12-16-2021

Exercise in patients with left ventricular devices: The interaction between the device and the patient

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Recommended Citation
Kerrigan DJ, Cowger JA, and Keteyian SJ. Exercise in patients with left ventricular devices: The interaction between the device and the patient. Prog Cardiovasc Dis 2021.

Progress in Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Exercise in patients with left ventricular devices: The interaction between the device and the patient

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ARTICLE INFO

Available online xxxx

Keywords:
Exercise testing
Exercise training
Mechanical circulatory support

ABSTRACT

Advances in the engineering of surgically implanted, durable left ventricular assist devices (LVAD) has led to improvements in the two-year survival of patients on LVAD support, which is now comparable to that of heart transplant (HT) recipients. And with the advent of magnetic levitation technology, both the survival rate and average time on LVAD support are expected to improve even further. However, despite these advances, the functional capacity of patients on LVAD support remains reduced compared to those who received a HT. A few small clinical trials have shown improvement in functional capacity with exercise training. Peak oxygen uptake improves modestly (10%–20%) with exercise training, suggesting a possible celling-effect linked to the ability of the LVAD to increase flow during exercise. This paper reviews both (a) the effect of the LVAD on the cardiorespiratory responses during a single, acute bout of exercise up to maximum and (b) the central and peripheral adaptations that occur among patients with an LVAD who undergo an exercise training regimen. We also address the tenets of the exercise prescription that are unique to patients with a durable LVAD.

Contents

Durable left ventricular (LV) assist device (LVAD) support is indicated for carefully selected individuals with advanced systolic heart failure (HF) refractory to medical optimization (American Heart Association/American College of Cardiology Stage D systolic heart failure).[1] To date, over 28,000 individuals have undergone Food and Drug Administration (FDA) approved LVAD implanted in the United States, as either a bridge to heart transplantation (HT) or for permanent ("Destination Therapy") support.[2] Currently, durable LV mechanical circulatory support (MCS) improves cardiac output (CO) and perfusion to vital organs using an electronically powered, continuous flow pump that removes blood from the LV via an inflow cannula, imparts kinetic energy as the blood traverses a motor, and then expels it through an outflow graft into the patient's ascending aorta (Fig. 1). Phasic blood delivery occurs during both the systolic and diastolic periods of the cardiac cycle, by means of either an axial (HeartMate II, Abbott, Inc) or centrifugal (HVAD, Medtronic, Inc.; HeartMate 3, Abbott, Inc) flow pathway within the pump casing. The early generation, FDA approved devices (HeartMate II and HVAD) were plagued by complications, including

Abbreviations: 6MWT, six minute walk test; BP, blood pressure; CO, cardiac output; CR, cardiac rehabilitation; FDA, Food and Drug Administration; HF, heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; HR, heart rate; HT, heart transplant; LV, left ventricle; LVAD, Left ventricular assist device; MCS, mechanical circulatory support; RV, right ventricle; VO_2, oxygen uptake.

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https://doi.org/10.1016/j.pcad.2021.12.002
0033-0620/

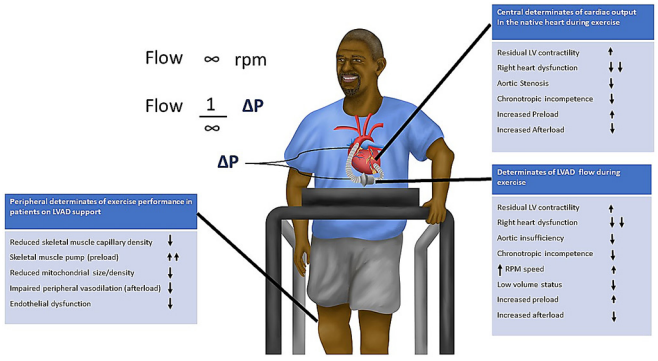

Fig. 1. Factors influencing exercise capacity in patients with a left ventricular assist device.

pump thrombosis and strokes, with average survival rates of 84% at 1 year and 46% at 5 years following implant. These early generation pumps were replaced by third generation HeartMate 3 (Abbott, Inc) continuous flow technology that uses magnetic levitation to move impellers within a pump housing that is located external to the pericardium. Clinical trial and registry data of patients on HeartMate 3 LVAD support demonstrate average survival rates of 88% at 1 year and 84% at 2 years, effectively mirroring that of HT over the short term.[3,4] The HeartMate 3 pump design has effectively eliminated pump thrombosis, reduced risk for stroke, and is expected to allow for an average survival time well beyond 5 years.[5]

Given the improvements in LVAD survival and the increased use of LVADs in the United States, the number of patients on LVAD support referred for exercise-based cardiac rehabilitation (CR) has commensurately increased. However, despite HF with reduced LV ejection fraction (HFrEF) representing a diagnosis covered by Medicare, in 2016 only 42% of eligible LVAD patients attended CR.[6] One potential barrier to CR in the LVAD patient population is the medical complexity of these patients, including difficulties with the monitoring of vital signs, equipment management, and small increases in the risk of complications (e.g., arrhythmias, hypotension) during exercise. Additionally, a survey of European CR facilities cited a lack of properly trained staff and staff safety concerns as two other reasons why patients on LVAD support are not enrolled into their CR facility.[7] It is likely that the above concerns, coupled with the complex interaction between the LVAD and the native cardiovascular system during exercise, both contribute to staff hesitancy and low enrollment into CR. In this paper we address the exercise physiology of the LVAD patient to a single bout of exercise, the central and peripheral of adaptations to an exercise training regimen, and how to establish an effective exercise prescription that mitigates potential safety concerns in these unique patients.

The exercise physiology of the LVAD

Continuous flow LVADs provide resting flow rates of 3–6 L/min, peaking at ~10 L/min with exercise.[8] Present FDA approved continuous flow LVADs operate at a fixed speed, independent of rest or exercise.[8] Therefore, any increase in flow through the pump or through the aortic valve is dependent on augmentation of native right and left heart function. Durable LVAD technology is typically set at a speed (measured in revolutions per minute) that can provide adequate end organ perfusion at rest that is indexed to body surface to yield a flow rate of 2.2–2.4 mL/min/m^2. This approach results in an appropriate unloading of the LV and does so without adverse impact on the neighboring right ventricle (RV) or instigation of LV suction.

Despite the discordance between the device and the body's native CV system, LVAD flow does increase with exercise but via mechanisms that differ from that of a healthy control (Figure 1). In patients without LVAD support, heart rate (HR) is a main determinate of CO in the native LV, increasing in a linear fashion during higher intensity aerobic-type-exercise (i.e., >50% peak oxygen uptake, VO_2).[9] In patients on LVAD support, augmentation of pump flow during exercise is reliant on native heart contractility and LVAD flow is only moderately correlated to HR during exercise.[10] This observation was reported by Muthiah et al., who showed that the contribution of various paced HRs on LVAD flow rate was negligible.[10] This suggests that among patients with an LVAD, it is likely that other factors have a greater impact on exercise capacity than chronotropic response.[11,12] Right heart dysfunction and pulmonary hypertension, for example, can critically limit LVAD output during exercise due to impairment in rapid LVAD filling. Additionally, many patients on continuous flow LVAD support have acquired aortic valve stenosis and/or complete aortic valve leaflet fusion (i.e., acquired aortic valve closure), preventing an increase in native CO via the aortic valve, and/or aortic insufficiency (AI) which leads to ineffective pump flow due to recirculation.[13] If systemic blood pressure (BP) substantially increases during exercise, the gradient driving this recirculation is increased, potentially contributing to exertional intolerance in the LVAD patient with AI.

Pump speed has a proportional relationship to pump flow, leading many to speculate about increasing speed as a method to bolster VO_2 peak.[14–16] However, there are limitations when increasing LVAD speed with respect to initiating potential RV complications. Additionally, exercise testing studies that adjusted pump speed have not consistently found improvements in peak VO_2, suggesting there are still other factors influencing peak VO_2.[17] Thus, since pump speed is fixed in contemporary LVADs, the largest contributor to pump flow both at rest and during exercise is the pressure gradient across the pump (i.e., pump head or differential pressure). The two main determinates affecting the pressure gradient across the pump are (a) systemic arterial BP and (b) LV end diastolic pressure.[18,19] Elevation of systemic arterial BP can lead to a marked reduction in LVAD pump flows in patients on modern centrifugal flow, continuous LVADs[20]. During exercise, total peripheral resistance, however, is usually reduced, leading to a subsequent increase in LVAD output. While this relationship between afterload and forward flow also happens in the non-LVAD supported native LV, the influence of afterload is 3–4 times more impactful relative to flow through the LVAD pump.[19] This finding was shown by Salamonsen et al. who reported that the afterload sensitivity of various continuous flow-LVADs was 0.09 ± 0.034 L/min/mmHg, compared to the known average values measured in the human LV of 0.03 ± 0.01 L/min/mmHg[21].

With respect to the LV end diastolic pressure during exercise, this is primarily driven by blood returning to the LV (i.e. preload) through a combined effect from the skeletal muscle pump and residual RV and LV contractility.[17] The influence of the skeletal muscle pump on preload was illustrated during a tilt-table study that found active ankle flexion in patients on LVAD support increased LVAD flow rate regardless of body position (i.e., supine versus upright).[10] Patient volume status also modulates LV end diastolic pressure, and LVAD flows can markedly drop when patients with centrifugal flow LVADs (HeartMate 3 and HVAD) are intravascularly volume depleted.

The exercise physiology of the native LV acting in concert with LVAD support

Adding to the complexity of the response of the LVAD during exercise is the contribution of the native LV during exercise. Specifically, residual contraction of the native LV contributes to pump flow in a variable manner, both at rest and during exercise. Residual LV contraction leads to increased LV filling pressures, which peaks during systole, resulting in LVAD flow rates during systole that are 3 times higher than during diastole.[8]

If LV pressure exceeds aortic pressure during systole, aortic valve opening will occur in LVAD patients without fused/stenotic aortic valves. In this scenario, the LVAD works in parallel with the native heart, contributing up to an additional 3 L/min of CO from the native

Table 1
Measures of functional capacity and other cardiopulmonary measures before and following LVAD implantation.

