Prognostic Value of Peak Oxygen Uptake in Patients Supported With Left Ventricular Assist Devices (PRO-VAD)

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ABSTRACT

OBJECTIVES The purpose of this study was to examine whether peak oxygen uptake (pVO₂) and other cardiopulmonary exercise test (CPET)-derived variables could predict intermediate-term mortality in stable continuous flow LVAD recipients.

BACKGROUND pVO₂ is a cornerstone in the selection of patients for heart transplantation, but the prognostic power of pVO₂ obtained in patients treated with a left ventricular assist device (LVAD) is unknown.

METHODS We collected data for pVO₂ and outcomes in adult LVAD recipients in a retrospective, multicenter study and evaluated cutoff values for pVO₂ including: 1) values above or below medians; 2) grouping patients in tertiles; and 3) pVO₂ ≤14 mL/kg/min if the patient was not treated with beta-blockers (BB) or pVO₂ ≤12 mL/kg/min if the patient was taking BB therapy.

RESULTS Nine centers contributed data from 450 patients. Patients were 53 ± 13 years of age; 78% were male; body mass index was 25 ± 5 kg/m² with few comorbidities (stroke: 11%; diabetes: 18%; and peripheral artery disease: 4%). The cause of heart failure (HF) was most often nonischemic (66%). Devices included were the HeartMate II and 3 (Abbott); and Heartware ventricular assist devices Jarvik and Duraheart (Medtronic). The index CPET was performed at a median of 189 days (154 days–225 days) after LVAD implantation, and mean pVO₂ was 14.1 ± 5 mL/kg/min (47% ± 14% of predicted value). Lower pVO₂ values were strongly associated with poorer survival regardless of whether patients were analyzed for absolute pVO₂ in mL/kg/min, pVO₂ ≤12 BB/14 mL/kg/min, or as a percentage of predicted pVO₂ values ($P \leq 0.001$ for all). For patients with pVO₂ >12 BB/14 and ventilation/carbon dioxide relationship (VE/VCO₂) slope <35, the 1-year survival was 100%.

CONCLUSIONS Even after LVAD implantation, pVO₂ has prognostic value, similar to HF patients not supported by mechanical circulatory support devices. (PROgnostic Value of Exercise Capacity Measured as Peak Oxygen Uptake [pVO₂] in Recipients of Left Ventricular Assist Devices [PRO-VAD]; [NCT04423562](https://doi.org/10.1016/j.jchf.2021.05.021)) (J Am Coll Cardiol HF 2021;■:■–■)
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**ABBREVIATIONS
AND ACRONYMS**

12 BB/14 = peak oxygen uptake cutoff (ml/kg/min) of 12 if taking beta-blocker therapy and 14 if not taking beta-blocker therapy

BB = beta-blocker

BTD/-T = bridge to decision/transplantation

DT = destination therapy

CO = cardiac output

CPET = cardiopulmonary exercise test

LVAD = left ventricular assist device

pVO₂ = peak oxygen uptake

QOL = quality of life

VE/VCO₂ = ventilation/carbon dioxide relationship

Survival rates after implantation with a durable left ventricular assist device (LVAD) have greatly increased over the last decade, and improvements in LVAD technology have lowered the risk of adverse events (1-3). In fact, recent studies have shown that short-term and intermediate term survival after LVAD implantation parallels that of cardiac transplantation (4). Furthermore, most LVAD recipients experience significant improvement in heart failure (HF) symptoms and quality of life (QOL) (5-7).

Although the preferred treatment for advanced, refractory HF remains heart transplantation, waiting time for donor organs is increasing in most countries. In a recent report from the ELEVATE (European registry of patients implanted with a full magnetically levitated LVAD) registry (3) of

Heartmate3 (Abbott Laboratories) recipients, <10% underwent transplantation after 2 years of device support, despite the fact that most received implants as a bridge-to-transplantation (BTT) (8). In the United States, the new allocation system (9) prioritizes patients on temporary mechanical circulatory support (MCS), which will likely increase waiting time for stable LVAD recipients. This highlights the potential need for prioritization of stable BTT LVAD recipients for organ allocation or even for consideration of the indication for transplantation, by risk stratification similar to guidelines applied for elective patients with advanced HF not supported with MCS (10). A cornerstone in selection of patients for heart transplantation listing is measurement of peak oxygen uptake (pVO₂) by means of a cardiopulmonary exercise test (CPET). In stable HF patients, pVO₂ has been shown to predict mortality with high accuracy (11), and other CPET-derived measurements such as ventilation/carbon dioxide relationship (VE/VCO₂) slope (12) may provide additional information. Recently, pVO₂ has been studied extensively in LVAD recipients and has been reported to remain reduced even in patients with significant symptomatic improvement (7). However, it is unknown whether pVO₂ maintains its prognostic power in patients with HF once they are supported with an LVAD.

