the bosentan group, in the placebo group in 1 patient. In the placebo group, there was a slight trend towards an increase in 6MWTD.
ENABLE [49]	HFrEF (n=1613); mean age for bosentan group of 67,5 years/mean age for placebo group of 66,9 years; LVEF <35%, NYHA class III-IV with median 6MWTD <375 m. Evaluation of RHC was not performed. Two patients were excluded from the analysis due to unwillingness to further participate in the study (total, 1611 patients).	Bosentan (n=804) 125 mg daily during the first month with an increase in dose after up to 250 mg per day or placebo (n=807) for median of 1,5 years.	Primary endpoint: change in clinical status at 9 months; all-cause death or hospitalization for HF.	Bosentan did not affect the clinical status of patients after 9 months. In the bosentan group, fluid retention was observed during the first 2-4 weeks of treatment. 321 patients in the placebo group and 312 patients in the bosentan group died or were hospitalized for HF.
MELODY-1 [50]	HFpEF and HFrEF (n=63); LVEF ⩾35% with NYHA class II-IV with mixed post-/precapillary PH (MPAP ⩾25 mm Hg, PAWP >15 mm Hg, DPG ⩾7 mm Hg, PVR >3 Wood units according to RHC).	Macitentan 10 mg (n=31) or placebo (n=32) for 12 weeks.	Primary points: safety and tolerability (fluid retention, deterioration in NYHA class). Hemodynamic changes, NT-proBNP, 6MWTD.	7 patients in the macitentan group had fluid retention/4 in the placebo group. There were no significant differences between groups in any of the study endpoints.

Abbreviations: DPG — diastolic pressure gradient, CI — confidence interval, PAWP — pulmonary artery wedge pressure, PAP — pulmonary artery pressure, 6MWTD — 6-minute walk test distance, RHC — right heart catheterization, PA — pulmonary artery, PAH — pulmonary arterial hypertension, PH — pulmonary hypertension, LV — left ventricle, PVR — pulmonary vascular resistance, OR — odds ratio, RV — right ventricle, ePASP — estimated pulmonary artery systolic pressure, CO — cardiac output, HF — heart failure, HFrEF — heart failure with reduced ejection fraction, HFpEF — heart failure with preserved ejection fraction, MPAP — mean pulmonary artery pressure, MRAP — mean right atrial pressure, EF — ejection fraction, Me — median, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association, TAPSE — tricuspid annular plane systolic excursio, VO_2peak — peak oxygen uptake.

The REDUCE-LAP-HF multicenter non-randomized study revealed that implantation of an interatrial shunt device in patients with HF and LVEF >40% (n=64) with a MPAP of 25 mm Hg was safe and resulted in a decrease in LV end-diastolic volume index, PAWP, improvement of RV systolic function, as a result of the functional status and quality of life of patients [31].

PA denervation in PH is still not fully understood, and is used in a few federal centers of the country, mainly as part of research areas for patients with chronic thromboembolic PH in addition to surgical treatment [32], as well as in cardiac surgery patients with acquired heart disease and PH [33]. Russian authors analyzed 8 studies on PA denervation in PH of various origins, including group 2 PH in world practice. It was demonstrated that the method of PA denervation contributed to a decrease in MPAP, the changes of which was -8,59 (95% CI -10,96 — -6,23) mm Hg, and an increase in the 6MWT distance on 60,0 (95% CI 35,74-84,27) meters in patients with PH [34].

The effect of PA denervation was studied in a separate group of patients with NYHA class II-IV HF and mixed post-/precapillary PH (n=98) in the PADN-5 study. In this study, the effectiveness of two approaches was compared: in the first group, PA denervation was performed, while in the second, sildenafil therapy 60 mg per day and PA denervation simulation in patients with mixed post-/precapillary PH on the background of standard medical therapy for HF. After 6 months in the PA denervation group, a significant and more pronounced changes in 6MWT distance was observed, as well as a pronounced decrease in PVR. In this group, clinical deterioration over 6 months was observed 2,4 times less frequently compared with patients in the group of sildenafil and simulated denervation [35].

Large multicenter studies devoted to the study of both short-term and prolonged effects of PA denervation in patients of various etiology and severity of PH should be conducted.

Pharmacotherapy

The potential of specific therapy in patients with PAH, such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators or prostacyclins, is a controversial and not fully resolved issue. However, the studies conducted indicate a safety risk, as well as a low expected efficacy from PAH-specific therapy for patients with PH with left heart pathology. So far, there is no multicenter study that would prove the safety and benefit of treatment with PAH-specific drugs in this group of patients.

Back in 1997, the first attempt to use pulmonary vasodilators for patients with PH on the background of left heart pathology was the The Flolan International Randomized Survival Trial. This study evaluated the effect of epoprostenol infusion therapy in patients with congestive NYHA class III-IV HFrEF FC. The effect of epoprostenol on improving cardiac index and reducing PAWP has been demonstrated, but the study was terminated early due to an increase in deaths with the use of epoprostenol in patients with group 2 PH [36].

The effect of sildenafil therapy in patients with both HFpEF and HFrEF is highly controversial due to the diverse results obtained in studies [37-44] (Table 1).

Lewis GD, et al. in patients with PH and HFrEF with LVEF <40% 12 weeks after sildenafil therapy at a dose of 25 to 75 mg 3 times/day demonstrated a significant improvement in functional status and a decrease in PVR in 17 patients with HF [37].

The prolonged effect of sildenafil at a dose of 50 mg 3 times was studied by Guazzi M, et al. in 16 patients with PH and HF with LVEF <45%. A significant improvement in peak oxygen uptake as measured by CPET from 9,6 to 13,2 ml/min/kg and a reduction in ventilatory carbon dioxide equivalent from 41,1 to 31,5 were demonstrated in addition to an improvement in hemodynamic characteristics, presented in the dynamics of MPAP from 34,8 to 24 mm Hg and PVR level from 360 to 255 dyn/s/cm^{-5} after a 1-year sildenafil therapt compared with the placebo group (p<0,01) [38].

For the first time, a multicenter, randomized, placebo-controlled study of SilHF demonstrated no effect of sildenafil at a dose of 40 mg 3 times/day on clinical and functional status, quality of life in patients with HFrEF (n=45) compared with placebo (n=24) after 24-week therapy [39].

In turn, in 22 patients with HFpEF and mixed post-/precapillary PH therapy with generic sildenafil at a dose of 50 mg 3 times a day within 6 months demonstrated a significant effect on the functional status, improvement of RV systolic function, reduction of PAWP and right atrial pressure [40].

Hoendermis ES, et al. revealed no effect of sildenafil therapy on the functional status and hemodynamic parameters of pulmonary circulation in patients with HFpEF. Against the background of 12-week sildenafil therapy at a dose of 20 mg 3 times/day (n=26) compared with placebo (n=26) in patients with HFpEF (LV EF ⩾45%), there was no significant change in MPAP level, cardiac output, PAWP and VO_2peak [41]. The randomized RELAX trial in a larger cohort of patients with HFpEF with a Me LVEF of 60% (with no invasively verified PH) also showed no effect of sildenafil therapy at a dose of up to 60 mg 3 times (n=113) compared with placebo (n=103) on clinical and functional status and quality of life of patients after 12-week treat-

ment [42]. However, these studies did not separate patients with mixed post-/precapillary PH.

Later studies, mainly including patients with mixed post-/precapillary PH and HFpEF, showed a significant improvement in the functional status and RV function both against the background of short-term use (3 months) and a year after sildenafil therapy in different dose regimens [43, 44] (Table 1).

The LEPHT randomized trial examined the effect of therapy with the soluble guanylate cyclase stimulator riociguat in 201 patients with PH and LV systolic dysfunction. The study whoed that 16-week riociguat therapy in different dose regimens had no effect on hemodynamic parameters of the pulmonary circulation [45].

A representative of the group of soluble guanylate cyclase stimulators, vericiguat, has also been studied in patients with HFrEF and HFpEF. However, the criterion for PH was not a key criterion for including patients with HF in studies. Thus, in the SOCRATES-REDUCED study [46], the safety and effect of vericiguat therapy in different dose regimens (from 1,25 to 10 mg per day) were evaluated in patients with HF with LVEF <45% (n=351) within 12 weeks. During therapy with vericiguat at a maximum dose of 10 mg, syncope was observed in 4,4% of patients, and significant hypotension occurred in 15,4%. Significant NT-proBNP level changes over 12-week vericiguat therapy was not detected. However, the authors attribute this to the presence of included patients with atrial fibrillation, which additionally contributes to the absence of myocardial strain biomarker improvement. At the same time, taking higher doses of riociguat was reflected in a more pronounced decrease in NT-proBNP level.

In 2021, the European guidelines for HF, vericiguat therapy should be considered to reduce the risk of CV death and hospitalizations due to HF in patients with NYHA class II-IV HFrEF [22]. In the SOCRATES-PRESERVED study [47], 12-week therapy with vericiguat 10 mg in patients with HFpEF had a good tolerability profile, with no significant effect on blood pressure changes, but had no effect on either NT-proBNP changes or LA volume reduction. At the same time, in patients with HFpEF, vericiguat therapy significantly improved the quality of life of patients, which encouraged researchers to further study longer-term vericiguat therapy in this cohort of patients with HF [47].

Turning to another class of drugs of specific therapy that has proven effect on patients with PAH, the results of studies on the safety and efficacy of endothelin receptor antagonist therapy in patients with PH and left heart pathology should be highlighted.

