

Advanced heart failure

Kalyuzhin V.V.¹, Teplyakov A.T.², Beshpalova I.D.¹, Kalyuzhina E.V.¹, Terentyeva N.N.³, Sibireva O.F.^{1,4}, Grakova E.V.², Usov V.Yu.², Osipova M.A.⁵

¹ Siberian State Medical University

2, Moscow Trakt, Tomsk, 634050, Russian Federation

² Cardiology Research Institute, Tomsk National Research Medical Center (TNRMC), Russian Academy of Sciences
111a, Kievskaya Str., Tomsk, 634012, Russian Federation

³ Surgut State University

1, Lenina Av., Surgut, 628412, Russian Federation

⁴ Regional Clinical Hospital

96, I. Chernykh Str., Tomsk, 634063, Russian Federation

⁵ Federal Government Health Care Institution "Medical department of the Ministry of Internal Affairs of the Russian Federation for the Tomsk region" (FGHCI "MD of the Ministry of Internal Affairs of the Russian Federation for the Tomsk region")

48/5, Elizarovskaya Str., Tomsk, 634012, Russian Federation

ABSTRACT

The authors of the article have analyzed the problem of advanced heart failure (AHF). Despite significant and, without exaggeration, revolutionary achievements in clinical pharmacology, cardiac surgery, and implantation arrhythmology, the number of patients with chronic heart failure (CHF) in many countries is not decreasing, and in some states, for example, in Russia, it is increasing. At the same time, unfortunately, immediate and long-term results of the so-called optimal therapy of CHF are often disappointing for both the patient and the doctor. In 2007, experts from The Heart Failure Association of the European Society of Cardiology proposed the term advanced heart failure (AHF) to refer to CHF in which optimal drug therapy, as well as cardiac resynchronization therapy, are not effective, which causes repeated hospitalizations and justifies the need for advanced treatment methods such as heart transplantation and mechanical circulatory support, and/or transition to palliative care. The opinions of experts from the established cardiological communities in the Old and New Worlds on the definition, diagnostic criteria, and treatment of AHF have been changing over time. Unfortunately, this evolution has not yet arrived at a consensus. The lecture consistently addresses the issues of terminology, diagnosis, prognostic stratification, and routing of patients with AHF, as well as short- and long-term strategies for treating these patients.

Key words: advanced heart failure, definition, indicators, prognostic stratification, clinical markers, biomarkers, imaging, exercise test, co-morbidity, management strategies, mechanical circulatory support, heart transplantation

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✉ Kalyuzhin Vadim V., e-mail: kalyuzhinvv@mail.ru.

Прогрессирующая (advanced) сердечная недостаточность

Калюжин В.В.¹, Тепляков А.Т.², Беспалова И.Д.¹, Калюжина Е.В.¹, Терентьева Н.Н.³, Сибирева О.Ф.^{1,4}, Гракова Е.В.², Усов В.Ю.², Осипова М.А.⁵

¹ Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, Томск, Московский тракт, 2

² Научно-исследовательский институт (НИИ) кардиологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634012, Томск, ул. Киевская, 111

³ Сургутский государственный университет (СурГУ)
Россия, 628412, Сургут, пр. Ленина, 1

⁴ Томская областная клиническая больница (ТОКБ)
Россия, 634063, г. Томск, ул. И. Черных, 96

⁵ Медико-санитарная часть Министерства внутренних дел России по Томской области (МСЧ МВД России по Томской области)
Россия, 634012, Томск, ул. Елизаровых, 48/5

РЕЗЮМЕ

Приводится анализ проблемы прогрессирующей сердечной недостаточности (ПСН). Несмотря на существенные, не будет преувеличением сказать – революционные, достижения клинической фармакологии, кардиохирургии и имплантационной аритмологии, число пациентов с хронической сердечной недостаточностью (ХСН) во многих странах не сокращается, а в некоторых, например в России, увеличивается. При этом, к сожалению, нередко непосредственные и отдаленные результаты так называемой оптимальной терапии ХСН вызывают разочарование как у пациента, так и у врача. В 2007 г. эксперты Ассоциации сердечной недостаточности Европейского общества кардиологов предложили термин ПСН для обозначения ХСН, при которой оптимальная медикаментозная терапия, а также сердечная ресинхронизирующая терапия не являются эффективными. Это является причиной повторных госпитализаций и обосновывает необходимость применения таких передовых методов лечения, как трансплантация сердца и механическая поддержка кровообращения, и (или) перехода к паллиативной помощи. Согласованные позиции экспертов авторитетных кардиологических сообществ в Старом и Новом Свете, касающиеся определения, критериев диагностики и лечения ПСН, менялись со временем, но, к сожалению, их эволюция до сих пор не завершилась полным консенсусом. В лекции последовательно рассматриваются вопросы терминологии, диагностики, прогностической стратификации и маршрутизации пациентов с ПСН, а также краткосрочной и долгосрочной стратегии лечения этих больных.

Ключевые слова: прогрессирующая сердечная недостаточность, определение, индикаторы, прогностическая стратификация, клинические маркеры, биомаркеры, визуализация, тест с физической нагрузкой, сопутствующие заболевания, стратегии ведения, механическая поддержка кровообращения, трансплантация сердца.

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

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INTRODUCTION

Chronic heart failure (CHF) is a notorious medical and social problem that belongs to the priorities of national health systems in almost all developed and developing countries [1, 2]. This is explained by the fact that despite the significant and even revolutionary achievements in clinical pharmacology, cardiac surgery, and implantation arrhythmology, the number of patients (especially those with heart failure with preserved left ventricular (LV) ejection fraction (EF)) with this disabling, costly, and often deadly condition does not decrease in many countries. In some countries, for example in Russia, it increases [3–6]. At the same time, immediate and long-term results of the so-called optimal therapy of heart failure are, unfortunately, often disappointing for both the patient and the doctor [7, 8].