Study	Participants Age	Device type (n)	Time of testing before LVAD implant (days)	Time of testing after LVAD implant (days)	Preoperative LVAD Exercise metrics	Postoperative LVAD Exercise metrics	*P* Value
Benton et al. (2015)	56 + 12	10 HM II	**121**	178	pVO_2 = 11.6 ± 5.0 mL/kg/min % pVO_2 = 40%	pVO_2 = 15.4 ± 3.9 mL/kg/min % pVO_2 = 54%	**0.009** **0.010**
Cowger et al. (2018)	60 ± 12	135 HM 3	N/A	180	6 MW = 173 (0–290 m)	6 MW = 312 (215–407)	**<0.0001**
Cowger et al. (2018)	59 ± 12	127 HM II	N/A	180	6 MW = 39 (0–259 m)	6 MW = 358 (259–415)	**<0.0001**
Gallastegi et al. (2020)	52 ± 2	25 HVAD 5 HM 3	**29**	109	pVO_2 = 11.0 ± 0.53 mL/kg/min Ex time = 7.2 ± 0.6 min VE/VCO_2 = 45.4 ± 1.6	pVO_2 = 12.7 ± 0.61 mL/kg/min Ex time = 8.9 ± 0.5 min VE/VCO_2 = 40.3 ± 1.3	**0.001** **0.003** **<0.001**
Leibner et al. (2013)	55 ± 9	21 HM II 4 HVAD	N/A	30–90	pVO_2 = 10.1 ± 3.4 mL/kg/min %pVO_2 = 34%	pVO_2 = 13.4 ± 5.5 mL/kg/min %pVO_2 = 44%	**<0.05** **<0.05**
Rosenbaum et al. (2018)	63 ± 10	43 HM II 6 HVAD	**36**	350	pVO_2 = 11.8 ± 2.9 mL/kg/min Ex time = 5.1 min VE/VCO_2 = 39.2 ± 6.5 6 MW = 344 ± 77 m	pVO_2 = 12.4 ± 3.0 mL/kg/min Ex time = 5.8 min VE/VCO_2 = 36.0 ± 6.3 6 MW = 393 ± 81 m	0.26 **0.02** **0.001** **<0.001**
Slaughter (2009)	62 ± 12	50 HM II	N/A	90	6MWT = 182 ± 140	6MWT = 319 ± 191	**<0.0001**

Abbreviations: 6MWT, six-minute walk test; HMII, Heart Mate II; HM3, Heart Mate 3; HVAD, Heart Ware; pVO_2, peak oxygen uptake; %pVO_2, Percent predicted peak oxygen uptake; VE/VCO_2, Slope of the ratio of minute ventilation to carbon dioxide production. Bold values indicate a p value < 0.05

heart (via ejection through the aortic valve).[22] Evidence of this parallel blood flow, which was also reported in first generation pulsatile LVADs, is supported by exercise studies showing CO values that exceed the known parameters of the device.[22–24]

In patients with fixed/fused aortic valve leaflets or marginal residual LV contractility, the LVAD continues to work in series with the heart during exercise. In this scenario, residual isovolumic LV contraction does not allow for aortic valve opening during exercise, but the pressure gradient between the LVAD inflow and aorta is still reduced, promoting increased flow through the pump during ventricular systole.

The effect of mechanical LVAD support on exercise capacity

Peak VO_2 is an important predictor of survival in patients on LVAD support.[25] A recent analysis found survival cut-off values for risk stratification in LVAD patients that are similar to patients with HFrEF (i.e. ≤ 12 mL/kg/min on a beta-blocker or ≤ 14 mL/kg/min without a beta-blocker).[25] Despite several studies examining peak VO_2 before and after LVAD implant, uncertainty remains whether continuous flow-LVADs alone improve peak exercise capacity (Table 1). In one of the largest cohorts of patients to perform cardiopulmonary exercise testing before and after LVAD implant ($n = 49$), Rosenbaum et al. reported a non-significant increase in peak VO_2 of 0.6 mL/kg/min ($p = 0.26$) at 12 months following implant.[26] While clinically and/or statistically significant increases in peak VO_2 were not observed, significant improvements in peak exercise time (+0.7 min), six-minute walk test (6MWT) distance (+49 m), and ventilatory efficiency [minute ventilation / volume of carbon dioxide expired slope] were noted. Other smaller studies have demonstrated significant improvements in peak VO_2 after LVAD implant; however, the reported increases were modest at best[17,27,28].

One factor likely contributing to persistently low age-predicted peak VO_2 levels is the presence of peripheral maladaptations seen in patients with advanced HF, such as reduced muscle capillary density, endothelial dysfunction, myocyte atrophy, and downregulation in aerobic enzyme activity (e.g., citric synthase, etc.).[29–31] Additionally, extended hospitalization before and after LVAD implant (16–20 day postoperative and 20–30 days for total length of stay) can markedly exacerbate deconditioning and lead to delays in starting CR. In fact, a report by Richey et al. found that the average time to begin CR following LVAD implant was 140 days, which was 90 days longer than the average delay for patients undergoing coronary artery bypass graft surgery and 74 days longer than observed for HT patients.[6] Serial exercise testing after LVAD implant suggests there may be a small increase in peak VO_2 within the first few months following LVAD implantation, but over a longer period peak VO_2 remains relatively unchanged.[32–34] Therefore, important implications arise relative to the potential role for exercise training in helping partially restore peak VO_2 and other measures of functional capacity.

Measures of submaximal functional capacity after LVAD implant

Despite the mixed results for improvement in peak VO_2 after LVAD, improvements in submaximal measures of exercise tolerance and quality of life have consistently been noted in clinical trials.[35–38] In a recent clinical trial of patients on HM3 LVAD support, average 6 MWT distance increased by 94 m by 6 months postoperative.[37]

One challenge with such comparisons is that many patients are simply unable to perform any assessment of exercise tolerance or functional capacity just prior to LVAD implant. This limitation was illustrated by Rogers et al. (2010) and Cowger et al. (2018), both of which utilized 6MWT distance to measure functional improvements. In these two studies, if a patient was unable to perform a 6MWT prior to LVAD implant, they were assigned a 6MWT distance of zero at baseline, thus potentially inflating the magnitude of improvement in functional capacity after LVAD implant. However, because the vast

majority of LVAD patients are intensive care unit confined prior to LVAD implant due to various degrees of cardiogenic shock, it is likely that the gains noted in 6MWT distance following LVAD implant are clinically relevant.