The effect of therapy with bosentan at a dose of 250 mg per day for 12 weeks was studied in the BADDHY single-center study in 9 patients with HFpEF. Therapy with bosentan did not improve the functional status of patients and ePASP level according to echocardiography, causing acute HF in 3 patients in the treatment group [48].

Long-term bosentan therapy at a dose of 250 mg per day in the ENABLE study after 9-month treatment did not improve the outcome of patients with NYHA class III-IV HFrEF (LVEF <35%), while causing severe decompensated HF despite the intensification of diuretic therapy. This study was terminated early [49].

The MELODY-1 prospective multicenter study (Macitentan in Subjects With Combined Pre- and Postcapillary Pulmonary Hypertension (CpcPH) Due to Left Ventricular Dysfunction) was the only study that had inclusion criteria specifically for patients with mixed post-/precapillary PH in the presence of left heart disease [50]. During the first month of follow-up in this study, macitentan 10 mg therapy resulted in a 10,1% increased risk of fluid retention in patients with mixed post-/precapillary PH compared with placebo. Fluid retention, most likely, can be explained by insufficient medical leveling and compensation of the postcapillary component, as well as its prevalence over the precapillary component of PH at the time of therapy initiation. After 3 months there were no significant changes in PVR, mean right atrial pressure, and PAWP compared to placebo when taking macitentan.

Until now, we are waiting for the results of multicenter SERENADE (Macitentan is an Effective and Safe Treatment for Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease) and SOPRANO (Macitentan in Patients With Pulmonary Hypertension After Left Ventricular Assist Device Implantation) studies on the efficacy and tolerability of macitentan 10 mg therapy in patients with mixed post-/precapillary PH on the background of HF with preserved LVEF[1] and in patients with mixed post-/precapillary PH after implantation of left ventricular assist device[2].

[1] ClinicalTrials.gov. A multi-center, double-blind, placebo-controlled phase 2b study to evaluate the efficacy and safety of macitentan in subjects with heart failure with preserved ejection fraction and pulmonary vascular disease (SERENADE). https://clinicaltrials.gov/ct2/show/NCT03153111. Date last updated: July, 2018.

[2] ClinicalTrials.gov. A prospective, multicenter, double blind, randomized, placebo-controlled, parallel group study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation (SOPRANO). https://clinicaltrials.gov/ct2/show/NCT02554903. Date last verified: February, 2018.

Considering no clear evidence of a positive effect of PAH-specific therapy for patients with group 2 PH according to the pilot studies and single multicenter studies, while demonstrating a high risk of pulmonary edema, in the current national clinical guidelines, the appointment of pathogenetic therapy for PAH in patients with PH due to left heart pathology is contraindicated [1]. However, the ESC/ERS guidelines for the diagnosis and treatment of PH recommend individual approach to the choice of therapy for patients with left heart pathology with mixed post-/precapillary PH with a pronounced precapillary component in the form of an increase in PVR ⩾5 Wood units. In this case, the drug of choice for such patients is a phosphodiesterase type 5 inhibitor — tadalafil or sildenafil (registered in the Russian Federation). For these patients, the decision to prescribe sildenafil should be made only with optimal drug therapy for heart failure within the expert PH center, where a comprehensive examination with RHC will be carried out [3].

Thus, the potential of pulmonary vasodilators from the group of PAH-specific therapy for patients with left heart pathology remains controversial. However, in some cases, attempts are being made to prescribe off-label PAH-specific therapy to this cohort of patients. There are following key factors justifying the prescription of pulmonary vasodilators: a combined post-/precapillary PH verified by an invasive diagnostic method with a eliminated/compensated post-capillary component of PH in a patient receiving optimal drug therapy for left heart disease; a personalized approach to prescribing and choosing a treatment, making a decision on prescribing a specific drug only by a multidisciplinary team of highly qualified specialists.

Conclusion

The complex phenotype of patients with PH on the background of left heart pathology implies the need for an integrated approach to assessing the prognosis of this cohort of patients, taking into account their comorbidity status, using both invasive and non-invasive parameters. This will make it possible to timely treat left heart pathology and/or achieve medical compensation. Attempts to use PAH-specific drugs for group 2 PH patients have been unsuccessful in most studies. However, studies are ongoing to study the safety and efficacy of modern drugs in mixed post-/precapillary PH.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Left ventricular global function index: diagnostic and prognostic value in cardiovascular diseases

Kapustina A. Yu.[1,2], Alekhin M. N.[1,2]

Left ventricular global function index (LVGFI) is a novel indicator for assessing LV function, considering the main components of cardiac remodeling, obtained using magnetic resonance imaging and echocardiography. Works with the assessment of normal LVGFI values were analyzed. The review provides data on the diagnostic and prognostic efficacy of LVGFI in various cardiovascular diseases, such as heart failure, myocardial infarction, cardiomyopathy, and amyloidosis. Examples of LVGFI calculation in healthy patients and in those with listed pathologies are also presented.

Keywords: left ventricle, function, global function index, ejection fraction, left ventricular remodeling, echocardiography.

Relationships and Activities: none.

[1]Central Clinical Hospital with a polyclinic of the Administrative Directorate of the President of the Russian Federation, Moscow; [2]Central State Medical Academy of the Administrative Directorate of the President of the Russian Federation, Moscow, Russia.

Kapustina A. Yu.* ORCID: 0000-0002-7072-9783, Alekhin M. N. ORCID: 0000-0002-9725-7528.

*Corresponding author: nast.capustina@yandex.ru

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Key messages

- We demonstrated the potential of a novel indicator of left ventricular function — global function index for assessing the prognosis of various cardiovascular diseases.

In most European countries, the incidence of cardiovascular diseases (CVD) decreases; recently, the main risk factors (RFs) for these diseases have been identified. However, they still remain the leading cause of morbidity and mortality. In this regard, the search for new risk factors and improving the prevention of CVDs does not lose relevance [1]. Modern imaging techniques occupy an important place in the diagnosis, choice of treatment and prognosis of patients with CVDs [2].

Assessment of left ventricular (LV) systolic function remains an important issue in clinical decision making and risk stratification in various CVDs [3]. The LV ejection fraction (EF) is by far the most important and widely used echocardiographic parameter for assessing heart failure (HF). It is also important to note that LVEF is the main criterion for inclusion in most randomized clinical trials related to cardiology [4].

However, despite the importance and widespread use of LVEF, there are some limitations in assessing cardiac function in HF [5-8]. First, a decrease in LVEF does not reflect its underlying process, since various heart diseases can lead to LVEF [9]. Secondly, the normal LVEF values are influenced by physiological factors, such as, for example, age

and sex [10]. Thirdly, there are limitations of echocardiography itself, including poor imaging, interobserver variability, and dependence on geometric assumptions of the Simpson method.

In addition to the above limitations, LVEF does not fully take into account LV myocardial remodeling.

Pathological LV remodeling is closely associated with the activation of neuroendocrine, paracrine, and autocrine secretion after myocardial injury under conditions of increased LV wall tension and hemodynamic disorders [11]. Modern outlooks say that the sequence of these events is a compensatory response to various pathological influences; however, the remodeling process is favorable for a short time [12]. The development of any of the LV remodeling patterns (concentric remodeling, eccentric hypertrophy, concentric hypertrophy) is associated with a gradual increase in the risk of composite endpoints [13].

Thus, along with the importance of assessing LV volumes, the evaluation of LV remodeling has additional information for prognosis.

Concentric and eccentric LV hypertrophy (LVH) are the predominant phenotypes associated with LV remodeling in patients with HF [14]. Modern echocardiography makes it possible to quantify the mass and left ventricular geometry as part of a routine diagnostic examination [15]. The detection of increased LV mass is a strong independent predictor of cardiovascular risk in adults [16].

Concentric LVH is more common in HF patients with preserved EF. This is explained by maintenance of normal myocardial torsion function, despite impaired longitudinal and circumferential strain [17]. In addition, progression of LV diastolic dysfunction contributes to HF with preserved EF [18].

Eccentric LVH, on the contrary, is more often associated with HF with reduced EF, which occurs due to myocardial infarction (MI), dilated cardiomyopathy and LV volume overload (for example, with mitral or aortic regurgitation) [19]. Fibrosis and synthesis of new sarcomeres predominate, elongating myocardial fibers [11, 20, 21], resulting in a change in LV geometry in the form of a transition from an elliptical to a spherical configuration of LV chamber with its subsequent expansion [22, 23] and a loss of cardiomyocyte orientation with impairment of all types of LV strain [24, 25].

LVH increases the risk of cardiovascular events and is the most important risk factor compared to other risk factors for morbidity and mortality [26]. Currently, echocardiography is a common, widely used in everyday diagnostic practice and a simple method for diagnosing LVH.

Taking into account the above data, such an important echocardiographic indicator as LVEF does not completely take into account LV remodeling, including LV mass.

Mewton N, et al. [27] in 2013 for the first time proposed a novel parameter — LV global function index (GFI), obtained using magnetic resonance imaging (MRI), which includes stroke volume (SV), end-diastolic volume (EDV), end-systolic volume (ESV), as well as LV mass.

LV GFI was calculated by the following equation:

$$\text{LV GFI} = \frac{\text{SV}}{\left(\frac{\text{LV EDV}+\text{LV ESV}}{2}\right) + \text{LV myocardial volume}} * 100\%,$$

where SV is stroke volume, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume. LV volume was calculated as LV mass/LV density, where LV density was 1,05 g/mL.