The aim of this lecture was to consider contemporary views on the problem of advanced heart failure (AHF), the prevalence of which in the population of patients with CHF ranges from 1 to 10% [9, 10].

TERMINOLOGY

In 2007, experts from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) proposed the term AHF to refer to heart failure, in which optimal drug therapy, including diuretics, renin-angiotensin-aldosterone system

(RAAS) inhibitors, beta-blockers (unless these drugs are not contraindicated and are well tolerated), and cardiac resynchronization therapy (if there are appropriate indications) are not effective. It is considered not effective if the following persist: objective signs of severe cardiac dysfunction, such as severe systolic and/or diastolic LV dysfunction, high ventricular filling pressure and increased natriuretic peptide blood levels, which are associated with heart failure corresponding to III-IV functional class (FC) according to NYHA (New York Heart Association), dyspnoea and/or fatigue at rest or with minimal exertion, as well as episodes of fluid retention and/or peripheral hypoperfusion at rest.

All of the above is the reason for repeated hospitalizations (≥ 1 case over the past six months) and justifies the need for using such advanced treatment methods as heart transplantation and mechanical circulatory support, and/or the transition to palliative care [11]. The studied cases included not yet fatal patients with refractory heart failure requiring consideration of the use of a circulatory assist device and/or heart transplantation and patients with end-stage heart failure in which irreversible changes in the end-organs cause contraindications to surgery and palliative care is the only possible option (for example, inotropic drug infusions, ultrafiltration or peritoneal dialysis and end-of-life care) were in question.

	AHF		
	Moderate CHF	Severe CHF	Refractory CHF
NYHA class*	III	IV	
CHF stage**	C		D

Fig. 1. Position of advanced heart failure (AHF) in chronic heart failure (CHF) classifications [11]: * Classification of the New York Heart Association; ** Classification by the American Heart Association and the American College of Cardiology

Well-known difficulties of precise CHF functional class (FC) diagnosis, associated with the subjectivity of a patient and a doctor in determining what limitation to physical activity is slight or significant and what exertion is habitual for the patient, were described many times in the «Bulletin of Siberian Medicine» among other sources [12–14]. This subjectivity naturally leads to low reproducibility of the results of assessing CHF FC in the same patient by different doctors. CHF affects mainly elderly people. Taking into account polymorbidity, the infor-

mativity of the exercise test performed to objectify FC (a 6-minute walk test, for instance) is often unacceptably low in these patients, since the distance traveled by the patient can be affected not only by myocardial, but also by coronary or respiratory failure and other factors [14].

At the same time, some doctors and researchers give a rather subjective interpretation of the NYHA classification. They identify intermediate FC values (for example, III-IV) and attempt to introduce additional gradations into the classification. One of these

is IIIB class which is not categorically identified as “advanced”. This class is vaguely characterized as a more serious disturbance of the functional status than in FC III, on the one hand, but not as severe as in CHF corresponding to FC IV, on the other hand [14, 15]. Medicine does not belong to exact sciences, but such an argument cannot be understood, as if you are being convinced that more than two results are possible after flipping a coin – not only “heads” or “tails”, but also the coin’s hanging in the air.

As for repeated hospitalizations, this is a controversial criterion, since some patients with AHF may often seek unplanned medical care and receive it in an outpatient setting (for example, in the United States in the emergency department), and some patients are hospitalized for reasons not directly related to CHF (for example, exacerbation of the underlying disease or comorbid pathology, or disturbances of heart rhythm and conduction). Most often, unplanned hospitalizations in these patients are caused by acute heart failure (including so-called acute decompensated heart failure) [8] and circumstances related to refractory CHF [11].

It is important not to allow for confusion of concepts. AHF is a form of CHF, which even in rapidly developing decompensation is fundamentally different from acute heart failure [1]. D.V. Preobrazhenskiy et al. [12] rightly consider the concepts of “heart failure” and “chronic heart failure” as synonyms, since speaking of acute heart failure, it is customary to indicate its specific form, such as pulmonary edema, cardiogenic shock, or acute pulmonary heart (it does not matter whether this preceded CHF or not). Nevertheless, in the special medical literature, there is also an opposite point of view, according to which acute heart failure includes episodes of acute cardiac decompensation in patients with CHF in the absence of the clinical presentation of pulmonary edema and cardiogenic shock. We quote what we cannot understand: “Acute decompensated heart failure (first-time, decompensation of CHF) – poorly expressed symptoms of acute heart failure that do not meet the criteria for cardiogenic shock, pulmonary edema ...” [16]. Apparently, all clinicians have encountered primary and secondary refractory disease in patients with CHF (it is important to recall pseudo-refractoriness that can be associated with the patient’s non-compliance) with the treat-

ment. There are no generally accepted criteria for verifying this condition (similar to those for resistant hypertension [17]). This is probably why repeated attempts to introduce the refractory phase (stage) of CHF in its classification are met with reasonable resistance from the leading cardiologists of Russia. Yu. N. Belenkov at the “Classification of chronic heart failure” round table at the annual (14.12.2001) conference of the Society of Specialists in Heart Failure, objected to such a proposal as follows: “You cannot introduce a refractory phase. Refractory to what? We do not make a classification for ourselves, but a classification for everyone. Your refractory patient and my refractory patient are different patients because we have plasmapheresis, ultrafiltration, and artificial LV” [18].

Finally, the final (terminal) stage of CHF should be distinguished from AHF. According to ESC experts [11], the main difference between them is the presence of a certain degree of reversibility in the severity of CHF manifestations when applying cutting-edge treatment methods. The ambiguous phrase “a certain degree of reversibility” dictates the need to search for informative discriminant signs. Doctors in the absence of the latter should not rush to pronounce a sentence on a patient with CHF.

