Srce i krvni sudovi 2022; 41(4): 190-193

Review article

Clinical application of cardiopulmonary exercise stress test for the recommendations for physical activity in patients with chronic heart failure

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Abstract Physical activity (PA) according to current guidelines is an important adjunctive therapy for patients with chronic heart failure (CHF) with reduced and preserved ejection fraction (HFrEF and HFpEF) which is level of evidence class 1A. However, as with any therapy, PA must be dosed according to the patient's own characteristics, so an individual assessment and prescription of exercise intensity is necessary. Different types of PA (endurance and resistance) and intensity levels (mild, mild to moderate, and high to moderate) are used in programs in patients with CHF.

The assessment can be carried out through indirect (heart rate reserve) or direct metabolic measures (VO2 reserve, anaerobic threshold) where precision is ensured by direct assessment of VO2 kinetics at constant work speed protocols of various loads - ergospirometry. Ergospirometry enables a direct assessment of the occurrence of anaerobic metabolism and real fatigue of the patient towards the limits of his position under different loads. In addition, the effect of exercise can be monitored on the basis of control tests. In this way, evidence-based efforts are prevented that a person with CHF cannot sustain or that would not lead to progress and improvement in symptoms and effort tolerance. Also, it enables a gradual increase in intensity and further progress in exercise.

Key words chronic heart failure, cardiopulmonary exercise test, functional capacity, anaerobic threshold, oxygen consumption, training prescription

Exercise is a key element in the prevention and treatment of cardiovascular diseases (CVD), and leads to improved quality of life, mortality, disability and prevention of comorbidities. Therefore, regular physical activity (PA) with at least 150 minutes of moderate-intensity aerobic exercise or at least 75 minutes of high-intensity exercise per week is recommended, with additional health benefits as minutes per week increase[1].

According to the current guidelines, PA is also adjunctive therapy for patients with chronic heart failure (CHF) with reduced and preserved ejection fraction (HFrEF and HFpEF), which is the level of evidence class 1A. However, like any therapy, it must be dosed according to the CHF severitiy and the capabilities of the patient himself, so individual assessment and prescription of exercise intensity is necessary. Different types of PA (endurance and resistance) and intensity levels (mild, mild to moderate, and moderate to high) are used in programs in patients with CHF[1-5].

For the objective assessment and determination of functional capacity, the gold standard is cardiopulmonary exercise test- ergospirometry (CPET)[6]. On the basis of CPET, patients with CHF are precisely stratified, which is the starting point for prescribing PA and monitoring the effects of exercise (Table 1).

CPET-based parameters for the assessment of the degree of CHF

Improvement in functional capacity is the most immediate and objective result of an effective training program for patients with CHF. [6,7.]

Peak oxygen consumption - maximum functional capacity (PeakVO$_2$)[7]. VO2max is a parameter that describes the maximum amount of energy that can be produced from aerobic metabolism in a unit of time (aerobic power). Normal values of VO2max depend on age, sex, and are influenced by body weight, level of physical activity and genetic predisposition. In patients it is represented as a

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Table 1. Prognostic and diagnostic stratification of patients with heart failure[9]

PRIMARY PARAMETERS CPET			
VE/VCO_2 slope	$PeakVO^2$	EOV	$PetCO_2$
Ventilatory class I VE/VCO_2 slope <30	Weber class A $PeakVO_2$ >20 ml/kg/min	Bez EOV	$PetCO_2$ at rest ≥33 mmHg Increase 3-8mmHg during CPET
Ventilatory class II VE/VCO_2 slope = 30-35.9	Weber class B Peak VO_2= 16-20 ml/kg/min		
Ventilatory class III VE/CO_2 slope = 36-44.9	Weber class C $PeakVO_2$= 10 – 15.9 ml/kg/min	Sa EOV	$PetCO_2$ at rest < 33 mmHg <3mmHg increase during CPET
Ventilatory class IV VE/VCO_2 slope ≥ 45.0	Weber class D $PeakVO_2$ < 10 ml/kg/min		
Standardni paremetri testa fizičkim opterećenjem			
Hemodynamic	EKG		Oporavak srčane frekvence
Normal increase in SBP during CPET	Without rhythm disturbances; No ST segment changes during the test		>12 bpm at 1 min recovery
Poor response of SBP during CPET	Rhythm disorders; ST-segment changes not due to test termination		≤ 12 bpm at 1 min recovery
SBP drop during CPET	Arrhythmias and/or ST-segment changes that are the reason for stopping the test		
Subjective reasons for stopping the test			
Leg fatigue	Angina		Dyspnea