The present authors hypothesized that pVO₂, as well as other CPET-derived variables, could predict mortality in stable recipients with a continuous flow LVAD, which could make the test potentially useful to select patients for cardiac transplantation listing also in this group of patients.

METHODS

A retrospective multicenter study was designed to collect data for pVO₂ in LVAD recipients. Based on earlier published reports (described elsewhere [7]), 34 centers performing CPET in LVAD recipients, either as part of research projects or as standard of care, were identified and invited to participate in this study. Adult patients supported by LVAD with at least 1 post-implantation CPET (with available pVO₂) were eligible for inclusion. All CPET protocols were accepted for inclusion regardless of initial workload and duration of workload steps used (stepwise increase every 2 or 3 minutes or continuous increase every second). Exclusion criteria included concomitant right ventricular assist devices and partially implanted LVADs. At the end of data collection (September 2020), 9 centers (Supplemental Table 1) had provided anonymized data to the database located at Rigshospitalet, Copenhagen, Denmark.

The following outcomes were collected: ongoing on-device, transplantation, explantation caused by cardiac recovery, pump exchange caused by thrombosis, and death. The primary endpoint was death, censoring for explantation for recovery and transplantation. Time to any endpoint was calculated as time elapsed from the first CPET performed after LVAD implantation (the index CPET) until the outcome of interest.

Beta-blocker dosages were reported in equivalents of metoprolol succinate. Doses were calculated as 100 mg of metoprolol succinate, ~5 mg bisoprolol, ~25 mg of carvedilol, ~200 mg of labetalol, ~80 mg of propranolol, and ~160 mg of sotalol. Loop diuretic agents were reported in equivalent doses of furosemide. Doses were calculated as 40 mg of furosemide; ~20 mg of torsemide, and ~1 mg of bumetanide. Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure + $\frac{1}{3} \times$ [systolic blood pressure – diastolic blood pressure].

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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Exercise tests were performed using protocols and LVAD settings as defined by the local center and staff. The LVAD settings were kept constant throughout the exercise test.

Percentage of predicted pVO_2 (%Pred pVO_2) was calculated using the Hansen formula (13,14). The contributing centers were asked to provide a VE/VCO_2 slope for CPET according to local methods of calculation, and if VE/VCO_2 was not used, the value was calculated by regression analysis (15) throughout the entire CPET (16), because we planned to use this value in case of suboptimal pVO_2 (respiratory exchange ratio [RER] <1.05) in accordance with current criteria for transplant listing (10). Neither anaerobic threshold nor periodic breathing was included in the analyses.

The study was conducted in accordance with the Declaration of Helsinki. Danish approval numbers were H-1-2012-092, H-3-2013-010, H-150- 21-598, H-17029488, 3-3013-1365/1, 3-3013-1365-2. The study was registered in the U.S. Clinical.trials.gov (NCT04423562).

STATISTICS

Continuous variables were expressed as mean $\pm$ SD if parametric, as median and interquartile range (IQR) if nonparametric, and categorical variables were described with frequencies and percentages. Relationships between continuous variables were evaluated using Pearson's and Spearman's rank correlation coefficient as appropriate.