Subsequently, a number of researchers also published data, including LV GFI obtained by MRI in various pathological conditions [28-33], including in MI, hypertrophic cardiomyopathy (HCM), and cardiac amyloidosis. Given that the parameters required for LV GFI can be obtained using transthoracic echocardiography, there were studies appearing from 2019 on this method, analyzing healthy individuals, patients with MI and chronic HF (CHF) [34-37].

The aim of this review is to analyze the potential and limitations of LV GFI in clinical practice.

Literature search was performed using electronic bibliographic databases (Medline, PubMed, Elibrary) without publication date range.

LV GFI in healthy individuals

To date, there have been no targeted studies to determine the normal LV GFI values. There are several publications related to LV GFI, which include groups of relatively healthy people [27, 30, 34].

Mewton N, et al. (2013) [27] for the first time presented LV GFI assessed by MRI as a novel marker for the prediction of cardiovascular events using the database of a Multi-Ethnic Study of Atherosclerosis. In 4425 patients of the control group with a mean age of 61±10 years and approximately the same ratio of men and women, LV GFI was 40±7%.

In addition, in the study on the differential diagnosis of amyloidosis and HCM by MRI [30], there was a control group of patients, quantitatively significantly inferior to the previous publication. Thirty-five relatively healthy patients aged 51±9 years with a uniform sex distribution with LV GFI 51±7,3% were included. It is possible that higher LV GFI values were obtained due to the younger age of patients in the group.

LV GFI by echocardiography in relatively healthy individuals was proposed in a publication investigating the predictive value of LV GFI in relation to HF and CVD in young adults [34]. After analyzing 3900

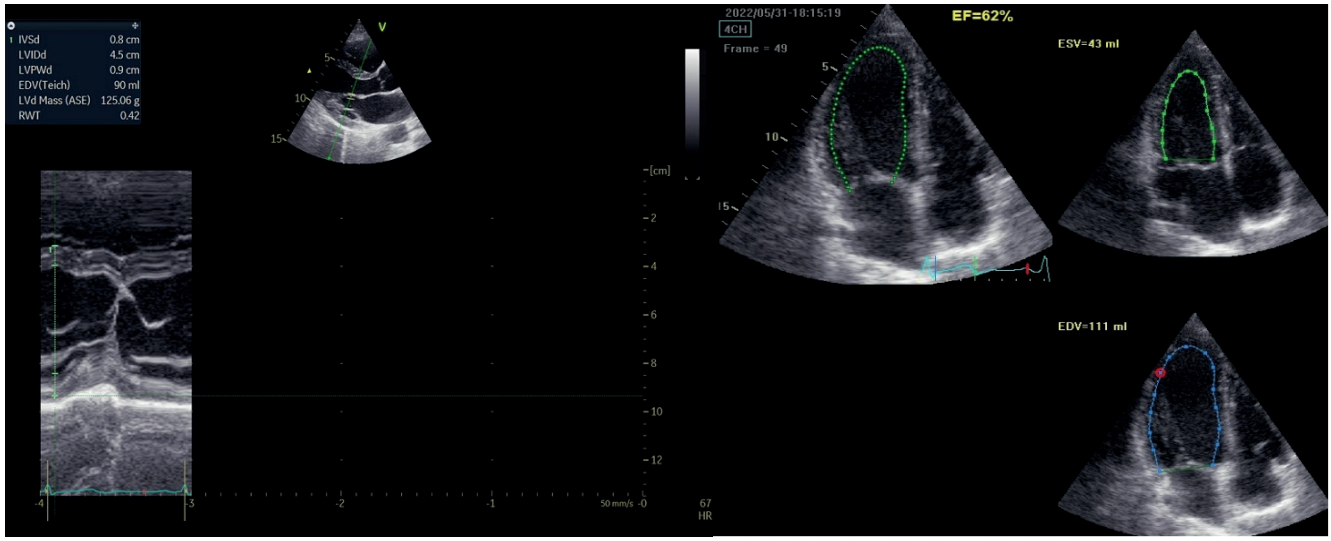

Figure 1. Estimation of LV mass and LVEF in a healthy patient.

people in the control group aged 29,9±3,6 years, LV GFI of 34,6±6,4% were obtained. Apparently, the lower values in comparison with the previous data are due to different methods of LV GFI assessment — MRI and echocardiography.

Figure 1 shows the parameters for calculation and an example of calculating the LV GFI in a healthy 35-year-old patient with the following echocardiographic parameters — LV EDV — 111 ml, LV ESV — 43 ml, LV SV — 68 ml, LV mass — 147 g, LVEF — 62%, LV GFI — 31%.

Thus, the search for reference values of LV GFI remains relevant, including the dependence of these values on the method (echocardiography or MRI), age and sex.

LV GFI in HF

Mewton N, et al. (2013) [27] in a multiethnic study of atherosclerosis revealed the significance of a decrease in LV GFI and LVEF in relation to HF development, along with an increase in myocardial mass, heart rate, N-terminal pro-brain natriuretic peptide, and the presence of diabetes in patients with an average age of 68±8 years. In addition, LV GFI <35% was associated with a 1,5-fold increased risk of HF.

Similar study but in young people (29,8±3,7 years) [34], for 25 years, showed that with LV GFI <30,7%, there is a significantly higher risk of HF. When comparing LV GFI with LVEF, the former showed the best predictive value for HF risk as follows: AUC, 0,80 and 0,66, respectively.

There are data on the significance of LV GFI in patients with HF with preserved EF over 60 years [35], for which LV GFI below 21,1% had an independent predictive value in relation to a death and had greater sensitivity and specificity compared to LVEF (sensitivity: 73,3% vs 66,7%; specificity: 70,0% vs 68,0%).

LV GFI in MI

The first study of LV GFI using MRI in patients with acute MI [28] included 795 patients who underwent coronary artery stenting (within 12 hours from the onset) followed by repeat MRI a week later. The follow-up period was 1 year. LV GFI <31,2% in multivariate analysis proved to be an independent predictor of adverse endpoints (all-cause mortality, recurrent MI, HF). Only the Thrombolysis In Myocardial Infarction (TIMI) score showed similar predictive value. Compared with LVEF, LV GFI showed a greater predictive value for all-cause mortality (AUC, 0,73 and 0,65, respectively, p=0,05).

In a study of patients with acute ST-segment elevation MI [29], which included 200 people, the incidence of adverse cardiovascular events (all-cause death, recurrent MI, HF) was analyzed during 3,1-year follow-up. In total, 20 such cases were identified, among which there were significantly lower values of both LV GFI and LVEF in comparison with the group without adverse cardiovascular events. In the ROC analysis, LV GFI and LVEF also showed comparable predictive values — AUC 0,73 and 0,74, respectively. Thus, LV GFI was a strong predictor of adverse cardiovascular events over 3 years in post-MI patients, but was inferior to LVEF.

In another publication [31], 235 patients with coronary artery disease were examined and, according to MRI, 3 following groups were identified: patients with MI (n=67), without a history of MI, but detected on MRI (n=48) and without MI (n=120). There were no

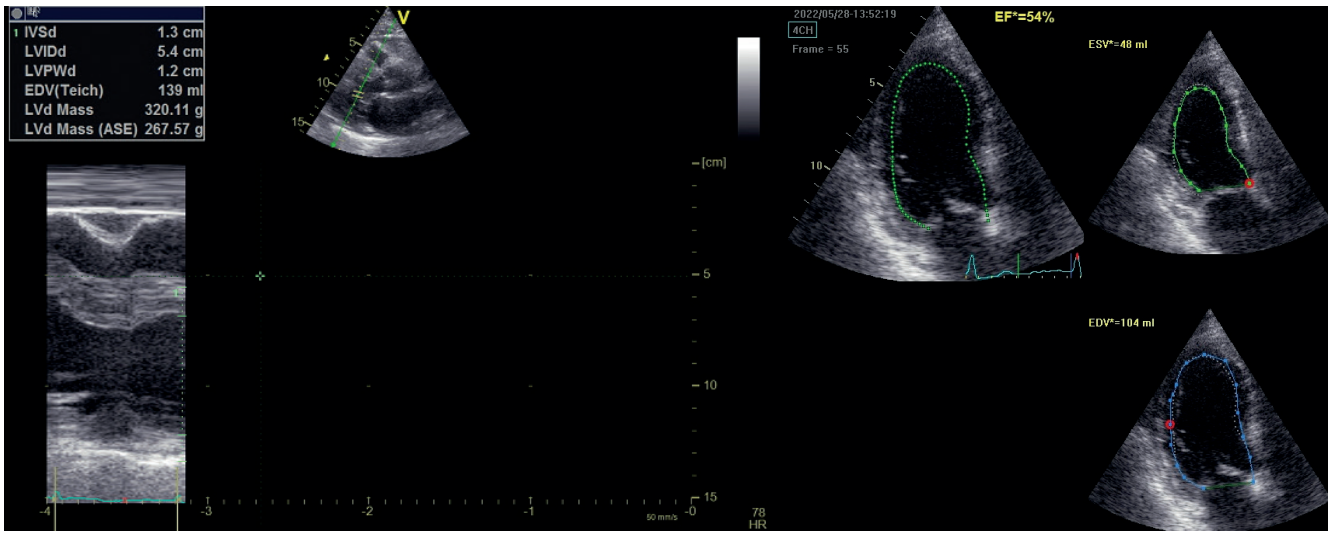

Figure 2. Estimation of LV mass and LVEF in a patient with impaired local contractility.
Note: LV EDV — 104 ml, LV ESV — 48 ml, LV SV — 56 ml, LV mass — 320 g, LVEF — 54%, LV GFI — 16%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

