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COMPREHENSIVE NON-INVASIVE EVALUATION OF THE FUNCTIONAL STATUS OF PATIENTS WITH CHRONIC HEART FAILURE

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The emergence of new groups of medications used in the treatment of chronic heart failure (CHF) has made it possible to optimize treatment regimens, changing the clinical status and prognosis in this patient cohort. In this regard, the relevance of individual prognostic markers and risk assessment scales for heart failure (HF) is losing its value. The aim of our review is to summarize the currently available evidence on modern methods of evaluating the functional capabilities of the body and exercise tolerance in CHF patients on the background of systolic dysfunction before heart transplantation.

Keywords: heart failure, heart transplantation, cardiopulmonary exercise test, 6-minute walk test, atrial natriuretic peptide, asthenia, waiting list.

With the increasing number of chronic heart failure (CHF) cases [1, 2], timely detection of the moment the disease transits from stable to end stage is crucial for the choice of further treatment tactics and assessment of survival prognosis in this category of patients [3]. To date, various prognostic risk scales have been developed and used in assessing CHF patients [4, 5]. However, statistics has shown that doctors are reluctant to use them in their daily practice, and the scales themselves do not provide complete information on patient survival prognosis [6, 7].

The previously developed Heart Failure Survival Score (HFSS), which was widely used in selection of patients for inclusion in the heart transplant waiting list, is now losing its relevance due to the emergence of new approaches to drug therapy in CHF patients [8]. Today, quadruple therapy is the gold standard treatment for patients with reduced left ventricular ejection fraction (LVEF). The concept of quad therapy includes the use of a combination of the following drug groups: beta-blockers, sodium-glucose co-transporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists, and renin-angiotensin-aldosterone system (RAAS) inhibitors. Large, randomized studies have shown that quadruple therapy significantly reduces the frequency of hospitalizations for decompensated HF and improved the survival prognosis in this patient cohort [9].

Although heart transplantation (HT) remains the only effective curative treatment for end-stage CHF and the waitlist criteria have expanded significantly in recent decades, organ shortages do not fully meet the need for curative treatment of patients with end-stage HF [10]. In this regard, there is a need to develop new approaches for assessing CHF severity and a personalized approach for choosing further treatment tactics.

The aim of our review was to summarize the currently available data regarding modern methods of assessing the functional capacity of the body and exercise tolerance in CHF patients.

Self-assessment of physical condition by the patient and/or by the treating physician depends mainly on what the patient perceives as limitations in their daily activities. The currently widely used New York Heart Association (NYHA) functional classification (FC) allows HF severity to be determined based on patient's complaints (Table 1).

However, this classification is based solely on symptoms and does not include prognostic indicators derived from various functional tests; therefore, it cannot serve as a reliable predictor of adverse events in CHF patients [11–13].

It is important to note that patients with mild symptoms of CHF may have poor survival prognosis despite the apparent perceived well-being of the condition [14].

Cardiopulmonary exercise testing (CPET) remains the gold standard and established tool for assessing the functional capacity in HF. CPET measures variables such as volume of oxygen consumed by the body (VO_2), volume of carbon dioxide produced by the body (VCO_2) and pulmonary ventilation (PV) at rest and during exercise.

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During exercise, the human body can be visualized as an integrated system that provides oxygen (O_2) delivery to the mitochondria for aerobic exercise [15–17]. Oxygen delivery depends on interaction between components of the electron transport chain and its adequate release in working muscles. Table 2 summarizes the main variables obtained during testing, which need further interpretation.

The main parameters derived from CPET

Respiratory exchange ratio (RER) is the ratio between peak VCO_2 production and peak VO_2 consumption. RER values of 1.05–1.15 indicate achievement of a maximal exercise effort in CPET [18].

Workload is the maximum workload a patient can perform during a CPET session. It is measured in watts. Maximum workload >90% predicted indicates that the patient has a high exercise tolerance [19].

Maximum heart rate. CPET is considered complete when the patient reaches a heart rate (HR) ≥90% of the predicted maximum HR, depending on the patient's age. It should be noted that patients under chronotropic medications are not sometimes capable of meeting this criterion. In this case, a maximal exercise may be completed as it is indicated by the interpretation of RER and workload [20].

Peak oxygen consumption (Peak VO_2) is the most important parameter derived from a CPET and at the same time is the gold standard to objectively assess functional limitations in HF patients [21]. Peak VO_2 can be reported as an absolute value (mL/min) or indexed by body weight (mL/min/kg) or as a percentage of predicted value (%) normalized to sex, age, height, and weight measurement [22, 23].

To date, a peak VO_2 <14 mL/kg/min is one of the risk factors for adverse cardiovascular events [24]. Heart transplant guidelines report that HF patients with peak VO_2 ≥12 mL/min/kg (while taking beta-blockers (BB)) or ≥14 mL/kg/min (while discontinuing BB 24 hours before testing) may be safely assigned UNOS status 7 [25, 26].

