Working group on the preparation of the document:
Begrambekova Yu. L.[1], Arutyunov G. P.[2], Glezer M. G. [3,4],
Karanadze N. A.[1], Kolesnikova E. A.[2], Lelyavina T. A.[5],
Lishuta A. S.[4], Orlova Ya. A.[1], Belenkov Yu. N.[4]

[1] Medical Research and Educational Center, Lomonosov Moscow State University, Moscow, Russia
[2] Pirogov Russian National Research Medical University
[3] Vladimirsky Moscow Regional Research Clinical Institute, Moscow, Russia
[4] Sechenov First Moscow State Medical University, Moscow, Russia
[5] Almazov National Medical Research Center, St. Petersburg, Russia

Evaluation of the Functional Reserve and Exercise Tolerance in Patients with CHF in Clinical Trials (Consent Document of the Editorial board of the Journal of Cardiology, the Board of the Society of Specialists in Heart Failure (SSHF) and Working Group «Non-drug treatment methods» of SSHF)

Assessing the functional capacity and exercise tolerance is an important and widely used research tool in patients with heart failure. It is used not only in cardiac rehabilitation and physical therapy, but also for inclusion criteria and outcome measures in studies of drug interventions. This document outlines the scope, guidelines for the implementation and interpretation, and limitations of the methods for assessing the functional capacity and exercise tolerance in clinical trials in patients with heart failure.

Keywords Heart failure; exercise; hear failure myopathy; ergoreflex; cardiorespiratory endurance; cardiopulmonary stress test; FC; 6MWT; respiratory muscle strength; one-repetition maximum

For citations Working group on the preparation of the document: Begrambekova Yu. L., Arutyunov G. P., Glezer M. G., Karanadze N. A., Kolesnikova E. A., Lelyavina T. A., Lishuta A. S., Orlova Ya. A., Belenkov Yu. N. Evaluation of the Functional Reserve and Exercise Tolerance in Patients with CHF in Clinical Trials (Consent Document of the Editorial board of the Journal of Cardiology, the Board of the Society of Specialists in Heart Failure (SSHF) and Working Group «Non-drug treatment methods» of SSHF). Kardiologiia. 2024;64(7):4–26. [Russian: Рабочая группа по подготовке документа: Беграмбекова Ю.Л., Арутюнов Г.П., Глезер М.Г., Каранадзе Н.А., Колесникова Е.А., Лелявина Т.А., Лишута А.С., Орлова Я.А., Беленков Ю.Н. Методология оценки функционального резерва и переносимости физической нагрузки при проведении клинических исследований у пациентов с ХСН (согласительный документ редколлегии журнала «Кардиология», Правления ОССН и Рабочей группы ОССН «Немедикаментозные методы лечения»). Кардиология. 2024;64(7):4–26].

Corresponding author Begrambekova Yu. L. E-mail: julia.begrambekova@ossn.ru

Background

The objective of clinical research is to generate valid scientific knowledge that will contribute to the advancement of medicine and the optimization of clinical practice. The quality of the design, organization, and presentation of the results of a clinical trial is of the utmost importance to ensure the reproducibility and validity of the findings, and thus their relevance to clinical practice. In the process of planning and conducting studies on cardiac rehabilitation, researchers encounter a number of additional challenges, in particular when attempting to meet the rigorous methodological standards that are necessary to produce evidence of the highest quality. These difficulties include the heterogeneity of the study population, the often complex nature of the intervention, the difficulty, and often impossibility of, organizing a true patient-blinded and physician-blinded study, the heterogeneity of patient outcomes, and the challenge of selecting an appropriate comparison group. Furthermore, the person-centered approach inherent to rehabilitation interventions frequently presents a challenge when attempting to adhere to standardized research protocols.

In light of the aforementioned considerations, the Editorial Board of the Cardiology Journal, the Board of the Society of Heart Failure Specialists (OSSN), and the OSSN Working Group «Nonmedication Methods of Treatment and Patient Education» have determined that the development of consensus documents is a crucial step towards establishing unified methodological approaches to the design, conduct, interpretation, and publication of clinical trials that assess exercise tolerance. The document presented describes methodological approaches to assessing functional reserve and exercise tolerability in clinical trials in patients with chronic heart failure (CHF) and represents the inaugural publication in a series of papers.

The assessment of functional capacity and exercise tolerance represents a crucial and extensively utilized research instrument in the context of patients diagnosed with CHF. The applications of this approach extend beyond the domain of cardiac rehabilitation and physical therapies for patients with HF. They also encompass the criteria for inclusion and the assessment of outcomes in a range of pharmacological interventions. It is, therefore, our hope that this paper will prove a valuable resource for all researchers whose scientific interests include CHF.

The objective of this consensus document is to delineate the scope of application, recommendations for performance and interpretation, and limitations of methods for assessing functional capacity and exercise tolerance in clinical trials in patients with HF.

Terminology Definitions of functional capacity, exercise tolerance, and cardiorespiratory endurance

Exercise tolerance can be defined as «the amount of exercise a person can perform without experiencing significant fatigue».

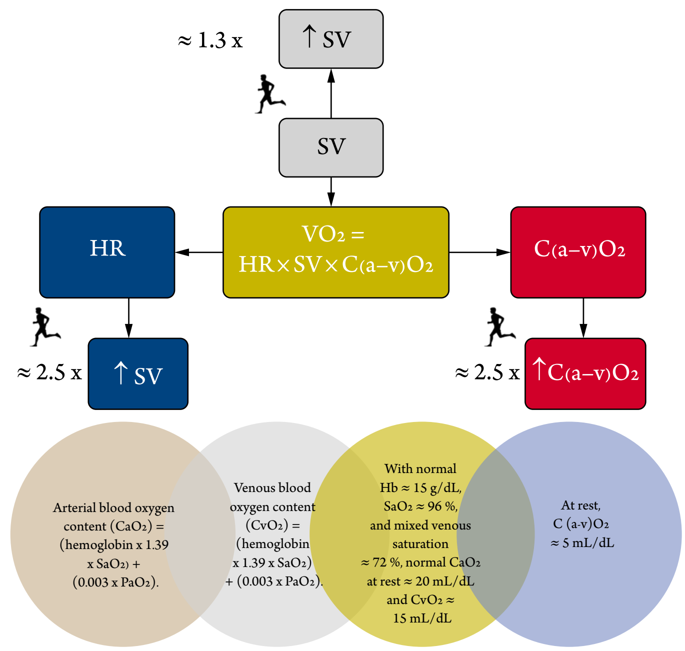
Functional capacity can be defined as «the ability to perform daily activities in which energy expenditure is primarily provided by aerobic metabolism».

Cardiorespiratory endurance is an assessment of the maximum amount of oxygen the body can take in during maximal or submaximal exercise. Thus, cardiorespiratory endurance is a complex index that quantifies a person's functional capacity and depends on an interrelated chain of processes, including pulmonary ventilation and diffusion, right and left ventricular function (both systole and diastole), ventricular-arterial interaction, the ability of the vascular system to efficiently transport blood from the heart to the working muscle, and the ability of muscle cells to receive and utilize oxygen and nutrients delivered by the blood (Figure. 1).

Assessment of heart failure class according to the New York Heart Association (NYHA) classification

The most common method of subjective clinical assessment of functional capacity in patients with CHF is undoubtedly the assessment of heart failure class according to the New York Heart Association (NYHA) classification. The first version of the classification was published in 1928, at a time when there were no objective methods for assessing cardiac function. The purpose of the methodology was to provide physicians with a uniform system to classify patient severity. Over time, the classification system has been refined and updated. The ninth edition of the NYHA classification, published in 1994 by the American Heart Association

Figure 1. Oxygen consumption at rest and the mechanisms of increased oxygen delivery and consumption during exercise



SV, stroke volume; HR, heart rate; Hb, hemoglobin; SaO_2, oxygen saturation; C (a-v), arteriovenous oxygen content difference; PO_2, partial pressure of oxygen; CvO_2, venous blood oxygen content.

Criteria Committee, is currently used in clinical practice [1]. The method of HF classification is ubiquitously used in the clinical setting and in clinical trials, not only as an inclusion criterion but also as an outcome measure. Patients are classified based on the severity of HF-related limitations to usual physical activity. Which class the clinician or researcher decides to assign the patient to depends on their interpretation of what they and/or the patient mean by «normal physical activity», «mild» and «severe» limitations in physical activity. The highly subjective nature of the method results in low reproducibility. For example, in the study by Goldman et al., the class of HF was determined independently by two physicians. Reproducibility was only 56%, and only 51% of the assessments agreed with the objective data from the stress tests [2]. In the same study, no consistent and uniform method of NYHA classification was found in a survey of 30 cardiologists. For example, HF class II and III assessments were consistent only 54% of the time. The authors also conducted a systematic review of the literature, which showed that although at least 90% of the available studies used NYHA class as an inclusion criterion and 50% used it as an outcome measure, 99% of the studies did not mention the methods or questions used to determine HF class. The authors of the study conclude that the identification of class I (asymptomatic) and class IV (symptomatic at rest) patients a relatively straightforward process and that there is a «gray area» in the definition of HF class within the class II–III range [3]. A survey was conducted in the Telegram channel of the Society of Heart Failure Specialists, the results of which demonstrated that the classification of HF is not a standardized procedure in Russian clinical practice. In the study, physicians were asked to respond to a question about how they determine the class of HF. More than one answer was possible. The survey included 485 physicians. The survey revealed that the majority of physicians (76%) rely on the patient's evaluation of their physical capabilities, approximately one-third of physicians (27%) utilize the 6 minute walk test (6MWT), while 10% of physicians consider dyspnea, and another 3% rely on a general impression of the patient's condition.

Therefore, it is important to note that HF class serves as an indicator of functional status, which is defined in classical terms as «the patient's ability to function in daily life». However, both the functioning of the patient and their subjective perception can be determined by a variety of personal and social factors. These factors may include, but are not limited to, individual perceptions of symptoms and the disease, depressive symptoms, and the availability of social support. It is crucial to recognize that the notion of functional status is discrete from the related yet not identical concepts of functional capacity. Functional capacity is typically evaluated through cardiopulmonary exercise testing (CPET) or other exercise tolerance assessments, such as the 6MWT A meta-analysis comprising 37 studies revealed significant heterogeneity in 6MWT distance across all studies and across all classes. The mean distance with a 95% confidence interval (CI) for classes I, II, III, and IV was as follows: 420 (379–462), 393 (362–424), 325 (296–354), and 225 (115–336) m, respectively. The following levels of heterogeneity in 6MWT outcomes across studies for each class were identified. Class I Q = 934.2; P < 0.001), Class II Q = 1658.3; P < 0.001), Class III Q = 1020.1; P < 0.001), and Class IV Q = 335.5; P < 0.001) [4].

It can thus be concluded that the NYHA classification is an effective tool for assessing patients with a significant number of symptoms (class III/IV) but is less reliable in asymptomatic patients or those with mild symptoms and exercise limitations (NYHA class I/II). The NYHA classification is a valuable first-line tool in routine clinical practice due to its accessibility and extensive experience of use. However, it is important to consider its potential subjectivity in clinical trials and comparisons between studies.

Most commonly used objective methods in clinical practice for assessing exercise tolerance and cardiorespiratory endurance

6-minute walk test

The 6MWT was initially proposed in 1982 by Butland et al. as a more straightforward alternative to the previously utilized 12-minute walk test in patients with chronic lung disease [5], and the first application of the test in patients with CHF was subsequently documented by G. H. Guyatt et al. in 1985 [6].

The primary objective of the 6MWT is to determine the distance (in meters) that a patient is able to walk in six minutes. The 6MWT protocol necessitates the provision of a corridor, defined as an area of flat hard surface, with a minimum length of 30 m and markings at intervals of 3 m. The methodology of the 6MWT is presented in Appendix 1 to this document. The absolute contraindications for 6MWT include the presence of unstable angina or a myocardial infarction that has occurred within the previous month. The following are the relative contraindications for the test: a resting heart rate (HR) exceeding 120 bpm, systolic blood pressure (SBP) above 180 mm Hg, and/or diastolic blood pressure (DBP) above 100 mm Hg. Stable angina pectoris does not constitute an absolute contraindication for the 6MWT; however, the test may be conducted in patients with this condition after the administration of antianginal medications and if nitroglycerin agents are available.

Utilizing 6MWT to evaluate the prognosis

In 2020, a meta-analysis was published examining the prognostic role of functional capacity in patients with CHF. The meta-analysis encompassed 33 studies that employed the 6MWT to evaluate exercise tolerance. Patients with HFrEF and HFpEF who demonstrated low exercise tolerance at the 6MWT faced an elevated risk of all-cause mortality [HR = 2.29; 95% CI: 1.86–2.82, p < 0.001] and HF mortality [HR = 2.39; 95% CI: 2.21–2.59, p < 0.001]. Furthermore, they exhibited an elevated risk of hospitalization due to HF [HR = 1.68; 95% CI: 1.20–2.33, p = 0.002] [7].

Furthermore, the 6MWT is a commonly utilized tool for monitoring disease progression and assessing the efficacy of therapeutic interventions. In the context of utilizing the test to evaluate the efficacy of interventions, it is crucial to acknowledge that despite the apparent objectivity of the test, the results may be influenced by the patient's subjective perception of their own abilities. It seems plausible that this is related to the rather pronounced variability of the test results, which may be attributed to the «learning effect,» whereby the distance covered increases when the test is retaken. This is likely due to the fact that many patients tend to underestimate their abilities at the first attempt.