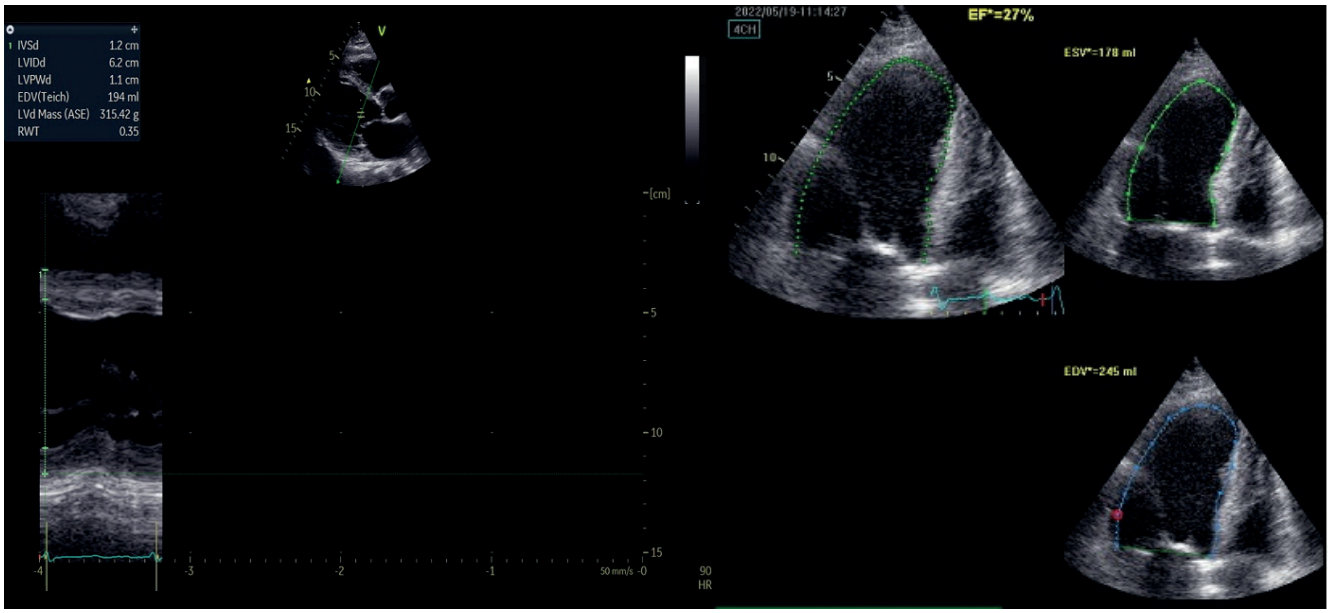

Figure 3. Estimation of LV mass and LVEF in a patient with reduced LVEF and eccentric LVH.
Note: LV EDV — 245 ml, LV ESV — 178 ml, LV SV — 67 ml, LV mass — 398 g, LVEF — 27%, LV GFI — 12%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

significant differences between groups 1 and 2 for either LVEF or LV GFI, but there was a significant difference between the groups 1+2 and group 3. Thus, the role of LV GFI as an additional parameter in the assessment of LV function in patients with coronary artery disease was shown, which, along with the data already presented, speaks in favor of greater prognostic value.

The studies assessing LV GFI in patients with acute coronary syndrome showed that a decrease in LV GFI <22,6% [36] is associated with an unfavorable outcome of ACS, correlates with the risk of all-cause death and adverse coronary events, along with age, prior MI, HF, diabetes and peripheral atherosclerosis. There was no significant difference in LVEF between the groups of survivors and deceased patients, in contrast to the LV GFI. LV GFI <27% [37] predicted obstructive coronary artery disease and had a high predictive value (AUC, 0,80) when

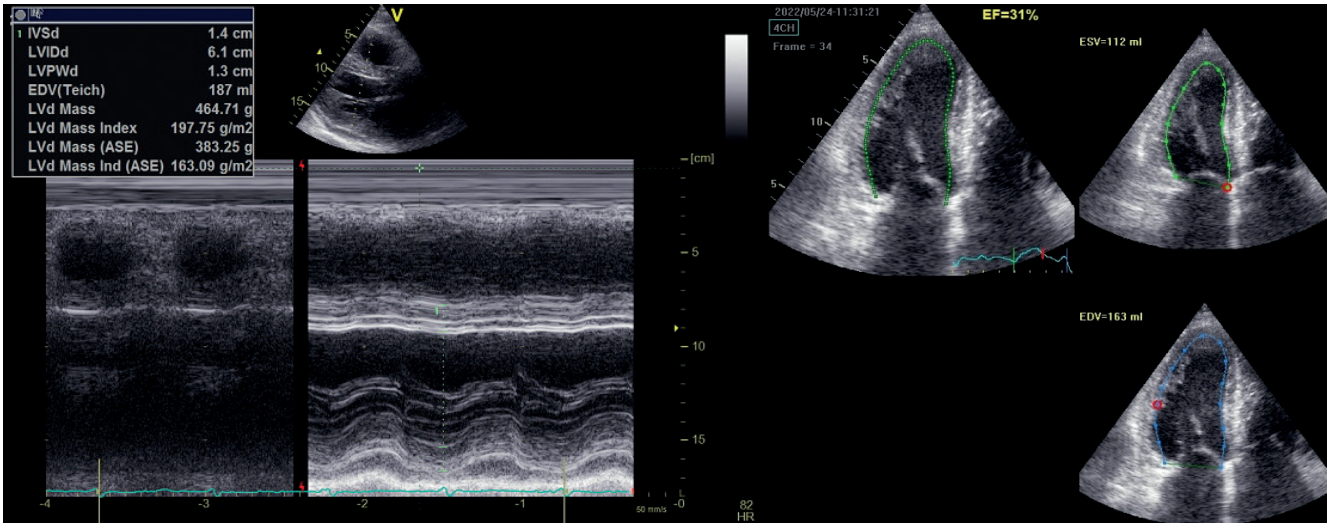

Figure 4. Estimation of LV mass and LVEF in a patient with reduced LVEF and concentric LVH.
Note: LV EDV — 163 ml, LV ESV — 112 ml, LV SV — 51 ml, LV mass — 465 g, LVEF — 31%, LV GFI — 9%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

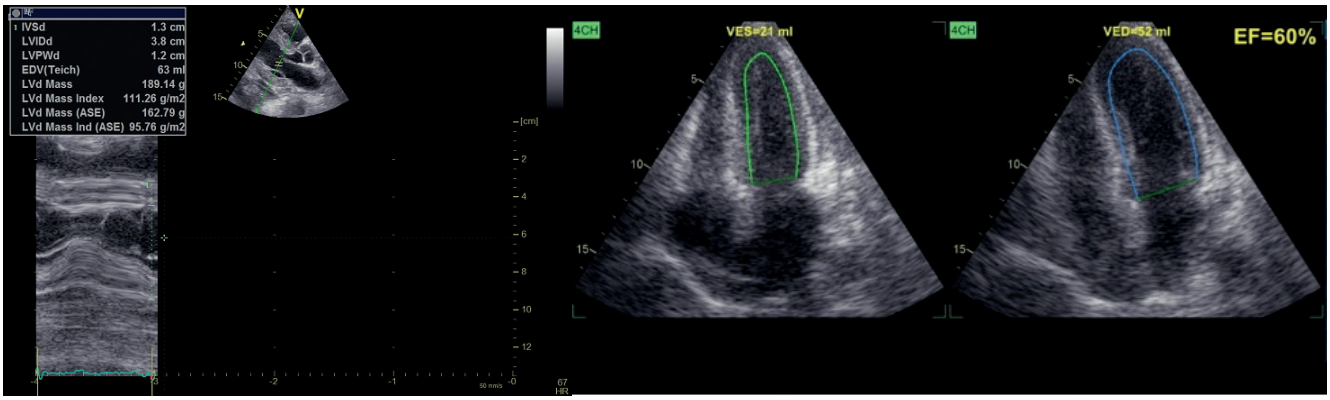

Figure 5. LV mass and LVEF in a patient with amyloidosis.
Note: LV EDV — 52 ml, LV ESV — 24 ml, LV SV — 28 ml, LV mass — 179 g, LVEF — 60%, LV GFI — 13%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

combined with LVEF, LV global longitudinal systolic strain, low-density lipoprotein level, and age.

Figure 2 shows an example of LV GFI calculation in a 73-year-old patient with concentric LVH, impaired local LV contractility (hypokinesia of the middle anterolateral and middle posterolateral segments) with a history of myocardial infarction, type 2 diabetes, and grade 3 hypertension, lower limb peripheral arterial disease.

Noteworthy is a significant decrease in LV GFI with normal LVEF and normal LV volumes.

Figures 3 and 4 illustrate the calculation of LV GFI in patients 77 and 67 years old with reduced LVEF, LVH (eccentric and concentric, respectively), prior MI, grade 3 hypertension, and multivessel coronary disease.

The calculations showed a significant decrease in LV GFI in patients with reduced LVEF in both eccentric LVH and concentric LVH.

