JACC: HEART FAILURE VOL. ■, NO. ■, 2020

PUBLISHED BY ELSEVIER

Hemodynamic Response to Exercise in Patients Supported by Continuous Flow Left Ventricular Assist Devices

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ABSTRACT

OBJECTIVES This study sought to characterize the hemodynamic response to exercise in LVAD-supported patients and identify parameters most strongly associated with peak oxygen consumption (VO_2).

BACKGROUND Despite improved survival for heart failure patients afforded by continuous flow left ventricular assist devices (LVADs), peak exercise capacity remains impaired. Mechanisms underlying this reduced functional capacity remain poorly understood.

METHODS Patients referred for post-VAD hemodynamic optimization from December 2017 through June 2019 were enrolled. Swan Ganz catheters were inserted and upright incremental bicycle ergometry with respiratory gas analysis was performed. Hemodynamic measurements, mixed venous saturation, and arterial blood pressure were recorded every 3 min during exercise. Linear correlations were performed between peak VO_2 (ml/min) and peak Fick cardiac output (CO), peak device flow, the assumed intrinsic CO derived as Fick CO-device flow, peak pressure differential across the LVAD (mean arterial pressure−pulmonary capillary wedge pressure), peak pressure differential across right ventricle (mean pulmonary artery pressure − right atrial pressure) and systemic vascular resistance.

RESULTS Forty-five patients supported by axial flow pumps (n = 12) and centrifugal flow pumps (n = 33) were studied. There were 34 men and 11 women. Age averaged 60 ± 10 years. Peak VO_2 averaged 10.6 ± 3.1 ml/kg/min. Fick CO had the greatest correlation with peak VO_2 with $r = 0.73$ ($p < 0.0001$) followed by intrinsic CO ($r = 0.67$; $p < 0.0001$). Multivariate model that best predicted peak VO_2 included Fick CO and peak arterial venous oxygen (AVO_2) difference.

CONCLUSIONS LVAD supported patients have severely impaired peak exercise capacity. The peak Fick cardiac output was the best correlate of peak exercise performance. (J Am Coll Cardiol HF 2020;■:■-■)

Despite the impressive improvement in survival and quality of life for patients with advanced heart failure afforded by left ventricular assist devices (LVADs), peak exercise capacity remains impaired (1-6). Several studies have reported significantly lower than normal peak oxygen consumption (VO_2) during cardiopulmonary exercise testing for patients on LVAD support (7-9). The mechanism underlying this impairment of functional capacity despite restoration of resting blood flow on LVAD support remains poorly understood (7-9). The current generation devices use continuous flow technology with axial (Heartmate II, Abbott, Abbott Park, Illinois) (1,2) and centrifugal flow mechanics with partial (Heartware, HVAD, Medtronic) (3,4) or fully (Heartmate 3, Abbott) (5,6) magnetically levitated rotor. None of the current devices have the ability to modify rotational speed based on workload. The

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Manuscript received September 4, 2019; revised manuscript received October 9, 2019, accepted October 10, 2019.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2019.10.013

ABBREVIATIONS AND ACRONYMS

AVO_2 = arterial venous oxygen

CHF = congestive heart failure

CO = cardiac output

LVAD = left ventricular assist device

mPAP = mean pulmonary artery pressure

MAP = mean arterial pressure

OUES = oxygen uptake efficiency slope

PAP = pulmonary artery pressure

PCWP = pulmonary capillary wedge pressure

RAP = right atrial pressure

SVR = systemic vascular resistance

TPR = total pulmonary resistance

VCO_2 = carbon dioxide production

VO_2 = peak oxygen consumption

VE = minute ventilation

VE/VCO_2 = ventilatory slope

original generation of pulsatile LVADs accomplished this using an "eject on full" algorithm with which flow increased physiologically in response to increases in venous return and native heart rate. The output of each current device is dependent on the instantaneous pressure differential that occurs across the pump, namely, the pressure difference between mean arterial pressure (MAP) and left ventricular end-diastolic pressure or between mean arterial pressure and pulmonary capillary wedge (PCWP) when PCWP is used as a surrogate for left ventricular end-diastolic pressure (MAP-PCWP) (8). During normal exercise, there is an increase in preload and a variable change in afterload. In patients on LVAD support, these changes may not occur to the same extent. How hemodynamic parameters change in response to exercise and then correlate with VO_2 is poorly understood. We sought to characterize the hemodynamic response to exercise in patients on LVAD support and identify those hemodynamic parameters most highly correlated with peak VO_2.

METHODS

All prospective patients at a single university center who were referred for routine post-LVAD hemodynamic optimization from December 2017 through June 2019 were approached for participation in this study. Over this period, 45 patients were enrolled. Only 11 patients did not participate in the study (5 patients refused participation, 6 patients were too ill to participate [i.e., 3 with acute decompensated heart failure, 1 in sustained ventricular tachycardia, and 2 with severe deconditioning). Five patients supported by centrifugal Heartware were also excluded.

Resting echocardiographic data including left ventricular ejection fraction, left ventricular end-diastolic dimension, right ventricular size and function, and presence of mitral, tricuspid, and aortic insufficiency were included from the nearest study within 3 months of the exercise test.

A Swan Ganz catheter was placed under fluoroscopy in the cardiac catheterization laboratory. After placement, the patient was transported with the Swan Ganz catheter to the cardiopulmonary exercise laboratory. Patients underwent upright incremental bicycle exercise on a cycle ergometer (Lode, Groningen, the Netherlands) with respiratory gas analysis (Med Graphics Ultima O_2) beginning at unloaded exercise and increasing by 25 Watts every 3 min. Hemodynamic measurements, VO_2, carbon dioxide production (VCO_2), minute ventilation (VE), perceived level of exertion (Borg Scale), pulse oximetry, mixed venous saturation, and blood pressure measurements (Terumo) (10) were recorded during exercise.