Such indistinct criteria were the subject of deserved criticism and the reason for revising the definition of AHF for it to take into account the evaluation of the effectiveness of new classes of drugs (such as sinus node If-channel inhibitors and angiotensin receptor and neprilysin inhibitors), characteristics of comorbid pathology, the condition of the end-organs, and other variables neglected by the ESC experts in 2007. The opinions of experts of reputed cardiological communities in the Old and New Worlds regarding the definition and criteria for diagnosis and treatment of AHF have changed over time, but, unfortunately, their evolution has not yet ended in full consensus, and none of the proposed interpretations are indisputable [9, 19]. In this regard, it is worth quoting the titles of the works of well-known cardiologists, who vividly designated the problem: “Advanced heart failure and end-stage heart failure: does a difference exist?” [20], “A changing trend toward destination therapy: are we treating the same patients different-

ly?” [21], “Rise of the machines? Left ventricular assist devices for treatment of severe heart failure” [22], “Mechanical ventricular assistance as destination therapy for end-stage heart failure: has it become a first-line therapy?” [23].

DIAGNOSTIC CRITERIA

Obviously, in order to speak about AHF with confidence, it is necessary to justify the presence of heart failure itself in the patient first. The principles of CHF diagnosis are well developed and described in numerous recommendations [3, 5, 24]. Modern criteria for the diagnosis of AHF, as a rule, include signs first formulated in 1998 by K.F. Adams Jr. and F. Zannad [25]: LV EF value determined at rest is less than 30%, CHF corresponds to FC III-IV, or maximum oxygen consumption is less than 14 ml / kg / min. However, even among patients hospitalized with acute heart failure, at least half have normal LV FV values. The absence of LV global contractile dysfunction should not contradict the diagnostic conclusion about AHF in the presence of other symptoms and signs of this condition [9].

Detailed criteria for the diagnosis of AHF, formulated in current memorandums of the HFA ESC [9], the American Heart Association (AHA) and the American College of Cardiology (ACC) [26], as well as the Heart Failure Society of America (HFSA) [27], are presented in Table 1.

After reviewing the criteria presented in Table 1, many clinicians are likely to have questions. The greatest list of questions, perhaps, is caused by AHF criteria presented in AHA/ACC recommendation, since they do not specify whether all criteria are obligatory for verification of AHF, they contain inaccurate wording (e.g., “frequent”, “usually”) and do not include any characteristics of a state of cardiac contractile and lusitropic functions. It should be noted that the North American experts focused strictly on CHF and discussed AHF briefly in the context of CHF [26]. However, in the absence of information about the presence and severity of global (segmental) systolic and diastolic ventricular dysfunction, as well as their remodeling, detection of CHF is not always infallible, and the diagnosis itself is not irreproachable [14, 28–32].

In this regard, the recommendations of the HFA ESC 2018 look more reasonable [9]. They emphasize a thorny path at differential diagnosis, since the symptoms and signs indicated in paragraphs 1 and 4 (Table 1) can be the result of not only cardiac dysfunction, but other conditions (for example, severe lung disease, non-cardiac cirrhosis of the liver, or, most often, renal failure of mixed etiology). However, these patients have a low quality of life and a bad prognosis and require the same attention as someone in whom heart failure is the only existing illness.

Table 1

Most common criteria for diagnosing AHF [9, 26, 27]		
HFA ESC, 2018	AHA / ACC, 2013	HFSA, 2015
<p>All the following criteria must be present despite optimal guideline-directed treatment:</p> <ol style="list-style-type: none"> 1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV]. 2. Severe cardiac dysfunction defined by reduced LVEF $\leq 30\%$, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data on severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF. 3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visits or hospitalizations over the last 12 months. 	<ol style="list-style-type: none"> 1. Repeated (≥ 2) hospitalizations or ER visits for HF in the past year 2. Progressive deterioration in renal function (e.g. rise in BUN and creatinine) 3. Weight loss without other cause (e.g. cardiac cachexia) 4. Intolerance to ACE inhibitors due to hypotension and/or worsening renal function 5. Intolerance to beta-blockers due to worsening HF or hypotension 6. Frequent systolic blood pressure <90 mmHg 7. Persistent dyspnoea with dressing or bathing requiring rest 8. Inability to walk 1 block on the level ground due to dyspnoea or fatigue 	<p>The presence of progressive and/or persistent severe signs and symptoms of HF despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalizations, severely limited exertional tolerance, and poor quality of life and is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the HF syndrome.</p> <p>Indicators of advanced HF in the setting of optimal medical and electrical therapies that should trigger consideration of referral for evaluation of advanced therapies include:</p> <ul style="list-style-type: none"> • Need for intravenous inotropic therapy for symptomatic relief or for maintaining end-organ function • Peak $VO_2 < 14$ mL/kg/min or $<50\%$ from the predicted value • 6MWT distance <300m • ≥ 2 HF hospitalizations in the last 12 months • >2 unscheduled visits (e.g. ER or clinic) in the last 12 months

Table 1 (continued)

HFA ESC, 2018	AHA / ACC, 2013	HFSA, 2015
<p>4. Severe impairment of exercise capacity with inability to exercise or low 6MWT (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.</p> <p>In addition to the criteria mentioned above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.</p>	<p>9. Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/day and/or use of supplemental metolazone therapy</p> <p>10. Progressive decline in serum sodium, usually to <133 mEq/L</p> <p>11. Frequent ICD shocks</p>	<ul style="list-style-type: none"> • Worsening right ventricular HF and secondary pulmonary hypertension • Diuretic refractoriness associated with worsening renal function • Circulatory–renal limitation to RAAS inhibition or beta-blocker therapy • Symptoms of progressive/persistent CHF (NYHA functional class III–IV) • Increased 1-year mortality (e.g. 20–25%) predicted by HF survival models (e.g. SHFS, HFSS, etc.) • Progressive renal or hepatic end-organ dysfunction • Persistent hyponatraemia (serum sodium <134 mEq/L) • Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks • Cardiac cachexia • Inability to perform ADL