The impact of pVO_2 on survival was assessed by use of the Kaplan-Meier method both for absolute pVO_2 and %Pred pVO_2 data. The following cutoff values for pVO_2 were tested for outcome analyses: 1) above or below median pVO_2 ; 2) grouping tertiles of pVO_2 ; and 3) $pVO_2 \leq 14$ ml/kg/min if intolerant to beta-blockers and $pVO_2 \leq 12$ ml/kg/min if the patient was taking beta-blockers (10). Cases with missing values were excluded from the respective analyses, and no imputations were performed. Cox regression analysis was used to adjust for the impact of age, body mass index, and indication for therapy (ie, destination therapy [DT] vs. not DT) on the relationship between pVO_2 and survival. To assess whether time from LVAD implantation to the time of the index CPET modified the predictive power of pVO_2 on mortality, an interaction analysis was performed containing the interaction term pVO_2 less than versus greater than the median (ie, $</\geq$ median) $\times$ time from implantation to CPET performed earlier than versus later than the median time from implant (ie, $</\geq$ median).

TABLE 1 Baseline Characteristics (N = 450)

Age, y	53.0 $\pm$ 13.0
Females	97.0 (22)
Whites	399.0 (89)
Body mass index, kg/m ²	25.0 $\pm$ 5
Nonischemic cardiomyopathy	292.0 (66)
Co-morbidity	
Stroke	46.0 (11)
Diabetes	78.0 (18)
Peripheral artery disease	18.0 (4)
LOS after LVAD implantation, days	45.0 $\pm$ 26
Duration of HF prior to LVAD implantation, y	3.7 (1-10)
MAP, mm Hg	78.0 $\pm$ 11
Resting HR, min ⁻¹	88.0 $\pm$ 18
Cardiac implantable-defibrillator device	279.0 (64)
Destination therapy	102.0 (23)
Device	
Heartmate II	173.0 (38)
Heartmate 3	102.0 (23)
Heartware	155.0 (34)
Jarvik	18.0 (4)
Duraheart	2.0 (<1)
Days from LVAD implantation to CPET	189.0 (154-225)
Medications	
Beta-blocker	206.0 (48)
Metoprolol equivalent dose, mg	68.7 $\pm$ 64
Loop diuretics	248.0 (58)
Furosemide equivalent dose, mg	60.0 $\pm$ 69
CPET variables	
pVO_2 , ml/kg/min	14.1 $\pm$ 5.0
Percentage of predicted peak oxygen uptake	47.1 $\pm$ 13.9
Respiratory exchange ratio	1.16 $\pm$ 0.12
VE/VCO_2 slope	37.1 (32.7-42.2)
Test duration, s	563.0 $\pm$ 226
Power, W	89.0 $\pm$ 38

Values are mean $\pm$ SD, n (%), or interquartile range (IQR), unless otherwise stated.

CPET = cardiopulmonary exercise test; CPET = cardiopulmonary exercise test; HF = heart failure; LOS = length of (hospital) stay; LVAD = left ventricular assist device; MAP = mean arterial blood pressure; pVO_2 = peak oxygen uptake; VE/VCO_2 = ventilation/carbon dioxide relationship; W = watts.

Statistical analyses were performed using SPSS software statistics (IBM) for Windows version 25.0 (Microsoft), and statistical significance was defined as a 2-tailed P value < 0.05. R Studio software version 1.3.1093 (R Foundation for Statistical Computing) was used for statistical presentation.

RESULTS

This study included 450 adult LVAD recipients with a postimplant CPET with pVO_2 . This corresponds to 41% of all patients who received implants during the data collection period in the participating centers (Supplemental Table 2). The index CPET was

performed on average 251 ± 259 days after LVAD implantation (Table 1). The most commonly implanted devices were HeartMate II (Abbott) and Heartware ventricular assist device (HVAD) (Medtronic Inc). Patients were most often middle aged, White males (Table 1). Cause of HF was non-ischemic for most patients and peri-implant heart rhythm was most often sinus. More than one-half of the patients were implanted with pacing devices (64%), of which most were implantable cardioverter-defibrillators (72%). The burden of co-morbidities (eg, stroke, diabetes, or peripheral artery disease) was relatively low as shown in Table 1. Six-minute walk test was available from 87 patients, and the walking distance was 404 ± 132 m.

At the time of the CPET, only a little more than one-half of the patients received loop diuretic agents with an average dose of 60 mg (furosemide equivalents), and beta-blockers were prescribed to fewer than one-half of the patients with an average dose of 69 mg (metoprolol equivalents).