Peak VO_2 was defined as the highest 30-s average of oxygen consumption. The ventilatory threshold was identified as the point at which the ventilatory equivalent for O_2 (VE/VO_2) is minimal, followed by a progressive increase. Ventilation was assessed by correlation of VE VCO_2 throughout exercise. Oxygen uptake efficiency slope (OUES) was determined using the following equation: $VO_2 = a \log_{10} VE + B$. VO_2 in ml/min was plotted on the y-axis and BE in l/min was plotted on the semilog transformed x-axis (11). The slope of this linear relationship, "a," represents the OUES.

The study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai. All patients provided informed consent.

DATA AND STATISTICAL ANALYSIS. All continuous variables are presented as mean ± SD. Categorical variables are summarized as frequencies and percentages. Comparison of baseline characteristics and rest and peak exercise variables between device types were performed using 2-sample Student's *t*-tests and chi-square tests. Pearson's correlation coefficients were used to assess the linear association between peak VO_2 and peak Fick cardiac output (CO), peak LVAD flow, assumed peak intrinsic CO derived as Fick CO − LVAD flow, peak pressure differential across the right ventricle (mean pulmonary artery pressure [PAP] - right arterial pressure [RAP]), peak pressure differential across the LVAD (MAP−PCWP), and systemic vascular resistance ([MAP−RAP]/CO·80), pulmonary artery pulsatility index ([PA systolic − PA diastolic pressure]/RAP), right ventricular stroke work index (mean PAP − mean RAP) × stroke volume index, where the stroke volume index was calculated as the cardiac index divided by the heart rate.

Multivariate linear models were used to predict peak VO_2 from other exercise parameters. A forward stepwise approach was used to include and retain variables in the multivariate model. All variables that showed a statistically significant association at the 0.1 level with peak VO_2 at the univariate level were used in the multivariate model. The model with the highest adjusted R^2 was chosen as the final model. Mixed linear models were used to compare the slopes of the Fick CO and the LVAD flow response during exercise.

All comparisons were conducted at the 0.05 2-sided significance level.

RESULTS

BASELINE CHARACTERISTICS. Forty-five patients were included in the study. Twelve patients were supported by axial flow pumps and 33 patients were supported by magnetically levitated centrifugal flow pumps (Heart Mate 3). The clinical characteristics of the patients are shown in Table 1. Patients supported by the axial flow pumps were more frequently bridge-to-transplant candidates and male compared with centrifugal flow pump patients. The axial flow supported patients were younger. The distribution of treatment with beta-blockers and angiotensin inhibitors was similar between the 2 groups as was the etiology of heart failure. For the patients in the axial flow group, 7 patients received carvedilol at an average daily dose of 22 mg and 2 received metoprolol XL at 25 mg. Of the patients supported with the centrifugal pumps, 15 patients received carvedilol at a daily dose of 22 mg, and 9 received metoprolol XL at 36 mg daily. More than 50% of patients in the centrifugal pump group had concomitant valve surgery including tricuspid and mitral valve repair/replacement. Based on the echocardiogram closest in proximity to the exercise test, 2 of the 45 patients had moderate to severe mitral regurgitation, none had moderate to severe aortic insufficiency, and 1 patient had moderate to severe tricuspid insufficiency. Left ventricular ejection fraction averaged 20.1 ± 6.3%; left ventricular end-diastolic dimension was 5.9 ± 1.2 cm. Eight patients had severe right ventricular dysfunction.

TABLE 1 Clinical Characteristics of Patient Cohort

	All (N = 45)	Axial (n = 12)	CF (n = 33)
Age (yrs)	59.8 ± 10.2	54.6 ± 11.1	61.2 ± 9.3*
Sex*			
Male	34 (76)	12 (100)	22 (67)
Female	11 (24)		11 (33)
Race			
White	22 (49)	6 (50)	16 (48)
Black	13 (29)	3 (25)	10 (30)
Hispanic	7 (18)	3 (25)	4 (15)
Asian	3 (4)		3 (7)
Etiology of CHF			
DCM	27 (60)	8 (66.7)	19 (58)
CAD	18 (40)	4 (33.3)	14 (42)
Indication for LVAD			
BTT	25 (56.0)	11 (91.7)	14 (42.0)
DT	20 (44.0)	1 (8.3)	19 (58.0)
Duration of implant (days)	241 ± 271	259 ± 336	234 ± 249
Device RPM		9,400 ± 120	5,384 ± 219
Hemoglobin (gm/dl)		12.1 ± 2.0	11.5 ± 1.5
Medications			
Digoxin	7 (15.5)	2 (16.7)	5 (15.0)
Beta-blocker	33 (73.3)	9 (75.0)	24 (73.0)
ACE/ARB/ARNI	24 (55)	9 (75)	15 (45)
Aldosterone inhibitor	26 (58.0)	5 (41.7)	21(64.0)
Diuretics	31 (69.0)	7 (58.3)	24 (73.0)
Amiodarone	6 (13.0)	1 (8.3)	5 (15.0)
Ancillary LVAD surgery			
TVR	27 (60)	3 (25)	24 (73)
AV Park Stitch/AVR	6 (15.4)	2 (16.7)	4 (14.8)
MV repair/replacement	23 (51.0)	1 (8.3)	22 (67.0)
Less invasive surgery	13 (29.0)	8 (66.7)	5 (15.0)

Value are mean ± SD or n (%). *p < 0.05, axial vs. CF.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitors; AV = aortic valve; AVR = aortic valve replacement; BTT = bridge to transplant; CF = centrifugal; CHF = congestive heart failure; CAD = coronary artery disease; DCM = dilated cardiomyopathy; DT = destination therapy; LVAD = left ventricular assist device; MV = mitral valve; RPM = revolutions per min; TVR = tricuspid valve repair.

REST AND EXERCISE HEMODYNAMICS. Patients exercised for an average of 8.51 ± 2.8 min (10.5 ± 2.8 with axial flow vs. 7.8 ± 2.5 with centrifugal devices; $p < 0.001$) to an average of 57 ± 23 Watts (71 ± 26 with axial flow vs. 52 ± 21 with centrifugal devices; $p < 0.01$).

Table 2 and Figure 1 show the rest and peak exercise hemodynamic parameters for all patients and those stratified by device type. Resting hemodynamics were notable for significantly lower filling pressures for both RAP and PCWP with axial versus centrifugal flow pumps. LVAD device flow was lower at rest in the centrifugal group though Fick CO and arterial venous oxygen (AVO_2) difference were similar in both groups. The peak pressure differential across the LVAD at rest (MAP-PCWP) was higher in the axial flow pumps at rest but similar at peak exercise. Patients supported by axial flow pumps achieved significantly higher maximum heart rates ($p < 0.01$), higher Fick ($p < 0.01$) and LVAD device flows ($p < 0.0001$), and higher peak VO_2 ($p < 0.01$) than centrifugal patients.

Figure 2 shows the peak mean PAP versus the peak Fick CO for all patients with a line dividing the peak exercise hemodynamic response to zones of exercised-induced pulmonary hypertension defined by a mean pulmonary artery pressure (mPAP) ≥ 30 mm Hg and a total pulmonary resistance (TPR [i.e., mPAP/CO]) >3 Wood Units (12). TPR represents the serial resistance of the heart and pulmonary vasculature. For this cohort, the majority of patients exhibited exercise-induced pulmonary hypertension.

The Fick and LVAD device flow for all the patients at each workload is shown in Figure 3. There was a steeper slope for the Fick CO versus the LVAD flow

TABLE 2 Rest and Peak Exercise Hemodynamics in All Patients and Those With Axial and Centrifugal Pumps

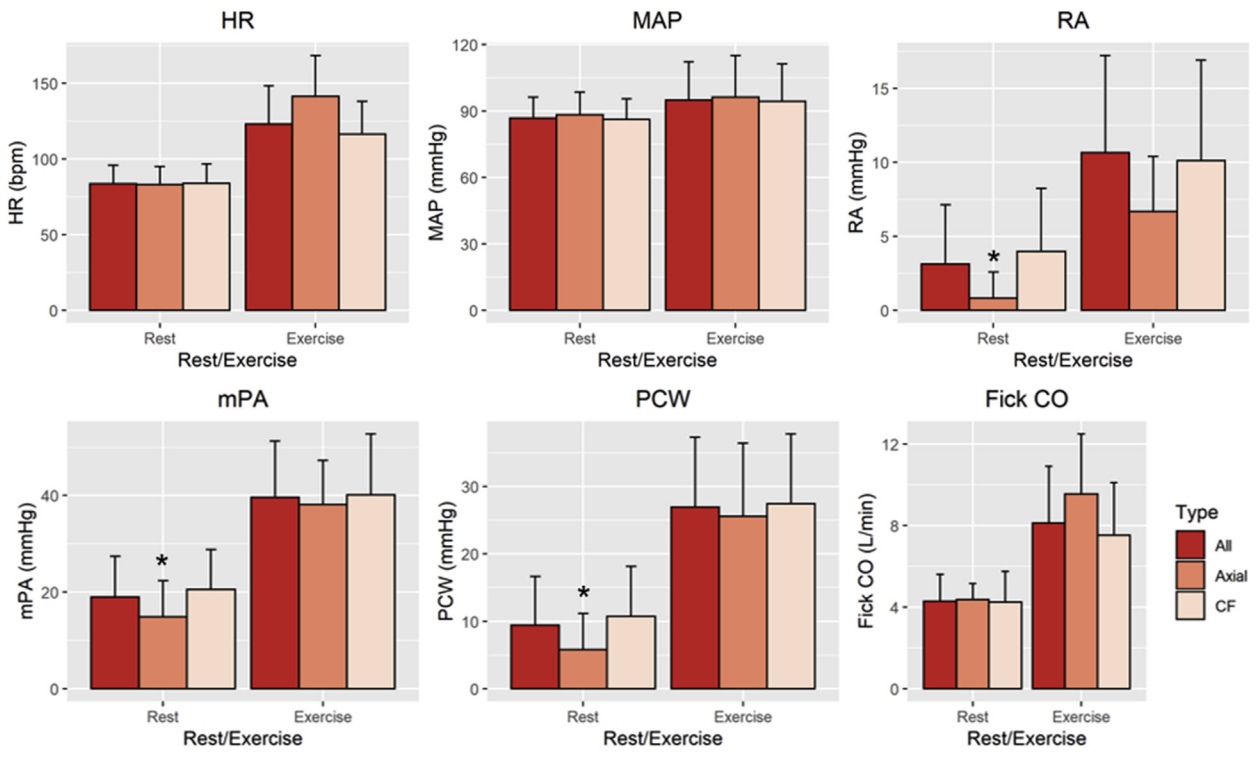
	All		Axial		Centrifugal	
	Rest	Peak Exercise	Rest	Peak Exercise	Rest	Peak Exercise
HR (beats/min)	83.7 ± 12.3	123.0 ± 25.0	83.2 ± 12.0	141.6 ± 27.0†	84.0 ± 13.0	117.0 ± 22.0†
MAP (mm Hg)	86.8 ± 9.5	94.7 ± 17.39	88.4 ± 10.0	96.3 ± 19.0†	86 ± 9.0	94.0 ± 17.0
RA (mm Hg)	3.1 ± 4.0	10.7 ± 6.5	0.8 ± 1.7*	6.7 ± 3.8†	4.0 ± 4.3*	12.1 ± 6.8†
mPA (mm Hg)	19 ± 8.4	39.6 ± 11.7	15 ± 7.5*	38 ± 9.2	21 ± 8.2*	40.1 ± 12.6
PCWP (mm Hg)	9.4 ± 7.2	26.9 ± 10.4	5.8 ± 5.3*	25.6 ± 11.0	11 ± 7.4*	27.4 ± 10.3
Fick CO (l/min)	4.3 ± 1.3	8.10 ± 2.8	4.4 ± 0.8	9.5 ± 2.9†	4.21 ± 1.5	7.53 ± 2.56†
AVO_2 diff	6.8 ± 1.2	11.6 ± 1.9	7.2 ± 1.3	12 ± 2.4	6.7 ± 1.1	11.4 ± 1.8
LVAD flow (l/min)	4.1 ± 0.8	5.0 ± 1.3	4.7 ± 1.0*	6.5 ± 0.9†	3.8 ± 0.6*	4.5 ± 0.9†
MAP-PCWP (mm Hg)	76.7 ± 11.0	65.7 ± 20.7	82.6 ± 10.0*	70.7 ± 22.4	74.2 ± 10.6	63.3 ± 19.7
mPA-RA (mm Hg)	15 ± 6.6	27.6 ± 9.0	14.1 ± 6.7	31.4 ± 7.5	15.4 ± 6.6	25.9 ± 9.2
Fick-LVAD flow	−0.07 ± 1.5	2.7 ± 2.3	−0.3 ± 1.2	3.4 ± 3.3	0.08 ± 1.7	2.3 ± 2.9
SVR	1,625.0 ± 361	886.0 ± 302	1,650.0 ± 343	838.0 ± 379	1,610.0 ± 378	911.7 ± 258

