



Article

Early Cardiopulmonary Fitness after Heart Transplantation as a Determinant of Post-Transplant Survival

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Abstract: Background: Decreased peak oxygen consumption during exercise (peak VO_2) is a well-established prognostic marker for mortality in ambulatory heart failure. After heart transplantation, the utility of peak VO_2 as a marker of post-transplant survival is not well established. Methods and Results: We performed a retrospective analysis of adult heart transplant recipients at the Hospital of the University of Pennsylvania who underwent cardiopulmonary exercise testing within a year of transplant between the years 2000 to 2011. Using time-to-event models, we analyzed the hazard of mortality over nearly two decades of follow-up as a function of post-transplant percent predicted peak VO_2 (% VO_2). A total of 235 patients met inclusion criteria. The median post-transplant % VO_2 was 49% (IQR 42 to 60). Each standard deviation ($\pm 14\%$) increase in % VO_2 was associated with a 32% decrease in mortality in adjusted models (HR 0.68, 95% CI 0.53 to 0.87, $p = 0.002$). A % VO_2 below 29%, 64% and 88% predicted less than 80% survival at 5, 10, and 15 years, respectively. Conclusions: Post-transplant peak VO_2 is a highly significant prognostic marker for long-term post-transplant survival. It remains to be seen whether decreased peak VO_2 post-transplant is modifiable as a target to improve post-transplant longevity.

Keywords: transplant; exercise; survival; prognosis



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1. Introduction

Diminished exercise capacity is a cardinal feature of advanced heart failure, and a strong association between decreased peak oxygen consumption (VO_2) and increased mortality has been recognized in ambulatory heart failure patients for decades [1,2]. Given its association with mortality, peak VO_2 is commonly used to estimate prognosis, and current practice guidelines recommend its use as a threshold for advanced heart failure therapies [3]. Mechanistically, however, the relationship between VO_2 and mortality in heart failure with reduced ejection fraction (HFrEF) is confounded by multiple convergent pathophysiologic processes resulting in the diminished consumption of oxygen. While it is plausible that decreased peak VO_2 in HFrEF reflects, at least in part, inadequate tissue oxygen delivery during exercise due to a reduced cardiac output [4], a dissociation between peak VO_2 and hemodynamic dysfunction has long been observed [5].

Hypothetically, if cardiac output were the main limitation barring further increases in peak VO_2 then peak VO_2 should increase dramatically after heart transplantation, and VO_2 would no longer distinguish risk for mortality. Yet, across the population of heart-transplant

recipients, post-transplant VO_2 is highly heterogeneous [6,7]. Peak VO_2 only improves in a small number of individuals, and those with the lowest pre-transplant peak VO_2 often have the lowest post-transplant VO_2 [8]. The reasons for this and the usefulness of VO_2 as a marker of short- or long-term survival are not well understood. Significant extracardiac parameters may mediate the link between mortality and peak VO_2 , and advanced heart failure therapies that treat cardiac failure may not directly influence these parameters, including mechanical circulatory support and heart transplantation.

Because multiple comorbidities factor into the peak VO_2 , there may be significant information captured in this metric post-transplant, even after transplant. This information could be clinically useful, improving risk-stratification and shedding new light on causal mechanisms for patient decline and transplant outcomes, with the potential for intervention. In this study, we sought to (1) quantify the association between post-transplant peak VO_2 and mortality and (2) identify potential pathophysiologic processes that may explain this association.

2. Materials and Methods

The first and last authors (T.C.H. and E.Y.B.) had full access to all the data in the study and take responsibility for its integrity and the data analysis. Requests to access deidentified data from qualified researchers trained in human subject confidentiality protocols should be sent to the corresponding author. Unidentified Stata code for this analysis is available upon request.

2.1. Design and Participants

We performed a retrospective analysis of all adult heart transplant recipients who were transplanted from March 2000 to November 2011 at the Hospital of the University of Pennsylvania, excluding multiorgan recipients and patients undergoing cardiac retransplantation. Survival status was observed through October 2019 using data merged from the Penn Transplant Institute. This era was selected due to a clinical protocol at the time in which all patients underwent a post-transplant cardiopulmonary exercise test (CPET) within one year of transplant if clinically able. Patients who underwent CPET outside of their first post-transplant year were excluded, as were four patients with missing peak VO_2 . Baseline pre- and post-transplant clinical data were recorded from the electronic medical record, including demographics, pre- and post-transplant comorbidities up to the time of CPET, laboratory values at the time of CPET, post-transplant echocardiographic data up to one year post-CPET, the incidence of acute cellular rejection grade 2R or 3R or antibody mediated rejection prior to CPET, and the CPET results themselves. This study was approved by the University of Pennsylvania Institutional Review Board with a waiver of informed consent.

2.2. Cardiopulmonary Exercise Metrics

Data from CPET were acquired retrospectively from the electronic medical record. All patients performed one symptom-limited CPET within the first post-transplant year according to our standard clinical practice, using a treadmill with a low- or moderate-intensity ramped protocol until exhaustion, the onset of limiting symptoms, or the development of a contraindication to continued exercise. Breath-by-breath expired gas analysis was used to obtain continuous estimates of VO_2 and carbon dioxide production (VCO_2) at peak exercise. Studies were interpreted by an advanced heart failure cardiologist.

Absolute peak VO_2 was determined as the highest 10-s averaged samples obtained during exercise. We estimated the % of predicted peak VO_2 using the Fitness Registry and the Importance of Exercise National Database (FRIEND) equation based on age, sex, and weight [9]. Peak VO_2 is conventionally standardizing for total body mass; however, because VO_2 is influenced primarily by muscle mass and can be reduced out of proportion to heart failure severity in obese subjects [10], we examined values of VO_2 indexed separately for total body mass in kilograms ($\text{peak VO}_2, \text{body mass}$) and estimated lean body mass (peak

$VO_{2, \text{lean}}$). Lean body mass was estimated from weight, height, age, and ethnicity using a formula validated against dual-energy X-ray absorptiometry (i.e., DXA scan) in a sample of 14,000 US adults [11]. Heart rate, systolic blood pressure, and diastolic blood pressure were recorded at rest and at peak exercise. O_2 pulse was calculated as the ratio of absolute peak VO_2 to peak heart rate.

The respiratory exchange ratio (RER) was determined from the ratio of VCO_2 to VO_2 at the time of exhaustion. Maximal Volitional exercise was determined using a peak $RER \geq 1.0$, based on guideline recommendation and application in recent large studies of exercise in HFref [12–15]. Only studies demonstrating evidence of maximal effort were used in analyses. The first post-transplant transthoracic echocardiogram obtained up to one year after CPET was used to compare peak VO_2 to the left ventricular ejection fraction.

2.3. Statistical Analysis

Continuous data are expressed as mean \pm standard deviation (SD), while categorical data are expressed as frequency and proportions. We compared baseline characteristics between patients who had peak VO_2 values above and below the sample median using the two-sample *t*-test for continuous variables (irrespective of normality due to large sample size) and the Chi-squared test or Fisher's exact test as appropriate for categorical variables. All time-to-event analyses considered the time to death or re-transplantation from the time of transplant, referred to hereafter as simply "mortality" given the low incidence of re-transplantation. Differences in mortality over time in relation to absolute peak VO_2 , $\%VO_2$, peak $VO_{2, \text{body mass}}$, peak $VO_{2, \text{lean}}$ and O_2 pulse were assessed in univariate and multivariable models as described below.

Three Cox proportional hazard models were constructed for each VO_2 parameter to quantify its crude and adjusted association with mortality. Model 1 was unadjusted. Model 2 was adjusted for demographics including age, race/ethnicity, sex, and the number of days from transplant to CPET. Finally, model 3 was adjusted for model 2 variables plus pre-transplant pulmonary vascular resistance (PVR), type 2 diabetes, ischemic cardiomyopathy, peripheral vascular disease, chronic obstructive pulmonary disease and post-transplant hemoglobin (measured at the time of CPET) [16]. All independent variables were normalized as a Z-score to their underlying SD to allow direct comparison of relative effect size. The proportional hazard assumption for each model was tested with Schoenfeld residuals [17]. A two-sided Type I error rate of 0.05 was used, without adjustment for multiple comparisons. The rate of missing data for each covariate did not exceed 15%. Missing values for covariates were imputed via multiple imputation with chained equations.

Next, we modeled survival at 1, 5, 10 and 15 years post-transplant as a function of post-transplant $\%VO_2$ using flexible parametric survival models [18]. The $\%VO_2$ cutoffs for predicted survival below 80% are presented at 5, 10, and 15 years post-transplant. One-year survival was also modeled, but a cutoff for 80% survival at 1-year did not exist within the measured range of $\%VO_2$. All analyses were performed in Stata version 16 (College Station, TX, USA: StataCorp LLC).

3. Results

3.1. Characteristics of the Sample Population

A total of 367 patients underwent single-organ, first-time heart transplantation at the University of Pennsylvania during the study period (Figure 1). Of these, we obtained peak VO_2 measurements on 235 patients. Reasons for missing peak VO_2 measurements were: 4 died prior to one year without undergoing CPET, 38 performed CPET after the 1-year cutoff, 4 performed CPET but were missing peak VO_2 , 67 were unable to perform CPET due to prolonged index hospitalizations or severe deconditioning, and 19 performed CPET with submaximal exercise. The RER for the patients excluded for submaximal exercise ranged from 0.8 to 1.0, while the RER for patients performing maximal exercise ranged from 1.0 to 1.44.

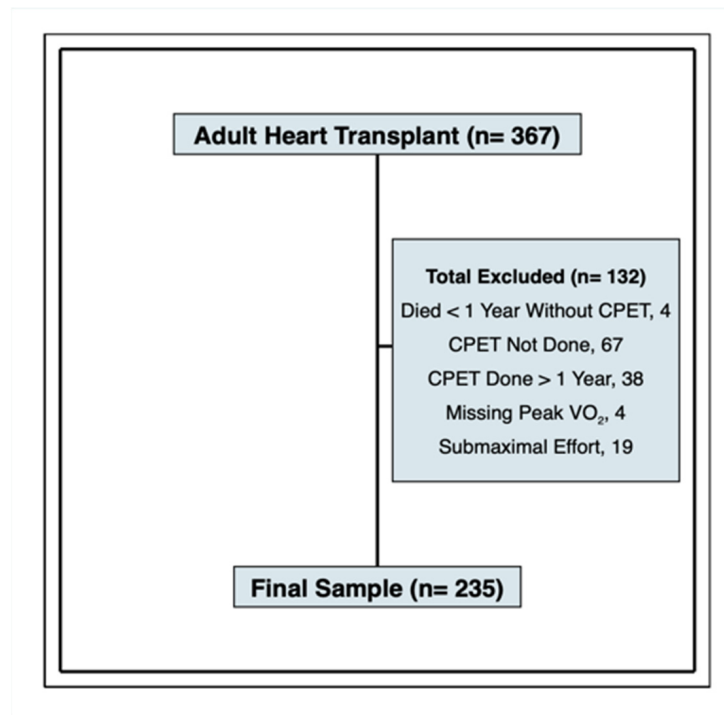


Figure 1. Study Inclusion and Exclusion. The final sample consists of 235 patients who had peak VO_2 measured within the first post-transplant year. Acronyms: CPET, cardiopulmonary exercise test; RER, respiratory exchange ratio.

During follow-up of the 235 patients in the cohort, there were 93 deaths (40%) and 4 retransplants (1.7%). The range of follow-up was 115 days to 18.9 years (mean 10.5 years, $SD \pm 4.4$ years). Figure 2 shows the distributions of post-transplant absolute peak VO_2 , $\%VO_2$, and VO_2 indexed to body mass or lean mass. The median $\%VO_2$ was 49% (IQR 42 to 60%).

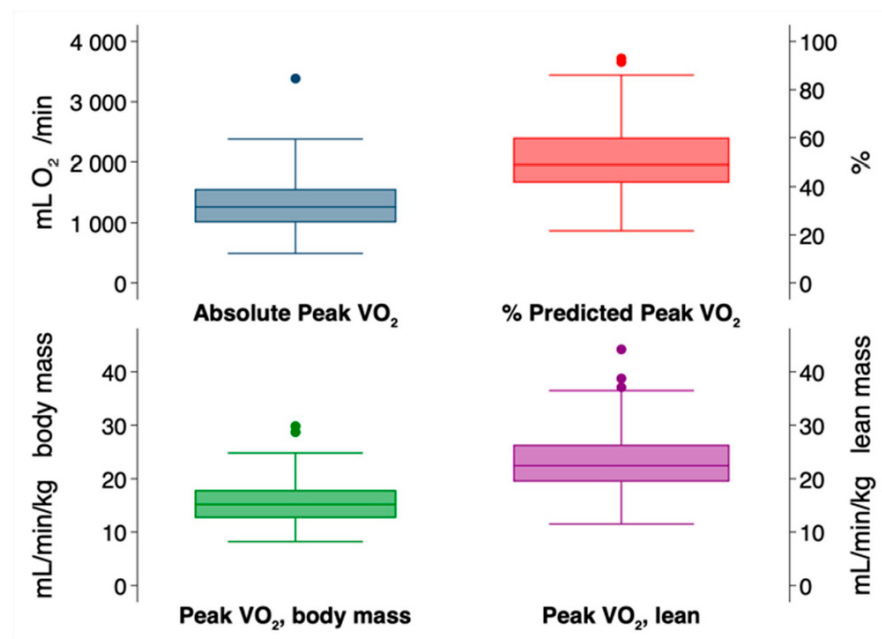


Figure 2. Distribution of Post-Transplant Peak VO_2 Indices. Box plots displaying the median, $1.5 \times$ interquartile range, and outliers for each VO_2 metric.

Several baseline parameters were associated with a %VO₂ below median (Table 1). This included younger age (50 vs. 56 years, *p* < 0.001), male sex (87 vs. 77%, *p* = 0.038), lower peak heart rate (116 vs. 125 bpm, *p* < 0.001), lower weight (82 vs. 88 kg, *p* = 0.013), and lower BMI (26 vs. 29 kg/m², *p* < 0.001). Some of these relationships may seem paradoxical (i.e., younger age), but this is because younger patients tended to have lower peak VO₂ relative to their age-predicted values than older patients, in spite of having greater absolute peak VO₂ measurements. O₂ pulse, the ratio of absolute VO₂ to peak heart rate, was also lower in individuals with %VO₂ below median (10 vs. 12 mL/beat, *p* < 0.001), suggesting impairments in the arteriovenous O₂ content or stroke volume at peak exercise. Distributions of pre-transplant comorbidities and ethnicity were similar. No differences in post-transplant LVEF were observed between the groups (64% vs. 66%, *p* = 0.34), and there was no association between acute cellular rejection and %VO₂ (35% vs. 35%, *p* = 0.97). No patients who performed maximal exercise CPET had experienced antibody mediated rejection prior to CPET.

Table 1. Baseline Characteristics of Patients Above and Below Median % Predicted VO₂.

	% Predicted Peak VO ₂ , <Median of 48.6% n = 118	% Predicted Peak VO ₂ , ≥Median of 48.6% n = 117	<i>p</i> -Value
Baseline Characteristics			
Age at CPET, years	50 ± 13	56 ± (9)	<0.001
Sex, % male	103 (87%)	90 (77%)	0.038
Ethnicity			0.066
Non-Hispanic White	91 (77%)	95 (81%)	
Non-Hispanic Black	20 (17%)	22 (19%)	
Hispanic	4 (3%)	0 (0%)	
Other	3 (3%)	0 (0%)	
Diabetic Pre-Transplant	52 (44%)	43 (37%)	0.25
Ischemic Etiology Pre-Transplant	51 (43%)	47 (40%)	0.64
PVD Pre-Transplant	8 (8%)	3 (3%)	0.12
COPD Pre-Transplant	9 (9%)	8 (8%)	0.82
PVR Pre-Transplant, dynes * s * cm ⁻⁵	146 ± 114	128.5 ± 72	0.19
Serum Creatinine (mg/dL)	1.6 ± 0.9	1.5 ± 1.0	0.39
Daily Prednisone Dose, mg	3.5 ± 3.5	3.1 ± 3.0	0.40
Cyclosporine Use	18 (15.3%)	16 (13.8%)	0.75
CPET Parameters			
Days from Transplant to CPET	88 ± 70	103 ± 79	0.12
Absolute Peak VO ₂ , mL O ₂ /min	1095 ± 283	1528 ± 412	<0.001
% Predicted Peak VO ