An overview of the cardiopulmonary exercise testing assessment in patients with left ventricular assist devices and heart failure with reduced ejection fractions

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ABSTRACT

Background: *Patients with advanced heart failure with reduced ejection fractions have decreased life expectancies. Treatment options include cardiac transplantation, left ventricular assist device (LVAD) insertion as a destination therapy, and palliative care. These LVADs do prolong survival and improve their quality of life. However, their effect on the maximum exercise capacity seems limited. This study reviewed recent literature reporting cardiopulmonary exercise testing in patients with LVADs to better understand the clinical benefits with these devices and the post insertion factors affecting exercise performance.*

Methods: *The PubMed database was searched using the MeSH terms "heart-assist device," "exercise test," and "heart failure." Search filters included English language publication. The focus was to identify articles which reported VO_2 max pre and post LVAD insertion, identified limiting factors in VO_2 max post LVAD, and analyzed the VO_2 burden during activities of daily living in patients with LVADs.*

Results: *This analysis used 11 articles which reported results in the 346 patients. The mean age was 53.1 ± 6.7 years, and 77% of the patients were male. The mean peak VO_2 was 14.0 ± 2.5 L/kg/min. The VO_2 max did not increase post LVAD insertion. Multiple factors were associated with the limitation in the VO_2 max in these patients post insertion. These included characteristics of the LVAD device, right heart function, chronotropic responses, tricuspid and aortic valve function, gas exchange, and hemodynamic stress based on BNP levels. Some patients who underwent cardiac rehabilitation had significant increases in VO_2 max, 6-minute walk distance, muscle strength, and quality of life questionnaire scores. In 1 study with 15 patients, the VO_2 increased from 16.8 ± 3.7 to 19.3 ± 4.6 mL O_2/kg/min. The 6-minute walk distance increased from 462 ± 88 m to 527 ± 76 m. Measurement of VO_2 during routine activities of daily living in these patients demonstrated that they used a significant fraction of their VO_2 max in activities; for example, walking upstairs required 66 ± 10% of peak VO_2.*

Conclusion: *Patients with advanced heart failure and LVAD insertion continue to have low peak VO_2 max on cardiopulmonary exercise testing. A complex set of factors, especially right ventricular dysfunction, are associated with exercise limitation. These patients do improve with cardiac rehabilitation but still use a significant fraction of their peak VO_2 to undertake routine daily activities.*

Keywords: Left ventricular assist device, heart failure, cardiopulmonary exercise test

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INTRODUCTION

Ventricular-assist devices (VADs) were originally developed as a temporary support to sustain patients until they could undergo heart transplant surgery. Nearly all patients with VADs have a baseline New York Heart Association (NYHA) class IV and VO_2 max below 14 mL/kg/min and are potential candidates for heart transplantation.[1,2] These assist devices have also become a long-term treatment option for patients with end-stage heart failure and can increase survival rates and improve quality of life. Specifically, VADs increase survival rates to 81% and 70% at the 1 and 2-year marks, respectively.[1] In patients with end-stage heart failure with reduced ejection fractions (HFrEF), LVADs decrease the pressure and volume in the left ventricle and increase cardiac output (CO).[3,4] Despite the hemodynamic benefits with LVADs in these patients, their functional capacity remains low and is often below 50% of the predicted VO_2 max measured by a cardiopulmonary exercise testing (CPET).[4] This testing is the gold standard for the evaluation of functional capacity in cardiac patients and can help identify the most important cardiac parameter associated with exercise limitation. Recent studies have demonstrated that LVADs have an inconsistent and limited effect on exercise performance measured by either CPET or the six-minute walk tests in these patients.[5]