Inter-test variability of 6MWT

In the study conducted by L. Hanson et al., the relative (intraclass correlation) and absolute (in meters) variability of 6MWT distance in patients with CHD was investigated [8]. It was demonstrated that although the

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

relative inter-test variability was good (0.84), the absolute variability was considerable. The authors note that for intragroup 6MWT changes, a difference of at least 45 meters would be considered valid for a group, whereas for individual changes, a difference of less than 99 meters is within the measurement error range. In light of these findings, the authors conclude that the 6MWT, performed in triplicate within a relatively short period of time, did not yield reliable results for the study population of patients with CHD. The distance covered increased with each successive test, which may be attributed to a «learning effect» [9]. The results of this study are in accordance with those previously reported by Hamilton et al. [10]. It is noteworthy that, based on the findings of analogous studies, there is little or no «learning effect» in patients with CHF. For example, in the study conducted by C. Lans et al., the relative inter-test variability was found to be greater than 0.90, which corresponds to an excellent level. The absolute variability was found to be a clinically insignificant difference of 9 m [11]. It is possible that including patients with more severe symptoms and more severe symptom-related limitations may result in a reduced likelihood of observing a «learning effect» and less inter-test variability.

Age-related variability of the six-minute walk test

The distance covered in the 6MWT may be influenced by age. As demonstrated by M. Yu. Sitnikov et al., there is a notable correlation between the distance covered in the 6MWT and the age of the patient [12]. Middle-aged patients (aged less than 65 years) completed a distance during the test that was significantly greater than both the 6MWT values for assessing CHF class according to the RSC Guidelines [13] and the results of patients older than 75 years, despite a comparable functional class of CHF (Table 1).

When performed correctly, the 6MWT offers a number of advantages, including simplicity, safety, and good patient tolerance. The test does not necessitate the involvement of personnel with a high level of training. The outcome of the test is a comprehensive evaluation of the patient's exercise tolerance (overall response to physical exertion on the cardiovascular, respiratory, and nervous systems, as well as muscle tissue and other organ systems) and the patient's subjective perception of their own abilities. The 6MWT is a tool used to assess the patient's submaximal level of exercise capacity, at which the majority of activities of daily living are performed. The 6MWT does not ascertain the factors that constrain the execution of the load. It is thus recommended that the data obtained from the 6MWT be regarded as an additional measure to that obtained from CPET, rather than as a substitute for it. A relatively strong correlation exists between peak 6MWT and peak oxygen consumption. Based on this correlation, formulas have been proposed for the indirect determination of peak VO_2 using 6MWT data. The specifics and constraints of the application of these formulas will be addressed in the section on indirect methods for determining peak oxygen consumption.

Table 1. Comparison of the results of the 6MWT (m) in patients with CHF of varying ages

CHF class	Group		
	Reference group, age > 75 years	Main group, age 45 ± 65 years	6MWT distances for HF class assessment according to the Guidelines
Class II	175 ± 8#	457 ± 2*#	301–425
Class III	145 ± 4	374.7 ± 4*	151–300
Class IV	89 ± 6#	271 ± 2*#	< 150

* Significance of differences between similar parameters of middle-aged and elderly patients with CHF – $p < 0.05$;
# Significance of differences between the adjacent CHF classes in the same study group – $p < 0.05$.

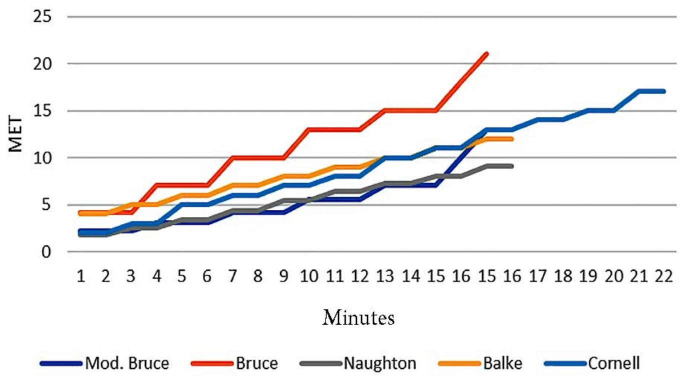
A multitude of factors influence the distance covered in the 6MWT (Table 2).

Cardiorespiratory stress testing

In the Russian and international scientific literature, a number of terms are employed to describe stress testing with simultaneous analysis of gas exchange, including ergospirometry, spiroergometry, cardiopulmonary stress testing, and cardiorespiratory stress testing. The term «respiratio» is derived from Latin and signifies the act of breathing. In light of the current understanding of the processes that ensure exercise performance, it is our opinion that the most accurate term is «cardiorespiratory stress testing.» This term reflects not only the assessment of external respiration or isolated lung function, but also the analysis of intracellular and mitochondrial respiration, the intensity of which changes when performing an exercise stress test. By analyzing these changes, the physician is able to more accurately determine which links in the oxygen transport and utilization pathway are most affected. Accordingly, the term «cardiorespiratory stress testing» will be employed in this paper.

CPET represents the gold standard for assessing the functional status of patients. In contrast to other stress tests, it permits the analysis of changes in multiple gas exchange parameters, including oxygen uptake (VO_2), carbon dioxide excretion (VCO_2), and ventilation (VE), which are altered during exercise. In comparison to other stress tests, CPET requires a greater investment of time and costly equipment. This methodology presents a significant challenge to researchers, both in terms of the methodology itself and the interpretation of the resulting data. Consequently, the clinical application of CPET is currently limited to patients with end-stage CHF to determine whether they should be placed on the waiting list for heart transplantation, for

Figure 2. Treadmill testing protocols – METs



MET, metabolic equivalent.

Table 2. Factors affecting the outcomes of the 6MWT, adapted from [14]

Factors contributing to an underestimation of the 6MWT outcomes	Factors contributing to an overestimation of the 6MWT outcomes
Shorter height Older age Overweight/obesity Female sex Cognitive impairment Shorter corridor (a greater number of turns) Comorbidities that further reduce exercise tolerance (chronic lung disease, CVD, musculoskeletal disorders) Depressive and anxiety symptoms	Taller height Male sex High level of motivation History of prior testing Taking medications prior to the test

6MWT, 6-minute walk test; CVD, cardiovascular disease.

differential diagnosis of dyspnea in HF, and as a control during cardiac rehabilitation [13, 15].

The aforementioned difficulties in performing and interpreting CPET results highlight the necessity for thorough planning of clinical trials that utilize CPET parameters as endpoints. This pertains to the selection of the loading protocol, the criteria for evaluating the patient's level of exertion, and the necessities for both the documentation and the peer review of the data obtained, in addition to the importance of careful consideration when determining the endpoints of the study, based on the objective and the characteristics of the study population. The standard procedures of the CPET are set forth in a number of documents [16–18].

The CPET may be conducted using either a treadmill or a cycle ergometer. From the perspective of safety, the cycle ergometer is the preferred option due to the stationary position of the upper half of the torso, which facilitates more convenient electrocardiogram (ECG) registration. Furthermore, the most compelling rationale for the cycle ergometer is its linear load increase. When testing on a treadmill, only the incline and speed can be modified; it is not possible to implement a linear increase in exercise load. The advantages of treadmill testing include the fact that walking is a familiar activity for patients, whereas pedaling may present difficulties for those who are untrained.

Selecting the CPET protocol

The selection of an appropriate stress protocol is a crucial aspect of the successful implementation of CPET on a treadmill. The most prevalent testing protocols are listed and described in Appendix 2 to this document. The first four protocols entail a stepwise augmentation of the load through an increase in both the speed and/or incline of the track. The fifth protocol employs a gradual increase in the exercise load (ramp protocol) to enhance the adaptation of patients with clinically significant heart failure to exercise and augment the probability of attaining submaximal effort during testing.

Figure 2 presents a comparison of the most commonly utilized protocols in clinical practice in accordance with the load profile they provide. As illustrated in the chart, in instances where there is uncertainty regarding the patient's ability to complete the test due to detraining, if the patient is over 75 years of age, or if there are relative contraindications to exercise testing, the modified Bruce and Naughton protocols are frequently employed. The aforementioned protocols facilitate the most seamless load escalation through the implementation of small incremental steps.

In addition to the aforementioned protocols, treadmill testing protocols that may also be appropriate for patients with low exercise tolerance include those proposed by Cornell, McNaughton, and Balke [19, 20]. These protocols are distinguished by a gradual increase in load.

It is regrettably only possible to ascertain that a selected protocol is unsuitable for a specific patient once the protocol has been completed. In patients with CHF, the most common issue with an inappropriate protocol is the inability to complete the protocol. The following factors indicate that this patient was tested using an inappropriate protocol: the testing duration was less than two minutes, the protocol was completed at the patient's request at an early stage (steps 2–3), and an RER ≥1.0 was not achieved. A sudden increase in heart rate, respiratory rate, changes in blood pressure, and other physiological parameters can occur when transitioning from one step to the next in the stepwise exercise protocol for patients with CHF. This can precipitate a rapid worsening of fatigue and premature termination of stress testing. For patients with severe HF, continuous-increasing exercise protocols, in which the increase in exercise capacity is gradual and nearly undetectable by the patient, may be considered (Appendix 2, Protocol 5).

It has been demonstrated that to obtain reliable outcomes, the duration of testing in patients CHF should be within the range of 10 to 14 minutes (steps 3–4 according to the

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

modified Bruce protocol). [21, 22]. Effort is measured in watts (W) (1 W = 6 km/min). The initial load for patients with CHF is typically 20–25 W, and this is increased by 15–25 W every two minutes until the maximum load is reached. As an alternative, the load can be regulated by a computer for electronically braked cycle ergometers, with a linear protocol (e.g., 10 W/min) frequently employed in such instances.

It is evident that all patients participating in a clinical trial should be subjected to the same protocol. In this regard, the selection of the most appropriate study protocol represents one of the most challenging and critical aspects of planning a study using CPET.

In selecting a study protocol, it is essential to conduct a comprehensive review of existing literature on a comparable cohort of patients, taking into account their clinical and demographic characteristics and analyze the advantages and limitations of the protocols employed in these studies. In addition to the challenges associated with the selection of appropriate protocols, issues encountered in the conduct and interpretation of studies are frequently linked to the condition of the CPET equipment. This equipment requires daily calibration, and instances of malfunction can result in the generation of inaccurate data. It is also of great importance to ensure that the patient is adequately prepared for the study. The most crucial elements of CPET to ensure the attainment of optimal outcomes, along with the methods of self-control employed by the researchers, are summarized in Figure 3.

Main parameters recorded during CPET

During the CPET, a face mask (or mouthpiece) with connected gas and flow (or volume) sensors is utilized to measure O_2 and CO_2 concentrations in exhaled air and minute ventilation ($\dot{V}E$ = tidal volume × respiratory rate). A number of key variables are derived from these measurements, as well as heart rate (HR) and exercise intensity monitoring.

A critical initial step in the analysis of CPET results is the assessment of the patient's attainment of the maximum possible workload. The respiratory exchange ratio (RER) has traditionally been regarded as an indicator of the proximity of the patient's exertions to their maximal capacity.

An RER value of ≥ 1.05–1.1 indicates that the patient is exerting themselves to a level that is both adequate and close to their maximal effort. Approximately 50% of patients with CHF fail to reach this threshold [23]. It is widely accepted that an HR of 85% or above is indicative of maximal effort. However, this is frequently unattainable in patients with HF who are taking beta-blockers and/or those with chronotropic insufficiency.

In the event that RER ≥ 1 is not attained, the interpretation of CPET measurements for the purpose of risk assessment may be compromised. It is evident that peak VO_2 and peak HR are particularly susceptible to the achievement of threshold effort. For example, Inge et al. demonstrated that VE/VCO_2 slope and peak VO_2 were not predictive of mortality in elderly patients with HF and peak RER < 1.0 [24]. Nevertheless, the estimation of patient effort is a more challenging task than the focus on RER, as a multitude of variables may exert an influence on this measure.

The utilization of RER as an indicator of exertion is founded upon the physiology of energy substrate metabolism. In a steady state, the RER is equal to the respiratory quotient (RQ), which is determined by the energy substrate that is the predominant substrate in metabolic processes. Given that muscle is the primary consumer of metabolic substrates, it is muscle that primarily influences the values of the respiratory exchange quotient and RER. RQ 0.7 indicates preferential fat metabolism, while RQ 0.8 indicates a mixed metabolism of carbohydrates and fatty acids.

In an unsteady state, the RER is additionally affected by CO_2 stores/buffering mechanisms, which result in a failure of the RER to reflect the actual RQ in such circumstances. It can be reasonably argued that an RER value of less than 1.1 at peak load does not necessarily indicate that the effort exerted was submaximal. In this case, it would be beneficial to analyze other factors that may have contributed to the observed low RER values. These could include a pattern of restricted breathing, a significant decrease in ventilatory efficiency, or a slight increase in effort relative to VO_2 [18]. Concurrently, an RER above 1.0 and/or an RER above 0.8 at the aerobic threshold is an unfavorable prognostic indicator, as it may also be caused by excess CO_2, which is produced during lactic acid metabolism, or by hyperventilation due to the more than 20-fold higher solubility of CO_2 in tissues compared with O_2. It is thus recommended that, in practical testing situations, the potential for both lactic acidosis and hyperventilation should be taken into account when the RER exceeds 1.0.

In consideration of the aforementioned, it is recommended that an assessment of patient effort include an evaluation of additional parameters beyond RER ≥ 1.10–1.15.

Onset of the respiratory compensatory point (RCP).

No observable increase in oxygen consumption and/or HR with an intensification of the exercise regimen and advancement to the subsequent step of the protocol.

Post-exercise blood lactate concentration ≥ 8 mmol/L.

Perceived load score ≥ 8 (on the 10-point Borg scale).

The respiratory compensation point is the moment of an increase in carbon dioxide ventilation (respiratory compensation) during continuously increasing exercise load in response to the development of acidosis in the blood, which arises due to the inherent limitations of the blood buffer systems (Figure 4).