Anaerobic threshold (AT) gives an idea of exercise tolerance under aerobic conditions. The point of anaerobic metabolism initiation (submaximal exercise) is determined using concentrations of inhaled oxygen and released carbon dioxide during a CPET session [27, 28].

So, CPET is currently the most comprehensive technique for evaluating patients with cardiopulmonary diseases. It may provide supporting information for differential diagnosis in the presence of symptoms such as shortness of breath and poor exercise tolerance between cardiac and respiratory failure and/or physical detraining of the patient. The disadvantages of this method are the need for specialized equipment, training of personnel, and the very high cost of the method itself, which is associated with limited accessibility in most hospitals, as well as the inability of some patients to perform this test due to the severity of their clinical condition. Where CPET cannot be performed, the 6-minute walk test (6MWT) is a simple, inexpensive test that can be performed for risk stratification in CHF patients [29–31].

The 6MWT is a simple test that does not require special equipment and special training of physicians. This test allows assessing the submaximal level of a patient's functional capacity, while walking on a flat hard surface for 6 minutes [32]. Inability to assess the reactions of all organs and systems involved during this test, as in the case of CPET, constitutes a disadvantage [33].

Despite the significant correlation between 6MWT and peak VO_2, this test cannot be considered as an al-

Table 1

New York Heart Association Functional Classification

FC I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath
FC II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain
FC III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain
FC IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort

Table 2

CPET data

Parameters	Expected values at peak exercise
Exercise	
Duration (minutes)	8–12
Workload (% of predicted)	>80
RER	>1.15
Hemodynamic parameters	
Systolic blood pressure (mmHg)	<220
Cardiac cycle (% of predicted HR)	>90
Metabolic indicators	
Peak VO_2 (% of predicted peak VO_2)	>84
Anaerobic threshold (% of predicted VO_2)	>40
Pulse O_2 (%)	>80
VO_2/work (mL/min/W)	9–11
Ventilation	
Respiratory rate (breaths/min)	<60
$PETCO_2$ at baseline (mmHg)	>33
$PETCO_2$ at anaerobic threshold (mmHg) vs. baseline	>3–6
O_2 desaturation (%)	<4
Prognostic	
VE/VCO_2 slope	<34
O_2 recovery slope	>650

ternative to CPET, as the results obtained are not a reliable predictor of changes in peak VO_2 in CHF patients [34–36].

Previous studies have shown that there is an inverse correlation between NYHA FC II–IV and the 6-minute walk distance (6MWD) [37–39]. Table 3 shows the correlation between physical activity parameters assessed via 6MWT, peak VO_2 by CPET and NYHA FC [40].

Several studies have shown that in CHF patients being evaluated for transplantation, a 6MWD <350 meters has a sensitivity of 71% and specificity of 60% for predicting peak VO_2 <14 ml/kg/min during a CPET session [41, 42].

Thus, 6MWT can be used as an alternative to measure the functional status of patients with HF and comorbid pathology, such as chronic obstructive pulmonary disease, when exercise testing is not feasible [43–47].

Modern biomarkers for assessing the severity of CHF and predicting the course of the disease include natriuretic peptides [48, 49].

Recent guidelines from the European Society of Cardiology (ESC) on diagnosis and treatment of heart failure [50] and the American Heart Association (AHA) [51] include brain B-type natriuretic peptide (BNP) and its precursor N-terminal pro b-type natriuretic peptide (NT-proBNP) were included as mandatory markers in HF diagnosis.

Determination of other diagnostic biomarkers, such as inflammatory marker ST2, oxidative stress marker – growth-differentiation factor-15 (GDF-15) – and cardiac remodeling marker – galectin-3 – may be useful in prescribing therapy aimed at HF treatment but are not mandatory in making this diagnosis [51].

In their work, Hogenhuis et al. analyzed a number of indicators of 229 patients who had been admitted for decompensated CHF at the time of hospital discharge. The following parameters were included in the analysis: BNP level 6MWD, LVEF, and NYHA FC. The authors revealed that BNP shows weak correlation to LVEF ($r = –0.29$, $P < 0.01$) and NYHA ($r = 0.20$, $P < 0.01$). There is also no correlation between BNP and 6MWT ($r = –0.01$, $P = 0.87$). Thus, the authors concluded that BNP level reflects the state of cardiac function to a greater extent, whereas 6MWD reflects the functional capacity of the body, and these two indicators represent different aspects of the clinical syndrome of CHF [52].