Many patients with heart failure have normal cardiac output at rest, but it does not increase during physical activity. The peak oxygen uptake (VO_2) in heart failure is directly related to peak cardiac output and perfusion of exercising muscles. When cardiac output fails to increase, this decreases perfusion to the muscles, causing anaerobic metabolism and muscle fatigue at lower workloads.[5] These patients often cannot reach their predicted maximum VO_2, and their VO_2 at the end of exercise is called "peak VO_2." Cardiopulmonary exercise testing provides an objective method for determining the functional capacity of heart failure patients and measures several variables that have prognostic implications, including peak VO_2 and the VE/VCO_2 slope during exercise. Peak VO_2 is an excellent prognostic index in heart failure patients and is used to establish a patient's candidacy for transplantation. Additional studies have shown that the VE/VCO_2 slope has equivalent or even superior prognostic value compared to peak VO_2 in heart failure patients.[5]

Routine evaluation of patients with cardiac disorders often includes questionnaire, such as a New York Heart Association classification or in the Kansas City Cardiomyopathy Questionnaire. These instruments provide an overview of the patient's clinical status but do not necessarily identify a specific activity which has an important effect in an individual patient. Portable equipment can measure VO_2 during 6-minute walk tests and other activities and can help relate a patient's symptoms to the oxygen demand for that particular activity. For example, Mirza et al. found that recipients of durable LVADs performed activities of daily living (ADL) with oxygen consumption (VO_2) levels much closer to their peak VO_2 than healthy age-matched controls.[6] The proportion of peak VO_2 was significantly higher in LVAD recipients, regardless of the ADL task. As a compensatory measure, LVAD recipients prolong the time needed to complete the task, leading to an impaired quality of life (QOL) for simple, non-demanding tasks, such as tying one's shoes. This study also confirmed that the mean peak exercise capacity of LVAD recipients was less than half of that of the controls.[6]

This review summarizes the clinical benefits and limiting factors associated with LVADs in patients with HFrEF using CPET and 6-minute walk tests as assessment tools and provides an overview for non-specialist clinicians.

METHODS

The literature search for this review in PubMed used the MeSH terms "exercise test," "heart failure," and "cardiac-assist devices". Other searches used the phrase left ventricular mechanical support. Relevant references in the identified articles were also reviewed.

RESULTS

This search identified 11 articles which provided representative information about the use and benefits of LVADs in patient with chronic heart failure with reduced ejection fractions (Table 1).[6–16] These articles reported results in the 346 patients (77% male) with a mean age of 53.1 ± 6.7 years. The average peak VO_2

Table 1. Maximum O_2 Consumption Post Left Ventricular Assist Device Insertion

Author	Year	# LVAD Patients	Male %	Age Years Mean	LVAD Flow at Rest (l/min)	Peak VO_2 Post LVAD	Primary Study Emphasis
Buchanan[7]	2024	10	90%	60	NA	10.8 ± 2.5	VO_2 max pre and post LVAD
Fresiello[8]	2020	83	78%	52	4.5	14.8 ± 4.5	Limiting factors in VO_2 max
Tran[9]	2020	26	92%	56	5.2	12.5 ± 3.2	RV function with LVADs
Sailer[11]	2021	12	83%	60	NA	10.5 ± 2.7	Autonomic nervous system with LVAD
Grosman-Rimon[10]	2020	15	53%	51	NA	13.5 ± 2.0	Neurohumoral responses post LVAD
Kaya[12]	2023	43	93%	53	NA	NA	Aortic valve function post LVAD
Wernhart[13]	2023	89	85%	53	NA	13.4 ± 3.5	Ventilation post LVAD
Laoutaris[14]	2011	21	8%	37	NA	19.3 ± 4.5	Rehabilitation post LVAD
Hayes[15]	2012	14	85%	48	NA	14.8 ± 4.9	Rehabilitation post LVAD
Kerrigan[16]	2014	18	61%	53	NA	15.3 ± 4.4	Rehabilitation post LVAD
Mirza[6]	2022	15	100%	61	4.8	14.9 ± 3.3	VO_2 during ADLs

LVAD – left ventricular assist device; NA – not available; ADLs – activities of daily living.

in these studies was 14.0 ± 2.5 L/kg/min. The VO_2 max did not increase post LVAD insertion. Multiple factors were associated with the limitation in the VO_2 max in these patients post insertion, and these included characteristics of the LVAD device, right heart function, chronotropic responses, tricuspid and aortic valve function, gas exchange, and hemodynamic stress based on BNP levels. Most patients but not all who underwent cardiac rehabilitation had an increase in VO_2 max, 6-minute walk distance, muscle strength, and quality of life questionnaire scores. In one study with 15 patients, the VO_2 increased from 16.8 ± 3.7 to 19.3 ± 4.6 mL O_2/kg/min, and the 6-minute walk distance increased from 462 ± 88 m to 527 ± 76 m. Measurement of VO_2 during routine activities of daily living in these patients demonstrated that they used a significant fraction of their peak VO_2 during routine activities. These studies are discussed in more detail in the following paragraphs.