LV GFI in cardiomyopathies and amyloidosis

LV GFI is of particular interest in patients with HCM, because EF does not take into account the relationship between LV mass and dimension. In a publication [30] including 90 patients with HCM and 68 patients with amyloidosis (66% with AL-amyloidosis), LV GFI demonstrated a comparable ability to late gadolinium uptake in the differential diagnosis of amyloidosis and HCM, superior to LVEF.

Figure 5 shows an example of LV GFI calculation in a 67-year-old patient with amyloidosis.

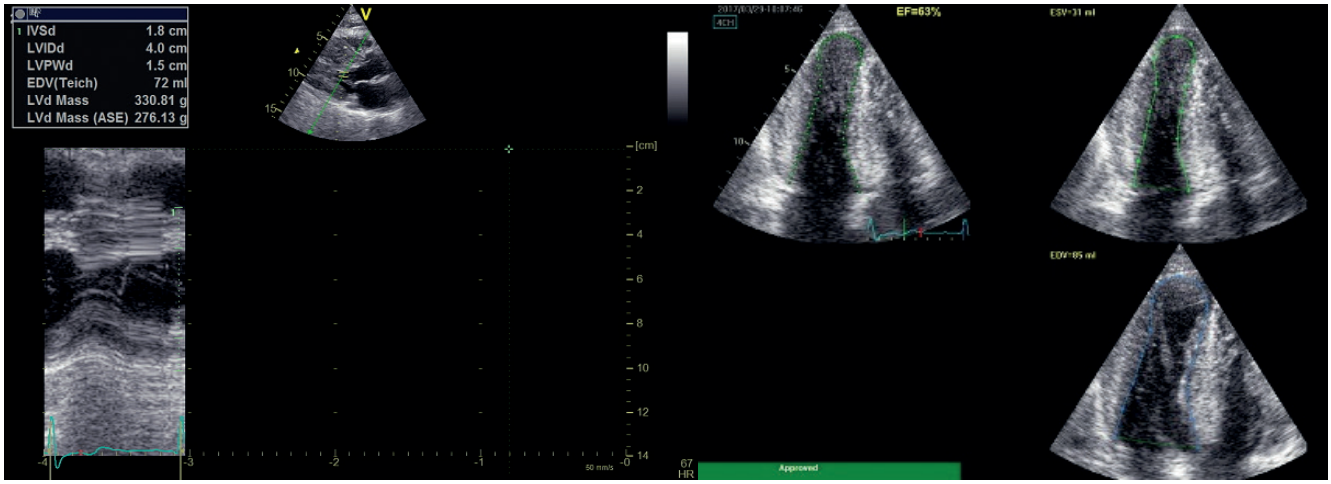

Figure 6. LV mass and LVEF in a patient with HCM.
Note: LV EDV — 85 ml, LV ESV — 31 ml, LV SV — 54 ml, LV mass — 331 g, LVEF — 63%, LV GFI — 15%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

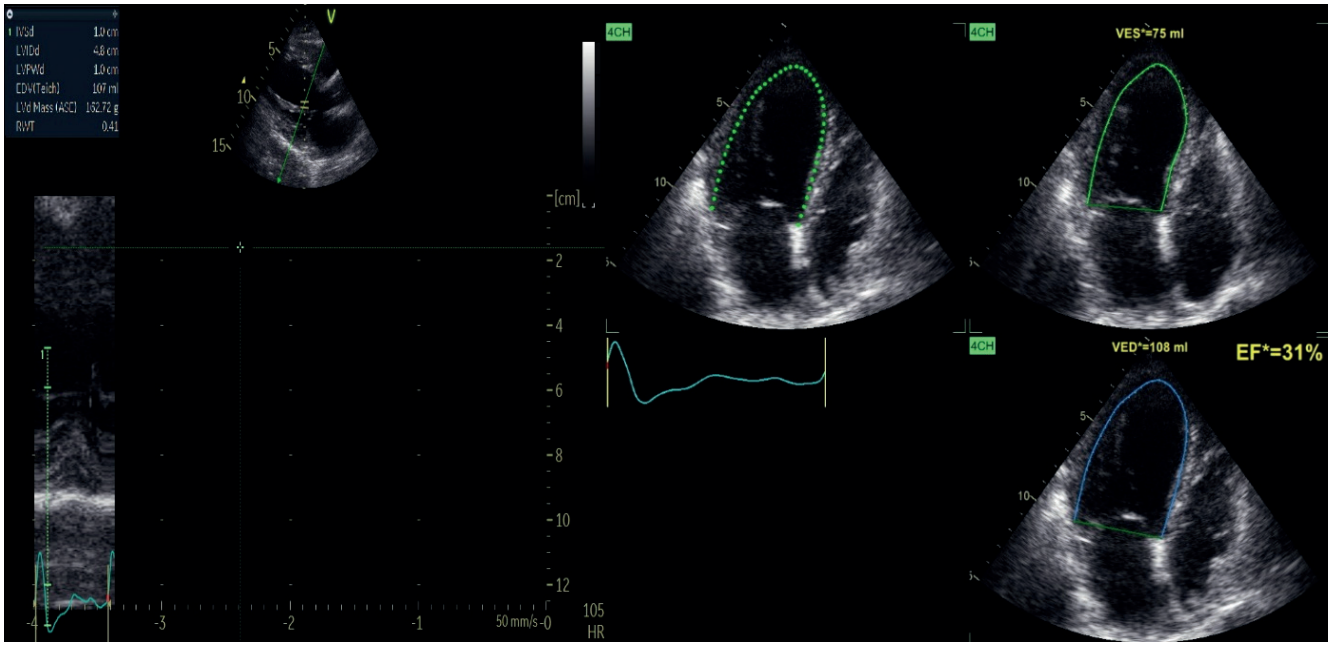

Figure 7. LV mass and LVEF in a patient with takotsubo cardiomyopathy.
Note: LV EDV — 108 ml, LV ESV — 75 ml, LV SV — 33 ml, LV mass — 163 g, LVEF — 31%, LV IGF — 10%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

As shown in Figure 5, LV GFI is significantly reduced, while LVEF and myocardial mass are normal, and LV volumes are low.

With a larger sample of patients (n=681), an analysis of LV GFI in HCM with LVEF >55% [33] was conducted during a 6,1-year follow-up period. LV GFI <37% was associated with the risk of all-cause death and ICD shock.

Figure 6 shows the parameters for calculating the LV GFI in a 68-year-old patient with HCM.

The presented calculations show a decrease in LV GFI with normal LVEF and LV volumes, but with increased myocardial mass.

Separate publications [32] showed differences in LV GFI in patients with myocarditis and takotsubo cardiomyopathy, which were more pronounced

when using LV GFI modification. However, the authors noticed significantly complicated estimation of this indicator.

Figure 7 shows the parameters for calculating LV GFI in a 68-year-old patient with takotsubo cardiomyopathy.

There is a decrease in LV GFI with a normal LV volume and mass, but with a decrease in LVEF.

Thus, LV GFI is an indicator of LV function, which can be easily estimated using standard echocardiography and does not require any additional methods. This is a huge advantage of LV GFI for wide diagnostic use. There is evidence of its prognostic significance in the development of adverse cardiovascular events in healthy individuals, patients with myocardial infarction, heart failure, heart failure with preserved LVEF, HCM. In addition, the effectiveness of LV GFI in the differential diagnosis of HCM and cardiac amyloidosis has been shown.

However, LV GFI also has a number of mathematical, methodological, and clinical limitations. Of course, LV GFI is mathematically related to LVEF and has similar disadvantages. For example, dependence on the quality of cardiac imaging on ultrasound is a major limitation for both EF and LV GFI. Impaired intracardiac hemodynamics with LV volume overload can also significantly affect both EF and LV GFI. Despite these limitations, the additional predictive value of LV GFI and its advantages mentioned above allow its wider use in a number of clinical situations.

According to the available data, LV GFI is not evaluated in routine diagnostic practice, not included in current guidelines, and currently purely research in nature. More studies are needed to evaluate in healthy groups of people and in various CVDs. In sum, these results indicate that LV GFI, which combines structural changes and LV functional state, can be useful and promising both in predicting subsequent cardiovascular events and as an indicator of LV structural and functional remodeling.

Relationships and Activities: none.

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Practical aspects of managing patients with cardiogenic shock

Novosadov M. M.[1], Novosadov V. M.[2], Dzhioeva O. N.[1,3], Drapkina O. M.[1]

[1]National Medical Research Center for Therapy and Preventive Medicine, Moscow; [2]V. V. Veresaev City Clinical Hospital, Moscow; [3]A. I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia.

Novosadov M. M.* ORCID: 0000-0002-7080-7438, Novosadov V. M. ORCID: 0000-0003-3753-9328, Dzhioeva O. N. ORCID: 0000-0002-5384-3795, Drapkina O. M. ORCID: 0000-0002-4453-8430.

*Corresponding author:
pegasustimi@gmail.com

Cardiogenic shock is the leading cause of death among patients with acute coronary syndrome. This pathology is characterized by high rates of inhospital and annual mortality. In Russian literature, data on the prevalence, diagnosis and treatment of patients with cardiogenic shock are limited. Therefore, the main aim of this publication is to increase the awareness of specialists about modern approaches to the diagnosis and treatment of this condition. This review discusses in detail the main causes of cardiogenic shock, aspects of pathophysiology, modern classification, diagnosis, and algorithms for pharmacological and non-drug therapy in patients with cardiogenic shock.