Note. HFA – Heart Failure Association; ESC – European Society of Cardiology; AHA / ACC – American Heart Association /American College of Cardiology; HFSA – Heart Failure Society of America; 6MWT – 6-minute walk test; ACE – angiotensin-converting enzyme; ADL – activities of daily living; BNP – B-type natriuretic peptide; BUN – blood urea nitrogen; CRT – cardiac resynchronization therapy; ER – emergency room; HF – heart failure; HFSS – Heart Failure Survival Score; ICD – implantable cardioverter-defibrillator; LV – left ventricular; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal pro-B-type natriuretic peptide; HfmrEF – heart failure with mid-range ejection fraction; HfpEF – heart failure with preserved ejection fraction; ARVC – arrhythmogenic right ventricular cardiomyopathy; NYHA – New York Heart Association; PCWP – pulmonary capillary wedge pressure; RAAS – renin-angiotensin-aldosterone system; RAP – right atrial pressure; SHFS – Seattle Heart Failure Score; pVO_2 – peak exercise oxygen consumption.

PROGNOSTIC STRATIFICATION

Accurate and timely prognosis is important for any disease, but in such a severe pathology as AHF, the results of predictive stratification are of particular importance. In order to justify referring the patient with chronic heart failure in a specialized center (e.g., heart failure clinic), it is enough to detect pronounced decompensation. However, to select patients requiring the use of advanced treatment methods, such as heart transplantation and artificial left ventricle, and to determine the optimal time for this therapy, it is necessary at first to have a substantiated assumption on unacceptably high risks of death in the absence of aid from an organ transplant surgeon or specialists in mechanical circulatory support [9].

A fairly extensive list of indicators of adverse prognosis in AHF is presented in Table 2 [9]. It is logically grouped by ESC experts according to the method of obtaining information (markers obtained in a clinical study and by performing simple instrumental tests; biomarkers evaluated in the laboratory; results of heart and vascular imaging; and exercise testing) and the presence of comorbid pathology.

As you can see, the prognosis in AHF patients is associated with a large number of factors with

an obvious linear relationship (from weak to almost functional) between many of them. For example, the quality of life in a patient with CHF is related to gender, parameters of LV remodeling (geometric and electrophysiological) and its functional state, the level of asthenia and the severity of depression, as well as the presence of metabolic syndrome (obesity and indicators reflecting the severity of systemic inflammation and oxidative stress), iron deficiency, and coronary insufficiency [33–39]. Depression of heart rate variability in these patients is directly related to age, heart remodeling, the degree of systolic and diastolic LV dysfunction, the presence of diabetes mellitus and diabetic autonomic neuropathy, as well as the clinical severity of heart failure, and, conversely, the effectiveness of CHF treatment [40–43]. Hyperuricemia can be one of the manifestations of metabolic syndrome or chronic kidney disease [44–46]. The number of cardiac and extra-cardiac factors affecting the level of the so-called cardiac biomarkers is generally difficult to calculate [47–53].

Due to the multicollinearity between risk factors, the partial prognostic value of each of them is difficult to determine and, therefore, it is not easy to distinguish significant independent predictors from

randomly detected and not carrying any additional information ones. The way out of the problematic situation in clinical practice can be the use of

multi-factor models of prognosis, which, for obvious reasons, have their advantages over monofactor models [9, 54, 55].

Table 2

Clinical markers and parameters obtained by instrumental research		
General clinical		
Age	↑ HR in sinus rhythm but not in atrial fibrillation	Reduced peripheral muscle strength
Male sex	Reduced HR variability	Rales
↑ QRS duration	Recent /recurrent HF hospitalizations	Edema
Longer HF duration	Changed haemodynamic profiles*	JVD
Higher NYHA class	Cardiomegaly	Hepatomegaly
Lower and labile SBP and lower DBP and MAP	S3	Ascites
Lower pulse pressure	Poor quality of life	
Biomarkers		
Copeptin		- ESR
Low sodium		Oxidative stress and fibrosis
Cardiomyocyte injury		- ST2
- Troponin		- Galectin-3
Cardiomyocyte stress		- GDF-15
- Higher BNP and/or NT-proBNP		- MR-proADM
- Increased NT-proBNP over time		- Lower LDL
- ANP		- Uric acid
- MR-proANP		- Low T3
Inflammation		- Albuminuria
- CRP		
Imaging		
Echocardiography		- Low LV RS at rest
- Lower LVEF		- No LV GLS increase in the dobutamine stress test
- Large areas of hypo/akinesis		- Pulmonary congestion by lung ultrasound
- LV dilatation		- Inflammation and fibrosis on CMR
- Diastolic dysfunction		- Poor viability of the myocardium on stress echocardiography and CMRR
- Mitral regurgitation		- Reduced miBG uptake
- Aortic stenosis		
- LV hypertrophy		
- LV mass		
Cardiopulmonary exercise test		
tests		
pVO ₂		
Short distance in the 6-min walk test		
V _E /V _{CO2} slope		
Co-morbidity		
Cardiovascular		- Smoking
- Ischemic heart disease/prior myocardial infarction		- Anemia
- Prior transient ischemic attack/stroke		- Higher red cell distribution width
- Peripheral arterial disease		- Higher white blood cell count
- Atrial fibrillation		- Iron deficiency
- Ventricular arrhythmia, sudden cardiac death, ICD shocks		- Liver dysfunction and low albumin
Non-cardiovascular		- Depression
- Chronic kidney disease		- Senile asthenia
- Diabetes		- Cachexia
- Chronic obstructive pulmonary disease		- Cognitive dysfunction
- Sleep apnoea and Cheyne–Stokes breathing		- Diuretic resistance

Note. ANP – atrial natriuretic peptide; BNP – B-type natriuretic peptide; CMR – cardiovascular magnetic resonance; CRP – C-reactive protein; DBP – diastolic blood pressure; ESR – erythrocyte sedimentation rate; GDF-15 – growth differentiation factor 15; HF – heart failure; HR – heart rate; ICD – implantable cardioverter-defibrillator; JVD – jugular venous distention; LDL – low-density lipoprotein; LV – left ventricular; LVEF – left ventricular ejection fraction; miBG – metaiodobenzylguanidine; MAP – mean arterial pressure; MR-proADM – mid-regional pro-adrenomedullin; MR-proANP – mid-regional pro-atrial natriuretic peptide; NT-proBNP – N-terminal pro-B-type natriuretic peptide; NYHA – New York Heart Association; pVO₂ – peak exercise oxygen consumption; SBP – systolic blood pressure; VE/VCO₂ – minute ventilation–carbon dioxide production relationship; S3 – gallop rhythm.