Figure 3. Preparing and Performing the CPET

Preparing patients for the test

- Patients should be informed and motivated to give their maximum effort.
- On the day of the examination, patients should take their usual medications, wear comfortable sports clothes and shoes, and eat their last meal at least 2–3 hours before the examination.
- Patients should be clinically stable, avoid smoking or vaping, s trenuous exercise, and alcohol consumption 24 hours prior to testing.

Selecting an exercise protocol

- It is recommended that stepwise load increments last for 10 ± 2 minutes or a minimum of 5 minutes in the case of patients with the most severe conditions.
- It is not recommended to begin an ascent at a rapid pace, as this often results in significant hyperventilation, difficulty in determining the lactate threshold (LT), and premature cessation of the exercise due to lactate acidosis.
- The results of a cycle ergometer test are typically approximately 10% higher than those of a treadmill test.

Verification of data validity to identify and rectify any anomalies in the equipment functioning

- Adequate minute ventilation. Lacking reliability when the increase in V*E does not align with the corresponding rise in the exercise rate. Potential causes: mask leaks, anxiety, inadequate effort.
- Adequate V*O2. Verification may be accomplished by employing resting values (5–6 mL/min/kg). Causes of inadequacy: mask leaks.
- Adequate respiratory exchange rate (RER). Lacking reliability when resting RER < 0.7 or RER > 1 at start of test. Possible causes: voluntary or preemptive hyperventilation, malfunctions of the gas analyzer, sample tube blockage, mask leaks.

Ve, minute ventilation; LP, lactate threshold;
VO_2 – oxygen consumption.

The failure to attain maximal effort by the patient does not preclude the interpretation of test results. In light of the high rate of failure to reach maximal effort among patients with CHF, it is recommended that clinical trials incorporate the analysis of measures that are less dependent on reaching maximal effort, in addition to peak measures.

Figure 5 illustrates the principal CPET measures and their derivatives at their maximum and minimum values, dependent on the achievement of maximum effort.

Measurements taken at the point of maximum load. Peak oxygen consumption (VO_2 peak)

The most commonly utilized CPET parameter is the oxygen consumption (VO_2) at peak (maximal) workload [18]. In patients with CHF, the severe limitations of exercise capacity preclude the attainment of maximum oxygen consumption, which corresponds to the state when continuous increases in load does not result in increases in VO_2. In the context of CHF, the sole relevant variable is the peak VO_2 value. It is crucial to consider that the VO_2 peak is approximately 10% higher when exercising on a treadmill in comparison to a cycle ergometer.

The calculation of oxygen consumption is performed using the Fick equation, which is a product of HR, cardiac output, and arteriovenous oxygen content difference. The values of peak/maximum VO_2 vary considerably between individuals and are influenced by a number of factors, including age, sex, genetics, lifestyle and exercise habits, and the presence of co-morbidities. For instance, in young athletes engaged in cyclic sports, the VO_2max can reach a level of >80 mL O_2 kg^{-1}•min^{-1}, whereas in patients in the terminal stages of CHF, it can be observed to be below 8 mL O_2 kg_{-1}•min^{-1} [25]. The Fitness Registry and the Importance of Exercise National Database (FRIEND) have recently published data that provide reference standards for peak VO_2 for adult men and women (20–79 years old) [26].

A peak VO_2 of less than 14–15 (less than 10–13 in patients with HFrEF treated with beta-blockers) [23, 27–31] is indicative of an unfavorable prognosis. Even slight elevations in peak oxygen consumption resulting from exercise have clinical and prognostic significance. In an additional analysis of the HF-ACTION trial, it was demonstrated that a 6% increase in peak VO_2, adjusted for other significant predictors, was associated with a 5% reduction in the risk of cardiovascular death (OR = 0.95; CI: 0.93–0.98; $p < 0.001$) The risk of cardiovascular mortality or hospitalization for HF was reduced by 8% (OR = 0.92; 95% CI: 0.88–0.96; $p < 0.001$), and all-cause mortality by 7% (OR = 0.93; 95% CI: 0.90–0.97; $p = 0.001$) [32]. Furthermore, the prognostic significance of VO_2 peak has been demonstrated in patients with HFpEF [33].

The Weber classification [34], which remains a valuable tool for assessing prognosis [35], was developed using peak oxygen uptake data (Table 3).

A limitation of peak VO_2 is its reliance on achieving the maximum possible protocol steps, which may be susceptible to numerous factors, including patient motivation, orthopedic impairment, and limiting symptomatology.

A circulatory power (CP) index, defined as the product of peak VO_2 and peak SBP, was proposed. The greater prognostic value of CP over VO_2 peak has been demonstrated in numerous scientific publications [36–39].

Indicators moderately dependent on the achievement of maximal effort. Ventilatory efficiency index (VE/VCO_2) and oxygen uptake efficiency slope (OUES)

A reduced ventilatory efficiency (high VE/VCO_2 slope) is associated with an increased pulmonary vascular resistance at rest and during exercise. Furthermore, there is a negative relationship between this efficiency and right ventricular ejection fraction (RVEF) and tricuspid annular plane systolic excursion (TAPSE) [40–42]. The

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

VE/VCO_2 slope is a robust prognostic factor in patients with HF, irrespective of the ejection fraction [43]. R. Arena et al. proposed a widely used classification based on ventilatory efficiency, in which four ventilation classes (VC) were distinguished (Table 4) [44].

The OUES, defined as the ratio between VO_2 and log VE, exhibits high reproducibility. The values achieved at test durations of 75%, 90%, and 100% of the expected duration differed by less than 2% and demonstrated superior prognostic value compared to peak VO_2 in a multivariate analysis of predictors of outcome in 243 patients with HFrEF. A nearly twofold increase in mortality was observed at OUES values below 1.47 L/min [45].

In 2012, D.E. Forman et al. [46] presented and evaluated the prognostic use of a new index, ventilatory power, which was calculated by dividing peak SBP by the ventilatory efficiency index VE/VCO_2. A number of authors have proposed that a more favorable prognosis is associated with higher BP values, i.e., higher SBP and/or lower VE/VCO_2 slope [46, 47].

CPET indicators not dependent on the achievement of maximal effort or the duration of the study

VO_2 at the lactate threshold

The use of oxygen consumption at lactate threshold (VO_2 LT) to assess the severity of HF or the effects of therapy, or to assess cardiovascular risk in the case of surgery, has been proposed as an alternative to peak VO_2 because it is independent of patient motivation, exercise protocol, and duration of testing [48, 49]. Inability to determine VO_2 LT is most common for patients with severe HF and is a predictor independent of other factors [50].

Intermittent breathing (IB). The determination of IB represents a significant challenge in terms of recording, yet it is also one of the most robust predictors of unfavorable outcomes in HF. The presence of IB is associated with 1 year mortality > 20% in patients with HFrEF [51, 52]. In accordance with the criteria established by Corrá et al., IB can be identified as cyclic ventilatory fluctuations that persist for a duration exceeding 60% of the exercise period, exhibiting an amplitude exceeding 15% of the mean amplitude of cyclic fluctuations observed at rest.

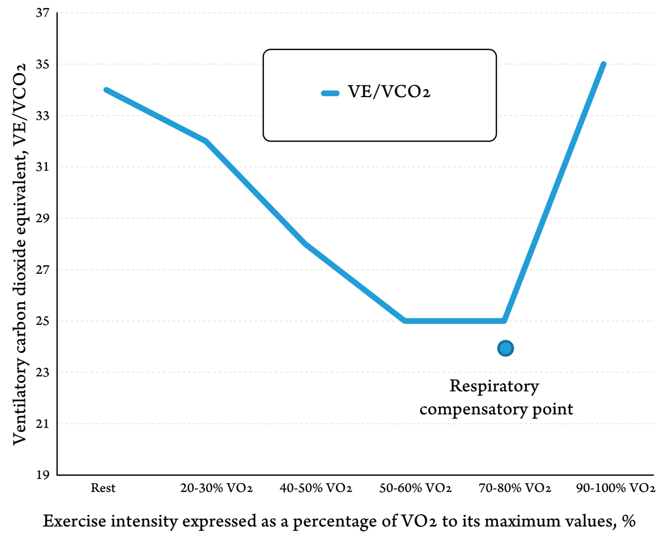
It has been demonstrated that the presence of IB markedly worsens the prognosis, regardless of LVEF and the testing protocol employed. A meta-analysis of studies reporting risk ratios for cardiovascular events revealed that patients with HF and the presence of IB exhibited a fourfold increased risk of adverse events in comparison to HF patients without IB.

As previously stated, the distinctive aspect of CPET is its capacity to diagnose the presence and extent of functional

Table 3. Weber classification of disease severity

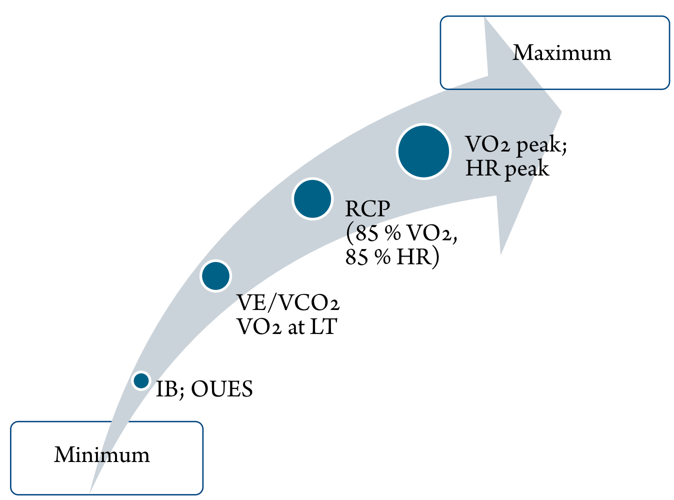
Severity of CHF	Class	VO_2 peak, mL/kg/min
Mild or absent	I	> 20
Mild to moderate	II	16–20
Moderate to severe	III	10–16
Terminal stage	IV	< 10

Figure 4. Characteristic changes in ventilatory CO_2 equivalent (VE/VCO_2) during continuously increasing exercise load



The point – corresponds to the beginning of the increase in ventilatory carbon dioxide equivalent (VE/VCO_2) – the respiratory compensatory point, VO_2 – volume of oxygen absorbed, X-axis – exercise intensity expressed as a percentage of VO_2 to its maximum values.

Figure 5. Dependence of data reliability on the achievement of submaximal and maximal effort



IB, intermittent breathing; OUES, oxygen uptake efficiency slope; LT, lactate threshold; VE/VCO_2, ventilatory efficiency; VO_2 peak, peak oxygen consumption; HR peak, heart rate at the point of maximal exertion during the exercise.

Table 4. Prognosis of patients with different ventilation class (VC)

VE/VCO_2 slope			
VC I, VE/VCO_2 ≤ 29.9	VC II, VE/VCO_2 = 30.0–35.9	VC III, VE/VCO_2 = 36.0–44.9	VC IV, VE/VCO_2 ≥ 45
2-year risk			
Negligible risk (< 5 %)	Low risk (~ 15 %)	Moderate risk (~ 30 %)	High risk (~ 50 %)

capacity decline, as well as to ascertain the influence of multiple factors that contribute to exercise intolerance. These include decreased cardiac output, pathological remodeling of the respiratory system, and skeletal muscle dysfunction. Figure 6 illustrates various alterations in CPET associated with the dysfunction of distinct links in the oxygen metabolism chain within the body during exercise.

Table 5 provides a description of the CPET measures and presents some of the indices calculated from them that are most commonly utilized in clinical trials involving patients with CHF.

Researchers are currently directing their attention toward alternative indicators of patients' functional status. One such indicator is the determination of lactate threshold (Appendix 3). The method enables the assessment of the functional capacity of a patient with heart failure by examining the stages of energy expenditure compensation during exercise and determining the biological reserves of adaptation to exercise load. Figure 7 illustrates the alterations in blood lactate concentration during a gradual increase in exercise load. At an exercise intensity corresponding to 27 [25;30] % VO_2max, the lactate level will increase. At the exercise peak, its value in healthy individuals is 9.7 mmol/L (9.1, 11.7 mmol/L). In patients with CHF class II, III, and IV, the lactate levels are 5.3 [4.6; 6.1], 4.4 [3.9; 4.9], and 3.2 [2.9; 3.5] mmol/L, respectively. Therefore, at an exercise intensity corresponding to 27 [25; 30] % VO_2max, there is a notable increase in blood lactate content, which indicates that the body's capacity for absorption of the formed lactate ion by muscle fibers, the liver, and the myocardium has been reached. In this instance, a pronounced (threshold) divergence in the lactate concentration curve is observed, which reflects the lactate threshold. Subsequently, there is a gradual increase in blood lactate content.

An elevation in blood lactate is associated with an increase in the respiratory exchange ratio, volume of CO_2 excretion, and lung minute volume. The achievement of lactate threshold in 100% of cases in all patients with CHF serves as the basis for determining the appropriate training intensity at the lactate threshold level physiologically justified for patients with CHF. At present, patient blood sampling is no longer a prerequisite for LT determination. However, the necessity for additional consumables and an extended study period has led to a more rigorous selection of indications for its implementation.

Inter-test variability of CPET

The inter-test variability of CPET in patients with CHF was investigated by A. Barron et al. They demonstrated that the majority of CPET variables exhibited low inter-test variability. The highest reliability was observed for peak VO_2, ventilatory efficiency index, and OUES.

Age, sex, and BMI, as well as the use of diverse protocols and inter-test interval, had no statistically significant effect on the inter-test variability of the indicators [54].