The effects of exercise training in patients with LVAD support

While limited by a small number of single site trials, aerobic exercise training does appear to improve peak VO_2 by roughly 10%–20% in this population.[32,39–41] Most of the training studies to date that measured peak VO_2 in patients on LVAD support have involved 6–12 weeks of supervised, continuous aerobic-type exercise at a moderate intensity utilizing either cycle ergometers or treadmills (Table 2). A meta-analysis of 4 randomized trials involving 74 patients on LVAD support reported improvements in peak VO_2 (+1.94 mL/kg/min, 95% CI 0.63–3.26, $p = 0.004$).[42] However, not all training studies in LVAD patients have noted similar gains in peak VO_2. Additionally, some trials reported improvements in peak VO_2 based on paired analysis within the training groups but found no significant change when measured against a comparison group. This may be a result of small sample sizes, variable patient phenotypes, or to the timing of the intervention, which if it occurred shortly after implant, might have masked changes in peak VO_2 unique to exercise training because of improvements attributable to the LVAD itself. As mentioned earlier, another possibility as to why peak VO_2 has been found not to improve or improve modestly with training may be due to the limitations of the LVAD, as well as concomitant right heart dysfunction.

However, despite absent or modest improvements in peak VO_2 following exercise training, gains in muscular strength, quality of life, and improvements in measures of submaximal exercise have been noted in LVAD patients who have entered exercise training programs (Table 2). A qualitative meta-analysis of three randomized exercise training trials showed an average 60 m increase in the 6MWT (95% CI, 22.61–97.50, $P = 0.002$) following training[43] with or without improvements in peak VO_2.[34,36,39] In a prospective, non-randomized trial of patients on long-term LVAD support (i.e. time on LVAD support ~18 months), Villela et al. reported no change in peak VO_2 but a significant improvement in VO_2 at ventilatory threshold [7.1 (6.5, 9.1) to 8.5 (7.7, 9.3) mL/kg/min, $P = 0.04$] following 5 weeks of higher intensity interval training.[36] Similarly, in a long-term study of LVAD patients who participated in CR, Marko et al. also showed improvements in ventilatory threshold (5%) and time to exhaustion (33%) despite the absence of any significant change in peak VO_2.[34]

Patient reported health outcomes has also improved with exercise training and such changes are independently associated with clinical outcomes. And while there are many reports showing improvement in these measures following LVAD implantation alone, there is evidence that exercise training further improves patient reported health outcomes. In a randomized trial comparing usual care to 18 visits in CR (i.e., 3 days/wk. for 6 weeks), the CR group reported improved scores on the Kansas City Cardiomyopathy Questionnaire (mean increase = 14.4 points compared to no change in the usual care group).[39] Laoutaris et al. found similar improvements using the Minnesota Living with Heart Failure Questionnaire, while a training study by Karapolat et al. reported reductions in symptoms of depression in patients with LVADs as measured by the Beck depression questionnaire, showing an average improvement from 11.3 ± 7.4 to 5.0 ± 6.0.[44] What is presently unknown about these improvements in patient reported health outcomes, is if a particular exercise mode or intensity of exercise modifies or accentuates the response. Additionally, presently unknown is the influence that social support, such as occurs in CR, has on patient reported outcomes.

Muscular strength, which is a known correlate to patient reported health outcomes and disability, is also associated with improved KCCQ scores in patients on LVAD support.[38,45] In addition, muscular strength (as measured by a hand grip test) was found to be associated with reduced hospital length of stay in patients hospitalized for LVAD implantation.[46,47] Despite the positive associations between strength and outcomes, resistance training studies in this patient population are sparse. The few exercise training studies that did incorporate resistance exercises did not report any issues and reported improvements in muscular strength and endurance similar to other HF patients.[32,34,40] To our knowledge there has not been a comparison study between aerobic exercise training and strength training.

Prescribing exercise in patients with LVAD support

Based on the above training studies, exercise seems to be well tolerated and safe in patients on LVAD support. While many exercise trials in the LVAD population have not disclosed adverse effects, those that have, report very few untoward events.[39,41] Examples of these is a study by Karapolat et al. that reported only 1 occurrence (i.e., non-sustained ventricular tachycardia) in over 1600 exercise hours and another study by Kerrigan et al., reporting a single syncopal episode after exercise out of 313 training sessions.[39,41]

The training stimulus needed to improve functional capacity appears to be the same as patients with HFrEF not on LVAD support. Thus, performing aerobic exercise 3–5 days/week, for 20–60 min, at intensities starting as low as 40% of peak VO_2 reserve (depending on exercise capacity) and gradually progressing up to 80% peak VO_2 reserve would be appropriate for patients on LVAD support. Heart rate reserve (HRR) can be used as a surrogate measure of peak VO_2 reserve to guide exercise intensity, despite the discordance between the LVAD and native heart. An exception to this would be in patients who display chronotropic incompetence or rely on a permanent pacemaker to increase rate.[48] For these patients there is a weaker association between VO_2 and HR during exercise; therefore, the use of other methods to guide intensity such as the Borg rating of perceived exertion (6–20 scale) or the Talk Test method would be more appropriate.[48]