Table 3

Exercise and oxygen consumption in patients with different functional classes of CHF

NYHA FC	6MWD (m)	Peak VO_2 (mL/min/m^2)
0	>551	>22.1
I	426–550	18.1–22.0
II	301–425	14.1–18.0
III	151–300	10.1–14.0
IV	<150	<10.0

In contrast, a study by Norman et al. conducted a correlation analysis to assess the relationship between BNP levels and peak VO_2 during CPET and LVEF in 22 subjects with compensated HF. The results suggested that plasma BNP levels may be a useful clinical measure for evaluating both global functional capacity and myocardial specific work capacity in individuals with HF [53].

In their study, Kato et al. evaluated peak VO_2 in combination with BNP in 424 potential recipients examined before HT. All patients were divided into three groups depending on peak VO_2. The first, second and third groups included 167, 146, and 111 patients, respectively. Peak VO_2 was >14 mL/min/kg in group 1, 10 to 14 mL/min/kg and <10 mL/min/kg in groups 2 and 3, respectively. The comparison group included 743 recipients after de novo HT. Multivariable analysis revealed that high BNP and low peak VO_2 were independently associated with death, HT, or ventricular assist device (VAD) systems (hazard ratio, 3.5 and 0.6; 95% CI, 1.24–9.23 and 0.03–0.71; $P = 0.02$ and <0.0001, respectively). One-year survival without VAD or without HT in patients with peak VO_2 between 10 and 14 mL/min/kg was comparable to one-year survival after HT. Given these findings, the authors divided the second group into two subgroups based on those with BNP ≥506 pg/mL and those with <506 pg/mL. One-year survival of patients with HF and low BNP levels was comparable to post-HT survival (1 year: 90.8% versus 87.2%; $P = 0.61$), whereas those with BNP ≥506 showed worse VAD-free or HT-free survival (1 year: 79.7%; $P < 0.001$ versus post-HT). It was concluded that a comprehensive evaluation of peak VO_2 during exercise in combination with BNP levels can determine the optimal time frame for inclusion of patients on the HT waiting list [54].

Shyh-Ming Chen et al. analyzed the survival of 377 patients hospitalized for decompensated HF and showed that the risk of adverse events at two years in patients with peak VO_2 of 10.2 mL/kg/min on optimal medical therapy was 20% for the entire cohort of patients. Based on these data, the authors proposed a scheme of an optimized strategy for predicting adverse events, determining the timing and indications for inclusion on the waiting list for HT or continuation of therapy for CHF (Fig. 1) [55].

Current clinical guidelines for the management of HF patients suggest that peak VO_2 obtained during CPET should be used as one of the criteria for determining whether a patient should be listed for HT. In the 1990s, Mancini et al. showed that peak VO_2 of 14.0 mL/kg/min is an indication for inclusion of patients in the HT waitlist [56]. In the 2000s, against the background of the beginning of widespread use of beta-blockers in CHF therapy, the threshold value was reduced to 12.0 mL/kg/min [57]. Recently, due to better survival prognosis

on the background of quad therapy application, the prognostic threshold was reduced to 10.2 mL/kg/min [58].

Recently, increasing importance has been attached to the frailty score in assessing the prognosis of CHF patients and in selecting patients for HT and/or mechanical circulatory support [59, 60].

Yasbanoo Moayedi et al. evaluated the prognostic significance and impact on survival prognosis of frailty in combination with peak VO_2 as a prognostic indicator for assessing the severity of heart failure. Frailty was assessed using modified criteria according to the Fried Frailty Phenotype (FFP) scale. The results were interpreted as frail, prefrail and nonfrail. The study included 201 HF patients. The median follow-up was 17.5 months (11 to 29.2 months). During the follow-up period, overall mortality was 25 patients (12.4%). One-year survival among patients with frail, prefrail and nonfrail were 78%, 94%, and 100%, respectively. Thus, the authors showed that frailty was associated with a twofold increased risk of death (HR 2.01, $P < 0.0001$, 95% CI 1.42–2.84). In a comparative analysis of the effect of this syndrome in combination with peak VO_2 on survival prognosis, it was shown that peak VO_2 <12 mL/kg/min, in combination with frailty, was associated with increased risk of mortality compared with patients with VO_2 >12 mL/kg/min (HR 1.72, $P = 0.006$). It was concluded that the severity of generalized weakness syndrome is one of the risk factors for poor prognosis of 1-year survival in patients with low peak VO_2 [61].