Value are mean ± SD. *p < 0.05 axial vs. centrifugal at rest. †p < 0.05 axial vs. centrifugal at peak exercise.

AVO_2 = atrial venous oxygen difference; CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; mPA = ; PCWP = pulmonary capillary wedge pressure; RA = right atrium; SVR = systemic vascular resistance; other abbreviations as in Table 1.

response with exercise (p < 0.001). Analysis of measurements by workload for axial and centrifugal pumps at each workload showed higher heart rate response, higher Fick CO, and higher LVAD flow in the axial versus centrifugal patients (p < 001) and lower RAPs with the axial flow pumps (p < 0.01). There was a tendency for lower mean PAP and PCW pressures, but these differences were not significant (Table 3).

FIGURE 1 Histograms

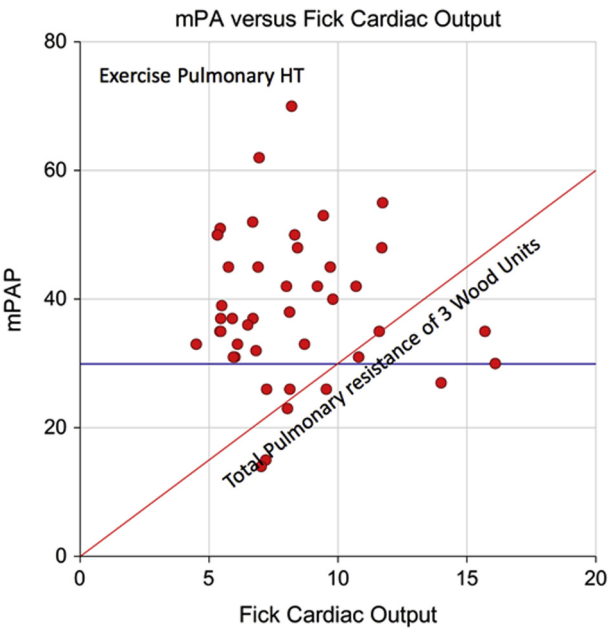


Heart rate (HR), mean arterial blood pressure (MAP), right atrial, mean pulmonary artery (PA), mean pulmonary capillary wedge (PCW), Fick, and LVAD cardiac outputs for all patients and those with axial and centrifugal pumps at rest and peak exercise (*p < 0.05 axial vs. centrifugal). CF = centrifugal; LVAD = left ventricular assist device.

CARDIOPULMONARY PARAMETERS. Peak VO_2 averaged only 10.6 ± 3.1 ml/kg/min, consistent with Class IIIB-IV congestive heart failure (CHF). Percent predicted VO_2 was 46 ± 13%. Similarly, submaximal parameters of exercise performance were severely abnormal in all patients. Ventilatory slope (VE/VCO_2) was elevated, and oxygen uptake efficiency slope and VO_2 at anaerobic threshold were severely reduced. Peak VO_2, peak heart rate reserve, and peak workload were all significantly higher in patients supported with the axial flow pumps (Table 4). The intensity of exercise measured by perceived exertion (Borg Scale), respiratory exchange quotient, and AVO_2 difference were comparable between the groups. There were significant differences in the slope of the parameter versus workload for LVAD flow ($p < 0.001$), Fick CO rise ($p < 0.001$), and heart rate ($p < 0.001$) for the axial versus centrifugal pumps. The rate of rise of RA pressure was less in the axial versus centrifugal pumps ($p < 0.01$), but the slope of the changes in mean BP, mPAP, and PCWP were the same for both groups (p = NS for all).

CORRELATION BETWEEN PEAK VO_2 AND EXERCISE HEMODYNAMIC MEASUREMENTS. Peak Fick CO (Figure 4), peak intrinsic CO (Fick-LVAD flow), peak systemic vascular resistance (SVR), and peak AVO_2 difference were all strongly correlated with peak Vo_2. However, there was only a weak correlation with peak LVAD flow and peak VO_2. There was no correlation between the change in pressure across the RV and VO_2 (Table 5). A multiple regression model for best correlates of peak VO_2 included peak Fick CO and peak AVO_2 difference. The adjusted R^2 for this model was 0.95.

FIGURE 2 Exercise-Induced Pulmonary Hypertension With Exercise in All Device Patients



Lines are drawn to the denote region of exercise pulmonary hypertension (i.e., mPAp ≥ 30 mm Hg and TPR >3 Wood Units). mPAP = mean pulmonary artery pressure; TPR = total pulmonary resistance (mPAP/cardiac output).