CARDIOPULMONARY EXERCISE TEST. Most tests were performed using an upright bicycle (93%), followed by a test on a treadmill (6%). Data were missing for 2 tests (0.4%). Exercise capacity was severely reduced with an average pVO_2 in the total cohort of 14.1 ± 5 ml/kg/min, equivalent to 47% of the expected value. The average RER indicated a maximal or near maximal effort (average RER = 1.16). Considerable variations were seen in test durations (563 ± 226 s) and test intensities (maximal power achieved: 89 ± 38 W). A total of 49% of the patients had pVO_2 below the accepted values for heart transplant listing (10). The VE/VCO₂ slope was missing from 50 (11%) of the tests; median (IQR) VE/VCO₂ slope was 37.1 (32.7-42.0); 62% had VE/VCO₂ slope >35.

SURVIVAL. After an average of 795 ± 666 days from index pVO_2 to the end of follow-up, the following distribution of outcomes was observed: ongoing on device: 179 (40%); transplantation: 169 (37.5%); explantation: 16 (3.5%); death: 86 (19%). Comparing baseline characteristics of BTT patients who received transplants with those who were ongoing on device at the end of follow-up (excluding explanted patients), the authors found no significant differences in age, race, sex, body mass index, HF duration prior to LVAD implantation, presence of cardiac implantable-devices or comorbidities (stroke, diabetes, peripheral artery disease, data not shown).

Dividing patients into tertiles by peak VO_2 clearly demonstrated that a lower pVO_2 was significantly associated with poorer survival ($P < 0.001$) (Figure 1A). Similar results were found when patients

were divided according to percentage of predicted pVO_2 values ($P = 0.001$) (Figure 1B).

After exclusion of 67 tests with RER <1.05, the findings remained statistically significant ($P = 0.003$). Upon excluding 105 patients with test duration <300 s, the prognostic value of pVO_2 remained unchanged ($P = 0.001$), and the same was true after excluding 139 patients with test durations of <300 or >900 s ($P = 0.001$).

Using the accepted pVO_2 threshold for transplantation listing of 12 (beta-blocker) or 14 (no beta-blocker) ml/kg/min also resulted in a significant and large difference in mortality (Figure 1C). VE/VCO₂ slope values higher than the median were associated with lower survival rates ($P = 0.023$). Upon grouping patients into tertiles, this association became clearer ($P = 0.001$) (Figure 2A), and when dividing patients into subgroups according to the generally accepted VE/VCO₂ slope threshold of 35 (10), higher mortality in the higher VE/VCO₂ slope group was observed ($P < 0.001$) (Figure 2B). Combining pVO_2 and VE/VCO₂ slope provided excellent discrimination of patients with very low risk. Grouping patients as: 1) $pVO_2 > 12$ BB/14 ml/kg/min (no BB) and VE/VCO₂ slope ≤ 35 ; 2) $pVO_2 \leq 12$ BB/14 ml/kg/min (no BB) and VE/VCO₂ slope >35; and 3) the remaining patients demonstrated 100% 1-year survival and close to 100% survival after more than 3 years of follow-up in group 1 ($P < 0.0001$) (Supplemental Figure 1).

Excluding treadmill tests (6%) did not change the prognostic impact of pVO_2 grouping patients according to median, tertiles or when using the cutoffs of 12 BB/14 ml/kg/min with or without VE/VCO₂ slope ($P < 0.001$ for all, graphs not shown).

To determine if the association between pVO_2 and mortality was independent of patient age and anthropometric variables as well as device indication in Cox regression analysis age, sex, body mass index, and therapy indication (DT versus not DT) were adjusted for. Cox regression analysis confirmed a higher risk of death for patients with lower pVO_2 (Table 2). Furthermore, interaction analysis revealed no significant differences in the predictive power of pVO_2 on mortality for CPET performed early versus late (ie, before or after the median time to CPET) after LVAD implantation (p for interaction = 0.86). No interaction with flow type (centrifugal/axial) on the association between pVO_2 and survival was found (p for interaction = 0.39).

A combined endpoint of death or HF hospitalization was also explored. The combined outcome was strongly predicted by lower pVO_2 values ($P \leq 0.001$ for all) (Figure 3, Supplemental Figure 2).