Keywords: cardiogenic shock, myocardial infarction, acute heart failure, revascularization, inotropic support, mechanical support.

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Key messages

- Cardiogenic shock remains the leading cause of death despite advances in therapy.
- The review suggests the creation of a registry of patients with cardiogenic shock in the Russian Federation in order to further optimize treatment protocols.

Cardiovascular diseases in the 21st century retain dominance in the structure of mortality in developed countries [1]. Over 17,3 million people die each year due to cardiovascular disease. Atherosclerotic cardiovascular diseases remain one of the most complex and unresolved problems of modern cardiology, since acute coronary artery disease (CAD) are the cause of cardiogenic shock (CS) in 82% of cases [2, 3].

CS is the most severe and unfavorable complication of acute CAD. The true prevalence of CS is unknown, but the 2019 European Society of Cardiology consensus [4] provides data that 3-5% of all hospitalizations for acute heart failure (AHF) occur in patients with true CS. In-hospital mortality, even with modern therapeutic methods, is in the range of 30-60%, with most deaths occurring within 24 hours of admission. The annual mortality of patients after CS is 50-60%, and most of the deaths occur in the first 30-60 days after hospital discharge. CS rate in patients with acute coronary syndrome (ACS) is 30-40% [5]. Interestingly, a decade ago, medical community believed that CS occurs mainly

in ACS. However, large US registry on CS problems revealed natural decrease in the number of patients with CS associated with myocardial infarction (MI), from 65,3% to 45,6% between 2005 and 2014 [6]. A similar trend was shown in the Canadian intensive care registry as followed: only a third of patients with MI had shock at admission, while ~18% of patients were admitted with decompensated heart failure (HF) against the background of ischemic cardiomyopathy without acute MI, 28% had non-ischemic cardiomyopathy and other causes (recurrent ventricular tachycardia, severe valvular heart disease) [7]. The aim of this review was to draw the attention of specialists to this urgent problem, encourage the formation of interdisciplinary teams of cardiologists and intensivists, as well as to assess the potential of creating a unified registry of CS patients in our country.

Definition, classification and epidemiology of CS

The most severe form of CAD is ACS, which is classified into 2 main forms: ST segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI), which also includes unstable angina [8-12]. STEMI is a less favorable form of acute CAD due to the high incidence of complications [13], among which are arrhythmias, right ventricular (RV) involvement, AHF and mechanical complications: left ventricular (LV) free wall rupture, interventricular septal rupture, mitral valve papillary muscle rupture. AHF continues to be the most common complication of STEMI and appears to be one of the most important unfavorable prognostic factors [14]. The leading mechanism for AHF is LV contractile dysfunction caused by a large necrosis. There are following other causes of AHF: arrhythmias, mechanical complications, comorbidity factors. There are following unfavorable factors of AHF:

1. Severe manifestations of systemic congestion, characterized by pulmonary edema (Killip III).

2. Hypotension is a decrease in blood pressure (BP) <90 mm Hg. The causes can be both RV and LV dysfunction, arrhythmias, and mechanical complications. Long-term hypotension >30 min leads to acute kidney injury and other systemic complications.

3. Decrease in the cardiac index (CI) <2,2 l/min/m^2, leading to tissue hypoperfusion and cardiorenal syndrome followed by oligoanuria.

CS still remains the most severe complication of AHF, as well as the most common cause of death in patients in the cardiac intensive care unit [15]. The definition of CS reflects that this is a state of critical hypoperfusion and tissue dysoxia: a decrease in tissue oxygen saturation due to heart disease. In routine clinical practice, the diagnosis of CS is based on clinical criteria such as persistent hypotension <90 mm Hg without an adequate response to volemic load and accompanied by clinical signs of organ hypoperfusion: cold extremities, oligoanuria <20 ml/h and mental changes. In addition, there are following biological markers of tissue dysoxia: an increase in blood lactate level >2 mmol/l [16].

According to modern classification [17], CS has 3 stages:

1. Pre-CS: Patients with systolic BP (SBP) >90 mm Hg but with hypoperfusion signs: cold extremities, oligoanuria <20 ml/h, and altered mental status.

2. True CS with SBP <90 mm Hg for >30 min, need for pharmacologic or intraaortic balloon pump support, decreased CI <2,2 l/min/m^2, elevated filling pressures of the left, right, or both ventricles (increased pulmonary capillary wedge pressure (PCWP) and central venous pressure).

3. Refractory CS, which does not differ from stage 2 in hemodynamic characteristics, but there is no adequate response to ongoing therapy.

The e American College of Cardiology, the American Heart Association, the Society of Critical Care Medicine, and the Society of Thoracic Surgeons [18] proposed an extended version of A-E classification of CS (Figure 1). Stage A is a patient who is at risk of CS. Usually, there are no signs or symptoms of true CS. In such patients, there are no significant clinical and paraclinical abnormalities, but there is a risk of its development. Most often, these are patients with STEMI, as well as patients with decompensated HF, regardless of the LV ejection fraction (EF). Such patients require continuous round-the-clock monitoring of vital parameters in the intensive care unit.

Stage B: "Beginning" CS (pre-shock/compensated shock) describes a patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion. At this stage, there may be a mild volume overload, while lactate levels are normal.

Stage C: "Classic" CS, at this stage patients have signs of hypoperfusion and require pressor and inotropic support, often mechanical support or extracorporeal membrane oxygenation (ECMO) is often used. These patients have mean BP <60 mm Hg and SBP <90 mm Hg along with hypoperfusion. Laboratory findings may include signs of impaired renal function, elevated levels of lactate, natriuretic peptide, and liver enzymes. Invasive hemodynamics demonstrates a decrease in CI <2,2 l/min/m^2.

Stage D: "Deteriorating" CS describes a patient who has failed to stabilize despite intense initial efforts and further escalation is required. In addition, at least 30 minutes have elapsed but the patient has not responded with resolution of hypotension or end-organ hypoperfusion. Escalation consists in increasing the degree of vasopressor and inotropic

Figure 1. CS classification ([18], courtesy of Wiley).
Abbreviations: CS — cardiogenic shock, CPR — cardiopulmonary resuscitation, ECMO — extracorporeal membrane oxygenation.
Stage A — At risk. A patient who is not currently experiencing signs or symptoms of CS, but is at risk for its development. These patients may include those with large acute myocardial infarction or prior infarction acute and/or acute on chronic heart failure symptoms.
Stage B — Beginning CS. A patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion.
Stage C–Classic CS. A patient that manifests with hypoperfusion that requires intervention (inotrope, pressor or mechanical support, including ECMO) beyond volume resuscitation to restore perfusion. These patients typically present with relative hypotension.
Stage D — Deteriorating. A patient that is similar to category C but are getting worse. They have failure to respond to initial interventions.
Stage E — Extremis. A patient with circulatory collapse, frequently (but not always) in refractory cardiac arrest with ongoing cardiopulmonary resuscitation (CPR) or are being supported by multiple simultaneous acute interventions including ECMO-facilitated CPR. These are patients with multiple clinicians at bedside laboring to address multiple simultaneous issues related to the lack of clinical stability of the patient.

support to eliminate hypoperfusion and often the addition of mechanical circulatory support after the initial observation period. Colleagues from City Clinical Hospital № 52 in Moscow show that ECMO is actively used in refractory true CABG and in circulatory arrest, as a therapy for critical conditions [19].

Stage E: "Extremis" CS is the patient with circulatory collapse (refractory to treatment hypotension). Often (but not always), there is a circulatory arrest with ongoing cardiopulmonary resuscitation (CPR) or life support is provided by multiple simultaneous acute interventions, including ECMO-facilitated CPR. These are patients treated by a multidisciplinary team with doctors of various specialties, ranging from an intensive cardiologist to a cardiac surgeon. All of their work at the bedside is geared towards addressing multiple simultaneous issues related to the lack of clinical stability of the patient. Again, Russian specialists concluded that a cardiac intensivist is ideally suited to work in the cardiology unit, since he is equally competent in both clinical cardiology and intensive care [20].

Mechanism of CS development

The underlying mechanism for CS development is most often an acute decrease in LV contractility due to ischemia, which primarily causes a pronounced decrease in myocardial contractility, which first of all triggers a vicious circle of decreased CI, which further leads to the hypotension, which collectively worsen SI, and this further exacerbates coronary hypoperfusion [21]. RV contractile dysfunction and microcirculatory impairment can also contribute to the onset and worsening of CS course. A decrease in cardiac output (CO) affects coronary perfusion, which leads to impaired myocardial contractility and progression of CS. Impaired microcirculation in patients with decompensated HF and CS was already noted in the work [22], which showed that the proportion of perfused small (20 μm) vessels was lower in patients with HF and CS than in HF patients without CS (63% [46-65%] and 49% [38-64%] vs 92% [90-93%], p=0,001). Therefore, microcirculation disorders are quite common in patients with CS and are associated with a poor prognosis. The presence of obstructive CAD can further aggravate the decrease in coronary perfusion.

