Cardiopulmonary Exercise Test—The Revolving Door of Left Ventricular Assist Devices in Heart Failure

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Abstract: The prevalence of heart failure has an increasing tendency in the last years. Either heart failure with reduced ejection fraction (HFrEF) or with preserved ejection fraction, the treatment depends on the severity, cause, and symptoms.

In case of HFrEF, careful evaluation of patient is essential for proper diagnosis, risk stratification and treatment, which should always be individualistic. Except from daily measurements, medical treatment and eventually implantation of implantable cardioverter defibrillator or cardiac resynchronization therapy, implantation of left ventricular assist device (LVAD) belongs also to therapeutic armamentarium.

Other than invasive procedures, which are required for the evaluation of every patient with HFrEF, Cardiopulmonary exercise test emerges as one of the most effective noninvasive method for diagnosis, risk stratification, and treatment strategy for these patients.

Cardiopulmonary exercise test can provide means for a critical evaluation of cardiovascular system. One of the most important variables is the maximal oxygen consumption (peak VO2). Its high predictive and prognostic power makes peak VO2 essential for the evaluation of patients as candidates, not only for LVAD-implantation, but also for explantation. Furthermore,

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regarding cardiac rehabilitation and exercise protocols, robust literature supports a follow-up of LVAD-patients by means of cardiopulmonary exercise testing. (Curr Probl Cardiol 2021;46:100651.)

Introduction

The catalyst for the development of CPET and its implication in heart failure is found in 1960s. Heart failure was reaching epidemic proportions in the United States. Back on these days, Professor Karlman Wasserman has been asked, how heart failure could be detected in its earliest stages, noninvasively, in populations. He had the view that the major role of the circulation was to support cellular respiration. Thus, he responded that the earliest detection of heart failure would be under the physiological stress of exercise, when cellular (muscle) respiration was increased. The O2 uptake at which the circulation failed to track the O2 requirement of exercise would result in anaerobiosis and lactic acidosis. His incomparable passion and dedication gave rise to the development of CPET, a powerful noninvasive examination in cardiology, which combines cardiovascular, ventilator and gas-exchange physiology (Image 1, Table 1).

Nowadays, CPET is one of the most important methods for the diagnosis, evaluation, risk stratification and treatment planning of heart failure patients. As ultima ratio, left ventricular assist devices (LVADs) emerge as a great option for patients with severe heart failure, either as a bridging for heart transplantation or as a final destination therapy. Peak VO2 reflects the severity of heart failure and can be served as an implantation, as well as explantation criterion of LVAD.[1] It can also serve as a follow-up marker in sports cardiology,[2] for exercise protocols and cardiac rehabilitation.

Prognosis in heart failure patients

Robust experience confirms the prognostic value of peak VO2 in the evaluation of patients with heart failure.[3-5] A study from Weber et al. demonstrated that, except maximal cardiac output during exercise, maximal peak VO2 is poorly correlated with cardiac index, wedge pressure, left ventricular ejection fraction (LVEF), and radiographic heart.[6] Szlachik et al. reported that peak VO2 of less than 10 mL/min/kg predicted 77% 1-year mortality; if peak VO2 was between 10 and 18 mL/min/kg, 1-year mortality was only 14%. In 2012, HF-ACTION Trial

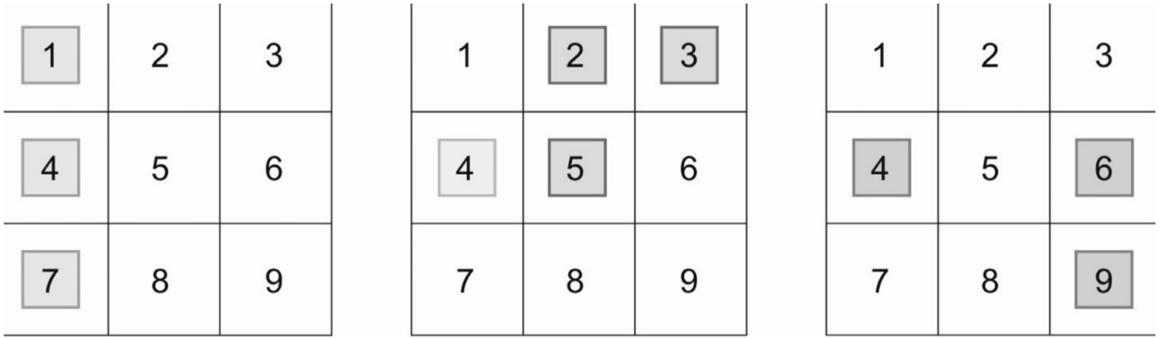

IMAGE 1. The signed panels on the left side represent ventilation. The signed panels in the middle demonstrate cardiovascular system. The signed panels on the right represent the gas exchange.

Table 1. Wasserman 9-Panel Plot informations and aspects. The presentation of the results should be systematic, concise and comprehensive

Panels	Information
Panel 1	VE and load against time
Panel 2	HR and O2-pulse against time
Panel 3	VO2, VCO2, and load against time
Panel 4	VE against VCO2
Panel 5	HR and VCO2 against VO2
Panel 6	EqO2 and EqCO2 against time
Panel 7	VTex against VE
Panel 8	RER and BR FEV% against tune
Panel 9	PETO2 and PETCO2 as well as PaO2 and PaCO2 against time

demonstrated, that for every 6% increase in peak VO2, a 5% lower risk of mortality or hospitalization was observed.[7]

Another study from Matsumura et al. demonstrated that the NYHA classification can be correlated with the AT and peak VO2, showing that symptoms and the ability to transport O2 were correlated.[8] Furthermore, 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.[9] A consensus conference for patients with heart failure as candidates for heart transplantation agreed with this more objective assessment.[10]

LVAD - Implantation and Explantation

Selection of patient and timing of surgery are crucial in terms of lowering postoperative morbidity and mortality. The delay of Implantation may give rise to worsening of clinical condition. The indications for durable VAD are bridge to therapy, bridge to decision, destination therapy and bridge to recovery.