FIGURE 1 Peak Oxygen Uptake

(A) Survival according to peak oxygen uptake (ml/kg/min) in tertiles. pVO_2 = survival according to peak oxygen uptake (pVO_2) in tertiles. **(B)** Kaplan-Meier plot shows survival according to the percentage of predicted peak oxygen uptake (%Pred pVO_2). Survival in patients with percentage of predicted peak oxygen uptake (%Pred pVO_2) less versus greater than the group median. **(C)** Kaplan-Meier plot shows survival according to peak oxygen uptake (ml/kg/min) using the ISHLT cutoffs for evaluating transplant listing. ISHLT = International Society of Heart and Lung Transplantation.

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Among the 289 patients still alive and ongoing on device 1 year after the index pVO_2 test (ie, excluding transplanted, explanted and patients who died within 1 year after the index CPET), the crude incidence of HF hospitalizations was 0.14 per patient year (ppy) in patients with $pVO_2 \leq 12$ BB/14 ml/kg/min and 0.05 ppy in those with $pVO_2 > 12$ BB/14 ml/kg/min ($P = 0.002$).

DISCUSSION

The current study is the first to demonstrate that lower values of pVO_2 are highly predictive of death (**Central Illustration**) and HF hospitalizations in LVAD recipients. It is further shown that another measure which can be obtained during CPET, VE/VCO₂ slope, predicts survival in LVAD recipients as is the case for patients with HF not supported by MCS.

The prognostic power of pVO_2 in heart failure patients considered for transplantation was demonstrated in the landmark study from 1991 by Mancini et al (11). Since then, several studies established the prognostic value of pVO_2 in advanced heart failure populations (17,18). The present results confirm that these

findings are valid in recipients of durable LVADs, as pVO_2 provided robust prognostic information in stable, ambulatory LVAD recipients, both in the early and late phases (>6 months) after implantation. The cutoff of 12 (if patients were taking BB) or 14 (if not taking BB) ml/kg/min is widely used in patients with advanced HF not supported by MCS to determine timing of transplantation (10), and we demonstrate that this threshold can also be applied in LVAD recipients. Interestingly, pVO_2 also predicted the risk of HF hospitalizations which is especially relevant for the growing population of DT patients (19).

Peak oxygen uptake is a reproducible, objective and dynamic parameter which assesses the cardiovascular reserve and peripheral adaptations to reduced cardiac output (according to Fick's principle) and as a direct consequence is highly predictive of outcome in HF (11,20,21). In LVAD recipients, total cardiac output (CO) is determined by blood flow through the pump and the native CO (through the aortic valve), the latter contributing in particular during exercise. Recently, Moss et al (22) presented exercise hemodynamic data and simultaneous VO₂ measurements

FIGURE 1 Continued

in 45 LVAD recipients. The authors confirmed that the main determinant of pVO_2 was patients' ability to increase total CO and, second, the capacity to extract oxygen peripherally (ie, arterial venous oxygen difference). Several factors contribute to the low CO and, consequently, pVO_2 observed in LVAD recipients. Although comorbidity and pump speed settings play a role (23), main determinants are LV function (ie, myocardial recovery) (24), aortic and mitral valve disease (25,26), and chronotropic incompetence (27,28). Although RV function has been shown to influence pVO_2 in some (29) but not all (27) studies, RV failure is clearly associated with increased risk of readmission (30,31) and poorer overall outcome in LVAD recipients (32,33). Taken together, these findings point to underlying mechanisms relating to incompletely treated heart failure as the main cause for low pVO_2 in LVAD recipients, which in turn, is consistent with the striking similarity between the pVO_2 , survival relationship observed in LVAD recipients in the current study, and that reported for patients with HF not supported by MCS.

Several studies (7) have reported pVO_2 in LVAD recipients with values ranging from 9.9 (34) to 20.3 (35) ml/kg/min in populations consisting mostly of middle-aged patients (ages range from 35 to 63 years old) (35-37). Although age ranges in earlier reports are comparable to those found in the PRO-VAD study, pVO_2 values in the current investigation ranged from 4.0 to 35.6 ml/kg/min. This indicates that the examined population is quite heterogeneous, including patients implanted with DT, BTT, and bridge-to-decision indications. We included all 3 categories for several reasons. First, a considerable number of patients designated DT regain candidacy after LVAD implantation and undergo transplantation, whereas conversely, some patients implanted with a BTT strategy develop contraindications to transplantation. Second, recent data suggest that an important difference in outcome in DT and BTT or bridge-to-candidacy patients do not exist, which, together with the crossover described, has led to the suggestion of abandoning the designations BTT and DT entirely (38). In the current study, it is further