In the position statement of the European Society of Cardiology [4], much attention in the CS development and its pathophysiology is paid to microcirculation and multiorgan dysfunction (Figure 2). This is primarily due to the fact that the microcirculation is

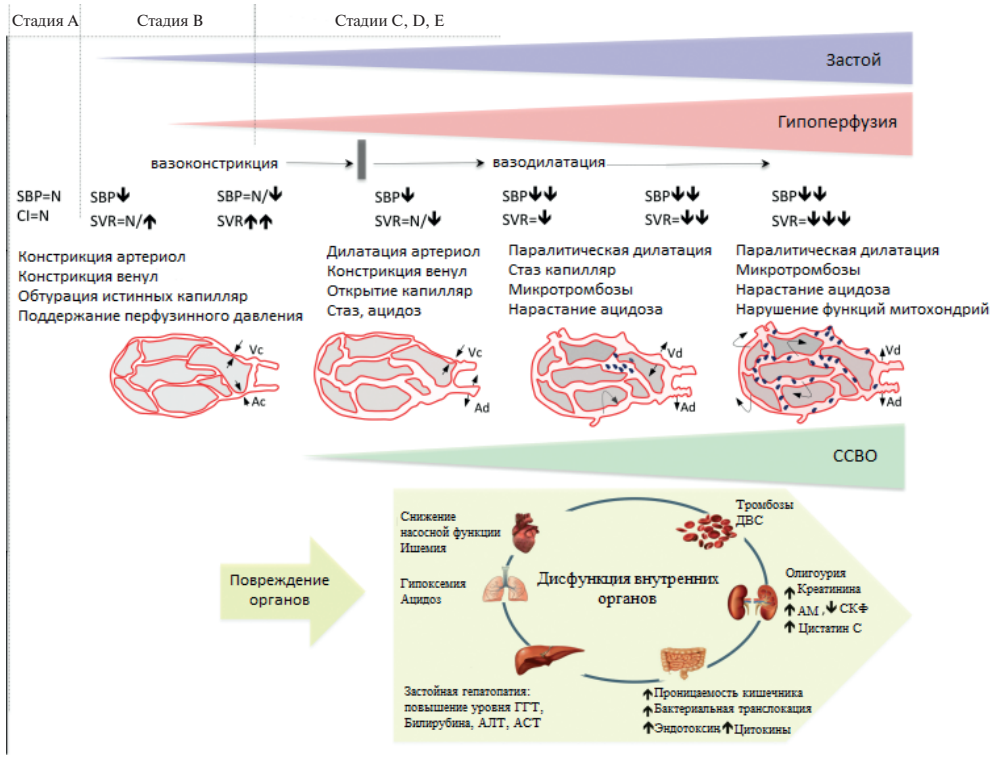

Figure 2. Organ dysfunction in CS ([4], courtesy of Wiley).
Abbreviations: ALT — alanine aminotransferase, AM — urea nitrogen, AST — aspartate aminotransferase, GGT — gamma-glutamyl transferase, DIC — disseminated intravascular coagulation, GFR — glomerular filtration rate, SIRS — systemic inflammatory response syndrome, Ac — arteriolar constriction, Ad — arteriolar dilatation, CI — cardiac index, SBP — systolic blood pressure, SVR — systemic vascular resistance, Vc — venular constriction, Vd — venular dilatation.

flow-dependent. A decrease in CO with a compensatory vascular tone increase reduces the sensitivity of capillaries, which does not meet the requirements of cellular metabolism, and this primarily leads to cellular hypoxia. However, even under severe hypoxia, mitochondrial viability and function are maintained for several hours, and animal models suggest initial activation of the mitochondrial transport chain to maintain normal functioning to support metabolic demands [23]. Subanalysis of the CULPRIT-SHOCK study [24] showed an independent correlation between microcirculatory perfusion and the composite endpoint of 30-day mortality, renal replacement therapy, especially in patients with a hemodynamic imbalance between microcirculation and macrocirculation characteristics [25]. Systemic inflammation also plays an important role in CS development and is observed in 20-40% of patients with CS, and ultimately leads to a decrease in systemic vascular resistance [26]. Elevated levels of cytokines (interleukin-1β, 6, 7, 8, and 10) were found in patients shortly after the CS onset, which is a predictor of death [27]. The production of nitric oxide and other inflammatory mediators leads to vasodilation, which impairs macrocirculation. Infection complicates the course of approximately 20-30% of CS cases [28]. Infection risks include vascular access as well as gastrointestinal mucosal damage associated with hypoperfusion and consequent bacterial translocation. Multiple organ dysfunction is the result of macrohemodynamic abnormalities and is associated with poor prognosis. Despite the fact that LVEF is a marker of poor prognosis in CS patients, contrary to popular belief, LV contractility is not always sharply reduced, which was shown, for example, in the SHOCK study [29], where most patients had EF >30%. An important factor is the presence of not only contractile dysfunction in these patients, but diastolic dysfunction with a restrictive pattern, leading to an increase in filling pressure. Reynolds HR, et al. [30] described in detail the echocardiographic patterns of CS. The pattern of increased filling pressure was observed in 60,9% of examined patients. Patients with this pattern had a lower LVEF (31,1% vs 39,0%, p=0,02) and a higher LV wall motion score index (2,1 vs 1,8, p=0,05). Patients with severe diastolic dysfunction were more likely to receive counterpulsation during echocardiography (73,7% vs 43,5%, p=0,03). The restrictive pattern had a positive predictive value of 80% for elevated PCWP ⩾20 mm Hg. Thirty-day survival was 53,9% with restriction versus 68,0%

without restriction (p=0,31). Therefore, restrictive filling pattern is common in patients with CS and is associated with its unfavorable course. CS can also occur with RV involvement, but the percentage of such patients is much less, because most of them are found with primary LV failure. Studying the registry for patients with CS, some researchers [31] conclude that patients with RV infarction have outcomes comparable to those in patients with CS and LV failure. There are following mechanism of LV failure: RV dysfunction affects LV contractility, not only by reducing LV preload, but also due to the effect of interventricular septum prolapse on LV geometry, which leads to a decrease in its contractility. The investigators made the following conclusions: patients with predominant shock in RV involvement were younger, with a lower rate of prior MI (25,5 vs 40,1%, p=0,047), anterior MI and multivessel disease (34,8 vs 77,8%, p=0,001), there was also less time spent from the diagnosis of MI to CI (2,9 vs 6,2 h, p=0,003) compared with patients with shock due to LV involvement. Inhospital mortality was 53,1% compared with 60,8% (p=0,296) for patients with predominance of RV and LV shock, respectively, and the effect of revascularization on mortality did not differ between groups. Therefore, CI against the background of RV failure has the same unfavorable prognosis as true LV CS. Thus, we see that true CS leads to macro- and micro-organ dysfunction, often leading to death. The instability of hemodynamic parameters and the severity of such a cohort of patients suggests the idea of decision-making speed and the timeliness of providing competent care.

Treatment of CS

To answer the question of what is the basis of therapy for such severe patients with true CS, it is important to understand the mechanism of CS development in each specific case, and one should try to influence the entire chain of organ dysfunction. Perhaps the most important is to perform revascularization in such patients, i.e. emergency percutaneous coronary intervention (PCI) should be performed [32]. In another review [33], the authors show that patients with return of spontaneous circulation after successful CPR should be taken to a PCI center as soon as possible. Early emergency echocardiography and laboratory tests (acid-base balance, lactate levels) are important and can be performed in the operating room, but only with limited delay without delaying PCI. Triage, stabilization and diagnostic evaluation of such patients are essential before invasive treatment. Stable patients with risk factors for shock (Stage A) or in the case of pre-CS (Stage B) can usually have immediate coronary angiography followed by infarct-related artery revascularization, with ongoing clinical, laboratory and physical reevaluation of patients for progression of shock every 60 minutes. Patients with more severe CS (Stages C-E) may generally need to be stabilized initially based on BP, target organ perfusion status, oxygenation, and acid-base status. However, in cases of STEMI, any necessary stabilization efforts should be accelerated to minimize the delay in reperfusion therapy, because every 10-min delay results in 3 deaths per 100 patients undergoing PCI [34].

What are the options for stabilizing the patient condition at the present time? Intravenous inotropic and pressor agents have been and remain the mainstays in the emergency treatment of CS. These agents can increase ventricular and CO contractility, decrease filling pressure, and maintain target organ perfusion. Among the most commonly used drugs, dobutamine can be distinguished, which is a direct agonist of β2-adrenergic receptors with a positive inotropic effect, in addition to it, norepinephrine can also be noticed, stimulating both α and β-adrenergic receptors, but more precisely with a vasopressor effect and minimal inotropic, as well as milrinone and levosimendan [35]. Norepinephrine is a fairly strong and reliable vasopressor with a minimal inotropic effect, which is important given compensatory tachycardia in this category of patients, and norepinephrine is often used in combination with dobutamine. The use of vasopressor agents in severe true CS is justified by the fact that in many patients the effectiveness of target organ perfusion directly correlates with BP: namely, with SBP or, as it is often called, perfusion BP, the level <60 mm Hg of which increases inhospital mortality. Norepinephrine in this case not only can maintain the perfusion of internal organs at an adequate level, but also stimulates a BP increase without concomitant increase in heart rate (HR). Currently, there are no comparative studies of pure inotropic and vasodilatory agents in CS. In clinical practice [36], three drugs can be used: dobutamine, which is a pure inotrope, as well as levosimendan and phosphodiesterase (PDE) inhibitors, both of which are combined inodilators. Interestingly, these three drugs act in different ways. Dobutamine is predominantly a β-1-agonist with weak activity at β-2 and α-1 receptors. PDE inhibitors prevents the breakdown of cyclic adenosine monophosphate (cAMP). In the myocardium, increased cAMP levels activate protein kinase A, which in turn produces calcium channel phosphorylation, increasing calcium influx into the cardiomyocyte, which in turn increases contractility. In smooth muscle, elevated levels of cAMP inhibit myosin light chain kinase, which primarily causes arterial and venous vasodilation. Levosimendan interacts with Ca^{2+}-saturated troponin C (cTnC) and this underlies Ca^{2+}-sensitizing mechanism. The

