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Cardiopulmonary Exercise Test in heart failure: A Sine qua non

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Abstract: A robust literature, over the last years, supports the indication of cardiopulmonary exercise testing (CPET) in patients with cardiovascular diseases. Understanding exercise physiology is a crucial component of the critical evaluation of exercise intolerance. Shortness of breath and exercise limitation is often treated with an improper focus, partly because the pathophysiology is not well understood in the frame of the diagnostic spectrum of each subspecialty. A vital field and research area have been cardiopulmonary exercise test in heart failure with preserved/reduced ejection fraction, evaluation of heart failure patients as candidates for LVAD-Implantation, as well as for LVAD-Explantation and ultimately for heart transplantation. All the CPET variables provide synergistic prognostic discrimination. However, Peak VO2 serves as the most critical parameter for risk stratification and prediction of survival rate.

Keywords: Cardiopulmonary exercise test, heart failure, heart transplantation, Peak VO2

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1. Introduction

CPET can simultaneously investigate the responses under the exercise of respiratory, cellular and cardiovascular systems. It is practically impossible to examine the heart or the lungs exclusively during exercise. There is always the need for coordination of both systems to meet the physiological demands in energy and oxygenation. The cardiopulmonary exercise test is unique in terms of combining ECG, measurement of gas exchange, blood pressure and spirometry. It has low morbidity and it is relatively inexpensive. Thus, it should be more often used in patients with both heart and lung diseases. The aim of this review is to get insight into the viability of cardiopulmonary exercise testing and to summarize the clinical applications in heart failure patients [1] as well as to demonstrate the utility in patients as candidates for LVAD implantation and explantation [2].

2. Heart Failure with reduced/preserved ejection fraction

Two of the most studied variables in cardiopulmonary exercise tests are Peak VO2 and the VE/VCO2 slope. Both have secure independent prognostic value in the group of patients with systolic heart failure [3]. Exercise oscillatory ventilation (EOV) and the partial pressure of end-tidalCO2 (PETCO2) during rest and exercise have also demonstrated strong prognostic value in patients with systolic heart failure (HF) [4-7]. There is also evidence, which indicates that a percent-predicted peak VO2 value below 50% indicates a poor prognosis [8]. Peak VO2, the VE/VCO2 slope, presence/absence of EOV, and PETCO2 in rest or during exercise should all be assessed. Pathological values increase the likelihood of major and minor adverse events, such as death, HF decompensation to the refractory stage as well as hospitalization due to HF, which is also likely to increase. Multiple studies have demonstrated that the above-mentioned CPET variables respond favorably to pharmacological, surgical and lifestyle interventions in patients with systolic HF [3].

It should always be taken into consideration the clinical image and the hemodynamic parameters that may reflect increased severity and favor a worse outcome, such as an abnormal hemodynamic response, alterations of electrocardiogram (ECG) and an abnormally low HR recovery (HRR) at one minute post-ET [9-13]. CPET has a prognostic value in heart failure with preserved ejection fraction. This has been established from a Project, the so-called The Henry Ford Hospital Cardiopulmonary Exercise Testing (FIT-CPX) project. Between 1997 and 2010, 173 Patients with HFpEF have been identified and included (45% women, 58% non-white, age 54 ± 14 years). Based on the Wald statistic from the Cox regression analyses adjusted for age, sex, and β-blockade therapy, ppMVO2 was the strongest predictor, followed by peak VO2. VE/VCO2 slope and EOV had no significant association [14]. CPET and echocardiography are considered as two essential tools for critical objective measurements concerning diastolic dysfunction.

In patients with chronic heart failure, CPET can detect a reduced peak VO2 and AT, reflecting reduced O2 transport. In the case of moderate to severe dysfunction, an increase in VE/VCO2 can be identified. Because the increase in VE/VCO2 is due to increased VD/VT in proportion to the reduction in exercise tolerance and is not accompanied by hypoxemia [15], these findings must reflect decreased perfusion. There are numerous studies comparing the CPET results between patients with reduced and preserved ejection fraction. A survey from Farr et al. interpreted cardiopulmonary exercise testing and echocardiographic findings. The VE/VCO2 slope was higher in patients with HFpEF, with, however, no differences in peak VO2 [16].

Another study from Kitzman et al. demonstrated that patients aged at least 60 years with diastolic heart failure had similar abnormalities. Still, not as severe as by patients with systolic heart failure, such as reduced exercise performance, reduced quality of life (QoL) and neuroendocrine activation (e.g. Norepinephrine and brain natriuretic peptide) [17]. Focused on the ventilatory response, a study from Witte et al. reported a significantly higher VE/VCO2 slope in heart failure patients with reduced ejection fraction compared with patients with preserved ejection fraction and an asymptomatic control group [18]. A critical study by Arruda et al. demonstrated that patients with diastolic heart failure had similar breathing patterns and gas exchange responses to patients with systolic heart failure. Echocardiographically observed, a large volume of left atrium or an altered E/E′ ratio were associated with reduced exercise capacity and elevated ventilatory responses, particularly in patients with HFpEF [19].