The selection criteria for Implantation in case of destination therapy were adopted from 2 landmark trials, REMATCH and Heart mate II and include patients who are not candidates for heart transplantation, significant functional limitations with chronic NYHA IV symptoms for 45 of 60 days despite use of optimal medical therapy, LVEF less than 25%, and peak VO2 of 14 mL/kg/min or less.[11]

Another landmark study from Stevenson et al. presented data on 68 heart transplantation candidates. The aim of the study was to determine the probability of excluding the patient for heart transplantation under optimizing heart failure treatment. All patients treated with the highest and most tolerable medical therapy. All 68 patients were involved in exercise rehabilitation training. Thirty-eight patients had an increase in peak VO2 with a value greater than 12 mL/kg/min. Of these, 7 patients reported no clinical improvement, but 31 were clinically improved. Fourty-five percent of the patients removed from the heart transplantation list, and the actual survival rate was 100%.[12]

Not all patients however with terminal heart failure can benefit from heart transplantation, in the frame of insufficient donations compared to demand. Over the last years, implantation of LVAD has been an important and an effective alternative in long-term. CPET can be used in order to determine the exercise capacity of heart failure patients after LVAD-implantation. A prospective multicenter Study from Maybaum et al. demonstrated an improvement of Peak VO2 throughout the study period despite no change in peak LVAD flow.[13]

On the other hand, LVAD explantation evaluation protocols remain heterogeneous across institutions. Primarily peak VO2, but also filling pressures and cardiac output should be evaluated for explantation candidacy.

Proposed criteria for LVAD Explantation have included LVEF >45%, LV end diastolic dimension <60 mm, PAWP <12 mmHg, cardiac index >2.8 L/min/m^2, peak VO2 >16 mL/kg/min, or VE/VCO2 of <34 during low LVAD speed testing.[14]

In a study from Imamura et al., 33 patients were enrolled, after implantation of ECPF-LVAD. Cox regression analysis, E1 (maximum load ≥51W), E2 (minute ventilation/carbon dioxide output [$\dot{V}$ E/$\dot{V}$ CO2] slope ≤34), and E3 (peak oxygen consumption [P$\dot{V}$ O2] ≥12.8 mL·kg(-1)·min (-1)) significantly predicted explantation expectancy during 2 years after LVAD implantation ($P < 0.05$ for all). 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.[15]

Right ventricular failure after LVAD-Implantation

Right ventricular failure following implantation of a left ventricular assist device is associated with increased morbidity and mortality. Accurately predicting it can influence surgical decision-making. One of the mechanisms responsible for early RVF after LVAD placement is the increase in preload to the right ventricle (RV). This is similar to the increase in preload that occurs during exercise. VE/VCO2 slope at anaerobic threshold increases proportionately with mean pulmonary pressures and is inversely related with RV function.

In the study from Gosain et al., the calculation of the Right Ventricle Stress Score (RVSS): RVSS = VE/VCO2 (at AT)/peak heart rate has been used to predict a right ventricular failure after LVAD placement. RVF was defined as the necessity for inotropes (milrinone or dobutamine) for more than 14 days or need for mechanical RV support. Using a cut-off of 0.33 for RVSS, the sensitivity of the test was 87.5% and specificity was 62.5% for RVF. The negative predictive value was 91%.[16]

Furthermore, the association between VE/VCO2 and RV dysfunction has been evaluated in the study from Grinstein et al. Elevated preoperative VE/VCO2 slope has been proven as a predictor of postoperative mortality and was associated with postoperative hemodynamic markers of impaired RV performance in LVAD patients.[17]

Assessment of Effects of Exercise Training in LVAD-Patients based on peak VO2

Numerous studies have examined the effect of exercise training after LVAD implantation. The study from Hayes et al. demonstrated a trend toward greater improvement in peak oxygen consumption compared with the control group.[18]

A meta-analysis from Grosman et al. showed that exercise rehabilitation significantly improved peak VO2 and 6-minute walk test distance. No significant differences were found for the ventilatory equivalent slope (VE/VCO2) or ventilatory anaerobic threshold. Exercise rehabilitation is associated with improved outcomes in VAD recipients, and therefore should be more systematically delivered in this population.[19]

Conclusion and future aspects

CPET is considered as a powerful method in cardiology, especially for determining the prognosis and for risk stratification of heart failure patients. All the CPET variables provide synergistic prognostic discrimination. However Peak VO2 serves as the most important parameter for risk stratification and prediction of survival rate.

Although an invasive evaluation, based on eg, central oxygen saturation and cardiac output, should be considered in every candidate for LVAD-implantation and explantation, CPET is considered as one of the best tools for noninvasive evaluation, due to the fact that can objectively justify and reflect the physical and hemodynamic capacity in rest, but most importantly under exercise.

Larger and higher quality trials are needed to investigate the effects of exercise in patients with heart failure patients as well as in patients with LVAD. Exercise protocols should be always individualistic and designed based on the clinical image of each patient.

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