Formulas for predicting oxygen consumption based on other exercise stress tests

Given the limited availability of CPET, a number of equations have been proposed for the purpose of predicting maximum or peak VO_2. In apparently healthy individuals and those with only slight reductions in exercise tolerance, the Harvard Step Test and the treadmill test are employed. In patients with CHF, the most appropriate method for predicting VO_2 peak is based on the 6MWT distance. This is because numerous studies that have employed both the 6MWT and the CPET have demonstrated a sufficiently high level of correlation between the 6MWT distance and VO_2 peak. The models for predicting VO_2 peak demonstrate satisfactory accuracy in estimating mean VO_2 values but exhibit limited accuracy in determining individual values. Greater prediction accuracy is determined by the presence of similar clinical and demographic characteristics between the training and test populations. Additionally, models based on larger and more diverse populations may contribute to improved accuracy [55].

A number of formulas have been put forth for determining peak oxygen consumption based on the 6MWT (Table 6). Furthermore, the 6MWT distance conversion table [60], as presented in Appendix 4, may be utilized for this purpose.

Additional studies to determine functional capacity of patients with CHF

Evaluation of the functional status of skeletal muscles

It is well documented that the progression of CHF is characterized by pronounced morphological and functional abnormalities in skeletal muscle (SM). The mean prevalence of sarcopenia in patients with CHF is 20% higher than in healthy individuals of the same age [61, 62]. The excessive neurohumoral activation observed in CHF results in impaired mitochondrial function, which in turn reduces the production of respirasomes, the supramolecular structures of the respiratory chain [63]. The worsening of energy deficiency, coupled with chronic inflammation (elevated production of proinflammatory cytokines and tumor necrosis factor), and the progressive decline in the synthesis of anabolic hormones (testosterone,

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

Table 5. Main indicators of CPET

CPET parameters	Description and reference values	Prognostic value	Evaluation of the effectiveness of cardiac rehabilitation
VO_2 peak, mL/kg/min	The maximum amount of oxygen that an individual can consume at the peak of exercise (aerobic capacity) The amount of can vary considerably between healthy individuals from < 20 mL/kg/min in the elderly to > 90 mL/kg/min in elite endurance athletes.	The peak VO_2 < 14 (< 10 in patients treated with beta-blockers) is indicative of an unfavorable prognosis	A 6 % increase in peak VO_2 is associated with a 7 % reduction in the risk of all-cause mortality [32]
The VO_2 at the moment of achieving the respiratory compensatory point	A point at which carbon dioxide ventilation (respiratory compensation) increases in response to a continuous increase in exercise load. The VO2 at the lactate threshold level is typically observed to be within the range of 70–80 % of the VO2 peak	A low value is indicative of detraining or the presence of cardiovascular disease, whereas a high value is observed in the presence of a good training level.	–
VO_2 at the lactate threshold (VO_2 LT), mL/kg/min	The point at which an abrupt elevation in blood lactate is observed. The VO2 at the lactate threshold level is typically observed to be 25–30 % of the VO2 peak A low value is indicative of detraining or the presence of cardiovascular disease, whereas a high value is observed in the presence of a good training level.	The inability to achieve LT is indicative of an unfavorable prognosis [50]	It has been demonstrated that personalized aerobic training is associated with favorable changes
VE/VCO_2 slope. Ventilatory efficiency index	Tidal volume/carbon dioxide excretion; it reflects ventilation efficiency. Normal range is 25–30. In elderly patients without CVD or pulmonary disease, it may be slightly elevated (independently). An elevated value is indicative of ineffective ventilation or a ventilation-perfusion mismatch	Values of ≥ 34 indicate the presence of clinically significant CVD or pulmonary disease (HF; PH, and COPD). Values ≥34 are associated with the most unfavorable prognosis in patients with CHF	It has been demonstrated that RM training and complex training are associated with beneficial changes
Peak HR	It varies widely depending on age and level of training. A linear increase in this variable should occur in conjunction with an incremental increase in exercise load	In individuals who are not receiving BBs, prognostically unfavorable values ≤ 85 % of the predicted value. No prognostic significance has been shown in patients receiving BBs	–
Respiratory exchange ratio (RER)	VCO_2 to VO_2 ratio	RER ≥ 0.8 at the aerobic threshold is an unfavorable prognostic indicator	–
Circulatory power (CP)	Product of peak VO_2 and peak systolic blood pressure	A reduced value serves as an independent predictor of mortality [36, 37]	The greatest increase in CP is demonstrated for comprehensive RM training, strength training, and aerobic training [53]

CPET, cardiopulmonary exercise testing; VO_2 peak, peak oxygen consumption; LT, lactate threshold; CVD, cardiovascular disease; HF, heart failure; PH, pulmonary hypertension, COPD, chronic obstructive pulmonary disease; HR, heart rate, BBs, beta-blockers; CP, circulatory power; RM, respiratory muscle.

growth hormone, insulin-like growth factor) represent a pivotal element in the advancement of myopathy affecting skeletal and respiratory muscles – myopathy associated with heart failure [64]. One of the markers of SM status in patients with CHF is the activity of the ergoreflex.

The modulation of hemodynamics and ventilation is contingent upon the exercise intensity, which is the result of three highly integrated reflexes: the baroreflex, the chemoreflex, and the ergoreflex [65]. In response to the metabolic state of the SM, ergoreflexes regulate the intensity of blood flow in muscles and the cardiorespiratory response to exercise stress, thereby ensuring the adequate supply of oxygen and nutrients to contracting muscles. In this instance, there is an augmentation in lung ventilation and a series of circulatory alterations resulting from the heightened activity of the sympathetic nervous system. These include an increase in HR, BP, and the contraction of resistive vessels in non-working muscles (Figure 8) [66, 67]. The hyperactivation of the ergoreflex, which is associated with an increase in prostaglandin concentration, has been observed in patients with CHF [68].

Functional status of skeletal muscles

The assessment of SM endurance and strength in patients with HF represents a crucial yet underutilized aspect of functional status evaluation.

The gold standard for assessing muscle strength is the one-repetition maximum (1RM). The resistance may be provided by free weights or weight machines. While 1RM can be obtained in any weightlifting exercise, the two most common are the bench press (for determination of upper body strength) and the leg press (for determination of lower body strength). Unfortunately, there is a lack of consensus regarding the interpretation of 1RM values in patients with HF. The reliability of strength tests may be contingent upon a multitude of factors pertaining to potential inaccuracies in measurement, methodology, and exercise parameters. In a meta-analysis conducted by J. Grgic and colleagues, which included 32 studies, it was concluded that the 1RM test has excellent test-retest reliability regardless of previous strength training experience, sex, and age of subjects, as well as the inclusion of a familiarization session in the testing procedure and the testing of either the upper or lower body musculature [69]. Hand-held dynamometry represents a more straightforward and prevalent approach to the evaluation of muscle functionality. The procedure is relatively simple and requires the patient to exert the greatest possible force on the dynamometer handle for a three-second interval. Following a brief period of rest, the test is repeated on two further occasions, with each arm undergoing assessment. While there are no normative values that are specific to patients with HF, standards are available for large populations. A meta-analysis comprising seven studies (23,480 patients with cardiovascular disease) was conducted to investigate the correlation between hospitalization rates for CHF and skeletal muscle strength as assessed by 1RM [70]. A comparative analysis revealed that the highest quintile was associated with a lower incidence of HF in comparison to the lowest quintile (OR = 0.18; 95% CI: 0.08–0.43; p = 0.001) [71].

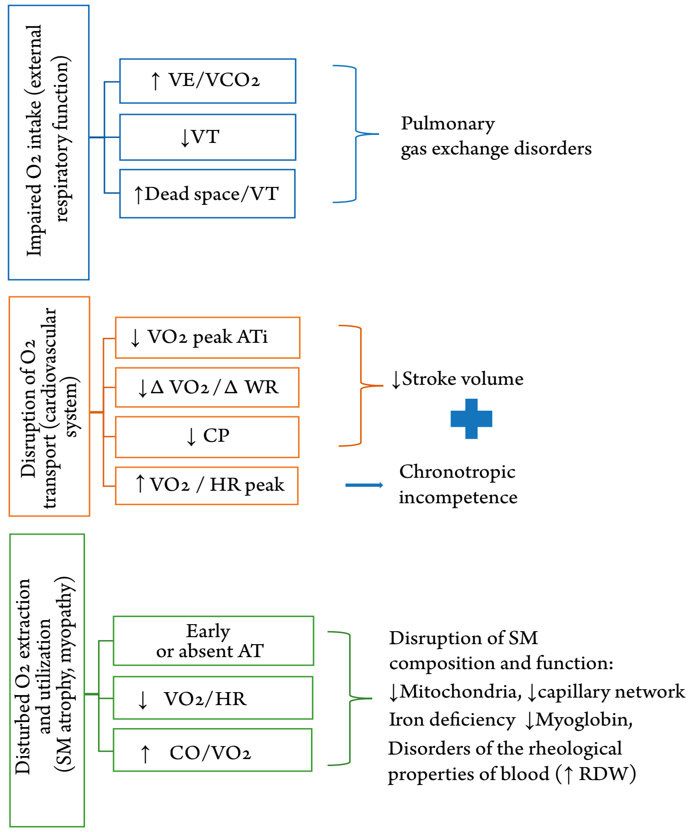
Furthermore, indirect methods of measuring muscle strength can be utilized as indicators of the functional capacity of the SM. The most prevalent approach is the Short Physical Performance Battery (SPPB), which was initially proposed by J.M. Guralnik et al. [72]. The approach comprises three components: a diagnosis of the patient's balance, a determination of the speed of walking a distance of four meters, and a lifting from a seated position. In the study conducted by T. Kitai et al., the prognostic value of the SPPB was evaluated in comparison to the 6MWT, when added to traditional prognostic factors. The incorporation of the 6MWT into the baseline model yielded superior risk prediction outcomes compared to the inclusion of the SPPB in the model. The incorporation of 6MWT into a model that includes traditional prognostic factors and SPPB resulted in a notable improvement in predictive efficacy. In contrast, the incorporation of SPPB into a model that included conventional prognostic factors and 6MWT did not lead to an enhancement in predictive accuracy [73].

Strength of the respiratory muscles

Respiratory muscle (RM) weakness is a prevalent phenomenon observed in patients with prolonged and severe CHF, and it is linked to an unfavorable prognosis [74–76].

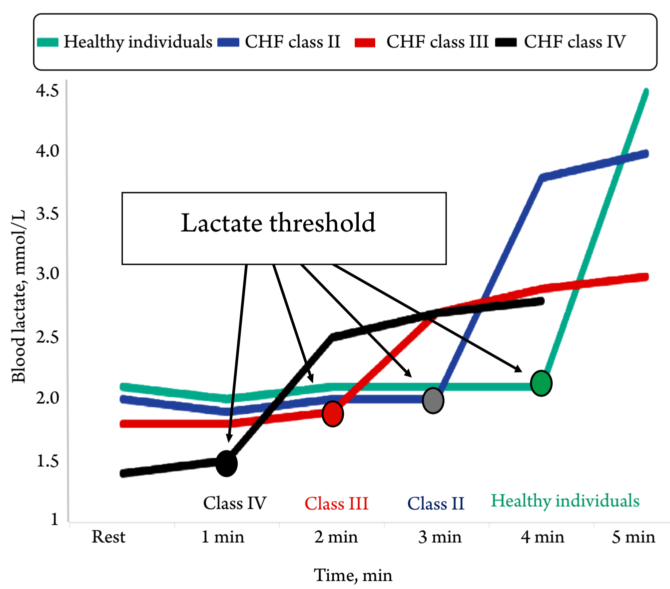
The RM dysfunction, including diaphragm dysfunction, occurs independently of the severity of CHF and significantly

Figure 6. CPET parameters that reflect the contribution of impairments in various systems involved in muscle function



AT, aerobic threshold; CP, circulatory power, VO_2 / WR, peak oxygen consumption to work rate ratio; HR, heart rate; SM, skeletal muscle; VT, tidal volume, ventilatory power index.

Figure 7. Changes in lactate content in venous blood during exercise



CHF, chronic heart failure;
X-axis, exercise intensity expressed as a VO_2 percentage of its maximum values;
Y-axis, lactate content in venous blood in mmol/L.