Resistance training is also recommended for patients on LVAD support, although due to the lack of research, there are no specific guidelines relative to repetitions, sets, and load (i.e., percent of one-repetition maximal). Studies in non-LVAD populations show that when compared to aerobic exercise, resistance exercises show a less pronounced reduction in total peripheral resistance and thus potentially, can negatively impact LVAD flow due to the device's sensitivity to afterload. Because of this, as well as other unknowns in this population, the resistance or intensity of work (i.e., amount of weight lifted) is generally conservative. This usually equates to performing resistance bands or light hand weights that can be done 10–15 repetitions, at an RPE of 11–13 on the 6–20 scale.

Due to the device itself, there are important precautions to consider beyond the standard wait of 8–12 weeks following sternotomy and LVAD implant.[49] One of these precautions includes restricting extensive trunk flexion (e.g., sit-ups, leg lifts), which may disrupt the integrity of LVAD powerline (aka driveline) at the site where it exists in the skin (i.e., a risk for infection) or increase intra-abdominal pressure (which can reduce LVAD flow rate). None of the equipment should be exposed to high levels of moisture (dampening from sweat is generally okay) or submersion in water. Another precaution needed for all LVAD patients is reliable driveline stabilization (e.g., abdominal binder or extensive driveline skin anchoring) to reduce the risk of trauma where the driveline exits the skin or distally, including entanglement of the driveline on exercise equipment.[50] While it is highly unlikely a patient will experience disconnection of power when power sources are securely fastened per device instructions for use, severe or repetitive kinking of the power line can damage wire integrity, leading to rare interruptions in power supply. Careful attention to fall risk is important for this population due to the extra weight of the device equipment (i.e., batteries and device controller) which can affect the center of gravity in the LVAD patient. As a result, choosing alternative exercises such as a sit-to-stand or wall squats, as opposed to a regular squat can help build leg strength

Table 2
Measures of functional capacity and other cardiopulmonary measures before and following exercise training in patients with an LVAD.