Interpretation of CPET
• Green color: excellent prognosis in the next 1-4 years (≥90% event-free survival)
- Optimal drug therapy and control test for 4 years.
• A greater number of CPET parameters and standard TFO red/yellow/orange indicates a progressively poor prognosis.
– All CPET parameters in red: risk for fatal outcome extremely high in the next 1-4 years (>50%)
• A greater number of parameters of CPET and standard TFO red/yellow/orange indicate an increase in the degree of heart failure
– All CPET parameters in red: significantly low cardiac output, elevated neurohormones, high potential for secondary pulmonary hypotension are expected.
• A greater number of parameters of CPET and standard TFO red/yellow/orange indicates a progressively poor prognosis and warns to consider more aggressive treatment and the option of surgical treatment

VE/VCO_2, ratio of minute ventilation vs carbon dioxide production; VO_2, oxygen consumption; EOV, oscillatory ventilation; PETCO2, partial pressure of end-tidal CO_2; SBP, systolic blood pressure; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; TFO, physical load test; HRR, heart rate recovery; RER, respiratory gas exchange index.

$peakVO_2$ as a maximal achieved valueof VO2 during the test. Pathological disturbance of the response of minute volume to physical load leads to a reduction of peakVO2 in relation to predicted values of VO2max.

Anaerobic threshold (VAT)[8]. When the metabolic needs during the exercise exceed the supply of oxygen to the working musculature, anaerobic metabolism is activated, which is also confirmed by the increase in lactate concentration. The ventilatory anaerobic threshold (VAT) is revealed by the metabolic increase in VCO_2 and VE in relation to VO_2. Usually, VAT occurs between 47% and 64% of predicted VO_2max of untrained healthy individuals and increases with training. VAT is the most important parameter in prescribing training and rehabilitation in patients with CHF because VO2 at AT indicates the ability to perform submaximal effort and daily activities, but also the degree of fitness and decreases with deconditioning. The effort up to the anaerobic threshold is a mild effort, defining the limit of mild and moderate effort for that patient (50-60% of peak VO_2), and the second anaerobic threshold (at the moment of intensive hyperventilation) is the limit of moderate to high intensity (60-80% of peak VO_2).

Work efficiency[7]. During symptom-limited exercise, the increase in VO2 is linearly related to the incremental workload (expressed in Watt/min) accurately reflecting the degree of aerobically regenerated adenosine triphosphate (ATP) and is called work efficiency. Under physiological conditions, the linearity of VO2 corresponds to an increase of 10 ml/min per watt, regardless of the load imposed and changes slightly depending on the duration of exercise. In addition, the change in VO2 intensity at the anaerobic threshold is monitored in terms of increasing the capacity for greater efforts and increasing peakVO2. In patients with CHF, this parameter is reduced depending on the severity of the disease, because the load is not accompanied by an increase in cardiac output, which results in the appearance of dyspnea, fatigue and exercise intolernce. In addition, the ECG and hemodynamic response are monitored during the test, so that in addition to symptoms, the symptomatic drop in pressure and the appearance of arrhythmias during exertion have prognostic significance.

Ventilatory efficiency (ventilation to CO_2 elimination ratio - VE/VCO_2 slope)[7] This parameter is perhaps the most important unique characteristic of CPET as the objective assessment of the ventilatory status - the ability of adequate ventilation and CO2 elimination. In the presence of pulmonary hypertension of varying degrees, this parameter is abnormal which allows the stratification. Improvement can be registered by reducing VE/VCO2slope in as the sign of improving ventilatory gas exchange. The mechanisms involved in this beneficial effect may be multifactorial, including modulating activity on chemoreflex sensitivity and improved perfusion of lung microvessels.