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

Table 6. Formulas for indirect determination of peak oxygen consumption using the 6MWT

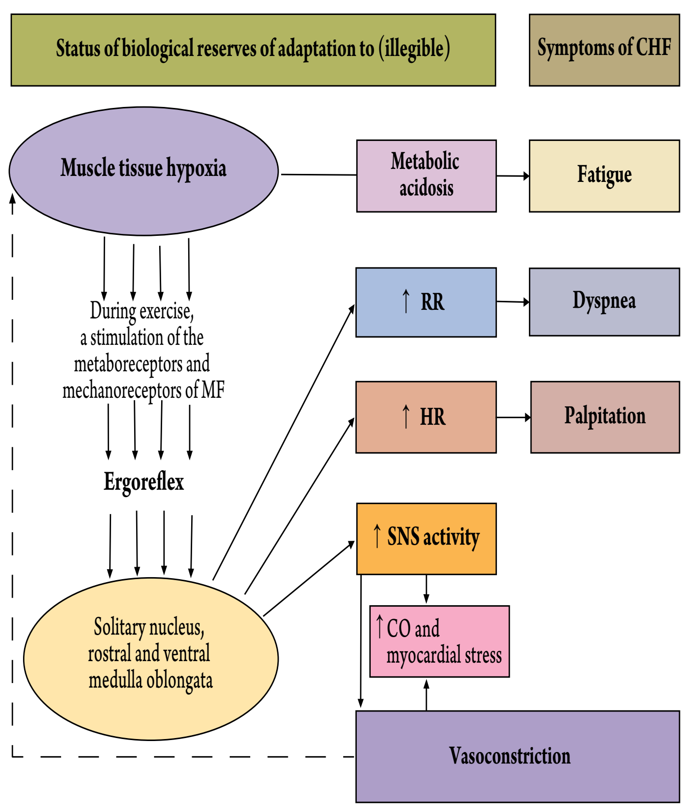
Author	Formula	Population
Burr et al. (2011) [56]	VO_2 max = 70.161 + 0.023 * 6MWT distance (m) – 0.276 * weight (kg) – 6.79 * sex (M = 0; F = 1) – 0.193 * Resting HR (beats per minute) – 0.191 * age (years)	Middle-aged healthy individuals
Ross et al. (2010) [57]	VO_2peak = 4.948 + 0.023 x mean 6MWT distance (m)	Combined cohort. Patients actually examined and data obtained by analyzing several studies that included patients with CHF and COPD
Adedoyin et al. (2010) [58]	VO_2 = 0.0105 × 6MWT distance (m) + 0.0238 age (years) 0.03085 weight (kg) + 5.598	HF class II–III
Cahalin et al. (1996) [59]	VO_2 peak = 0.03 * 6MWT distance (m) + 3.98	Patients with severe HF

6MWT, 6-minute walk test; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HR, heart rate; M, male; F, female.

contributes to reduced exercise tolerance. Morphological studies have demonstrated that diaphragm dysfunction in patients with sarcopenia and cachexia is associated with alterations in the ratio of muscle, connective tissue, and adipose tissue within the diaphragm. As heart failure progresses, there is a reduction in the quantity of muscular tissue, accompanied by an increase in the volume of adipose and connective tissue within the diaphragm. These changes are correlated with the CHF class, the maximum thickness of the diaphragmatic muscle during inspiration, and the maximum inspiratory pressure. Morphological changes are most pronounced in patients with CHF class III [77] and in the presence of comorbidities [78]. The results of the ultrasonography indicate a correlation between the increase in the volume of connective tissue in the diaphragm of patients with CHF and a reduction in the thickness of the diaphragmatic muscle. This impairs the ability of the diaphragm to participate fully in external respiration. As demonstrated by Yamada K. et al., a diaphragm thickness of less than 4 mm is indicative of a compromised function, exhibiting a strong correlation with the maximum inspiratory pressure. A reduction in the maximum thickness of the diaphragm at the end of inspiration to less than 3.9 mm is associated with a significantly shorter 6 minute walk distance and a worse prognosis for the patient [79]. Accordingly, an augmentation in the quantity of connective tissue and a diminution in muscle mass within the diaphragm give rise to its dysfunction, which is manifested as a superficial type of breathing. This, in turn, activates the sympatho-adrenal system, thereby increasing the risk of fatal arrhythmias. As the condition progresses, it results in an inability to cough effectively, an accumulation of sputum, and an increased risk of developing pneumonia [74, 80]. Moreover, the ratio of physiologic dead space to tidal volume (VD/VT) undergoes a change (normally it is 0.3) [81].

As the diaphragm's functionality is compromised, the tidal volume diminishes, thereby increasing the absolute value of the dead space ratio. The capacity for spontaneous breathing is compromised when the dead space ratio reaches 0.7–0.8, as the respiratory work increases (as a result of shallow breathing, the respiratory rate rises) and CO_2 is accumulated in greater quantities than can be removed. The most commonly employed measures for the diagnosis of RM strength are maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). MIP is significantly correlated with dyspnea during exercise [82, 83]. The most comprehensive investigation into the prevalence and prognostic implications of RM weakness was conducted

Figure 8. Mechanisms of ergoreflex activation in heart failure and formation of clinical symptoms of chronic heart failure



MF, muscle fiber; CO, cardiac output; SNS, sympathetic nervous system; CHF, chronic heart failure; HR, respiratory rate; HR, heart rate. The standard methodology for ergoreflex testing was standardized by M. Piepoli 25 years ago, in 1996 (Appendix 5). The ergoreflex activity has been demonstrated to be significantly correlated with the severity of CHF.

by N. Hamazaki et al. The study included 445 patients with HFrEF and 578 patients with HFpEF. RM weakness was observed in 42.7% of patients with HFrEF and 39.1% of patients with HFpEF. The mortality rate was significantly elevated in both patients with HFrEF and HFpEF and respiratory muscle weakness (RMW) in comparison to patients without RMW. RMW was associated with a twofold increase in the risk of all-cause mortality in patients with HFrEF and a threefold increase in patients with HFpEF. Concurrently, RMW served as an independent negative prognostic factor exclusively in patients with HFpEF [75]. Furthermore, morphologic alterations in the diaphragm impact MIP values, exhibiting a direct correlation with muscular tissue volume and an inverse correlation with adipose and connective tissue volume [84].

Maximal inspiratory pressure shows the most pronounced decline in patients with CHF class III, while remaining relatively stable in patients with class IV. The RM strength can vary considerably depending on the age, sex, and weight of the patient. It is thus advised that absolute values be avoided in favor of percentages in the analysis. A multitude of formulas have been put forth for determining the optimal values for maximum inspiratory and expiratory pressures. When selecting a formula, it is essential to consider the characteristics of the population on which the formula was based. The most appropriate formula for a given study will be that which aligns most closely with the characteristics of the study population, including mean age, BMI, and other parameters used in the formula. The diagnosis of RM weakness is further complicated by the considerable variability of the parameters. Indeed, the mean values of MEP and MIP in different studies exhibit only a weak correlation, with the correlation coefficients differing between men and women. Moreover, these indices are distinguished by inter-test variability, which can reach as high as 7–10% [85]. In diagnosing RM weakness, one may utilize the values of the «lower limit of normal,» as outlined by M.I. Polkey et al. [86]. For MIP, these values are 80 mm Hg in men and 60 mm Hg in women. In the case of MEP, the corresponding values are 150 mm Hg and 120 mm Hg, respectively. In accordance with alternative sources, a diagnosis of RM weakness should be considered when the values are approximately 40% below the predicted value for a given patient [87]. A general guideline for the application of formulas is provided in Figure 9.

Table 7 presents a summary of studies that have proposed formulas for both men and women. The most commonly employed variables in these formulas are age, weight, and height. In the study conducted by M. Moeliono et al., it was put forth that the movement of the rib cage at the level of the fourth intercostal space and the xiphoid process be employed as indicators.

Conclusion

- The methods of functional capacity assessment outlined in this document can, to varying degrees, address the challenges associated with the assessment of exercise capacity and functional reserve, prognosis, efficacy of drug and non-drug interventions, including those related to physical rehabilitation. Furthermore, they can also contribute significantly to the understanding of the pathophysiological processes involved in the development and progression of CHF.
- The design, conduct, and interpretation of studies to assess the functional status of patients represents a complex undertaking. This is due to the fact that functional impairment is the consequence of intricate pathogenic processes that involve a multitude of organs and systems within the body, occurring at both the organ and cellular levels.
- The following recommendations are proposed with the objective of enhancing the validity of research findings and the quality of papers in this complex and understudied area of clinical medicine.
- In the planning of studies that include an assessment of the functional status of patients, the selection of a specific method should be justified in accordance with the objectives of the study.
- The gold standard for the assessment of functional status in patients with congestive heart failure (CHF) is cardiopulmonary exercise testing (CPET). The use of the 6MWT as the primary methodology for functional status assessment is a reasonable approach when conducting studies on large samples. In other instances, it is recommended that additional methods for evaluating the functional status of patients, as outlined in this document, be employed to enhance the informative value of the study outcomes.
- The «Materials and Methods» section should include not only a comprehensive account of the study methodology but also an interpretation of the results in accordance with the specific reproducibility and variability inherent to the method employed.
- In the case of CPET results for parameters that are highly dependent on achieving the maximum level of workload (VO_2 peak), it is of the utmost importance to specify the criteria for attaining the requisite level of workload. It is further recommended that additional analysis be conducted on parameters that are less dependent on the achievement of maximal exercise levels, such as VO_2 at the aerobic threshold and OUES.
- It should be noted that the formulas used to predict oxygen consumption and respiratory muscle strength demonstrate satisfactory accuracy when estimating average values; however, they exhibit poor accuracy when determining individual values. Formulas developed based on larger

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

Table 7. Formulas for predicting the strength of DM

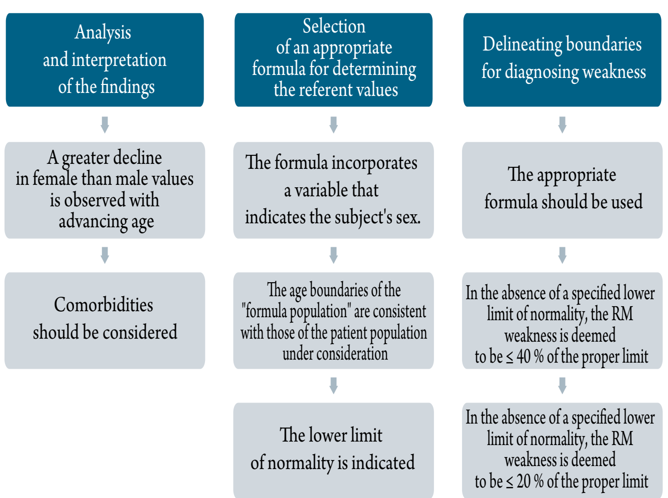
Author, year	Age	Sex F/M (N)	Formula (female)	Formula (male)
Black (1969) [88]	20–70	60/60	MIP = 104 – (0.51 × age) MEP = 170 – (0.53 × age)	MIP = 143 – (0.55 × age) MEP = 268 – (1.03 × age)
Wilson et al. (1984) [89]	18–70	87/48	MIP = – 43 + (0.71 × Height in cm) MEP = 3.5 + (0.55 × Height in cm)	MIP = 142 – (1.03 × age) MEP = 180 – (0.91 × age)
Enright et al. (1994) [90]	65–85	176/112	MIP = (0.133 Weight in lb) – (0.805 Age) + 96 MEP = (0.344 Wt in lb) – (2.12 Age) + –	MIP = (0.133 Weight in lb) – (0.805 Age) + 96 MEP = (0.250 Weight in lbs) – (2.95 Age) + 347
Hautmannet al. (2000) [91];	18–82	504/256	MIP = (– 0.024 × age) + 8.55	MIP = (0.158 × BMI) – (0.051 × age) + 8.22
Sachs et al. (2009) [92]	45–84	883 / 872	MIP = – 388 + (1.77 ×age) + (– 0.014 × age) + (0.41 × Weight in lb) + (– 0.0041 × Age × Weight (lb)) + (4.69 ×Height in cm) + (– 0.014 × Height in cm)	MIP = 9.8 + (– 0.31 × age) + (1.47 × Weight (lb)) + (– 0.0026 × Weight (lb)) + (–0.0059 × Age × Weight (lb))
Sanchez et al. (2018) [93]	18–89	229/124	Model 2: MIP = –94.75 + (0.816 × age) – (1.822 × BMI) MEP = 91.58 – (0.556 × age) + (0.798 × BMI) Model 3: MIP = –95.54 + (0.748 × age) – (0.688 × Weight in kg) MEP = 87.20 – (0.506 × age) + (0.350 × Weight in kg)	MIP = –108.16 + (1.307 × age) – (2.904 × BMI) MEP = 98.36 – (0.672 × age) + (1.759 × BMI) MIP = –110.07 + (1.208 × age) – (0.942 × Weight in kg) MEP = 98.84 – (0.610 × age) + (0.576 × Weight in kg)
Moeliono et al. 2022 [94]	20–40	42/35	MIP (L2*) MIP = 56.802 + 2.387 + L2 + 13.904 + Sex * MIP = 53.289 + 3.561 + L3** + 9.504 + Sex #	–

0 – female, 1 – male; * At the level of the fourth intercostal space (L2);
** At the level of the xiphoid process (L3). MIP, maximal inspiratory pressure;
MEP, maximal expiratory pressure; BMI, body mass index.

and more diverse populations (e.g., a formula by Ross et al.) should be preferred, and further validation on test populations should be conducted.

- The interpretation of study results must consider the inherent limitations of the methodologies employed. A comprehensive account of the study limitations should be provided in the section designated for such information.

Figure 9. Interpretation of the findings of a respiratory muscle strength assessment



List of Abbreviations

1RM, one-repetition maximum
6MWT, 6-minute walk test
AT, aerobic threshold
BMI, body mass index
C (a-v), arteriovenous oxygen content difference
CHF, chronic heart failure
CI, confidence interval
CP, circulatory power
CPET, cardiopulmonary exercise test
CRE, cardiorespiratory endurance
CvO_2, venous blood oxygen content
FC, functional class
Hb, hemoglobin
HFpEF, heart failure with preserved ejection fraction
HFrEF, heart failure with reduced ejection fraction
HR, hazard ratio
HR, heart rate
IB, intermittent breathing
LT, lactate threshold
MEP, maximal expiratory pressure
MET, metabolic equivalent
MIP, maximal inspiratory pressure
MR, metaboreflex
OUES, oxygen uptake efficiency slope

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

PO_2, partial pressure of oxygen
SaO_2, oxygen saturation
SV, stroke volume
VCO_2, carbon dioxide volume
VE/VCO_2, ventilatory efficiency
VO_2, oxygen consumption
VO_2/WR – oxygen uptake to work rate ratio

No conflict of interest is reported.