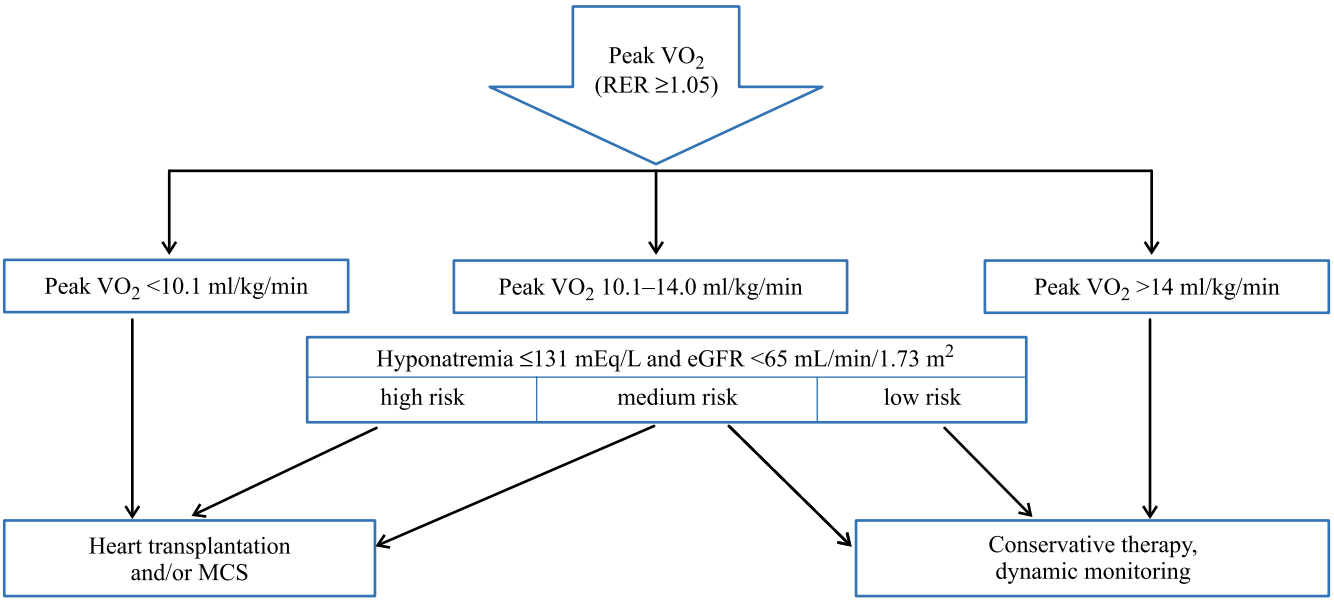

Fig. 1. Optimized strategy for predicting adverse events, timing, and indications for heart transplantation. eGFR, estimated glomerular filtration rate; RER, respiratory exchange ratio; MCS, mechanical circulatory support

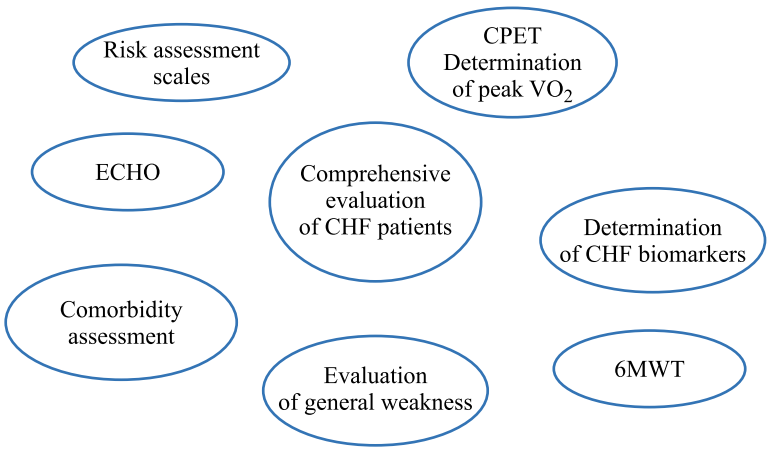

Fig. 2. Comprehensive non-invasive evaluation of the functional status of patients with chronic heart failure resulting from systolic dysfunction before heart transplantation. CHF, chronic heart failure; 6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test; ECHO, echocardiography

CONCLUSION

Today, there are a number of methods for assessing CHF severity. They allow a comprehensive assessment of the patient, determine the survival prognosis, as well as indications for continuation of drug therapy or the need for surgical treatment of the end-stage CHF, which involves resynchronization therapy, implantation of long-term mechanical circulatory support systems and/or heart transplantation. The prognostic risk assessment model for CHF patients is multiparametric, including many variables obtained during clinical and instrumental examination of the patient. However, the relevance of individual prognostic markers may vary depending on the severity of CHF symptoms and the presence of comorbidities.

Fig. 2 schematically shows the main parameters for assessing the prognosis and planning of further tactics, which, in our opinion, are widely available in the practice of medical institutions.

So, a personalized approach to choosing further treatment tactics for CHF patients largely depends on the survival prognosis for a particular patient. Predicting the future of a patient with heart failure is not a perfect science, but a quantitative assessment of risk factors, which is the beginning of choosing a treatment tactic.

The authors declare no conflict of interest.

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