Study	Participants Age (n)	Device type (n)	Study design	Time following LVAD implant (days)	Before training exercise metrics	After training exercise metrics	P Value (within group)
Laoutaris et al. (2011)	TG = 38 ± 18 CG = 42 ± 15	4 INCOR 10 pulsatile LVADs 17 EXCOR 11 BiVAD	Randomized control design. Combined home and supervised exercise on a cycle ergometer or treadmill for 45 min 3–5 day/wk.	TG = 198 ± 132 CG = 168 ± 114	**TG** pVO_2 = 16.8 ± 2.9 mL/kg/min VT = 12.0 ± 5.6 mL/kg/min Ex time = 9.7 ± 2.2 min VE/VCO2 = 40 ± 6.5 6 MW = 462 ± 88 m **CG** pVO_2 = 14.9 ± 4.0 mL/kg/min VT = 12.2 ± 4.4 mL/kg/min Ex time = 8.0 ± 2.9 min VE/VCO2 = 41.4 ± 6.5 6 MW = 430 ± 41 m	**TG** pVO_2 = 19.3 ± 4.5 mL/kg/min VT = 15.1 ± 4.2 mL/kg/min Ex time = 10.1 ± 1.9 min VE/VCO2 = 35.9 ± 5.6 6 MW = 527 ± 76 **CG** pVO_2 = 14.8 ± 4.2 mL/kg/min VT = 12.9 ± 3.4 mL/kg/min Ex time = 8.4 ± 2.9 min VE/VCO2 = 40.2 ± 7.3 6 MW = 448 ± 55 m	**0.008** **0.001** 0.3 **0.009** **0.005** 0.5 0.6 0.2 0.9 0.1
Hayes et al. (2012)	47 ± 15	14 VentrAssist	Randomized control design. Supervised training, 8 weeks on a cycle ergometer and treadmill for 30 min, 3 days/wk. 6 strength training exercises	Combined TG and CG = 32	**TG** pVO_2 = 10.5 ± 2.3 mL/kg/min Peak work = 42.0 ± 15.4 W 6 MW = 351 ± 77 m **CG** pVO_2 = 12.4 ± 1.7 mL/kg/min Peak work = 50.4 ± 21.6 W 6 MW = 367 ± 77 m	**TG** pVO_2 = 14.8 ± 4.9 mL/kg/min Peak workload = 74.5 ± 31.3 W 6 MW = 531 ± 131 m **CG** pVO_2 = 15.3 ± 4.4 mL/kg/min Peak workload = 79.4 ± 45.0 W 6 MW = 489 ± 95 m	**<0.05** **<0.05** **<0.05** **<0.05** **<0.05** **<0.05**
Karapolat et al. (2013)	46 ± 14;	3 EXCOR 8 HVAD	Retrospective study. 8-week training period. 90 mins, 3 days/wk. using various aerobic modalities and 8 upper and lower body resistance exercise. Aerobic exercise was at 60%–70% peak VO_2	TG = 84 ± 64	**TG** pVO_2 = 14.7 ± 3.6 mL/kg/min	**TG** pVO_2 = 15.1 ± 3.4 mL/kg/min	**<0.05**
Kerrigan et al. (2014)	TG = 53 ± 13 CG = 60 ± 12	20 HM II 6 HVAD	Randomized control design. Supervised training, six weeks 30 mins, 3 days/wk. of stationary cycling, treadmill, or recumbent stepper. Aerobic exercise was at 60% heart rate reserve.	TG = 91 ± 33 CG = 73 ± 32	**TG** pVO_2 = 13.6 ± 3.3 mL/kg/min VT = 10.0 ± 2.1 mL/kg/min Ex time = 7.9 ± 1.6 min VE/VCO2 = 36.8 ± 8.7 6 MW = 350 ± 65 m **CG** pVO_2 = 11.2 ± 2.0 mL/kg/min VT = 9.1 ± 0.7 mL/kg/min Ex time = 6.6 ± 2.7 min VE/VCO2 = 38.8 ± 8.0 6 MW = 337 ± 59 m	**TG** pVO_2 = 15.3 ± 4.4 mL/kg/min VT = 10.9 ± 2.1 mL/kg/min Ex time = 11.0 ± 2.1 min VE/VCO2 = 37.8 ± 8.8 6 MW = 402 ± 89 m **CG** pVO_2 = 11.8 ± 2.0 mL/kg/min VT = 9.3 ± 1.0 mL/kg/min Ex time = 7.4 ± 2.9 min VE/VCO2 = 37.2 ± 8.4 6 MW = 356 ± 52 m	**<0.05** **<0.05** **<0.05** >0.05 **<0.05** >0.05 >0.05 >0.05 >0.05 >0.05
Marko et al. (2015)	TG = 55 ± 12	9 HM II 32 HVAD	Retrospective analysis. ~32 Cardiac rehabilitation sessions using a combination of stationary cycling and free walking at an RPE of 13 on the Borg scale. Lower extremity strength training 2 sets, 12 reps	TG = 48 ± 38	**TG** pVO_2 = 11.3 ± 4.1 mL/kg/min Peak work = 37.8 ± 17.6 W VE/VCO2 = 37.8± 7.9	**TG** pVO_2 = 14.5 ± 5.2 mL/kg/min Peak work = 61.5 ± 24.6 W VE/VCO2 = 33.7± 5.8	**0.007** **0.004** **0.022**
Marko et al. (2017)	TG = 57 ± 9;	7 HM II 8 HVAD	Retrospective analysis of individuals who participated in CR twice, separated by over a year. Training was conducted within of cardiac rehabilitation	TG = 547 ± 197	**TG** pVO_2 = 12.3 ± 3.2 mL/kg/min Peak work = 55.7 ± 24.5 W	**TG** pVO_2 = 12.2 ± 4.0 mL/kg/min Peak work = 82.9 ± 26.2 W	0.906 **<0.001**
Villela et al. (2021)	TG = 51 (29–71)	12 HM II 3 HM 3	Prospective, observational study. 5 wk. Supervised training period, 3 days wk. of high intensity exercise training on a cycle ergometer. HIIT protocol: 30 s warm-ups Six 30-s-high intensity intervals followed by 4-min active recovery.	TG = 540 (90–1920)	**TG** pVO_2 = 11.9 (9.5–14.8) mL/kg/min VT = 7.1 (6.5–9.1) mL/kg/min Peak work = 99 (25–141) Watts VE/VCO2 = 40 (35–44)	**TG** pVO_2 = 12.0 (10–15) mL/kg/min VT = 8.5 (7.7–9.3) mL/kg/min Peak work = 100 (67–124) Watts VE/VCO2 = 42 (37–43)	0.6 **0.04** 0.18 0.88

Abbreviations: 6MWT, six-minute walk test; CG, Control group; EXCOR, extracorporeal; HMII, Heart Mate II; HM3, Heart Mate 3; HVAD, Heart Ware; INCOR, Intracorporeal; LVAD, Left ventricular assist device; pVO_2, peak oxygen consumption; $\%pVO_2$, Percent predicted peak oxygen consumption; TG, treatment group; VE/VCO_2, Ratio of minute ventilation to carbon dioxide production; RPE, Rating of perceived exertion; VT, Ventilatory threshold. Bold values indicate a p value < 0.05

while reducing the risk of falls. Finally, extended cool down periods and hydration during recovery are recommended to avoid provocation of hypotension, dizziness/orthostasis, or device low flow alarms related to BP dysregulation or dehydration. All patients should have an emergency bracelet or their LVAD labeled with clear information to contact their physician or LVAD coordinator for questions or urgencies that may arise.

Future considerations addressing exercise in patients on LVAD support

Exercise training has been shown to have short-term benefits for patients on LVAD support. As LVAD technology and outcomes continue to improve and the number of patients on long-term MCS increases, there will be more opportunities to look at the long-term effects of regular exercise on both patient-centered outcomes and LVAD function. Additionally, there is a need to examine the effects of CR participation and clinical outcomes in these patients; although a retrospective analysis by Bachmann et al. showed participation in CR was associated with a 23% lower adjusted one-year hospitalization risk (95% CI 11%–33%, $p < 0.001$) and a 47% lower adjusted one-year mortality risk (95% CI 18%–66%, $p < 0.01$), a data deficit remains relative to the impact of CR on risks for hospitalization and/or mortality[51] in patients with an LVAD.