* is detected according to the presence/absence of congestion (or hypoperfusion) signs.

Out of more than 100 multi-factor predictive models proposed for patients with CHF, the most well-validated are SHFM (Seattle Heart Failure Model), HFSS (Heart Failure Survival Score), MECKI (Metabolic Exercise test data combined with Cardiac and Kidney Indexes), INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure), BIO-STAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure), BCN Bio-HF (Barcelona Bio-Heart Failure), and UCLA score (University of California, Los Angeles) [9]. An unacceptably low survival rate during the year in most cases is indicated by an assessment of the prognosis at a level not exceeding 80% (for example, on the SHFM or MAGGIC model) [9].

ESC experts emphasize the prognostic value of the treatment-related factor [9]. Non-compliance by a doctor or patient with the provisions of modern recommendations for treatment of CHF (particularly refusal to use a β -blocker) is associated with a worsening prognosis. However, it should be understood that the term AHF is applicable only to describe the phenotype of treated CHF. If the patient for one reason or another did not receive optimal therapy, then regardless of the clinical severity of decompensation, it is too early to talk about this form of heart failure.

PATIENT ROUTING

All patients with CHF should undergo regular checkups for timely detection of progression of symptoms and signs. The described mnemonic "I need help" is useful for identifying patients with AHF who need a timely referral to a specialized center which uses advanced methods of heart failure treatment that are not available in an ordinary clinic. It stands for the following: I (Inotropes), N (NYHA class), E (End-organ dysfunction), E (Ejection fraction), D (Defibrillator shocks), H (Hospitalizations), E (Edema/escalating diuretics), L (Low blood pressure), P (Prognostic medication) [56].

Unfortunately, patients with AHF are often referred to advanced heart failure centers too late. The routing scheme developed within the framework of the active screening concept, the goal of which is timely referral of these patients to the ap-

propriate specialized medical centers, is presented in general form in Figure 2 [9]. The concept of active screening justifies referral (if there are appropriate indications) to a local heart failure clinic of patients with CHF symptoms corresponding to NYHA FC II.

When planning the timing of specialized medical care for patients with AHF, you can use the classification of heart failure severity phenotypes provided in the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support) [9, 57] (Table 3).

In general, only the 2nd, 3rd, and 4th phenotypes are unconditionally related to AHF, since the 1st type corresponds to acute heart failure and the 5th–7th types – to non-severe CHF.

SHORT-TERM TREATMENT STRATEGY

Since a reasonable conclusion about AHF leaves little hope for the success of pharmacotherapy aimed at hemodynamic, neurohumoral, volumetric, myocardial, and immune unloading of the heart, according to the figurative expression of V. Pernias et al. [58], the solution to the problem lies outside the heart (heart transplantation or implantation of a circulatory assist device). However, in a situation where the patient's clinical condition is rapidly deteriorating or there is a reason for assuming reversible dysfunction of end-organs, active pharmacotherapy or temporary mechanical circulatory support may be required. Such a short-term strategy can be lifesaving for a patient who is on the waiting list for a transplant or implantation of a circulatory assist device [9].

The use of non-glycosidic inotropes and vasoconstrictors should be limited to cases of acute decompensated heart failure, low cardiac output syndrome, and cardiogenic shock [9, 59–62]. Allowed medicines include vasoconstrictors (for example, norepinephrine and vasopressin), inotropes with vasoconstrictor properties (for example, dopamine and adrenaline), as well as inodilators, among which, according to some experts, the most promising is levosimendan (its use is permissible in the absence of a pronounced decrease in systolic blood pressure – >85 mmHg) [9, 60].

The cornerstone of congestion correction in these patients is loop diuretics. For the purpose of the so-called decongestion (not to be confused with

anticongestant therapy in the otorhinolaryngologic practice) in case of refractory edema syndrome, including the one associated with the “braking phenomenon”, they should be used (after or against the background of systemic arterial hypotension correction) intravenously at a high dose, in combination with one another, with neurohumoral modulators, and drugs improving renal filtration (for example, aminophylline or a “renal” dose of dopamine) and increasing oncotic blood pressure (albumin, blood plasma) [5, 9, 63, 64].

In patients with normal or elevated systemic blood pressure, a combination of diuretics with vasodilators may be effective, the most promising of which are serelaxin (a recombinant analog of human relaxin-2), low doses of nesiritide (a recombinant form of human brain natriuretic peptide), and the vasopressin antagonist tolvaptan (especially in case of hyponatremia of dilution) [63, 65, 66]. Finally, the use of drugs from the group of the sodium-dependent glucose co-transporter type 2 inhibitors (such as dapagliflozin or empagliflozin) in combination therapy can help to shift the process from the “dead point” and achieve the coveted euvolemia in refractory edema syndrome [63, 67, 68].

If other methods of dehydration are ineffective, it is possible to use extracorporeal ultrafiltration (gentle regimes using a minimum volume of extracorporeal blood and an ultrafiltration rate of no more than 250 ml / hour are preferable) and peritoneal dialysis [5, 9, 69, 70].