FIGURE 2 Ventilatory Efficiency **(A)** Survival according to VE/VO₂ slope in tertiles. **(B)** Survival according to VE/VO₂ slope less vs >35. VE/VO₂ slope = ventilation/carbon dioxide relationship.

reassuring to find that the mortality HR for pVO₂ remained unchanged upon adjusting for therapy indication (DT vs BTT or BTD). As such, pVO₂ was demonstrated its ability to readily identify patients with an excellent survival over several years regardless of the pre-implant intention of transplantation. In patients with pVO₂ >12 or 14 depending on BB use, it appears that heart transplantation can be safely deferred and re-evaluated at a later timepoint.

It is not clear whether the advanced HF community and patients are ready to adopt a strategy where stable LVAD recipients are prioritized for heart transplantation by their future mortality risk. However, in reality, a prioritization already occurs in some regions where urgent transplantations for acute LVAD complications such as stroke or infection are common. Hence, it might be more attractive to risk stratify patients before complications occur, as this would likely improve post-transplant outcomes. As shown in the current study, measuring pVO₂ in stable LVAD recipients at regular intervals may be a feasible strategy for risk stratification. Further studies would be required to understand the association between low pVO₂ and specific adverse events in LVAD recipients as this information may further qualify the decision of transplantation listing.

Potentially, pVO₂ measurements in LVAD recipients may identify patients who would benefit from more aggressive medical management. Indeed, therapy directed by invasive hemodynamic evaluation has been suggested to improve outcomes in LVAD recipients (39), and future studies should determine whether pVO₂ measurements could be used to noninvasively identify patients requiring

TABLE 2 Univariate and Multivariate Analysis of Predictors of Survival After CPET in LVAD Recipients

Covariate/Explanatory Variables	B	P Value	Hazard Ratio	95% CI
pVO ₂ , ml/kg/min (cont)	−0.13	<0.001	0.88	0.83–0.94
pVO ₂ , ml/kg/min (cont)	−0.11	<0.001	0.9	0.84–0.95
Age	0.013	0.224	1.01	0.99–1.03
Sex	−0.1	0.727	0.91	0.55–1.52
pVO ₂ , ml/kg/min (cont)	−0.14	<0.001	0.87	0.81–0.93
Age	0.01	0.304	1.01	0.99–1.04
Sex	−0.07	0.796	0.93	0.56–1.56
BMI	−0.04	0.088	0.96	0.92–1.01
Device indication	0.22	0.441	1.24	0.72–2.15

The table shows the risk (HR) of death for patients calculated per ml/min/kg increase in pVO₂ in a univariate analysis (first row). In the succeeding rows 2 multivariate analyses adjusting for age, sex, BMI and device indication are shown. See paper for details.

B = regression coefficient; BMI = body mass index; (cont) = continuous variable; pVO₂ = peak oxygen uptake (continuous variable), ml/kg/min.

hemodynamic assessment. Additionally, the CPET study may serve as an excellent tool in determining the need for additional physical training in these patients.

STUDY LIMITATIONS. Although the current study is strengthened by its multicenter design and the large sample size, some limitations remain. The data were collected retrospectively, leading to missing information of some datapoints for some patients, especially regarding test protocols, LVAD settings, and echocardiographic findings, etc. Information for cause of death was not available. The study did not rely on enrollment of consecutive patients and the results cannot be extrapolated to patients with characteristics different from those of our study population. Patients not able to perform exercise tests were not included, which may be a major prognosticator limiting the extrapolation of the results. Furthermore, the authors did not have access to information regarding adverse events or quality of life in this study. The patients did not undergo CPET at a pre-specified timepoint and exercise protocols differed between centers. Furthermore, the patients received implants from a wide range of durable LVADs, thus reflecting a large proportion of the current LVAD landscape. This, however, is not different from advanced patients with HF not supported with MCS

who may undergo CPET at any point in their disease journey, typically to assess if transplant listing is relevant. Reassuringly, the prognostic power of pVO_2 in the current study did not depend on the timing after LVAD implantation. Only 6% of patients were tested on a treadmill, and as such the findings of the current study should be applied with caution to patients subjected to this test modality.

CONCLUSIONS

In this large multicenter study, the authors demonstrated that the cardiovascular reserve expressed as peak oxygen uptake is of clear prognostic value in LVAD recipients, comparable to heart failure patients not supported by MCS. Risk stratification of patients with LVAD awaiting heart transplant by pVO_2 and VE/VCO_2 slope should be considered. Furthermore, since pVO_2 predicts HF hospitalizations after LVAD implantation, routine postimplant measurement of oxygen consumption and aggressive therapy in patients with poor results may be helpful to improve outcomes in this population.

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CENTRAL ILLUSTRATION Prognostic Impact of Peak Oxygen Uptake

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Low peak oxygen uptake ($pVO_2 < 12$ ml/kg/min (if treated with beta-blockers) or < 14 ml/kg/min (no beta-blocker) predicts mortality in stable recipients of a continuous-flow LVAD. The median time from LVAD implantation to the exercise test was approximately 6 months. The findings are remarkably similar to those observed for HF patients without LVAD support, where the same cutoff values for pVO_2 are used to inform decisions for listing heart transplantation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Cardiovascular reserve expressed as peak oxygen uptake is of clear prognostic value in LVAD recipients, comparable to that in heart failure patients not supported by MCS. As pVO₂ predicts HF hospitalizations after LVAD implantation, routine post-implant measurement of oxygen consumption and aggressive therapy in patients with poor results might be helpful to improve outcomes LVAD recipients. Risk stratification of patients with LVAD

supporting heart transplant listing decisions by pVO₂ and VE/VCO₂ slope should be considered.

TRANSLATIONAL OUTLOOK: In LVAD recipients the use of peak oxygen uptake can guide clinicians to select patients with increased risk of death and heart failure hospitalizations. Risk stratification of patients with LVAD supporting heart transplant listing decisions by pVO₂ and VE/VCO₂ slope should be considered.

REFERENCES

- Chatterjee A, Feldmann C, Hanke JS, et al. The momentum of HeartMate 3: A novel active magnetically levitated centrifugal left ventricular assist device (LVAD). *J Thorac Dis*. 2018;10:S1790-S1793.
- 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.
- Gustafsson F, Shaw S, Lavee J, et al. Six-month outcomes after treatment of advanced heart failure with a full magnetically levitated continuous flow left ventricular assist device: Report from the ELEVATE registry. *Eur Heart J*. 2018;39:3454-3460.
- Theochari CA, Michalopoulos G, Oikonomou EK, et al. Heart transplantation versus left ventricular assist devices as destination therapy or bridge to transplantation for 1-year mortality: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2018;7:3-11.
- 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 Transplant*. 2018;37:15-24.
- 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.
- Mirza KK, Gustafsson F. Determinants of functional capacity and quality of life after implantation of a durable left ventricular assist device. *Card Fail Rev*. 2020;6:e29.
- Zimpfer D, Gustafsson F, Potapov E, et al. Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry. *Eur Heart J*. 2020;41:3801-3809.
- Rogers JG. Changes in United States heart allocation: a community energized to improve policy. *J Thorac Cardiovasc Surg*. 2016;152:1484-1486.
- Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35:1-23.
- Mancini DM, Eisen H, Kussmaul W, Mull R, Edmonds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778-786.
- MacGowan GA, Janosko K, Cecchetti A, Murali S. Exercise-related ventilatory abnormalities and survival in congestive heart failure. *Am J Cardiol*. 1997;79:1264-1266.
- Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129:S49-S55.
- Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail*. 2009;2:113-120.
- Tabet JY, Beauvais F, Thabut G, Tartièr JM, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO₂ slope in chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2003;10:267-272.
- Corrà U, Piepoli MF, Adamopoulos S, et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role a position paper from the committee on exercise physiology and training of the heart failure association of the ESC. *Eur J Heart Fail*. 2014;16:929-941.
- Davies LC, Francis DP, Piepoli M, Scott AC, Ponikowski P, Coats AJS. Chronic heart failure in the elderly: Value of cardiopulmonary exercise testing in risk stratification. *Heart*. 2000;83:147-151.
- Cohen-Solal A, Caviezel B. Cardiopulmonary exercise testing in chronic heart failure. *Heart Fail*. 1994;10:46-57.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129-2200.
- Jessup Likoff M, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol*. 1987;59:634-638.
- Szlachet J, Masse BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol*. 1985;55:1037-1042.
- Moss N, Rakita V, Lala A, et al. Hemodynamic response to exercise in patients supported by continuous flow left ventricular assist devices. *J Am Coll Cardiol HF*. 2020;8:291-301.
- Park SJ, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Outcomes of extracorporeal life support for low cardiac output syndrome after major cardiac surgery. *J Thorac Cardiovasc Surg*. 2014;147:283-289.
- Birks EJ, Drakos SG, Patel SR, et al. Prospective multicenter study of myocardial recovery using left ventricular assist devices (RESTAGE-HF [Remission from Stage D Heart Failure]): medium-term and primary end point results. *Circulation*. 2020;142:2016-2028.
- McKellar SH, Deo S, Daly RC, et al. Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. *J Thorac Cardiovasc Surg*. 2014;147:344-348.
- Imamura T, Kinugawa K, Nitta D, et al. Opening of aortic valve during exercise is key to preventing development of aortic insufficiency during ventricular assist device treatment. *ASAIO J*. 2015;61:514-519.
- Mirza KK, Jung MH, Sigvardsen PE, et al. Computed tomography-estimated right ventricular function and exercise capacity in patients with continuous-flow left ventricular assist devices. *ASAIO J*. 2020;66:8-16.
- Alvarez Villela M, Guerrero-Miranda CY, Chinnadurai T, Patel SR, Jorde UP. Rate response pacing in left ventricular assist device patients. *ASAIO J*. 2020;66:e29-e30.