The article was received on 10/01/2024

REFERENCES

1. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. P. 253-256. Dolgin M, New York Heart Association, editors -Boston, Mass.: Little, Brown and Co, 1994. – 334p. ISBN 978-0-316-60538-0
2. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation. 1981;64(6):1227–34. DOI: 10.1161/01.CIR.64.6.1227
3. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476–82. DOI: 10.1136/hrt.2006.089656
4. Yap J, Lim FY, Gao F, Teo LL, Lam CSP, Yeo KK. Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance: A Systematic Review. Clinical Cardiology. 2015;38(10):621–8. DOI: 10.1002/clc.22468
5. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. BMJ. 1982;284(6329):1607–8. DOI: 10.1136/bmj.284.6329.1607
6. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Canadian Medical Association Journal. 1985;132(8):919–23. PMID: 3978515
7. Fuentes-Abolafio IJ, Stubbs B, Pérez-Belmonte LM, Bernal-López MR, Gómez-Huelgas R, Cuesta-Vargas AI. Physical functional performance and prognosis in patients with heart failure: a systematic review and meta-analysis. BMC Cardiovascular Disorders. 2020;20(1):512. DOI: 10.1186/s12872-020-01725-5
8. Hanson LC, McBurney H, Taylor NF. The retest reliability of the six-minute walk test in patients referred to a cardiac rehabilitation programme. Physiotherapy Research International. 2012;17(1):55–61. DOI: 10.1002/pri.513
9. Wu G, Sanderson B, Bittner V. The 6-minute walk test: How important is the learning effect? American Heart Journal. 2003;146(1):129–33. DOI: 10.1016/S0002-8703(03)00119-4
10. Hamilton DM, Haennel RG. Validity and Reliability of the 6-Minute Walk Test in a Cardiac Rehabilitation Population. Journal of Cardiopulmonary Rehabilitation. 2000;20(3):156–64. DOI: 10.1097/00008483-200005000-00003
11. Lans C, Cider Å, Nylander E, Brudin L. Test–retest reliability of six-minute walk tests over a one-year period in patients with chronic heart failure. Clinical Physiology and Functional Imaging. 2020;40(4):284–9. DOI: 10.1111/cpf.12637
12. Sitnikova M.Yu., Lelyavina T.A., Shlyakhto E.V., Ivanov S.G., Trukshina M.A., Fedotov P.A. et al. Effectiveness and prognostic value of diagnostic methods for the severity of chronic heart failure in patients of different ages. Arterial Hypertension. 2008;14(S1-2):5–11. [Russian: Ситникова М.Ю., Лелявина Т.А., Шляхто Е.В., Иванов С.Г., Трукшина М.А., Федотов П.А. и др. Эффективность и прогностическая ценность методов диагностики тяжести хронической сердечной недостаточности у пациентов разного возраста. Артериальная гипертензия. 2008;14(S1-2):5–11]
13. Tereshchenko S.N., Galyavich A.S., Uskach T.M., Ageev F.T., Arutyunov G.P., Begrambekova Yu.L. et al. 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020;25(11):311–74. [Russian: Терещенко С.Н. Галявич А.С., Ускач Т.М., Агеев Ф.Т., Арутюнов Г.П., Беграмбекова Ю.Л. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):311-74]. DOI: 10.15829/1560-4071-2020-4083
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the Six-Minute Walk Test. American Journal of Respiratory and Critical Care Medicine. 2002;166(1):111–7. DOI: 10.1164/ajrccm.166.1.at1102
15. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2022;79(17):e263–421. DOI: 10.1016/j.jacc.2021.12.012
16. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. Circulation. 2010;122(2):191–225. DOI: 10.1161/CIR.0b013e3181e52e69
17. Arutyunov G.P., Kolesnikova E.A., Begrambekova Yu.L., Orlova Ya.A., Rylova A.K., Aronov D.M. et al. Exercise training in chronic heart failure: practical guidance of the Russian Heart Failure Society. Russian Heart Failure Journal. 2017;18(1):41–66. [Russian: Арутюнов Г.П., Колесникова Е.А., Беграмбекова Ю.Л., Орлова Я.А., Рылова А.К., Аронов Д.М. и др. Рекомендации по назначению физических тренировок пациентам с хронической сердечной недостаточностью. Журнал Сердечная Недостаточность. 2017;18(1):41–66.]. DOI: 10.18087/rhfj.2017.1.2339
18. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. American Journal of Respiratory and Critical Care Medicine. 2003;167(2):211–77. DOI: 10.1164/rccm.167.2.211
19. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. United States Armed Forces Medical Journal. 1959;10(6):675–88. PMID: 13659732
20. Myers J, Bellin D. Ramp Exercise Protocols for Clinical and Cardiopulmonary Exercise Testing. Sports Medicine. 2000;30(1):23–9. DOI: 10.2165/00007256-200030010-00003
21. Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R и др. Work-rate affects cardiopulmonary exercise test results in heart failure. European Journal of Heart Failure. 2005;7(4):498–504. DOI: 10.1016/j.ejheart.2004.06.007
22. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. Journal of Applied Physiology. 1983;55(5):1558–64. DOI: 10.1152/jappl.1983.55.5.1558
23. Lala A, Shah KB, Lanfear DE, Thibodeau JT, Palardy M, Ambardekar AV et al. Predictive Value of Cardiopulmonary Exercise Testing Parameters in Ambulatory Advanced Heart Failure. JACC: Heart Failure. 2021;9(3):226–36. DOI: 10.1016/j.jchf.2020.11.008
24. Ingle L, Witte KK, Cleland JGJF, Clark AL. The prognostic value of cardiopulmonary exercise testing with a peak respiratory exchange ratio of <1.0 in patients with chronic heart failure. International Journal of Cardiology. 2008;127(1):88–92. DOI: 10.1016/j.ijcard.2007.04.075
25. Karanadze N.A., Begrambekova Yu.L., Borisov E.N., Orlova Ya.A. Red cell distribution width as a predictor of impaired exercise capacity in patients with heart failure. Kardiologiia. 2022;62(4):30–5. [Russian: Каранадзе Н.А., Беграмбекова Ю.Л., Борисов Е.Н., Орлова Я.А. Ширина распределения эритроцитов как предиктор низкой толерантности к физической нагрузке у пациентов с хронической сердечной недостаточностью. Кардиология. 2022;62(4):30-5]. DOI: 10.18087/cardio.2022.4.n1813
26. Ozemek C, Arena R. Cardiopulmonary Exercise Testing in Patients With Heart Failure and a Preserved Ejection Fraction: Filling the Prognostic Knowledge Gap. Revista Española de Cardiología (English Edition). 2018;71(4):237–9. DOI: 10.1016/j.rec.2017.08.012
27. Zugck C, Haunstetter A, Krüger C, Kell R, Schellberg D, Kübler W и др. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. Journal of the Ameri-

can College of Cardiology. 2002;39(10):1615–22. DOI: 10.1016/S0735-1097(02)01840-5
28. Guimaraes GV, d'Avila VM, Silva MS, Ferreira SA, Ciolac EG, Carvalho VO et al. A cutoff point for peak oxygen consumption in the prognosis of heart failure patients with beta-blocker therapy. International Journal of Cardiology. 2010;145(1):75–7. DOI: 10.1016/j.ijcard.2009.05.001
29. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak Oxygen Consumption as a Predictor of Death in Patients With Heart Failure Receiving β-Blockers. Circulation. 2005;111(18):2313–8. DOI: 10.1161/01.CIR.0000164270.72123.18
30. Sarullo FM, Fazio G, Brusca I, Fasullo S, Paterna S, Licata P et al. Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure: Prognostic Comparison from Peak VO_2 and VE/VCO_2 Slope. The Open Cardiovascular Medicine Journal. 2010;4(1):127–34. DOI: 10.2174/1874192401004010127
31. Corrà U, Giordano A, Piepoli M. Cardiopulmonary exercise testing in chronic heart failure patients treated with beta-blockers: Still a valid prognostic tool. International Journal of Cardiology. 2020;317:128–32. DOI: 10.1016/j.ijcard.2020.04.020
32. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L и др. Modest Increase in Peak VO_2 Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients: Results From Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training. Circulation: Heart Failure. 2012;5(5):579–85. DOI: 10.1161/CIRCHEARTFAILURE.111.965186
33. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. Journal of the American College of Cardiology. 2011;58(3):265–74. DOI: 10.1016/j.jacc.2011.02.055
34. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 1982;65(6):1213–23. DOI: 10.1161/01.CIR.65.6.1213
35. Guazzi M, Borlaug B, Metra M, Losito M, Bandera F, Alfonzetti E et al. Revisiting and Implementing the Weber and Ventilatory Functional Classifications in Heart Failure by Cardiopulmonary Imaging Phenotyping. Journal of the American Heart Association. 2021;10(5):e018822. DOI: 10.1161/JAHA.120.018822
36. Jaussaud J, Blanc P, Derval N, Bordachar P, Courregelongue M, Roudaut R et al. Ventilatory response and peak circulatory power: New functional markers of response after cardiac resynchronization therapy. Archives of Cardiovascular Diseases. 2010;103(3):184–91. DOI: 10.1016/j.acvd.2010.01.003
37. Cohen-Solal A. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. European Heart Journal. 2002;23(10):806–14. DOI: 10.1053/euhj.2001.2966
38. Giardini A, Specchia S, Berton E, Sangiorgi D, Coutsoumbas G, Gargiulo G et al. Strong and independent prognostic value of peak circulatory power in adults with congenital heart disease. American Heart Journal. 2007;154(3):441–7. DOI: 10.1016/j.ahj.2007.05.009
39. Madan N, Beachler L, Konstantinopoulos P, Worley S, Sun Z, Latson LA. Peak Circulatory Power as an Indicator of Clinical Status in Children After Fontan Procedure. Pediatric Cardiology. 2010;31(8):1203–8. DOI: 10.1007/s00246-010-9799-1
40. Methvin AB, Owens AT, Emmi AG, Allen M, Wiegers SE, Dries DL et al. Ventilatory Inefficiency Reflects Right Ventricular Dysfunction in Systolic Heart Failure. Chest. 2011;139(3):617–25. DOI: 10.1378/chest.10-0318
41. Nayor M, Xanthakis V, Tanguay M, Blodgett JB, Shah RV, Schoenike M et al. Clinical and Hemodynamic Associations and Prognostic Implications of Ventilatory Efficiency in Patients With Preserved Left Ventricular Systolic Function. Circulation: Heart Failure. 2020;13(5):e006729. DOI: 10.1161/CIRCHEARTFAILURE.119.006729
42. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of Ventilatory Efficiency in Heart Failure: The Role of Right Ventricular Performance and Pulmonary Vascular Tone. Circulation: Heart Failure. 2008;1(4):227–33. DOI: 10.1161/CIRCHEARTFAILURE.108.785501
43. Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. Heart Failure Reviews. 2013;18(1):79–94. DOI: 10.1007/s10741-012-9332-0
44. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P et al. Development of a Ventilatory Classification System in Patients With Heart Failure. Circulation. 2007;115(18):2410–7. DOI: 10.1161/CIRCULATIONAHA.107.686576
45. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. Journal of the American College of Cardiology. 2000;36(1):194–201. DOI: 10.1016/S0735-1097(00)00691-4
46. Forman DE, Guazzi M, Myers J, Chase P, Bensimhon D, Cahalin LP et al. Ventilatory Power: A Novel Index That Enhances Prognostic Assessment of Patients With Heart Failure. Circulation: Heart Failure. 2012;5(5):621–6. DOI: 10.1161/CIRCHEARTFAILURE.112.968529
47. Castello-Simões V, Minatel V, Karsten M, Simões RP, Perseguini NM, Milan JC et al. Circulatory and Ventilatory Power: Characterization in Patients with Coronary Artery Disease. Arquivos Brasileiros de Cardiologia. 2015;104(6):476–85. DOI: 10.5935/abc.20150035
48. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M et al. Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death. Circulation. 2002;106(24):3079–84. DOI: 10.1161/01.CIR.0000041428.99427.06
49. Corrà U, Giordano A, Mezzani A, Gnemmi M, Pistono M, Caruso R et al. Cardiopulmonary exercise testing and prognosis in heart failure due to systolic left ventricular dysfunction: a validation study of the European Society of Cardiology Guidelines and Recommendations (2008) and further developments. European Journal of Preventive Cardiology. 2012;19(1):32–40. DOI: 10.1177/1741826710393994
50. Agostoni P, Corrà U, Cattadori G, Veglia F, Battaia E, La Gioia R et al. Prognostic Value of Indeterminable Anaerobic Threshold in Heart Failure. Circulation: Heart Failure. 2013;6(5):977–87. DOI: 10.1161/CIRCHEARTFAILURE.113.000471
51. Corrà U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P и др. Sleep and Exertional Periodic Breathing in Chronic Heart Failure: Prognostic Importance and Interdependence. Circulation. 2006;113(1):44–50. DOI: 10.1161/CIRCULATIONAHA.105.543173
52. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: An unfavorable combination with high prognostic value. American Heart Journal. 2007;153(5):859–67. DOI: 10.1016/j.ahj.2007.02.034
53. Laoutaris ID, Piotrowicz E, Kallistratos MS, Dritsas A, Dimaki N, Miliopoulos D et al. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. European Journal of Preventive Cardiology. 2021;28(15):1626–35. DOI: 10.1093/eurjpc/zwaa091
54. Barron A, Dhutia N, Mayet J, Hughes AD, Francis DP, Wensel R. Test–retest repeatability of cardiopulmonary exercise test variables in patients with cardiac or respiratory disease. European Journal of Preventive Cardiology. 2014;21(4):445–53. DOI: 10.1177/2047487313518474
55. Begrambekova Yu.L., Fedotov D.A., Karanadze N.A., Lelyavina T.A., Bortsova M.A., Orlova Ya.A. Possibilities of Predicting Peak Oxygen Consumption in Patients With Chronic Heart Failure According to the 6-Minute Walk Test. Kardiologiia. 2024;64(2):34–42. [Russian: Беграмбекова Ю.Л., Федотов Д.А., Каранадзе Н.А., Лелявина Т.А., Борцова М.А., Орлова Я.А. Возможности прогнозирования пикового потребления кислорода у пациентов с хронической сердечной недостаточностью по данным 6-минутного теста ходьбы. Кардиология. 2024;64(2):34-42]. DOI: 10.18087/cardio.2024.2.n2551
56. Burr JF, Bredin SSD, Faktor MD, Warburton DER. The 6-Minute Walk Test as a Predictor of Objectively Measured Aerobic Fitness in Healthy Working-Aged Adults. The Physician and Sportsmedicine. 2011;39(2):133–9. DOI: 10.3810/psm.2011.05.1904
57. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six minute walk test accurately estimates mean peak oxygen uptake. BMC Pulmonary Medicine. 2010;10(1):31. DOI: 10.1186/1471-2466-10-31
58. Adedoyin RA, Adeyanju SA, Balogun MO, Adebayo RA, Akintomide AO, Akinwusi PO. Prediction of functional capacity during six-minute walk