Temporary (usually from several days to several weeks) mechanical circulatory support (mono- and biventricular) can be indicated in the development of cardiogenic shock, as well as in a situation where it is necessary to gain time deciding on a heart transplant or implantation of an artificial ventricle (ventricles). For this, percutaneous transluminal methods are currently available, including intra-aortic balloon counterpulsation and Impella® ventricular support systems, as well as paracorporeal devices (for example, the so-called tandem heart), including combining mechanical circulatory support with blood oxygenation (venoarterial extracorporeal membrane oxygenation) [9, 71–76].

The following terms are used to describe various technologies for temporary mechanical circulatory support in discrete clinical situations [24]:

1. “Bridge to decision” / “Bridge to bridge” – is used in patients with cardiogenic shock existing until haemodynamics and end-organ perfusion are stabilized to exclude contraindications for long-term mechanical circulatory support (for example, brain damage after resuscitation) and consider additional therapeutic options, including long-term ventricular assist device therapy or heart transplantation.

2. “Bridge to candidacy” – the use of temporary mechanical circulatory support can lead to improved function of the end-organs and give the right to heart transplantation to those patients for whom it was previously contraindicated;

3. “Bridge to transplantation” – mono- and biventricular mechanical circulatory support to keep alive patients at high risk of death waiting for a heart transplant (application may take several months or even years since only 10% of these patients will receive a donor heart within a year);

4. “Bridge to recovery” – mechanical circulatory support to keep patients alive until their cardiac function is restored to a level sufficient to remove the circulatory assist device (usually we are talking about a partially reversible cause of CHF, such as acute myocarditis or peripartum cardiomyopathy).

LONG-TERM TREATMENT STRATEGY

Conventional surgical treatment is aimed at correcting etiological factors, as well as the leading mechanisms underlying CHF. We are talking, for example, about revascularization of ischemic but viable myocardium in patients with LV EF < 35%, prosthetics of the aortic valve in severe symptomatic aortic valve stenosis with an average pressure gradient > 40 mm Hg. or in severe aortic regurgitation in all patients with symptoms and asymptomatic patients with LV EF ≤ 50%, as about surgery to correct mitral regurgitation (endovascular placement of the mitral valve clip theoretically looks more justified in a situation of high perioperative risk), including secondary (due to LV dilation) severe mitral insufficiency (especially in patients with LV EF < 30%), which cannot be corrected with the help of pharmacotherapy and electrophysiological methods of treatment [9].

Long-term mechanical circulatory support in the framework of “definitive treatment” technology can be considered as an alternative to heart transplantation in patients with end-stage CHF, in which

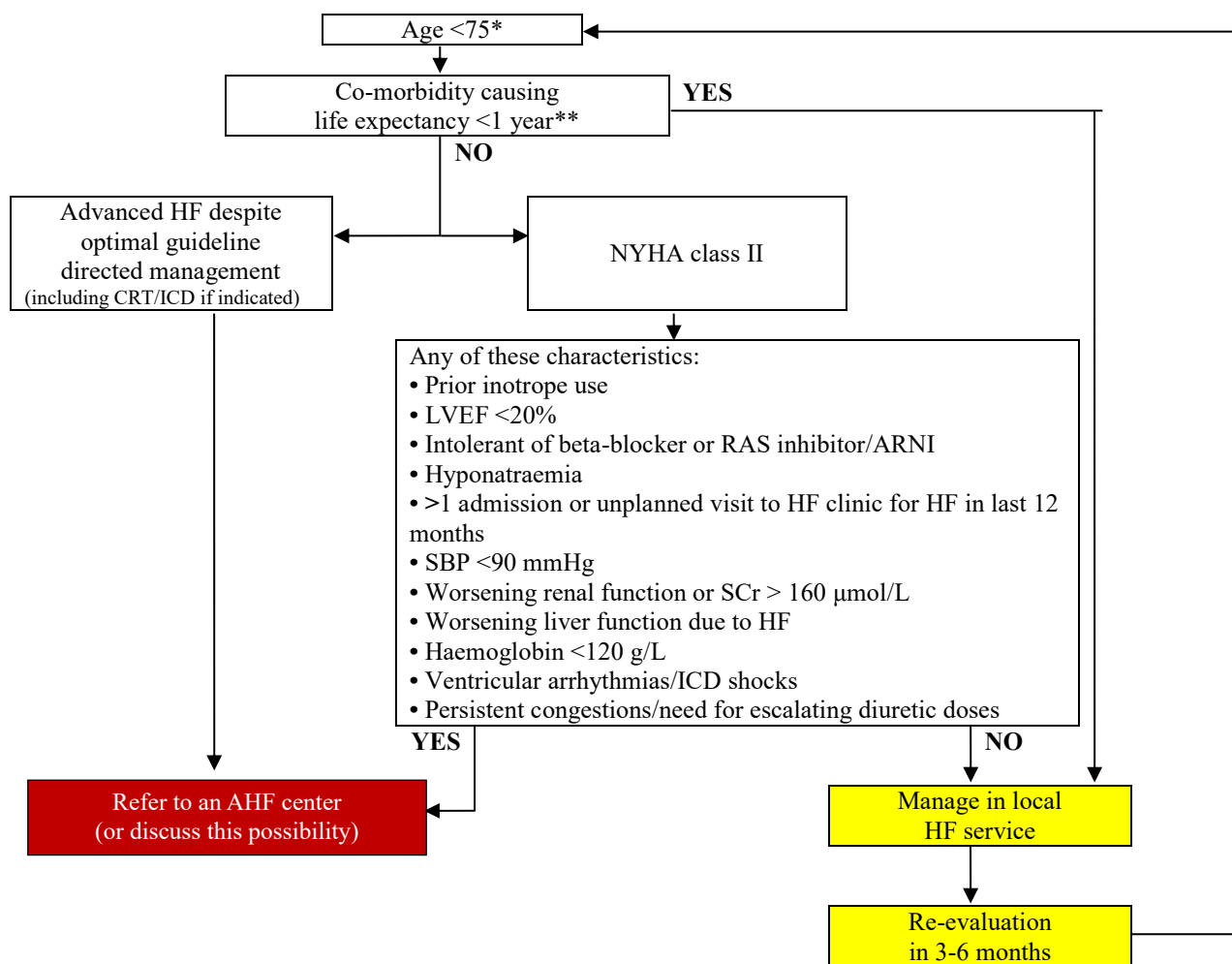


Fig. 2. Triage of patients with advanced heart failure (HF) and appropriate timing of referral [9]: ARNI – angiotensin receptor–neprilysin inhibitor; COPD – chronic obstructive pulmonary disease; CRT – cardiac resynchronization therapy; ICD – implantable cardioverter-defibrillator; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; RAS – renin-angiotensin system; SBP – systolic blood pressure; SCr – serum creatinine.

* >75 years with good functional status apart from HF (mono-organ disease); ** e.g. incurable cancer, dementia, severe COPD

for objective or subjective reasons, transplantation is not feasible (see below). Naturally, such devices must be implanted and administered only in centers with professionally educated doctors to reduce the risk of complications (secondary infection, pump thrombosis, bleeding, thromboembolism, and dysfunction of the device itself), which, despite continuous improvement in technology, remains a serious problem [9, 24, 77].

The results (patient survival and quality of life) of implantation of circulatory assist devices largely

depend on the correct selection of patients for this intervention and the type of device chosen. High survival rates are usually observed among people under 70 years of age, without diabetes, renal failure or cardiogenic shock. In carefully selected groups of patients, implantation of second- or third-generation continuous axial or centrifugal flow devices (that are more effective than devices that use pulsatile pumps) generally provides better results than optimal drug therapy in patients dependent on inotropes.

Table 3

Phenotypes in patients with heart failure [9, 24, 57]	
Phenotype	Time frame for intervention
INTERMACS 1: Critical cardiogenic shock Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. «Crash and burn»	Definitive intervention needed within hours: ECLS, ECMO, percutaneous support devices
INTERMACS 2: Progressive decline Patients with a declining function despite intravenous inotropic support, (may be manifested through worsening renal function, nutritional depletion, and inability to restore volume balance). Also describes declining status in patients unable to tolerate inotropic therapy. «Sliding on inotropes»	Definitive intervention needed within few days: ECLS, ECMO, LVAD
INTERMACS 3: Stable but inotrope-dependent Patients with stable blood pressure, organ function, nutrition, and symptoms with continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. «Dependent stability»	Definitive intervention elective over a period of weeks to few months: LVAD
INTERMACS 4: Resting symptoms Patients can be stabilized close to normal volume status but experience daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5. «Frequent flyer»	Definitive intervention elective over a period of weeks to few months: LVAD those in
INTERMACS 5: Exertion intolerant Patients feel comfortable at rest and with ADL, but are unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4 and require definitive intervention. «Housebound»	Variable urgency, depends upon maintenance of nutrition, organ function, and activity: LVAD
INTERMACS 6: Exertion limited Patients without evidence of fluid overload feel comfortable at rest, with ADL and minor activities outside the home but fatigue after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with haemodynamic monitoring to confirm the severity of cardiac impairment. «Walking wounded»	Variable, depends upon maintenance of nutrition, organ function, and activity level: LVAD / Discuss LVAD as option
INTERMACS 7: Advanced NYHA class III A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion. «Placeholder»	Transplantation or circulatory support may not currently be indicated

Note. ADL – activities of daily living; ECMO – extracorporeal membrane oxygenation; NYHA – New YorkHeart Association; ECLS – extracorporeal life support; ECMO – extracorporeal membrane oxygenation; INTERMACS – Interagency Registry for Mechanically Assisted Circulatory

The survival rate after this operation is comparable to the early survival rate after heart transplantation (2-year survival at the level of 76–85%) [9, 24, 77, 78].

The main pros and cons of long-term mechanical circulatory support, formulated by EACTS (European Association for Cardio-Thoracic Surgery) experts [79], are presented in Table 4.

Severe right ventricular dysfunction (for example, in the presence of significant tricuspid regurgitation) is usually considered as one of the main contraindications to implantation of a LV assist de-

vice, but it is not an obstacle to heart transplantation [24]. If it is predicted that severe right ventricular dysfunction will be potentially reversible, then temporary (from days to several weeks) extracorporeal devices for mechanical support of the right ventricle can be used in addition to an implanted LV assist device [24]. In patients with irreversible right ventricular dysfunction secondary to left ventricular heart failure, the use of long-term biventricular mechanical circulatory support (using two implantable / extracorporeal pumps or a so-called total artificial heart) should be considered [79–81].

Table 4

Recommendations for evaluation and selection of patients for long-term mechanical circulatory support* [79]

LT-MCS implantation should be considered in patients with the following (Class of recommendation IIa, level of evidence - B):

- New York Heart Association functional class IIIB–IV and
- Ejection fraction <25% and

At least one of the following criteria:

- INTERMACS 2–4**
- Inotrope dependence
- Progressive end-organ dysfunction
- $pVO_2 < 12$ ml/kg/min
- Temporary MCS dependence

LT-MCS implantation may be considered in patients with (Class of recommendation IIb, level of evidence - B):

- New York Heart Association functional class IIIB–IV and
- Ejection fraction <25% and a need:
 - To reverse elevated pulmonary vascular resistance or potentially reversible renal failure in potential heart transplant candidates
 - To allow time for transplant contraindications to be reversed, such as recent cancer, obesity, and recovering drug and alcohol dependence in potential heart transplant candidates

Patient characteristics associated with a high risk of poor outcome after implantation of a left ventricular assist device (Class of recommendation IIa–III, level of evidence – B–C):