29. Bouzas-Cruz N, Koshy A, Gonzalez-Fernandez O, et al. Markers of right ventricular dysfunction predict maximal exercise capacity after left ventricular assist device implantation. *ASAIO J*. 2020 [ahead of print].
30. Hasin T, Marmor Y, Kremers W, et al. Readmissions after implantation of axial flow left ventricular assist device. *J Am Coll Cardiol*. 2013;61:153-163.
31. Smedira NG, Hoercher KJ, Lima B, et al. Unplanned hospital readmissions after heartmate II implantation. Frequency, risk factors, and impact on resource use and survival. *J Am Coll Cardiol HF*. 2013;1:31-39.
32. Takeda K, Takayama H, Colombo PC, et al. Incidence and clinical significance of late right heart failure during continuous-flow left ventricular assist device support. *J Heart Lung Transplant*. 2015;34:1024-1032.
33. Goldstein DJ, Meyns B, Xie R, et al. Third annual report from the ISHLT mechanically assisted circulatory support registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. *J Heart Lung Transplant*. 2019;38:352-363.
34. Gross C, Marko C, Mikl J, et al. LVAD Pump flow does not adequately increase with exercise. *Artif Organs*. 2019;43:222-228.
35. Noor MR, Bowles C, Banner NR. Relationship between pump speed and exercise capacity during HeartMate II left ventricular assist device support: Influence of residual left ventricular function. *Eur J Heart Fail*. 2012;14:613-620.
36. Rosenbaum AN, Dunlay SM, Pereira NL, et al. Determinants of improvement in cardiopulmonary exercise testing after left ventricular assist device implantation. *ASAIO J*. 2018;64:610-615.
37. Schmidt T, Bjarnason-Wehrens B, Mommertz S, et al. Development of exercise-related values in heart failure patients supported with a left ventricular assist device. *Int J Artif Organs*. 2019;42:201-206.
38. Goldstein DJ, Naka Y, Horstmannshof D, et al. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the multicenter study of MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3. *JAMA Cardiol*. 2020;5:411-419.
39. Uriel N, Burkhoff D, Rich JD, et al. Impact of hemodynamic ramp test-guided HVAD speed and medication adjustments on clinical outcomes: the RAMP-IT-UP multicenter study. *Circ Heart Fail*. 2019;12:12-22.

KEY WORDS exercise, maximum oxygen uptake, outcome, prognosis, survival

APPENDIX For supplemental tables and figures, please see the supplemental version of this paper.