Table 2. Level of exercise intensity based on CPET[6]

Intensity	$\%VO_2$peak	$\%HR_{max}$	HRR	RPE scale	Trening zone
Low	<40	<55	<40	10-11	aerobic
Mild	40-60	55-74	40-69	12-13	aerobic
Moderate to high	70-85	75-90	70-85	14-16	aerobic -lactates
Very high	>85	>90	>85	17-19	Aerobna-anaerobic

HR_{max} = maximum pulse frequency; HRR = heart rate reserve; RPE = subjective feeling of exertion; VO_2peak = peak oxygen consumption.

Oscillatory ventilation (EOV)[7]. Another important parameter in stratification is oscillatory ventilation, a phenomenon characterized by cyclical fluctuation of ventilation and expired gas kinetics, which occurs in approximately 20-30% of patients with HF. When it is present, it is a sign of a worse prognosis. The proposed etiology includes prolonged circulation time with the absence of an adequate increase in cardiac output during exertion, causing a delay in circulation time and a decrease in chemoreflex sensitivity to blood gases. Studies have shown that physical activity has a better effect on improving EOV compared to drug therapy, suggesting that EOV is a phenomenon that may not respond to standard CHF therapy.

Determination of exercise intensity in CHF

The methodology for determining exercise intensity (EI) for exercise prescription is still being improved, especially in patients with CHF. Recently, the new 2020 ESC sports cardiology guidelines proposed a new classification of EI based on the exercise stress test[6] (Table 2). Of all the essential elements of exercise prescription in CHF, EI is considered to be the most critical for achieving aerobic fitness and to have the most beneficial effect on risk factors[6,7]. Absolute EI refers to the rate of energy expenditure during exercise and is usually expressed in kcal/min or metabolic equivalents (METs). Relative EI is usually prescribed as a % of maximal aerobic capacity (VO2max or VO2peak) based on CPET. Training intensity can also be expressed as a % of maximum heart rate (HRmax). during the exercise test or predicted based on the equation [HRmax = 220 - age]. There are caveats regarding the use of HR to prescribe and assess exercise intensity in individuals using beta-blockers. Intensity is also usually monitored using a rate of perceived exertion (eg 12 - 14 on Borg's 6 - 20 scale) or a 'talk test', eg 'to be able to talk while exercising'[6].

Risk stratification and training prescription

Physical activity in patients with CHF is initiated in a clinically stable individual after medical therapy for CHF has been optimized [6-10]. The main components before starting an exercise program and participating in sports include[6]:
(1) Exclusion of contraindications to exercise: hypotension or hypertension at rest or during exercise, unstable heart disease, worsening CHF symptoms, myocardial ischemia despite therapy (exercise may be allowed up to ischemic threshold), or severe and suboptimally treated lung disease.
(2) Detailed cardiology evaluation: assessment of comorbidities and severity of CHF (eg, by blood natriuretic peptide assessment and echocardiography). Mandatory exercise test - recommended just ergospirometry to assess functional capacity, exercise-induced arrhythmias and hemodynamic abnormalities. Based on the obtained anaerobic threshold and peak VO2 on the test, the exercise intensity is prescribed. When doing only ECG exercise test, prescription is based on the maximum HR achieved or Borg's rating of perceived exertion (RPE).
(3) Optimization of medical therapy: All persons with CHF should be treated according to current guidelines, including device implantation when necessary.
Based on CPET results, aerobic exercise is prescribed for stable patients [New York Heart Association (NIHA) Class I-III], due to its effectiveness and safety. In patients in NIHA class III, exercise intensity should be maintained at a lower intensity (<40% VO2peak), according to observed symptoms and clinical status during the first 1-2 weeks. This should be followed by a gradual increase in intensity up to 50-70% VO2peak, and if tolerated, up to 85% VO2peak which is the primary goal[6,7]. (Table 3)
Strength/resistance exercises are not prohibited and are complementary because they recover and maintain the mass of skeletal muscles, but without significant strain on the heart. The intensity level is adjusted so that the CHF patient can do 10 to 15 repetitions with an RPE on the Borg scale of up to 15[6]. (Table 3)

Identification of post-program progress/deterioration based on CPET results

Some patients do not show improvement after the PA program in terms of exercise tolerance and PeakVO2 increase and represent perhaps the most important population for analysis and correction of treatment approaches. There are studies addressing the clinical relevance of poor response to PA. They showed that PeakVO2 and natriuretic peptides are the most important for monitoring. Absence of improvement after PA programs was defined in those who:

- did not improve peakVO2 by > 5%
- did not increase workload by > 10%,
- did not reduce the VE/VCO2 slope by > 5%.