- LT-MCS in patients with advanced age, after careful evaluation of comorbidities and senile asthenia, should be considered.
- LT-MCS in patients with peripheral vascular disease, depending on its severity, may be considered.
- LT-MCS in patients with active systemic bacterial/fungal infection is not recommended.
- In patients with well-controlled HIV, hepatitis B or hepatitis C, LT-MCS should be considered.
- In patients with diabetes with poor glycaemic control or end-organ complications, LT-MCS may still be considered.
- LT-MCS may be considered in patients with chronic dialysis.
- LT-MCS implantation in patients with haemostatic deficiencies and coagulopathies may be considered.
- LT-MCS implantation in patients with untreated aortic regurgitation or mechanical aortic valve is not recommended.
- LT-MCS in patients with untreated severe mitral stenosis is not recommended.
- LT-MCS implantation in patients with irreversible liver dysfunction, as diagnosed by liver enzyme laboratory tests and the Model of End-stage Liver Disease score, is generally not recommended.
- In patients with poor neurological and cognitive function, LT-MCS implantation is not recommended.
- Frail patients and patients with limited mobility may be considered for LT-MCS implantation after careful evaluation.
- LT-MCS in patients who are living alone or who are suffering from depression should, after careful evaluation, be considered.
- LT-MCS implantation in patients who suffer from dementia is not recommended.
- LT-MCS implantation in patients with active substance abuse, not willing to cease the abuse, is not recommended.
- LT-MCS implantation in patients with malignancies may be considered, if expected survival is >1 year.

Note. LT-MCS – long-term mechanical circulatory support; INTERMACS – Interagency Registry for Mechanically Assisted Circulatory Support; pVO_2 – peak exercise oxygen consumption; HIV – human immunodeficiency virus.

* It is recommended that reversible causes of heart failure are ruled out; ** Patients with the INTERMACS 3 phenotype will benefit the most [9].

Despite the lack of well-organized controlled studies, the cardiological community is dominated by the view that heart transplantation at the final stage of CHF improves survival (1-year survival rate of about 90% and a median survival rate of 12.2 years), physical performance, and the quality of life to a much greater extent compared to conventional treatment, provided that the appropriate selection

criteria are carefully met (the gold standard of treatment for refractory CHF) [9, 82].

Indications for heart transplantation largely coincide with those for long-term mechanical circulatory support, and the list of contraindications is longer and includes additional points, such as high pulmonary vascular resistance or transpulmonary pressure gradient and recently treated cancer [9] (Table 5).

Table 5

Indications and contraindications to heart transplantation [9]	
Patients to consider	<ol style="list-style-type: none"> 1. End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options 2. Motivated, well-informed, and emotionally stable 3. Capable of complying with the intensive treatment required postoperatively
Contraindications	<ol style="list-style-type: none"> 1. Active infection 2. Severe peripheral arterial or cerebrovascular disease 3. Pharmacologic irreversible pulmonary hypertension (LVAD should be considered with a subsequent re-evaluation to establish candidacy) 4. Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence) 5. Irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min) 6. Systemic disease with multiorgan involvement 7. Another serious comorbidity with a poor prognosis 8. Pre-transplant BMI >35 kg/m² (weight loss is recommended to achieve a BMI <35 kg/m²) 9. Current alcohol or drug abuse 10. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting

Note. LVAD – left ventricular assist device; BMI – body mass index; HF – heart failure.

If we recall shortage of donor hearts, the problem of graft rejection, and lack of effective treatment for coronary artery disease of the transplanted heart, it becomes clear why the number of patients receiving permanent mechanical circulatory support is constantly increasing (for example, in Germany alone in 2016, 1,000 implantations of LV mechanical support devices were performed). At the same time, the number of heart transplants in the world has braked at the level of 1994 (about 5,000 per year) [5, 9, 83].

CONCLUSION

AHF is a form of CHF, progression of which has reached a stage where traditional evidence-based therapy becomes ineffective. Patients at this stage persist with symptoms and signs of severe heart failure, often accompanied by episodes of acute decompensation that are associated with an adverse prognosis. It is important to raise awareness of this form of heart failure, since its prevalence in the multilion population of patients with CHF can reach 10%,

and it requires timely application of advanced treatment methods, such as heart transplantation and mechanical circulatory support and/or transition to palliative care.

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Authors information

Kalyuzhin Vadim V., Dr. Sci. (Med.), Professor, Head of the Department of Advanced Internal Medicine, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0001-9640-2028.

Teplyakov Alexander T., Dr. Sci. (Med.), Professor, Principal Researcher, Cardiology Research Institute, TNRMC, Tomsk, Russian Federation. ORCID 0000-0003-0721-0038.

Bepalova Inna D., Dr. Sci. (Med.), Professor, Department of Advanced Internal Medicine, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-4513-6329.

Kalyuzhina Elena V., Dr. Sci. (Med.), Professor, Department of Advanced Internal Medicine, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-7978-5327.

Terentyeva Nadezhda N., Cand. Sci. (Med.), Associate Professor, Department of Internal Diseases, Surgut State University, Surgut, Russian Federation. ORCID 0000-0002-0462-3526.

Sibireva Olga F., Dr. Sci. (Med.), Professor, Department of Biochemistry and Molecular Biology, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-5651-8875.

Grakova Elena V., Dr. Sci. (Med.), Senior Researcher, Department of Myocardial Pathology, Cardiology Research Institute, TNRMC, Tomsk, Russian Federation. ORCID 0000-0003-4019-3735.

Usov Vladimir Yu., Dr. Sci. (Med.), Professor, Head of the Department of Radiological and Tomographic Methods of Diagnostics, Cardiology Research Institute, TNRMC, Tomsk, Russian Federation. ORCID 0000-0001-7978-5514.

Osipova Marina A., Cand. Sci. (Med.), Head of the Department of Functional Diagnostics, FGHC «MD of the Ministry of Internal Affairs of the Russian Federation for the Tomsk region», Tomsk, Russian Federation. ORCID 0000-0001-6759-8113.

(✉) **Kalyuzhin Vadim V.**, e-mail: kalyuzhinvv@mail.ru.

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