Pre and post implant insertion VO_2

Buchanan et al. studied ten patients who underwent CPETs before and after LVAD insertion.[7] This evaluation also included pulmonary artery catheterization. There was no increase in maximum oxygen uptake after LVAD insertion; the max VO_2 was 10.8 ± 2.5 mL/kg/min before insertion, 10.7 ± 2.2 mL/kg/min on second visit with constant pump speed, and 11.5 ± 1.7 mL/kg/min on the third visit with increased pump speed during exercise. Mean pulmonary artery (~45 mmHg at peak exercise) and pulmonary capillary wedge pressures (~20 mmHg at peak exercise) were increased significantly preimplantation and remain elevated post implantation. This study demonstrates that peak VO_2s were very low before implantation and did not improve post LVAD insertion.

Limiting factors in exercise performance

Multiple factors limit exercise capacity in patients with advanced heart failure and LVADs; these include device characteristics, residual native left ventricular function, right ventricular dysfunction, aortic valve abnormalities, skeletal muscle mass, physical deconditioning, and medical conditions, such as anemia and chronic renal disease.[1,3,17,18]

Fresiello et al. reported a detailed study on the functional impairment in 83 patients with LVADs to determine factors that limit exercise capacity.[8] They evaluated the exercise capacity of these patients using CPET and 6-minute walk test distance (6-MWD), measured the peak oxygen uptake and distance walked, and then expressed the results as percent predicted VO_2 and percent predicted 6-MWD. Both these functional parameters were reduced; the patients had a relatively higher percent predicted submaximal exercise capacity based on their 6-MWD (64 ± 16%) than percent predicted maximum exercise capacity based on peak VO_2 (51 ± 14 %). Several factors were associated with VO_2 % predicted, and these included LVAD parameters, chronotropic responses, the opening of the aortic valve at rest, tricuspid insufficiency, NT-proBNP levels, and the presence of a cardiac implantable electronic device. The 6-MWD % predicted was determined by general health factors, such as history of diabetes mellitus, baseline creatinine and urea, ventilation efficiency, and continuous flow-LVADs pulsatility index [8-Fresiello]. The patients with longer time intervals between the development of their cardiac disease and LVAD insertion had worse exercise capacity, presumably due to more advanced ventricular dysfunction. However, the results in this study were analyzed with univariable analysis to identify significant associations, and multivariable analysis might have identified fewer factors, questionably more important factors, associated with decreased performance.

Tran et al. studied 26 patients with LVADs using hemodynamic tests with either a conductance catheter in the right ventricle to measure pressure-volume relationships or a right heart catheter to measure pressures to evaluate right ventricular contractile function in LVAD patients.[9] They found that there was a limited contractile reserve, and no increase in RV contractility at peak exercise in comparison to submaximal exercise, and there were marked increases in pulmonary, left-sided filling, and right-side filling pressures during exercise. In addition, ventilator efficiency was very abnormal with a $V/VCO_2 > 40$. Other studies have also reported right ventricular dysfunction in patients with LVADs.[19–22]