3. CPET as a tool for measurement of cardiac output, assessing and grading the severity of heart failure

In a study published in 2017 from Agostoni P et al., based on gender and age, cardiac output is correlated with peak VO2. An equation has been formed, that can provide and predict peaked cardiac output: (4.4 × peak V˙o2) + 4.3 in the overall study cohort, (4.3 × peak V˙o2) + 4.5 in men, and (4.9 × peak V˙o2) + 3.6 in women [20]. A Study from Matsumura et al. demonstrated that the NYHA classification could be correlated with the AT and peak VO2, showing that symptoms and the ability to transport O2 were correlated [21]. Another Study from Weber and Janicki correlated more objectively the symptoms with peak VO2 and AT. An A through E Classification for VO2/kg has been established. It has been found that this classification for objectively assessing cardiac dysfunction was superior to NYHA Classification [22]. A consensus conference for patients with heart failure as candidates for heart transplantation agreed with this more objective assessment [23] (Table 1).

Table 1 Most important parameters of CPET for heart failure patients

Peak VO2(ml/kg/min)	Maximal Oxygen Consumption
VE/VCO2 Slope	Ventilatory efficiency, normal < 30
O2 Puls (ml/Heartbeat)	Surrogate Value for cardiac output
PetCO2 (mmHg)	End-tidal CO2, normal > 30
Peak RER	The ratio of exhaled CO2 and inhaled O2

3.1 Peak VO2 and Heart failure Prognosis

Over the last decades, it has been increasingly appreciated that peak VO2 more sensitively predicts prognosis than more classic heart failure risk factors such as left ventricular ejection fraction, NYHA Class IV symptoms and neurohormonal markers.

Increasing experience has confirmed the prognostic value of peak VO2 in the evaluation of patients with heart failure for cardiac transplantation [24-26]. A study from Weber et al. had demonstrated that, except maximal cardiac output during exercise, maximal peak VO2 is poorly correlated with cardiac index, wedge pressure (at rest or during exercise), left ventricular ejection fraction and radiographic heart [27]. Szlachik et al. reported that peak VO2 of less than 10ml/min/kg predicted 77% 1-year mortality; if peak VO2 was between 10 and 18 ml/min/kg, 1-year mortality was only 14% [28]. Back in 2012, HF-ACTION Trial demonstrated that for every 6% increase in peak VO2 (1 ml/kg/min), a 5% lower risk of mortality or hospitalization was observed [29].

3.2 Submaximal exercise parameters with high prognostic value

Anaerobic threshold (AT) represents the maximal sustainable VO2. It is an objective measurement and it can be derived from submaximal exercise testing without the need for maximal effort. Another Parameter that derives from submaximal testing and has a prognostic value for survival is the VE/VCO2 slope below the ventilator compensation point (VCP) [30-31]. A study from Gitt et al. has shown that peak VO2 and the submaximal parameters can serve as predictors of 6-month and 24-month patient survival rate in a cohort of 223 patients. As thresholds have been considered a peak VO2 of less than 14 ml/min/kg, AT or less than 11 ml/min/kg and VE/VCO2 slope below the VCP of more than 35 for high risk. It has been found that each of these parameters separates the high risk from low-risk patients [32]. The combination of AT and VE/ VCO2 below the VCP was found to be the best predictor of early death within 6 months in patients with left ventricular failure. Because both AT and VE/VCO2 below the VCP are determined at submaximal work levels and are not effort dependent, these are exceptionally valuable measurements. Sun et al. confirmed the 6-month findings showing increased early death or hospitalization rates if values were beyond the threshold values for severity. When adding oscillatory breathing pattern in assessing survival in stable patients with heart failure, death and early hospitalization rates within six months were even more marked [33].

4. Heart transplantation

4.1 Risk stratification and survival rate based on VO2 measurement

Multiple studies have outlined the important significance of peak VO2, serving as the most powerful predictor for survival rate in heart failure patients, which are candidates for heart transplantation. One study demonstrated that peak VO2 outperformed right heart catheterization data, exercise time, and the usual clinical variables used to assess heart failure patients in predicting outcomes. Direct measurement of VO2 should be made when a clinical or surgical decision needs to be made. Another study demonstrated that a group of patients who referred for heart transplantation with stable congestive heart failure and who had peak VO2 of 17.4+/4.3ml/kg/min, had a survival rate at 1 year of 98% and at least 4 years of 84%. This study had also demonstrated that patients have a favorable prognosis in case of stable symptoms and a relatively high peak exercise VO2 [34]. Macini et al. studied patients who were candidates for heart transplantation. Patients were divided based on peak VO2. Patients with peak VO2 greater than 14 ml/kg/min were considered too well for transplantation and had a 1-year survival rate of 94%. Patients with peak VO2 less than 14 ml/kg/min were accepted for transplantation and had a 70% 1-year survival rate with medical management. There was also a group of patients with peak VO2 less than 14 ml/kg/min that were not accepted for surgery for non-cardiac reasons [35]. In a study from Osada et al., 154 of 500 patients have been identified, who were referred for cardiac transplantation, with a peak VO2 equal to or less than 14ml/kg/min. In patients with an inability to reach a systolic blood pressure of 120mmHg, the 3-year survival rate was reduced from 83% to 55% [36].