The one of the best predictors was HR recovery in 1 min (in patients without atrial fibrillation), and people who did not meet at least one of the mentioned criteria were classified as non-responders (less than 30 beats/min for HR, less than 6 beats/min for HR recovery and less than 101 rpm for maximum HR).
Follow-up according to recommendations should be carried out for 3 to 6 months, more precisely depending on the severity of CHF, comorbidities, age and symptomatic status[6].

Conclusion

Ergospirometry represents the gold standard in the assessment of functional capacity and stratification of patients with CHF and is therefore a guide for prescribing physical activity. Because of its repeatability and

Table 3. Recommendations for physical activity in patients with CHF[6]

	Aerobic	resistance/strength
Frequency	3-5 days/week, Or every day	2-3 days/week, Or every day
Intensity	40-80%VO2peak	Up to RPE<15 40-60% , 1 RM
Duration	20-60 min	10-15 repetitions At least 1 set, with 8-10 upper and lower body exercises
Mode	Continuous or intermittent	
Progress	Progressive increase in intensity based on monitoring and evaluations at 3 to 6 months depending on effort tolerance	Progressive increase in intensity based on monitoring and evaluations at 3 to 6 months depending on effort tolerance

RM - the maximum load that a person can lift in one repetition; RPE = subjective feeling of exertion; VO_2peak = peak consumption of oxygen.

safety, it is also used to monitor the effects of training and further increase in intensity as fitness and clinical status progress. Thanks to that, for the last 10 years it has become an integral part of recommendations for heart failure, rehabilitation and sports cardiology.

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Sažetak

Klinička primena kardiopulmonalnog testa fizičkim opterećenjem u propisivanju fizičke aktivnosti kod bolesnika sa hroničnom srčanom insuficijencijom

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Fizička aktivnost (FA) prema važećim smericama predstavlja nezaobilaznu pomoćnu terapiju za pacijente sa hroničnom srčanom insuficijencijom (HSI) sa redukovanom i sa očuvanom ejekcionom frakcijom (HFrEF i HFpEF) što je nivo dokaza i klase 1A. Medjutim ka oi svaka terapija, FA se mora dozirati prema spsoosbnostima samog pacijenta, tako da je neophofdna indivisualna procena i propisivanje intenziteta vežbanja. Različiti tipovi FA (izdržljivost i otpor) i nivoi intenziteta (blagi, blagi do umereni i visoki do umereni) se koriste u programima kod pacijenata sa HSI.
Procena se može se izvesti putem indirektnih (rezerva otkucaja srca) ili direktnih metaboličkih mera (VO_2 rezerva, anaerobni prag) gde je preciznost obezbedjena direktnom procenom kinetike VO_2 pri protokolima konstantne brzine rada različitih opterećenja- ergospirometrijom. Ergospirometrija omogućava direktnu procenu pojave anaerobnog metabolizma i realnog zamora pacijenta kao i granica njegove tolerancije na napor. Pored toga, na osnovu kontrolnih testova može se pratiti efekat vežbanja. Na taj način se, zasnovano na dokazima, sprečava primena napora koji bi doveo do pogoršanja CHF ili koja ne bi dovela do napretka i poboljšanja simptoma/tolerancije napora. Takodje, omogućava postepeno povećanje intenziteta i dalji napredak u vežbanju.

***Ključne reči**: hronična srčana insuficijencija, kardiopulmonalni test fizičkim opterećenjem, funkcionalni kapacitet, anaerobni prag, potrošnja kiseonika, propisivanje treninga*