Chronotropic incompetence could also contribute to the reduced exercise capacity in these patients. Neurohormonal levels (norepinephrine [NE] and aldosterone) reflect sympathetic responses in exercise and are correlated with CPET parameters. In a study with 15 patients, CPET variables, such as peak VO_2 (13.6 mL/kg/min) and percentage of age and sex-predicted VO_2 max, were low; the minute ventilation/carbon dioxide output (VE/VCO_2) slopes were increased.[10] Furthermore, VO_2 at anaerobic threshold (VO_2 AT) and O_2 pulse values were negatively correlated with NE levels. The NE levels were positively correlated with chronotropic responses and heart rate recovery; aldosterone levels did not have any significant relationship with CPET measures. Despite the association of NE levels with chronotropic responses during peak exercise, neither NE levels nor chronotropic responses predicted peak VO_2. This suggests that chronotropic incompetence is probably not the primary factor responsible for the low peak VO_2. Nevertheless, patients with LVADs often have chronotropic incompetence, and this needs consideration during patient management.[10] Sailer et al. studied 12 patients before and after LVAD insertion and found that cardiac baroreceptor sensitivity was decreased both before and after placement.[11] Norepinephrine levels were elevated before placement and remained elevated after placement. Chronically increased catecholamine levels could have adverse effects on myocardial function.

The LVAD consists of a pump draining blood from the left ventricle and perfusing of blood into the aorta. This changes pressure gradients across the aortic valve and can influence aortic valve opening. In addition, the constant perfusion applied across the valve in the aortic arch can cause tissue damage. These 2 processes can change aortic valve function. Kaya et al. studied 43 patients before and after LVAD insertion to determine the effect of aortic valve opening patterns and on endothelial function measured with flow-mediated dilatation and the pulsatility index.[12] Patients with intermittently opened and not opened aortic valve had worse endothelial function at follow-up. Consequently, aortic valve dysfunction may contribute to the outcome in patients with LVADs, and LVADs may have unavoidable adverse effects on valve function. LVADs primarily support the left ventricle, but the right ventricle is indirectly forced to pump more blood, and this increased volume/

flow may exceed its capacity and they develop right heart failure.[19–21] This right ventricular dysfunction could contribute to the decreased exercise capacity of patients with HFrEF with LVADs. Wernhart et al. found that tricuspid annular plane systolic excursion (TAPSE), an index of right ventricular dysfunction and ejection fraction, was a major determinant of reduced exercise capacity.[13] Lower TAPSE was associated with a higher incidence of atrial fibrillation and valve dysfunction. Treatment of valve dysfunction and rhythm/rate control of atrial fibrillation in HFrEF requires attention, when possible, to delay the decline of exercise capacity and morbidity.[13]

Other possible limitations during exercise in LVAD patients could include abnormal alveolar ventilation and perfusion and respiratory system mechanics, which can be measured by changes end tidal CO_2 during CPETs. In an observational study with 89 patients, Wernhart et al. determined that LVAD patients had increased dead space ventilation despite increased alveolar perfusion during exercise.[13]

Activities of daily living and rehabilitation

Patients with LVADs usually do not have a significant increase in VO_2 during exercise. Mirza et al. studied 15 patients with an LVAD who had a peak VO_2 of 14.9 mL/kg/min.[6] They used a significant percentage of this peak VO_2 during activities of daily living; for example, walking on stairs required 66 ± 10 percent of their peak VO_2. This percentage was much higher than in control patients. Consequently, simple quality of life scales which provide an overall assessment may not adequately measure patients' limitations in specific routine activities.

Gobbo et al. evaluated 38 patients with LVADs using CPET, handgrip tests, isometric and isotonic strength testing of the knee and ankle, and the Romberg balance test.[23] Only 12 patients were able to complete all the assessments. The mean peak VO_2 was 12.4 ± 3.4 mL/kg/min. The mean handgrip strength was 30.1 ± 10.6 kg; 25 patients were below the 25th percentile of their reference population. This study indicates that these patients had significantly reduced functional capacity and decreased overall strength and suggests that rehabilitation should include a muscle strengthening protocol.

Patients with chronic heart failure and LVAD insertion often participate in pulmonary rehabilitation. Laoutaris et al. reported results in 10 patients post LVAD placement who underwent training using moderate intensity aerobic exercise and high intensity inspiratory muscle training.[14] Patients in this training group had increased VO_2 max, increased VO_2 at the ventilatory threshold, and decreased V/VCO_2 slope. Their 6-MWD increased, and the scores on a quality-of-life questionnaire improved. Hayes et al. compared outcomes in 7 patients post LVAD placement who participated in cardiac rehabilitation with both aerobic and strengthening exercises with 7 control post-LVAD patients (15-Hayes). There was a non-statistically significant increase in VO_2, 6-MWD, and quality of life scores in the patients who participated in comparison to control patients.