DISCUSSION

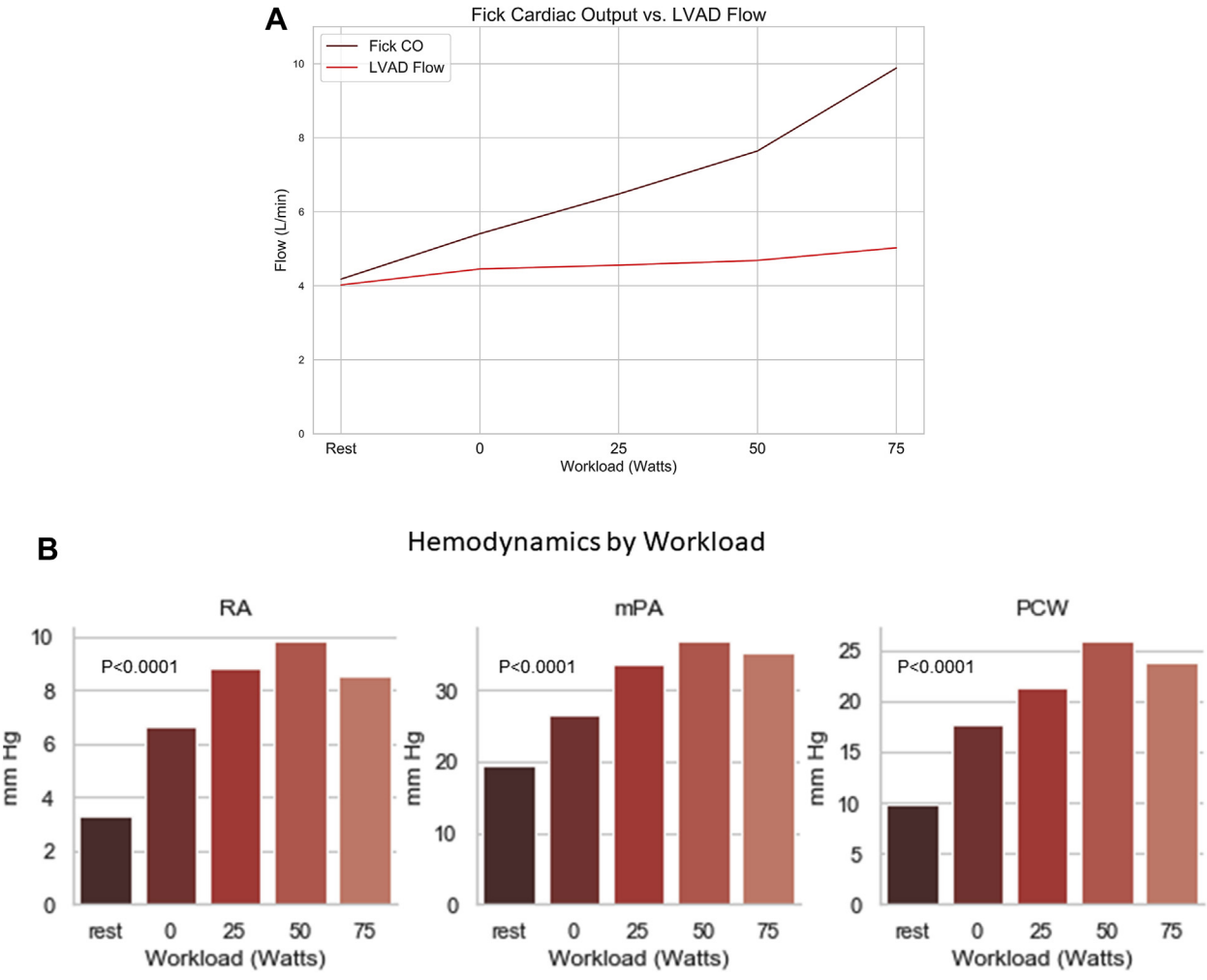
To the best of our knowledge, the current study presents the largest cohort of continuous flow LVAD-supported patients who had exercise hemodynamics were performed. In so doing, we were able to demonstrate the following findings: continuous flow pumps have minimal increase in device flow with exercise resulting in a markedly diminished peak exercise capacity. Submaximal exercise parameters also remain markedly abnormal. The major contributors to peak exercise performance in LVAD-supported patients were the ability of the patient to increase their Fick CO and their capacity to extract oxygen peripherally (AVO_2 difference) (Central Illustration).

Continuous flow LVAD devices have greatly affected the short and midterm survival in patients with Stage D heart failure and enhanced the quality of life of these patients (1-6). Six-min walk tests have also shown to be improved in several studies (1-6,13). However, though the distance walked is consistently improved, the actual distances reported remain reduced at levels associated with severe CHF.

There are fewer data on the cardiopulmonary response to maximal exercise in LVAD-supported patients but most reported studies demonstrate peak VO_2 that are in the range of 10 to 15 ml/kg/min (14-16). This measurement, again, is consistent with patients in New York Heart Association functional class III HF and generally in the range most HF physicians would begin to consider heart replacement therapies. In our study, we demonstrated extremely reduced peak VO_2 in both axial and centrifugal devices. This is the first report of peak VO_2 in Heart Mate 3 patients showing that the peak exercise capacity attained with this device remains severely impaired. This finding may be limited by the small number of patients and the number of destination therapy patients. Age is significantly related to VO_2, and inclusion of older patients may have contributed to the reduced VO_2 observed with this device.

The submaximal exercise parameters measured during cardiopulmonary exercise i.e. anaerobic

FIGURE 3 Workload



(A) Fick cardiac output and LVAD flow for all patients at each workload. **(B)** RA, mPAP. and PCWP at each workload. CO = cardiac output; PCWP = pulmonary capillary wedge pressure; RA = right atrial; other abbreviations as in Figure 1.

threshold (VO_2 AT), the ventilatory equivalent for VCO_2 (VE/VCO_2 slope), the OUES was severely abnormal in these patients, reflecting their very compromised functional status. Although we have no measurement of these submaximal measurements before device insertion, the values measured demonstrate impairment of local vasodilatory and muscle function that persists after device support.

Though reduced maximal and submaximal cardiopulmonary parameters persist following LVAD insertion, we did not measure the exercise endurance of the patients. The benefit derived and sensed by LVAD patients may be an improvement in their ability to sustain longer duration of submaximal exercise. This hypothesis needs testing in future studies.