among patients with chronic heart failure. Nigerian Journal of Clinical Practice. 2010;13(4):379–81. PMID: 21220849
59. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The Six-Minute Walk Test Predicts Peak Oxygen Uptake and Survival in Patients With Advanced Heart Failure. Chest. 1996;110(2):325–32. DOI: 10.1378/chest.110.2.325
60. ACSM's guidelines for exercise testing and prescription. Pescatello LS, American College of Sports Medicine, editor -Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014. – 456p. ISBN 978-1-60913-605-5
61. Zhang Y, Zhang J, Ni W, Yuan X, Zhang H, Li P et al. Sarcopenia in heart failure: a systematic review and meta-analysis. ESC Heart Failure. 2021;8(2):1007–17. DOI: 10.1002/ehf2.13255
62. Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N et al. Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). European Journal of Heart Failure. 2018;20(11):1580–7. DOI: 10.1002/ejhf.1304
63. Joseph GA, Wang SX, Jacobs CE, Zhou W, Kimble GC, Tse HW et al. Partial Inhibition of mTORC1 in Aged Rats Counteracts the Decline in Muscle Mass and Reverses Molecular Signaling Associated with Sarcopenia. Molecular and Cellular Biology. 2019;39(19):e00141-19. DOI: 10.1128/MCB.00141-19
64. Bossone E, Arcopinto M, Iacoviello M, Triggiani V, Cacciatore F, Maiello C et al. Multiple hormonal and metabolic deficiency syndrome in chronic heart failure: rationale, design, and demographic characteristics of the T.O.S.CA. Registry. Internal and Emergency Medicine. 2018;13(5):661–71. DOI: 10.1007/s11739-018-1844-8
65. Alam M, Smirk FH. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. The Journal of Physiology. 1937;89(4):372–83. DOI: 10.1113/jphysiol.1937.sp003485
66. Nobrega ACL, O'Leary D, Silva BM, Marongiu E, Piepoli MF, Crisafulli A. Neural Regulation of Cardiovascular Response to Exercise: Role of Central Command and Peripheral Afferents. BioMed Research International. 2014;2014:1–20. DOI: 10.1155/2014/478965
67. Crisafulli A, Marongiu E, Ogoh S. Cardiovascular Reflexes Activity and Their Interaction during Exercise. BioMed Research International. 2015;2015:1–10. DOI: 10.1155/2015/394183
68. Scott AC, Wensel R, Davos CH, Kemp M, Kaczmarek A, Hooper J et al. Chemical Mediators of the Muscle Ergoreflex in Chronic Heart Failure: A Putative Role for Prostaglandins in Reflex Ventilatory Control. Circulation. 2002;106(2):214–20. DOI: 10.1161/01.CIR.0000021603.36744.5E
69. Grgic J, Lazinica B, Schoenfeld BJ, Pedisic Z. Test–Retest Reliability of the One-Repetition Maximum (1RM) Strength Assessment: a Systematic Review. Sports Medicine - Open. 2020;6(1):31. DOI: 10.1186/s40798-020-00260-z
70. Pavasini R, Serenelli M, Celis-Morales CA, Gray SR, Izawa KP, Watanabe S et al. Grip strength predicts cardiac adverse events in patients with cardiac disorders: an individual patient pooled meta-analysis. Heart. 2019;105(11):834–41. DOI: 10.1136/heartjnl-2018-313816
71. Li R-M, Dai G-H, Guan H, Gao W-L, Ren L-L, Wang X-M et al. Association between handgrip strength and heart failure in adults aged 45 years and older from NHANES 2011–2014. Scientific Reports. 2023;13(1):4551. DOI: 10.1038/s41598-023-31578-9
72. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. Journal of Gerontology. 1994;49(2):M85–94. DOI: 10.1093/geronj/49.2.M85
73. Kitai T, Shimogai T, Tang WHW, Iwata K, Xanthopoulos A, Otsuka S и др. Short physical performance battery vs. 6-minute walking test in hospitalized elderly patients with heart failure. European Heart Journal Open. 2021;1(1):oeab006. DOI: 10.1093/ehjopen/oeab006
74. Begrambekova Yu.L., Karanadze N.A., Orlova Ya.A. Alterations of the respiratory system in heart failure. Kardiologiia. 2019;59(2S):15–24. [Russian: Беграмбекова Ю.Л., Каранадзе Н.А., Орлова Я.А. Нарушения системы дыхания при хронической сердечной недостаточности. Кардиология. 2019;59(2S):15-24]. DOI: 10.18087/cardio.2626
75. Hamazaki N, Kamiya K, Matsuzawa R, Nozaki K, Ichikawa T, Tanaka S et al. Prevalence and prognosis of respiratory muscle weakness in heart failure patients with preserved ejection fraction. Respiratory Medicine. 2020;161:105834. DOI: 10.1016/j.rmed.2019.105834
76. Frankenstein L, Nelles M, Meyer FJ, Sigg C, Schellberg D, Remppis BA et al. Validity, prognostic value and optimal cutoff of respiratory muscle strength in patients with chronic heart failure changes with beta-blocker treatment. European Journal of Cardiovascular Prevention and Rehabilitation. 2009;16(4):424–9. DOI: 10.1097/HJR.0b013e3283030a7e
77. Arutyunov A.G., Ilyina K.V., Arutyunov G.P., Kolesnikova E.A., Pchelin V.V., Kulagina N.P. et al. Morphofunctional Features of The Diaphragm in Patients With Chronic Heart Failure. Kardiologiia. 2019;59(1):12–21. [Russian: Арутюнов А.Г., Ильина К.В., Арутюнов Г.П., Колесникова Е.А., Пчелин В.В., Кулагина Н.П. и др. Морфофункциональные особенности диафрагмы у больных с хронической сердечной недостаточностью. Кардиология. 2019;59(1):12-21]. DOI: 10.18087/cardio.2019.1.2625
78. Sokolova A.V., Dragunov D.O., Arutyunov G.P. The prevalence of sarcopenia in patients with chronic heart failure and chronic kidney disease. Clinical Nephrology. 2023;3:18–23. [Russian: Соколова А.В., Драгунов Д.О., Арутюнов Г.П. Распространенность саркопении у пациентов с хронической сердечной недостаточностью и хронической болезнью почек. Клиническая нефрология. 2023;3:18-23]. DOI: 10.18565/nephrology.2023.3.18-23
79. Yamada K, Kinugasa Y, Sota T, Miyagi M, Sugihara S, Kato M et al. Inspiratory Muscle Weakness Is Associated With Exercise Intolerance in Patients With Heart Failure With Preserved Ejection Fraction: A Preliminary Study. Journal of Cardiac Failure. 2016;22(1):38–47. DOI: 10.1016/j.cardfail.2015.10.010
80. Thomsen RW, Kasatpibal N, Riis A, Nørgaard M, Sørensen HT. The Impact of Pre-existing Heart Failure on Pneumonia Prognosis: Population-based Cohort Study. Journal of General Internal Medicine. 2008;23(9):1407–13. DOI: 10.1007/s11606-008-0672-3
81. Balmain BN, Tomlinson AR, MacNamara JP, Sarma S, Levine BD, Hynan LS et al. Physiological dead space during exercise in patients with heart failure with preserved ejection fraction. Journal of Applied Physiology. 2022;132(3):632–40. DOI: 10.1152/japplphysiol.00786.2021
82. Killian KJ, Jones NL. Respiratory muscles and dyspnea. Clinics in Chest Medicine. 1988;9(2):237–48. PMID: 3292125
83. Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M et al. ERS statement on respiratory muscle testing at rest and during exercise. European Respiratory Journal. 2019;53(6):1801214. DOI: 10.1183/13993003.01214-2018
84. Lee Y, Son S, Kim D-K, Park MW. Association of Diaphragm Thickness and Respiratory Muscle Strength With Indices of Sarcopenia. Annals of Rehabilitation Medicine. 2023;47(4):307–14. DOI: 10.5535/arm.23081
85. Mcelvaney G, Blackie S, Morrison NJ, Wilcox PG, Fairbarn MS, Pardy RI. Maximal Static Respiratory Pressures in the Normal Elderly. American Review of Respiratory Disease. 1989;139(1):277–81. DOI: 10.1164/ajrccm/139.1.277
86. Polkey MI, Moxham J. Clinical Aspects of Respiratory Muscle Dysfunction in the Critically Ill. CHEST. 2001;119(3):926–39. DOI: 10.1378/chest.119.3.926
87. Caruso P, Albuquerque ALPD, Santana PV, Cardenas LZ, Ferreira JG, Prina E et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. Jornal Brasileiro de Pneumologia. 2015;41(2):110–23. DOI: 10.1590/S1806-37132015000004474
88. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. The American Review of Respiratory Disease. 1969;99(5):696–702. DOI: 10.1164/arrd.1969.99.5.696
89. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax. 1984;39(7):535–8. DOI: 10.1136/thx.39.7.535
90. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. American Journal of Respiratory and Critical Care Medicine. 1994;149(2):430–8. DOI: 10.1164/ajrccm.149.2.8306041

91. Hautmann H, Hefele S, Schotten K, Huber RM. Maximal inspiratory mouth pressures (PIMAX) in healthy subjects – what is the lower limit of normal? Respiratory Medicine. 2000;94(7):689–93. DOI: 10.1053/rmed.2000.0802
92. Sachs MC, Enright PL, Hinckley Stukovsky KD, Jiang R, Barr RG, Multi-Ethnic Study of Atherosclerosis Lung Study. Performance of maximum inspiratory pressure tests and maximum inspiratory pressure reference equations for 4 race/ethnic groups. Respiratory Care. 2009;54(10):1321–8. PMID: 19796411
93. Sanchez FF, Araújo Da Silva CD, De Souza Pereira Gama Maciel MC, Rebouças Demósthenes Marques J, Brosina De Leon E, Lins Gonçalves R. Predictive equations for respiratory muscle strength by anthropometric variables. The Clinical Respiratory Journal. 2018;12(7):2292–9. DOI: 10.1111/crj.12908
94. Moeliono M, Marta Sari D, Nashrulloh T. Prediction for the maximum inspiratory pressure value from the thoracic expansion measurement in Indonesian healthy young adults. Canadian Journal of Respiratory Therapy. 2022;58:34–8. DOI: 10.29390/cjrt-2021-064
95. Lelyavina T.A., Sitnikova M.Yu., Galenko V.L., Bortsova M.A. Non-invasive method for detecting changes in the lactic acid content in the blood of patients with chronic heart failure using the treadmill test protocol with continuously increasing physical activity. Patent for the invention RU 2789272 C1 from 31.01.2023. Application No.2022102976A from 07.02.2022. Av. at: https://patents.google.com/patent/RU2789272C1/ru. [Russian: Лелявина Т.А., Ситникова М.Ю., Галенко В.Л., Борцова М.А. Неинвазивный способ выявления изменения содержания молочной кислоты в крови больных хронической сердечной недостаточностью при помощи протокола тредмил-теста с непрерывно возрастающей физической нагрузкой. Патент на изобретение RU 2789272 C1 от 31.01.2023. Заявка №2022102976A от 07.02.2022. Доступно на: https://patents.google.com/patent/RU2789272C1/ru]
96. Lelyavina T.A., Sitnikova M.Yu. Method for determining the biological reserves of the body's adaptation to physical activity. Patent for the invention RU 2574901 C1 from 10.02.2016. Application No. 2014139641/15 from 30.09.2014. Av. at: https://patenton.ru/patent/RU2574901C1?ysclid=lyjr58qcrc422915792. [Russian: Лелявина Т.А., Ситникова М.Ю. Способ определения биологических резервов адаптации организма к физической нагрузке. Патент на изобретение RU 2574901 C1 от 10.02.2016. Заявка № 2014139641/15 от 30.09.2014. Доступно на: https://patenton.ru/patent/RU2574901C1?ysclid=lyjr58qcrc422915792]

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

APPENDICES TO THE EXPERT OPINION

Appendix 1. Methodology for the 6-minute walk test (6MWT), adapted from [14]

The 6MWT protocol necessitates the provision of a corridor, defined as an area of flat hard surface, with a minimum length of 30 m and markings at intervals of 3 m.

In order to perform the 6MWT, the following are required: a countdown timer (or stopwatch), a mechanical/electronic lap counter, turn/U-turn point indicators, a chair that can be easily moved as one walks, an oxygen source, a sphygmomanometer, a phone, an automatic electronic defibrillator.

Patients must meet the following criteria.: Wear comfortable clothing and suitable footwear, use common walking aids, such as canes or walkers; have light meals in the early morning or afternoon. It is recommended that patients refrain from engaging in strenuous physical activity for two hours following the completion of the test.

To minimize intraday variability, repeat testing should be conducted at approximately the same time of day. The patient is required to sit quietly in a chair situated in close proximity to the starting point study for a minimum of ten minutes prior to the commencement of the test. During this period, the patient's clothing and footwear are evaluated, contraindications are identified, and vital signs, including pulse, blood pressure (BP), and oxygen saturation levels (if necessary), are assessed.

At the outset of the test, the patient's level of dyspnea and general fatigue are evaluated using the Borg scale, after which the patient is provided with instructions. Throughout the course of the test, the patient's condition is observed, and the remaining time is communicated to the patient.