interaction site for levosimendan on the cTnC molecule was located on the hydrophobic N-domain, in close proximity to so-called D/E linker. Levosimendan binding results in Ca^{2+}-saturated cTnC stabilization in the drug presence, thereby increasing the inotropic function of cardiomyocytes. This drug also has a vasodilation effect on vascular smooth muscle, mediated through the opening of adenosine triphosphate-sensitive potassium channels [37]. Despite the whole pool of favorable effects, levosimendan is usually considered as a second-line agent in CS therapy. Based on clinical experience, availability, and cost, dobutamine is generally recommended as a first-line drug. Dobutamine has been shown to significantly increase heart rate, CI, and mixed venous oxygen saturation (SvO_2) in CS, while decreasing both PCWP and lactate levels. Milrinone, a member of PDE inhibitors, was found not to significantly increase HR with a decrease in PCWP and an increase in CI, but no marked increase in SvO_2 or decrease in lactate was noted. In the end, both drugs were associated with arrhythmias and systemic hypotension. However, studies suggest that milrinone and dobutamine showed similar efficacy and safety profiles, but with little difference in side effects. The choice of milrinone or dobutamine as initial inotropic therapy in CS may depend more on the tolerability of adverse events [38]. Dopamine is an endogenous catecholamine, the cardiovascular effects of which are directly dependent on the dose. Small dose (2 μg/kg) cause vasodilation due to stimulation of dopamine D1 receptors of smooth muscles, which dominate in the endothelium of the celiac and renal arteries. In addition, stimulation of D1 receptors causes natriuresis due to inhibition of sodium-potassium ATPase, and due to the acceleration of renal blood flow during stimulation of renal artery receptors. In addition, a decrease in sodium reabsorption in the proximal tubule was also noted, which is especially important in patients with severe HF. At medium doses (2-5 μg/kg/min), dopamine stimulates cardiac β-receptors and vascular sympathetic receptors, causing an inotropic effect. At higher doses (5-15 μg/kg/min), alpha-adrenergic stimulation with peripheral arterial and venous constriction occurs. The effects of dopamine in CS include an increase in HR (+11%), CO (+40%), stroke volume (+30%) and PCWP (+2,4 mm Hg), but at high doses the drug increases systemic vascular resistance [39]. Therefore, dopamine is still better not to use in CS, despite all favorable effects. Dopamine has been shown to be associated with an increase in 28-day mortality compared to norepinephrine. The study [40] included 1679 patients, of which 858 received dopamine as the main line of pressor therapy and 821 — norepinephrine to restore and maintain perfusion pressure. There was no significant difference in mortality at 28 days (52,5% in the dopamine group and 48,5% in the norepinephrine group), but there were more life-threatening cardiac arrhythmias in the dopamine group (207 events (24,1%) vs 102 events (12,4%), p<0,001). A subanalysis showed that dopamine, compared with norepinephrine, was associated with increased mortality at day 28 among 280 patients with CS, but not among patients with septic shock or hypovolemic shock (p=0,03 for CS, p=0,19 for septic shock and p=0,84 for hypovolemic shock). Another meta-analysis on inotropic and pressor support showed [41] that norepinephrine was associated with a lower 28-day mortality rate, as well as a lower risk of arrhythmic events. This superiority of norepinephrine over dopamine is seen regardless of CS caused by CAD. As for vasopressin, it is not recommended for use due to lack of inotropic properties. Therefore, it does not improve the cardiac power index and CI, while norepinephrine increases CI. Therefore, norepinephrine is currently considered the best vasopressor agent, which has such a significant effect as an increase in systemic vascular resistance and maintenance of perfusion pressure at a target level, while dobutamine is the optimal inotropic agent. With regard to mechanical support methods, they should be used as early as possible when refractory to inodilator and vasopressor therapy. Available devices include a intra-aortic balloon counterpulsation (IABP), support devices Impella, Tandem Heart, and venoarterial ECMO (VA-ECMO) (Figure 3). According to a review on mechanical support devices [42], IABP is considered to be one of the best, most commonly used method. The device consists of an inflatable balloon, which is connected to a double-lumen catheter and a pump that helps with counterpulsation. The catheter is placed in the descending aorta, proximal to the renal arteries and distal to the left subclavian artery. The most used area is the femoral artery. IABP provides cardiac support by inflating during diastole with an increase in coronary perfusion with subsequent deflating during systole and creating a vacuum that greatly reduces aortic pressure and reduces LV afterload, synchronizing the device with the patient's electrocardiography. Despite the usability and availability, IABP is associated with a large number of vascular complications, often leading to patient immobilization. The Impella is a pump that unloads the LV by directing blood flow from the LV to the aorta and can provide flow up to >5 L/min, depending on the device used: Impella 2.5 and Impella CP can be rapidly implanted percutaneously in a catheterization laboratory, while the Impella 5.0 requires surgical implantation. Unlike IABP, Impella does not require electrocar-

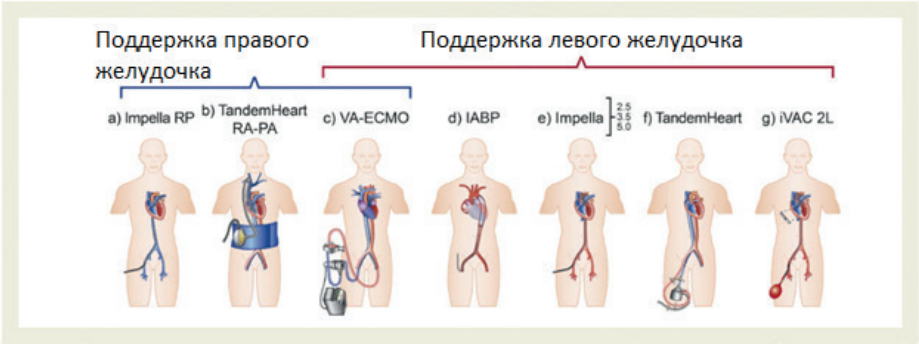

Figure 3. Devices for mechanical LV and RV support ([16], courtesy of the European Heart Journal).

diographic trigger, which contributes to stability even in the presence of tachyarrhythmias or electromechanical dissociation. Although it provides better hemodynamic support than IABP, there is no evidence of improved survival in CS, mainly due to vascular complications and bleeding [43]. VA-ECMO is a portable device that resembles a heart-lung machine. The device has a number of components including a membrane oxygenator, a controller, a heat exchanger, a centrifugal flow pump, a venous inflow cannula, and an arterial outflow cannula. During ECMO, deoxygenated blood from the right atrium (RA) is sent to a membrane oxygenator for oxygenation and then sent to a heat exchanger for warming and then to a controller for pumping back into the arterial system. In patients with RV failure, VA-ECMO can be cannulated from the RA into the pulmonary artery. The most commonly used is peripheral VA-ECMO, which increases left ventricular afterload directly affecting the elevated PCWP, which can ultimately increase pulmonary congestion. Decompression strategies for LV ventilation include additional procedures such as IABP, septostomy, and hybrid circuit. When cardiac recovery precedes lung recovery, an influx of deoxygenated blood into the ascending aorta results in upper body hypoxia, Harlequin syndrome, requiring CO reduction or reconfiguration of the apparatus until lung recovery. The use of VA-ECMO has a significant impact on the quality of life. The study [44] demonstrated that VA-ECMO was associated with a significant improvement in 30-day survival in both groups compared with IABP, and there was no difference in comparison with TandemHeart or Impella. It is worth noting that the idea of combining IABP and VA-ECMO is the best practice. IABP can neutralize the undesirable effects of VA-ECMO, such as a decrease in afterload, as well as an increase in coronary perfusion. With regard to mechanical ventilation, acute respiratory failure with or without the use of mechanical ventilation correlates with higher in-hospital mortality, and therefore a patient with CS should be intubated sooner. This is due to the fact that an additional energy consumption to maintain a high respiratory rate, which is not able to compensate for ventilation-perfusion mismatch with metabolic acidosis, can lead to CS progression. Particular care should be taken to ventilate the lungs under positive pressure in CS with RV dysfunction, since high levels of positive end-expiratory pressure may exacerbate RV failure [45]. Also, with the development of cardiorenal syndrome, renal replacement therapy should be performed. Continuous venovenous hemodiafiltration is recommended for severe acute kidney injury (creatinine $\geqslant$2 of the baseline and urine output <0,5 ml/kg/h for $\geqslant$12 h) or severe hypervolemia, electrolyte disbalance or pronounced acid-base balance changes [46].

Conclusion

CS is a complex multifactorial clinical syndrome with extremely high mortality, with rapid development of multiple organ failure and death. There are few clinical and registry studies in this area, the results of which remain not entirely satisfactory. Future multicenter trials should consider the timely therapy in an appropriately selected cohort of patients with CS [4]. Educational activities are also needed to increase the awareness of specialists about modern principles of therapy for patients with complicated coronary and non-coronary myocardial diseases.

Relationships and Activities: none.

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