There are many potential explanations for the limited exercise performance of centrifugal flow LVAD patients including the lack of support for the right ventricle (16), persistent frailty from their prolonged disease, alteration of vascular resistance from continuous flow devices, chronotropic incompetence, and the need for modifiable device output in response to physiological changes in work load (17-19). Early designed pneumatic pulsatile LVAD systems had an "eject when full" algorithm that automatically enabled a rise in CO with increased venous return and heart rate. Currently, there are no algorithms incorporated in modern-day devices that can augment device output with increase in activity levels other than are achieved by changes in pressure gradient

and, to a limited extent, changes in heart rate. Previous studies have attempted to optimize exercise performance by augmenting the speed of the LVAD during exercise testing (17-20). Some investigators noted small increase in peak VO_2, whereas others did not. The rate of increase in device speed has been variable with investigators concerned that too rapid an increase could result in suction.

For the current continuous flow devices, as noted, the major contributor to increase in pump flow is the change in the pressure head differential across the LVAD pump. With axial flow pumps, small changes in this pressure head differential can yield higher increases in pump flow. The centrifugal pumps have a flatter flow pressure curve; therefore, a higher pressure head differential is needed. In this patient cohort, the pressure head differential with exercise decreased less in the centrifugal than in the axial flow pumps. Subsequently, centrifugal device output with maximal effort increased minimally by <1 L of flow. This increase in device flow is inadequate to provide patients, especially younger patients, with reasonable exercise capacity.

A surprising finding was the degree of chronotropic incompetence with a diminished heart rate reserve, especially in the centrifugal flow pumps. However, the chronotropic incompetence seen in the centrifugal patients may simply be from their inability to exercise and not vice versa. There was no significant difference in the use of beta-blockers, amiodarone, or pacemaker in the axial and centrifugal pump patients.

Though LVADs generally provide marked decompression of the left ventricle and decrease in mitral regurgitation with resultant significant declines in resting hemodynamic pressures, our study was notable for rapid exercise-induced pulmonary hypertension and elevated PCWPs. Almost all patients exhibited exercise-induced pulmonary hypertension with a mean PAP >30 mm Hg and TPR above 3 Wood Units (12). This is consistent with the persistently elevated ventilatory response to exercise with a mean VE/VCO_2 slope >34 for all patients. Clearly, medical optimization of the LVAD patient is needed to alleviate this exercise response. Interestingly, pulmonary pressures during exercise remained elevated despite the high rates of associated ancillary valve surgery that was used in our patient population.

Examination of the correlation of the various hemodynamic parameters with peak VO_2 revealed that Fick CO, presumed intrinsic CO (peak Fick - LVAD flow), peak AVO_2 difference, and decrease in SVR had the greatest correlation. Total Fick CO and intrinsic CO reflect the ability of the native heart to contribute to exercise performance. Unfortunately, we do not have echocardiographic images demonstrating aortic valve opening to confirm this assumption. Also, we have to acknowledge that the VAD flow measurements are approximations and thus may underrepresent actual device flow.

The ability to decrease SVR to unload the native left ventricle as well as affect the pressure head across the pump requires recovery of peripheral factors. Endothelial function is abnormal in HF patients and

TABLE 3 Hemodynamics at Each Workload in Axial and Centrifugal Pump Patients

	Rest	0 W	25 W	50 W	75 W	p Value for Difference in Slopes
RA						0.03
All	3.3 ± 4.2	6.7 ± 5.5	8.8 ± 6.6	9.9 ± 6.4	8.6 ± 5.6	
Axial	1 ± 1.7	3.3 ± 2.5	5.2 ± 3.3	5.6 ± 3.8	7 ± 3.4	
CF	4.2 ± 4.4	7.9 ± 5.8	10.2 ± 7.1	11.4 ± 6.5	9.41 ± 6.59	
mPA						0.88
All	19.4 ± 8.7	26.5 ± 8.9	33.5 ± 13.6	37 ± 11.0	35 ± 9.7	
Axial	14.9 ± 7.5	23.3 ± 8.1	29.6 ± 11.1	33.4 ± 11.1	35.7 ± 8.6	
CF	21 ± 8.6	27.7 ± 9.0	35 ± 14.0	38.5 ± 10.8	35.1 ± 10.9	
PCW						0.35
All	9.8 ± 7.4	17.7 ± 8.6	21.24 ± 10.4	26.0 ± 9.8	23.9 ± 10.3	
Axial	6.2 ± 5.4	14.2 ± 8.4	18.5 ± 8.8	24 ± 11.1	25.7 ± 9.5	
CF	11.1 ± 7.6	18.9 ± 8.5	22.3 ± 10.9	26.8 ± 9.4	22.5 ± 11.2	
Fick CO						0.03
All	4.2 ± 1.2	5.4 ± 1.5	6.5 ± 2.0	7.6 ± 1.9	9.9 ± 2.6	
Axial	4.4 ± 0.8	5.77 ± 1.1	7.23 ± 1.7	8.3 ± 1.6	10.4 ± 1.3	
CF	4.1 ± 1.3	5.3 ± 1.6	6.2 ± 2.0	7.4 ± 2.0	9.5 ± 3.2	
VO_2						0.04
All	292 ± 61	478 ± 86	642 ± 108	824 ± 143	1,133 ± 182	
Axial	305 ± 48	497 ± 74	672 ± 54	858 ± 94	1,188 ± 23	
CF	287 ± 65	471 ± 89	632 ± 120	812 ± 157	1,092 ± 237	
SVR						0.21
All	1,711 ± 449	1,345 ± 393	1,046 ± 328	927 ± 291	7,279 ± 210	
Axial	1,620 ± 362	1,238 ± 418	918 ± 342	908 ± 344	738 ± 158	
CF	1,747 ± 479	1,399 ± 379	1,091 ± 320	935 ± 276	717 ± 268	
HR						0.01
All	83 ± 12	96 ± 16	105 ± 19	115 ± 17	127 ± 20	
Axial	83 ± 12	95 ± 9	110 ± 21	121 ± 14	140 ± 11	
CF	83.5 ± 12	97 ± 18	104 ± 19	112 ± 18	121 ± 11	
mBP						0.75
All	87 ± 11	94 ± 13	91 ± 17	94 ± 17	91 ± 17	
Axial	88 ± 12.0	97 ± 22.0	89 ± 22.0	90 ± 28.0	113 ± 7.5	
CF	86 ± 10	93 ± 8	91 ± 16	95 ± 11	90 ± 19	
LVAD						<0.001
Flow (all)	4.1 ± 0.81	4.45 ± 0.94	4.63 ± 1.04	4.79 ± 1.12	5.41 ± 1.45	
Axial	4.7 ± 1.03	5.6 ± 1.1	5.97 ± 1.0	6.3 ± 0.9	6.9 ± 0.9	
CF	3.9 ± 0.6	4.1 ± 0.5	4.2 ± 0.6	4.2 ± 0.5	4.2 ± 0.5	

Value are mean ± SD.

mBP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; VO_2 = peak oxygen consumption; other abbreviations as in Tables 1 and 2.