IMPORTANT! The 6MWT may be discontinued immediately in the event of the occurrence of any of the following: chest discomfort, severe dyspnea, leg cramps, unsteady gait, dizziness, perspiration, and pallor.

At the end of the 6MWT, heart rate, BP, oxygen saturation, subjective perception of exertion using the Borg scale, and severity of dyspnea using the modified Borg scale are also assessed. The number of stops and the reasons for stopping the test are also recorded. Any deviations from the protocol can significantly affect the results, especially when evaluating the efficacy of treatment or rehabilitation interventions, comparing data from other studies or data from other sites.

Appendix 2. The most common treadmill cardiopulmonary exercise testing (CPET) protocols

Table. Common treadmill cardiopulmonary exercise testing (CPET) protocols

Step	Speed (km/h)	Incline angle	Duration of the step (min)	Duration (min)	MET	Target group
Protocol 1. R. Bruce						
1	2.7	10.0	3	3	4,1	For patients with presumed high exercise tolerance. Commonly used in healthy individuals and patients under the age of 75 years in the absence of significant comorbidities and contraindications to stress testing.
2	4	12.0	3	6	7	
3	5.4	14.0	3	9	10	
4	6.7	16.0	3	12	13	
5	8.0	18.0	3	15	15	
6	9	20.0	3	18	18	
7	9	22.0	3	21	21	

Step	Speed (km/h)	Incline angle	Duration of the step (min)	Duration (min)	MET	Target group
Modified protocol. R. Bruce (MOD BRUCE)						
1	2.7	0.0	3	3	2.2	Patients with CHF and presumed low exercise tolerance
2	2.7	5.0	3	6	3.1	
3	2.7	10.0	3	9	4.1	
4	4.0	12.0	3	12	7	
5	5.4	14.0	3	15	10	
6	6.7	16.0	3	18	13	
7	8.0	18.0	3	21	15	
Protocol 2. Cornell						
1	2.7	0.0	2	2	2	
2	2.7	5.0	2	4	3	
3	2.7	10.0	2	6	5	
4	3.3	11.0	2	8	6	
5	4.4	12.0	2	10	7	
6	4.8	13.0	2	12	8	
7	5.4	14.0	2	14	10	
8	6.1	15.0	2	16	11	
9	6.7	16.0	2	18	13	
10	7.4	17.0	2	20	14	
11	8.0	18.0	2	22	15	
12	8.0	19.0	2	24	17	
Protocol 3. J. Naughton						
1	1.6	0.0	2	2	1.8	Frequently used in patients with CHF and other patients with very low exercise tolerance. Also commonly utilized for the prescription and monitoring of cardiac rehabilitation
2	3.2	0.0	2	4	2.5	
3	3.2	3.5	2	6	3.4	
4	3.2	7.0	2	8	4.4	
5	3.2	10.5	2	10	5.4	
6	3.2	14.0	2	12	6.4	
7	3.2	17.5	2	14	7.3	
8	3.2	19.0	2	16	8.0	
9	3.2	20.0	2	18	9.1	
10	3.2	22.5	2	20	10.1	
Protocol 4. B. Balke						
1	4.8	2.0	2	1	4	Patients with CHF and presumed low exercise tolerance
2	4.8	4.0	2	2	5	
3	4.8	6.0	2	3	6	
4	4.8	8.0	2	4	7	
5	4.8	10.0	2	5	8	
6	4.8	12.0	2	6	9	
7	4.8	14.0	2	7	10	
8	4.8	16.0	2	8	11	
9	4.8	18.0	2	9	12	
10	4.8	20.0	2	10	13	
11	4.8	22	2	11	14	
12	4.8	24	2	12	15	

Step	Speed (km/h)	Incline angle	Duration of the step (min)	Duration (min)	MET	Target group
Protocol 5. A stress protocol comprising a gradual increase in the intensity of physical exertion [95]						
Rest	0	0	2	2	0	Patients with CHF and presumed low exercise tolerance
1	1.2	0.5	15 sec	2:15	1-2.2	
2	1.4	0.5	15 sec	2:30		
3	1.6	1	15 sec	2:45		
4	1.8	1	15 sec	3		
5	2.0	1.5	15 sec	3:15		
6	2.2	1.5	15 sec	3:30		
7	2.4	1.5	15 sec	3:45		
8	2.6	1.5	15 sec	4 min		
9	2.8	2	15 sec	4:15	2.3-3.7	
10	3.0	2	15 sec	4:30		
11	3.2	2	15 sec	4:45		
12	3.4	2	15 sec	5		
13	3.6	2	15 sec	5:15		
14	3.8	2	15 sec	5:30		
15	4.0	2.5	15 sec	5:45		
16	4.2	2.5	15 sec	6		
17	4.4	2.5	15 sec	6:15	3.8-5.4	
18	4.6	3	15 sec	6:30		
19	4.8	3	15 sec	6:45		
20	5.0	3.5	15 sec	7		
21	5.2	4	15 sec	7:15		
22	5.4	4.5	15 sec	7:30		
23	5.6	5	15 sec	7:45		
24	5.8	5.5	15 sec	8		
25	6	6	15 sec	8:15	5.5-7.4	
26	6.2	6	15 sec	8:30		
27	6.4	6.5	15 sec	8:45		
28	6.6	6.5	15 sec	9		
29	6.6	7	15 sec	9:15		
30	6.6	7.5	15 sec	9:30		
31	6.8	7.5	15 sec	9:45		
32	7	7.5	15 sec	10		
33	7	8	15 sec	10:15		
34	7.2	8	15 sec	10:30	7.5-10.0	
35	7.4	8.5	15 sec	10:45		
36	7.6	9	15 sec	11		
37	7.6	9.5	15 sec	11:15		
38	7.8	10	15 sec	11:30		
39	8	10.5	15 sec	11:45		
40	8.2	11	15 sec	12:00		
41	8.4	11.5	15 sec	12:15		
42	8.6	12	15 sec	12:30		
43	8.8	12.5	15 sec	12:45	10.1-14	
44	9	13	15 sec	13		
45	9.2	13.5	15 sec	13:15		
46	9.4	14	15 sec	13:30		
47	9.6	14	15 sec	13:45		
48	9.8	14	15 sec	14		
49	9.8	14	15 sec	14:15		

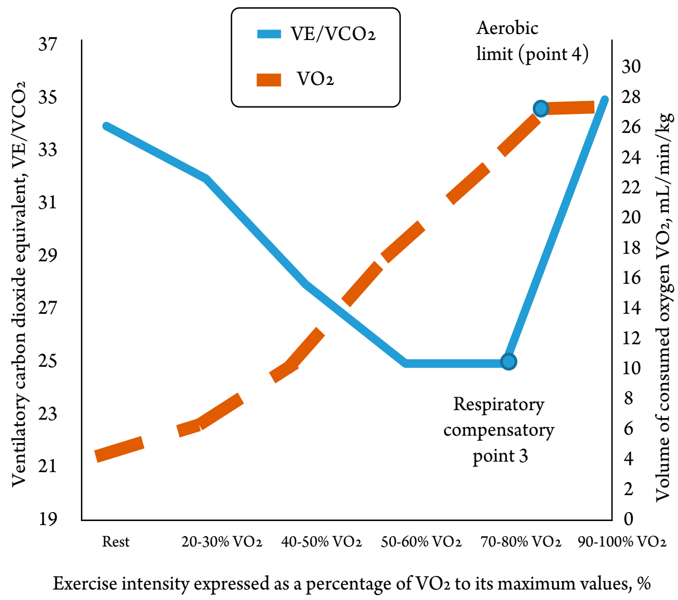
ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637

Appendix 3.
Determination of lactate threshold [96]

Point 3 corresponds to the beginning of the increase in ventilatory carbon dioxide equivalent (VE/VCO_2) – a respiratory compensatory point; Point 4 corresponds to the moment of exercise when aerobic metabolism has reached its limit and additional increase in energy production by aerobic way is further impossible – an aerobic limit; CHF, chronic heart failure; VO_2, volume of oxygen consumption; X-axis, exercise intensity expressed as a VO_2 percentage of its maximum values. VO_2 increases linearly as exercise intensity increases until a certain point, which is known as the aerobic limit or VO_2 plateau. Moreover, despite an increase in exercise intensity, there is only a minimal increase in VO_2 (see Figure).

VO_2 plateau is: 1) An indication that the cardiovascular and respiratory systems have reached their maximal capacity to deliver oxygen (O_2), as well as the limit of the working muscle mitochondria's capacity to utilize O_2; 2) An indication that the increase in energy production by aerobic means is no longer possible, and that the increase in exercise intensity from this point on is provided by additional intensification of anaerobic metabolism. Accordingly, four stages of compensatory adaptive reactions of the organism in response to exercise with increasing intensity can be distinguished in healthy individuals and patients with CHF: lactate threshold, pH threshold, respiratory compensatory point, and aerobic threshold [50, 52].

Figure. Characteristic changes in the volume of consumed oxygen (VO_2), ventilatory CO_2 equivalent (VE/VCO_2) during continuously increasing exercise load



Appendices 4.
Table of conversion of distances for the 6-minute walk test (6MWT) [14]

Table. Conversion of distances for the 6-minute walk test (6MWT)

Distance (m)	km/h	m/min	VO_2 (mL/kg/min)	METs	W
<150	<1.5	<25	<6	<1.7	<29
152	1.51	25	6.04	1.73	30
155	1.55	26	6.09	1.74	
159	1.58	26	6.14	1.75	
162	1.61	27	6.19	1.77	31
165	1.64	27	6.24	1.78	
168	1.67	28	6.29	1.80	
171	1.71	28	6.35	1.81	32
174	1.74	29	6.39	1.83	
177	1.77	29	6.45	1.84	
180	1.79	30	6.50	1.86	33
183	1.82	30	6.55	1.87	
186	1.85	31	6.59	1.89	
189	1.88	32	6.65	1.90	34
192	1.92	32	6.70	1.91	
195	1.95	33	6.75	1.93	
198	1.98	33	6.80	1.94	35
201	2.01	34	6.85	1.96	
204	2.04	34	6.90	1.97	
207	2.06	35	6.95	1.99	36
210	2.09	35	7.00	2.00	
213	2.13	36	7.06	2.02	
216	2.16	36	7.11	2.03	37
219	2.19	37	7.16	2.05	
223	2.22	37	7.21	2.06	
226	2.25	38	7.26	2.07	38
229	2.29	38	7.31	2.09	
232	2.32	39	7.36	2.10	
235	2.33	39	7.41	2.12	39
238	2.37	40	7.46	2.13	
241	2.40	40	7.51	2.15	
244	2.43	41	7.56	2.16	40

Distance (m)	km/h	m/min	VO_2 (mL/kg/min)	METs	W
247	2.46	41	7.62	2.18	
250	2.50	42	7.67	2.19	
253	2.53	42	7.72	2.20	41
256	2.56	43	7.77	2.22	
259	2.59	43	7.82	2.23	
262	2.61	44	7.87	2.25	42
265	2.64	44	7.92	2.26	
268	2.67	45	7.97	2.28	
271	2.70	45	8.02	2.29	43
274	2.74	46	8.07	2.31	
277	2.77	46	8.12	2.32	
280	2.80	47	8.17	2.34	44
283	2.83	47	8.22	2.35	
287	2.87	48	8.28	2.36	

Distance (m)	km/h	m/min	VO_2 (mL/kg/min)	METs	W
290	2.88	48	8.33	2.38	45
293	2.91	49	8.38	2.39	
296	2.95	49	8.43	2.41	
299	2.98	50	8.47	2.42	46
302	3.01	50	8.52	2.44	
305	3.04	51	8.58	2.45	47
335	3.35	56	9.08	2.60	
366	3.64	61	9.59	2.74	48
396	3.94	66	10.10	2.89	50
427	4.25	71	10.61	3.03	53
457	4.56	76	11.12	3.18	56
488	4.86	81	11.62	3.32	59
518	5.17	86	12.13	3.47	62
>551	>5.47	>91	>12.64	>3.61	>65

Appendices 5. Investigation of ergoreflex activity

The investigation is conducted with the use of specialized ergospirometric equipment. The standardized technique, as described by Piepolli et al. (1996), provides post-load regional circulatory occlusion. Prior to the test, the maximum hand grip force is evaluated through the utilization of a dynamometer. The test is conducted with the subject gripping the dynamometer with a force of 50% of the maximum force.

Two stress tests are conducted with a 60-minute interval of rest between each test:

The control test entails repeated gripping of the dynamometer with a force of 50% of the maximum for a period of three minutes. The patient is provided with a visual representation of the compression force curve, which serves to maintain an appropriate level of force.

The occlusion test is conducted after 30 minutes of rest. The same protocol is repeated, but 10 seconds before cessation of exercise, a cuff is placed on the forearm for 1 minute and inflated to a pressure 30 mm Hg higher than the maximum pressure achieved during the control test.

During the test, a 12-channel ECG is recorded, and the following parameters are measured: diastolic blood pressure (DBP), minute ventilation volume, and gas exchange.

The quantification of ergoreceptor sensitivity is determined by the percentage of the respiratory and hemodynamic response to stress that is maintained by circulatory occlusion during the third minute of the test, in comparison to the third minute of recovery during the control test. The sensitivity of ergoreceptors can be calculated using the following formula:

$$[(\text{Recovery}/\text{Stress}) + \text{RCO} - (\text{Recovery}/\text{Stress}) - \text{RCO}] * 100,$$

Stress is defined as minute ventilation volume (or diastolic blood pressure or volume of carbon dioxide excreted) averaged over the last 30 seconds of exercise; Recovery is defined as minute ventilation volume averaged over the past 30 seconds of the third minute of recovery; RCO is regional circulatory occlusion.

ISSN 0022-9040. Kardiologiia. 2024;64(7). DOI: 10.18087/cardio.2024.7.n2637