4.2 Proper treatment and re-evaluation of candidates for LV heart transplantation

Perhaps one of the most important studies, a landmark study from Stevenson et al. presented data on 68 heart transplantation candidates. All candidates repeated exercise tests at a mean 6 +/- months after initial evaluations. The goal was to determine the probability of excluding the patient for heart transplantation under optimizing heart failure treatment. All 68 patients were treated with the escalation of medical therapy, e.g. diuretics and afterload reduction. It was also addressed that all 68 patients were involved in exercise rehabilitation training. Thirty patients had no significant improvement. However, 38 patients had an increase in peak VO2 of more than 2ml/kg/min, to a value greater than 12 ml/kg/min. Of these, 7 patients reported no clinical improvement, but 31 were clinically improved. The study also demonstrated that AT, peak O2 pulse and exercise heart rate reserve was improved and resting heart rate was decreased. 45% of the patients removed from the heart transplantation list, and the actual survival rate was 100% [37].

4.3 Left ventricular assist device (LVAD)

Not all patients with an end-stage status can benefit from heart transplantation, due to the fact that the available donations are not sufficient for the demand. Over the last years, the implantation of left ventricular assist devices has been an important and effective alternative for the support of these patients in the long-term. Cardiopulmonary exercise test can be used in order to determine the exercise capacity of heart failure patients after LVAD-Implantation. A prospective multicenter Study from Maybaum et. demonstrated the progressive improvement of the Peak V̇ o2 throughout the study period despite no change in peak LVAD flow and a progressive reduction in resting LVEF [38].

On the flip side of the coin, cardiopulmonary exercise test can be served as a tool for prediction for myocardial recovery and as a predictor for weaning of LVAD. In a study from Imamura et al., 33 patients were enrolled, after implantation of ECPF-LVAD and symptom-limited CPX testing at three months after the operation, and who were followed between 2005 and 2014. Cox regression analysis, E1 (maximum load ≥51W), E2 (minute ventilation/carbon dioxide output [V̇ E/V̇ CO2] slope ≤34), and E3 (peak oxygen consumption [PV̇ O2] ≥12.8 ml·kg(-1)·min(-1)) significantly predicted explantation expectancy during 2 years after LVAD implantation ($P<0.05$ for all). Explantation score, the sum of positive E1-3, significantly stratified 2-year cumulative explantation rate into low (0 points), intermediate (1-2 points), and high (3 points) expectancy groups (0%, 29%, and 86%, respectively, $P<0.001$). When the scoring system was used for 45 patients with continuous-flow LVAD, the 2 patients who had explantation were assigned to the high expectancy group [39].

5. Conclusion and future aspects

Circulating metabolites and mRNAs in combination with CPET may provide valuable information and enlighten the genetic background as well as discover an initial stage of heart failure. The cardiopulmonary exercise test is potentially a potent diagnostic tool in cardiology. Combining numerous variables, blood gases, continuous ECG recording, blood pressure and heart rate monitoring, blood lactate and, in case of the invasive cardiopulmonary exercise test, measurement of invasive hemodynamic parameters, this test provides a wide spectrum of multiple diagnostic schemas in many different clinical cases. Heart failure accounts for one of the most important health issues worldwide. In cases whereby medical therapy, invasive and non-invasive therapeutic approaches as also as mechanical (such as left ventricular assist device) and resynchronization therapy, fail to improve outcome, heart transplantation may be the very last option. Perhaps as underused and underestimated diagnostic approach in clinical basis, cardiopulmonary exercise testing can essentially refine the grading of severity, prognosis and risk stratification of heart failure patients and can genuinely evaluate candidates for LVAD implantation and explantation.

Appendix

AT	Anaerobic Threshold
CPET	Cardiopulmonary exercise testing
CRT	Cardiac resynchronization therapy
EC-PF/-CF	Extracorporal-pulsatile flow/ -continuous flow
EOV	Exercise oscillatory ventilation
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HRR	Heart Rate recovery
LV	Left Ventricle
LVAD	Left ventricular assist device
LVEDD	Left ventricular end diastolic diameter
LVAD	Left Ventricular assist device
NYHA	New York Heart Association
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PETCO2	Partial pressure of end-tidalCO2
QoL	Quality of Life
RV	Right Ventricle
SCD	Sudden cardiac death
VCO2	Carbon dioxide output
VE	Ventilation
VO2	Oxygen uptake
VD/VT	Dead space over tidal volume
VCP	Ventilator compensation point

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Conflict of interest

None of the authors have any conflicts of interest to declare.

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