In addition to exploring more potential benefits of exercise for patients on LVAD support, there is also a need to reduce common exercise barriers. The delivery of home-based CR is an opportunity to circumvent a common barrier to exercise in this population. In a non-randomized trial by Kugler et al. patients on continuous flow LVADs were given cycle-ergometers and asked to follow a home-based exercise and nutrition program with telephone follow-ups.[52] Compared with a usual care control group, the home-based exercise group showed improvements in both predicted peak workload and percent predicted peak VO_2.[52] At minimum, this study demonstrated the feasibility of performing a home-based model in this population and with the recent expansion of telehealth strategies due the COVID pandemic, the capabilities to provide additional virtual methods of CR continue to expand.

Another important finding from the study by Kugler et al. was the attenuation of body mass index in the exercise group, while the control group reported 5-unit increase. This is important and an untapped area of research, because many studies report substantial increases in body mass index following LVAD implant, which can effect transplant status and potentially lead to further complications.[53] The above illustrates yet another need and opportunity to provide exercise and lifestyle interventions in the LVAD population. Future interventions will need to take into account the uniqueness of the LVAD population, considering both the interaction between the device and human physiology and the specific needs and characteristics of the patient supported by it. Lastly, as the LVAD technology evolves so must the exercise and lifestyle strategies used to improve the health and well-being of these patients.

Declaration of Competing Interest

None.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2013;128:1810-1852.
2. Molina EJ, Shah P, Kiernan MS, et al. The society of thoracic surgeons intermacs 2020 annual report. Ann Thorac Surg 2021;111:778-792.
3. Mehra MR, Goldstein DJ, Uriel N, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. N Engl J Med 2018;378:1386-1395.
4. Pagani FD, Cantor R, Cowger J, et al. Concordance of treatment effect: an analysis of the Society of Thoracic Surgeons Intermacs database. Ann Thorac Surg 2021;21.10.1016, Ahead of print.
5. Mehra MR, Uriel N, Naka Y, et al. A fully magnetically levitated left ventricular assist device — final report. New Engl J Med 2019;380:1618-1627.
6. Ritchey MD, Maresh S, McNeely J, et al. Tracking cardiac rehabilitation participation and completion among Medicare beneficiaries to inform the efforts of a National Initiative. Circ Cardiovasc Qual Outcomes 2020;13, e005902.
7. Ben Gal T, Piepoli MF, Corrà U, et al. Exercise programs for LVAD supported patients: a snapshot from the ESC affiliated countries. Int J Cardiol 2015;201:215-219.
8. Akimoto T, Yamazaki K, Litwak P, et al. Rotary blood pump flow spontaneously increases during exercise under constant pump speed: results of a chronic study. Artif Organs 1999;23:797-801.
9. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription. Tenth Edition ed.* Lippincott Williams & Wilkins. 2018.
10. Muthiah K, Gupta S, Otton J, et al. Body position and activity, but not heart rate, affect pump flows in patients with continuous-flow left ventricular assist devices. JACC Heart Fail 2014;2:323-330.
11. Fresiello L, Jacobs S, Timmermans P, et al. Limiting factors of peak and submaximal exercise capacity in LVAD patients. PLoS One 2020;15, e0235684.
12. Levine BD, Cornwell WK, Drazner MH. Factors influencing the rate of flow through continuous-flow left ventricular assist devices at rest and with exercise *. JACC: Heart Fail 2014;2:331-334.
13. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail 2010;3:668-674.
14. Vignati C, Apostolo A, Cattadori G, et al. Lvad pump speed increase is associated with increased peak exercise cardiac output and vo(2), postponed anaerobic threshold and improved ventilatory efficiency. Int J Cardiol 2017;230:28-32.
15. Jung MH, Hansen PB, Sander K, et al. Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. Eur J Heart Fail 2014;16:403-408.
16. Jung MH, Houston B, Russell SD, Gustafsson F. Pump speed modulations and submaximal exercise tolerance in left ventricular assist device recipients: a double-blind, randomized trial. J Heart Lung Transpl: Off Public Int Soc Heart Transpl 2017;36:36-41.
17. Fresiello L, Gross C, Jacobs S. Exercise physiology in left ventricular assist device patients: insights from hemodynamic simulations. Ann Cardiothoracic Surg 2021;10:339-352.
18. Severin R, Sabbahi A, Ozemek C, Phillips S, Arena R. Approaches to improving exercise capacity in patients with left ventricular assist devices: an area requiring further investigation. Expert Rev Med Dev 2019;16:787-798.
19. Lim HS, Howell N, Ranasinghe A. The physiology of continuous-flow left ventricular assist devices. J Card Fail 2017;23:169-180.
20. Slaughter MS, Pagani FD, Rogers JG, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transpl: Off Public Int Soc Heart Transpl 2010;29:S1-39.
21. Salamonsen RF, Mason DG, Ayre PJ. Response of rotary blood pumps to changes in preload and afterload at a fixed speed setting are unphysiological when compared with the natural heart. Artif Organs 2011;35:E47-E53.
22. Jacquet L, Vancaenegem O, Pasquet A, et al. Exercise capacity in patients supported with rotary blood pumps is improved by a spontaneous increase of pump flow at constant pump speed and by a rise in native cardiac output. Artif Organs 2011;35:682-690.
23. Brassard P, Jensen AS, Nordsborg N, et al. Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. Circ Heart Fail 2011;4:554-560.
24. Lai JV, Muthiah K, Robson D, et al. Impact of pump speed on hemodynamics with exercise in continuous flow ventricular assist device patients. ASAIO J (Am Soc Artif Intern Org: 1992) 2020;66:132-138.
25. Mirza KK, Szymanski MK, Schmidt T, et al. Prognostic value of peak oxygen uptake in patients supported with left ventricular assist devices (PRO-VAD). JACC Heart Fail 2021;10:758-767.
26. Rosenbaum AN, Dunlay SM, Pereira NL, et al. Determinants of improvement in cardiopulmonary exercise testing after left ventricular assist device implantation. ASAIO J (Am Soc Artif Intern Org: 1992) 2018;64:610-615.
27. Benton CR, Sayer G, Nair AP, et al. Left ventricular assist devices improve functional class without normalizing peak oxygen consumption. ASAIO J (Am Soc Artif Intern Org: 1992) 2015;61:237-243.
28. Gallastegi AD, Ozturk P, Demir E, Nalbantgil S, Yagdi T, Ozbaran M. Prospective evaluation of ventricula assist device risk scores capacity to predict cardiopulmonary exercise parameters. Interact Cardiovasc Thorac Surg 2020;30:223-228.
29. Vuckovic KM, Piano MR, Phillips SA. Effects of exercise interventions on peripheral vascular endothelial vasoreactivity in patients with heart failure with reduced ejection fraction. Heart Lung Circ 2013;22:328-340.
30. Duscha BD, Kraus WE, Keteyian SJ, et al. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. J Am Coll Cardiol 1999;33:1956-1963.
31. Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. Am J Physiol Heart Circ Physiol 2012;302:H1050-H1063.
32. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transpl: Off Public Intern Soc Heart Transpl 2012;31:729-734.
33. Leibner E, Cysyk J, Eleuteri K, El-Banayosy A, Boehmer J, Pae W. Changes in the functional status measures of heart failure patients with mechanical assist devices. ASAIO J 2013;59:117-122.