Kerrigan et al. studied 18 patients post LVAD placement who underwent aerobic exercise at 60% to 80% of heart rate reserve (16-Kerrigan). These patients had increased peak oxygen uptake, treadmill time, 6-MWD, and leg strength. These functional changes were significantly better than the control patients who did not undergo this training. Feuerstein et al. randomized 64 patients with heart failure and LVAD into a 12-week supervised exercise training or usual care study.[24] The mean increase in peak VO_2 after 12 weeks was 0.83 mL/min/kg (P = NS). Exercise training did increase his 6-minute walk distance with a mean increase of 43.4 m and increase to physical domain score on the Kansas City Cardiomyopathy questionnaire.

In summary, these studies indicate that many patients but not all with LVADs do benefit from cardiac rehabilitation. This rehabilitation needs to include strength training and balance exercises.

Complications

LVAD-related complications are important causes of morbidity and mortality in patients with end-stage HF. They can be classified into three major categories, i.e., complications related to the pump and its components (e.g., pump malfunction), complications related to the patient (ventricular arrhythmias, valvular insufficiency, and right ventricular failure), and pump-patient interface-related complications (acquired von Willebrand disease, infection, stroke, and pump thrombosis).[25,26] In the initial 60 days post-implantation, common complications include bleeding, infections, arrhythmias, respiratory and neurologic events, reoperations, and tamponade. Bleedings and arrhythmias usually occur right after the procedure; infections and neurologic issues have a later onset. Infections, ranging from local to systemic, can predict mortality and may require antibiotics or device explantation. Bleeding, affecting 30–60% of cases, often presents as gastrointestinal bleeding but also can involve critical events such as intracranial hemorrhage. Pump thrombosis can lead to urgent pump replacement, and arrhythmias like atrial fibrillation are common post LVAD insertion. Stroke is a primary cause of death post-LVAD and the risk increases over time. Aortic insufficiency is a common complication, especially with HeartMate 2 support.

Discussion

LVADs are designed to support cardiac function in patients with heart failure by reducing the work that a weak left ventricle has to perform during normal physiologic circumstances. These devices have shown that cardiac output and VO_2 are stable at rest in patients with heart failure, but recent studies using CPET parameters have shown that oxygen consumption and exercise capacity are not increased with these devices.[7] As a result, the quality of life in these patients likely varies depending on the particular activity under consideration. Oxygen demands will be higher than expected, and this will result in more fatigue.[6]

The use of LVADs to improve exercise capacity of heart failure patients has been studied in multiple centers with variable results. Some studies suggest that LVADs can increase physical activity levels by enhancing exercise capacity, but other studies have reported limited benefit with LVADs, especially in activities requiring higher levels of O_2 consumption or longer completion times.[14–16] These patients need a comprehensive evaluation prior to LVAD insertion. This should include chest x-rays, pulmonary function tests, and echocardiograms to determine cardiac chamber size and ventricular function. Right heart catheterization can determine important information about cardiac and pulmonary pressures and responses to either fluid loading or exercise during the catheterization procedure.[27] Advanced evaluation might include using an intraventricular conductance catheter insertion to measure pressure-volume relationships.[28] CPETs provide a global assessment of cardiopulmonary function following LVADs insertion and may help identify the most important limiting factors in physical performance. However, the 6-minute walk test may provide a better and more practical index of the patients' ability to perform routine daily activities.

Conclusion

In summary, LVADs can prolong life in patients HFrEF. However, their effect on maximum cardiopulmonary exercise capacity is limited. More research is needed to determine the benefits and limitations of LVADs in patients with heart failure, including their effect on exercise capacity and complications. The management of these patients requires a complex assessment of biventricular function, chronotropic responses, pulmonary function, and other comorbid medical conditions.

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