TABLE 4 Cardiopulmonary Exercise Variables for All Patients and Those Supported by Axial and Centrifugal Pumps

Exercise Variable	All	Axial	CF	p Value
Peak VO_2 (ml/kg/min)	10.6 ± 3.1	12.3 ± 3.6	9.8 ± 2.6*	<0.01
VO_2AT (ml/kg/min)	7.0 ± 1.9	7.9 ± 2.0	6.6 ± 1.8	0.05
VE/VCO_2	35.0 ± 7.9	31.6 ± 5.5	36.4 ± 8.3	0.08
OUES	1,039 ± 386	1,148 ± 458	997 ± 354	0.28
Reason for terminating exercise				
SOB	6	2	4	0.96
Fatigue	24	7	17	
Both	6	2	4	
Other	9	2	7	
RER	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.71
Heart rate reserve (beats/min)	37 ± 22	24 ± 25	42 ± 19*	0.02
Borg scale (6-20)	15.4 ± 2.6	14.5 ± 2.3	15.6 ± 2.7	0.32
Peak workload (Watts)	577 ± 22	71 ± 26	52 ± 21*	0.01
Exercise duration (min)	8.6 ± 2.8	10.5 ± 2.8	7.9 ± 2.6*	<0.01

Values are mean ± SD or n. *$p < 0.05$ axial vs. centrifugal.

OUES = oxygen uptake efficiency slope; RER = respiratory exchange ratio; VE/VCO_2 = ventilatory equivalent for carbon dioxide production; VO_2AT = oxygen consumption at anaerobic threshold; other abbreviations as in Table 3.

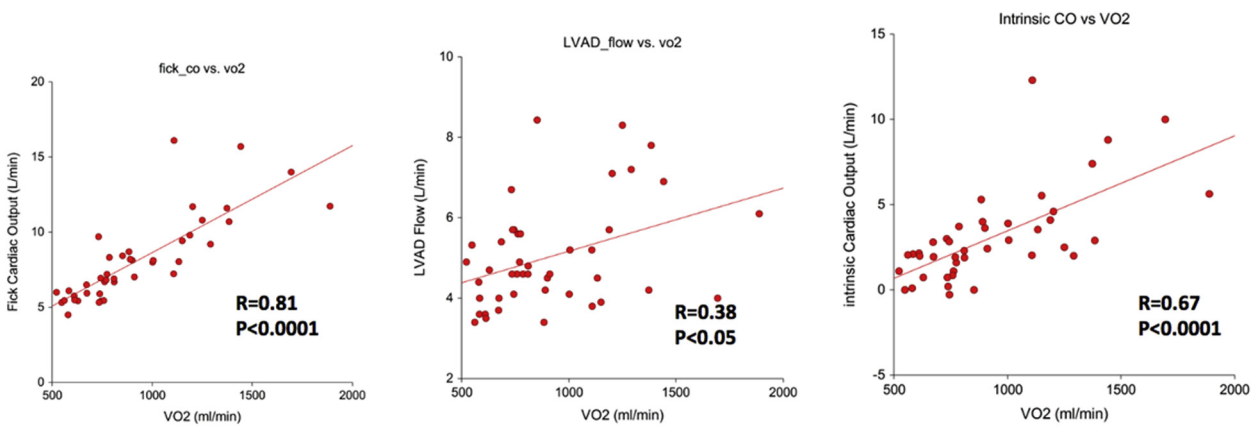
unfortunately does not improve with LVAD support (21). Arterial stiffness appears to worsen in patients with continuous flow devices as evidenced by increases in arterial wall thickness and less reactive hyperemia (21-23). AVO_2 difference along with peak Fick CO was the most powerful predictor of peak exercise performance; this emphasizes the importance of the peripheral musculature and its ability to use the delivered oxygen.

Exercise capacity can potentially be improved in LVAD patients by strategies to correct peripheral factors. A few cardiac rehabilitation studies have been reported in LVAD patients. A consistent improvement in peak VO_2 is observed with this intervention, in the range of 10% or 1 to 2 ml/kg/min (24-27). Correction of severe anemia, improvement of chronotropic incompetence by pacemaker optimization, and management of right heart failure are other potential effective strategies to enhance exercise performance in LVAD patients.

The multivariable model that best predicted peak VO_2 incorporated the elements that potentially can be addressed to improve exercise performance. Fick CO is enhanced by an appropriate heart rate response to exercise, native heart recovery, and treatment of right heart failure. The pressure differential across the pump can be improved with optimization of pump settings in response to changes in workload. Last, hemoglobin affects the oxygen-carrying capacity of the blood and is a key component of the AVO_2 difference. Manipulation of hemoglobin content has been demonstrated to affect VO_2 and has been used to enhance exercise performance in athletes as well as in patients with CHF.

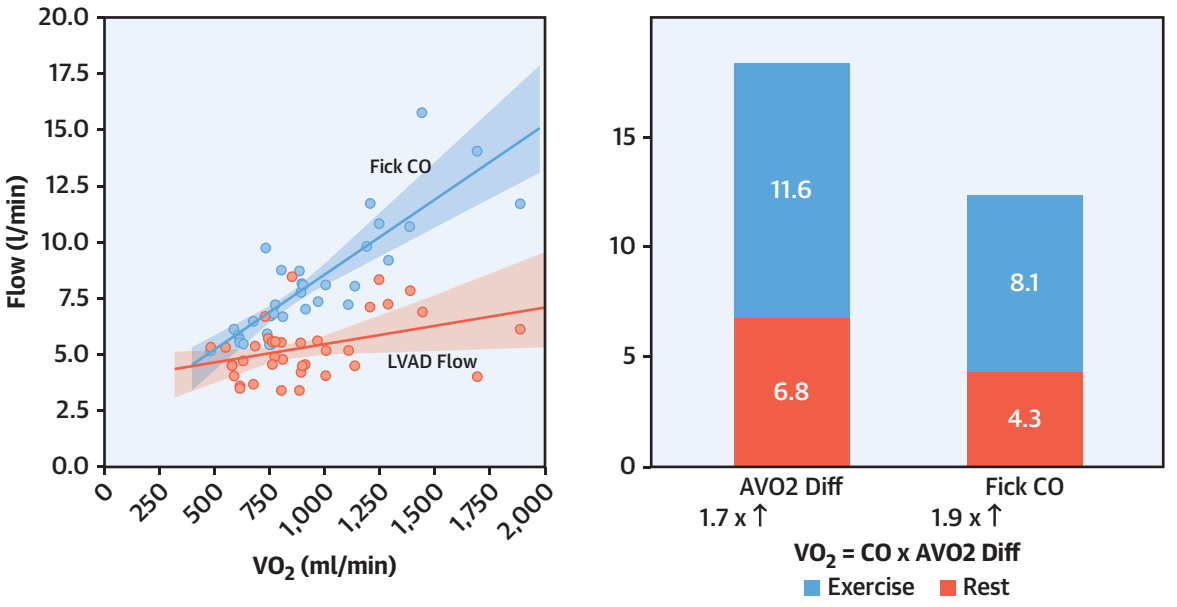
The intervention that may have a large impact on exercise performance in LVAD patients may be collaboration with engineers and industry to integrate biosensors in the devices and develop algorithms using the data to regulate the speed and output of pumps at varying work demands. In addition, devices that are able to achieve higher mean flow rates (>10 l/min) may also be a key element. This is an area of research that is still underdeveloped as neither patients nor physicians alone will be able to achieve the increase in cardiac

FIGURE 4 Correlation of Peak VO_2 to Peak Fick CO, Peak Lvad Flow, and Assumed Intrinsic Cardiac Output



VO_2 = peak oxygen consumption. Abbreviations as in Figures 1 and 3.

CENTRAL ILLUSTRATION **Determinants of Exercise Performance**



Moss, N. et al. J Am Coll Cardiol HF. 2020;■(■):■–■.

(Left) Correlation of peak VO_2 to peak Fick cardiac output and to peak LVAD flow. **(Right)** Two multivariate predictors of peak VO_2 and their relative contributions to peak exercise. Abbreviations as in Figures 1 and 3.

output needed to sustain higher workloads without the assistance of bioengineers.

STUDY LIMITATIONS. First, there was a diverse group of patients with a wide age range on 2 different LVAD pumps and with variable times after LVAD implantation. However, all patients were studied during periods of stability and at least 3 months after device implant, which would allow adequate time for recovery from the immediate surgery.

We used the slow cuff deflation device to better assess blood pressure in LVAD patients. Though use of this device has been correlated with arterial line readings at rest, it may not be as accurate during exercise. Use of an arterial line would have been ideal, but we were reluctant to perform arterial punctures on patients who were anticoagulated. Similarly, simultaneous echocardiographic images at peak exercise would have enabled us to confirm that native cardiac output was a key contributor to peak exercise performance and should be done in future studies. Some of the parameters reported are estimated or derived and not directly measured, which therefore also limits the analysis. Importantly, LVAD flow is an estimated value

TABLE 5 **Correlations With VO_2**

	r	p Value
Age	−0.56	0.0001
Hemoglobin	0.39	0.01
Height	0.35	0.02
Weight	0.30	0.045
Peak Fick CO	0.81	0.0001
Peak LVAD flow	0.38	0.01
Peak Fick CO-LVAD flow	0.670	0.0001
Peak MAP-PCWP	0.11	0.50
Peak mPAP-RAP	0.04	0.79
Peak SVR	−0.60	0.0001
HR reserve (maximum-rest HR)	−0.31	0.04
Peak AVO_2 difference	0.44	0.003
Peak HR	0.51	0.0005
Peak RA	−0.26	0.08
Peak mPAP	−0.11	0.46
Peak PCWP	0.02	0.89
PAPi rest	−0.03	0.86
PAPi exercise	0.021	0.89
Peak MAP	0.143	0.36

mPAP-RAP = mean pulmonary artery pressure minus mean right atrial pressure; PAPi = pulmonary artery pulsatility index; other abbreviations as in Tables 1 and 2.

that can have significant error. Our inability to precisely measure LVAD flow limits our accuracy in measuring intrinsic cardiac output.

Between-pump comparisons are limited by the small number of patients and different patient characteristics. Specifically, those patients who received axial flow pumps tended to be younger, were exclusively male, and were implanted as bridge to transplant. Thus, they probably represented a population with a higher aerobic capacity.

CONCLUSIONS

The best predictor of peak exercise performance in LVAD supported patients is the Fick cardiac output, which appears to be augmented primarily by the patient's own native cardiac capacity. Attention to correction of anemia and conditioning status could potentially improve aerobic function of these patients. Whether biomechanical enhancements with activity, volume, and pressure sensors embedded in the LVAD can enable the device to respond to increased workload of exercise and to improve functional capacity in LVAD supported patients remains to be investigated.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LVAD-supported patients have severely impaired peak exercise capacity despite improved survival. Presently, the best determinant of maximal exercise performance for these patients is Fick cardiac output. Future developments in LVAD technology need to focus on enhanced engineering with algorithmic approaches to maximize device performance during exercise.

TRANSLATIONAL OUTLOOK: In this study, we describe the hemodynamic response to exercise in patients supported by continuous flow left ventricular assist devices. Our study demonstrates the severely impaired exercise capacity and the need for future trials to optimize these patient's functional capacity. These studies will include the collaboration of cardiologists, surgeons, exercise physiologists and biomedical engineers.

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KEY WORDS CPET, exercise, heart failure, left ventricular assist device