34. Marko C, Xhelili E, Lackner T, Zimpfer D, Schima H, Moscato F. Exercise performance during the first two years after left ventricular assist device implantation. ASAIO J (Am Soc Artif Intern Org: 1992) 2017;63:408-413.
35. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-1834.
36. Villela MA, Chinnadurai T, Salkey K, et al. Feasibility of high-intensity interval training in patients with left ventricular assist devices: a pilot study. ESC Heart Fail 2021;8:498-507.
37. Cowger JA, Naka Y, Aaronson KD, et al. Quality of life and functional capacity outcomes in the MOMENTUM 3 trial at 6 months: a call for new metrics for left ventricular assist device patients. J Heart Lung Transpl: Off Public Intern Soc Heart Transpl 2018;37:15-24.
38. Dunlay SM, Allison TG, Pereira NL. Changes in cardiopulmonary exercise testing parameters following continuous flow left ventricular assist device implantation and heart transplantation. J Card Fail 2014;20:548-554.
39. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-659.
40. Karapolat H, Engin C, Eroglu M, al. e.. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. Transplant Proc 2013;42:1026-1032.
41. Marko C, Danzinger G, Kaferback M, et al. Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. Eur J Prev Cardiol 2015;22:1378-1384.
42. Grosman-Rimon L, Lalonde SD, Sieh N, et al. Exercise rehabilitation in ventricular assist device recipients: a meta-analysis of effects on physiological and clinical outcomes. Heart Fail Rev 2019;1:55-67.
43. Mahfood Haddad T, Saurav A, Smer A, et al. Cardiac rehabilitation in patients with left ventricular assist device: a systematic review and meta-analysis. J Cardiopulm Rehabil Prev 2017;37:390-396.
44. Karapolat H, Engin C, Eroglu M, et al. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. Transplant Proc 2013;45:3381-3385.
45. Savage PA, Shaw AO, Miller MS, et al. Effect of resistance training on physical disability in chronic heart failure. Med Sci Sports Exerc 2011;43:1379-1386.
46. Yost G, Bhat G. Relationship between handgrip strength and length of stay for left ventricular assist device implantation. Nutrit Clin Pract: Off Public Am Soc Parent Enteral Nutrit 2017;32:98-102.
47. Kerrigan DJ, Williams CT, Ehrman JK, et al. Muscular strength and cardiorespiratory fitness are associated with health status in patients with recently implanted continuous-flow LVADs. J Cardiopulm Rehabil Prev 2013;33:396-400.
48. Kerrigan DJ, Williams CT, Brawner CA, et al. Heart rate and V O2 concordance in continuous-flow left ventricular assist devices. Med Sci Sports Exerc 2016;48:363-367.
49. AACVPR. *Guidelines for Cardiac Rehabilitation Programs. 6th ed.* Champaign, IL: Human Kinetics. 2021.
50. Adamopoulos S, Corrà U, Laoutaris ID, et al. Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the committee on exercise physiology and training and the Committee of Advanced Heart Failure of the heart failure Association of the European Society of cardiology. Eur J Heart Fail 2019;21:3-13.
51. Bachmann JM, Duncan MS, Shah AS, et al. Association of cardiac rehabilitation with decreased hospitalizations and mortality after ventricular assist device implantation. JACC Heart Fail 2018;6:130-139.
52. Kugler C, Malehsa D, Schrader E, et al. A multi-modal intervention in management of left ventricular assist device outpatients: dietary counselling, controlled exercise and psychosocial support. Eur J Cardio-thoracic Surg: Off J Eur Assoc Cardio-thoracic Surg 2012;42:1026-1032.
53. Coyle LA, Ising MS, Gallagher C, et al. Destination therapy: one-year outcomes in patients with a body mass index greater than 30. Artif Organs 2010;34:93-97.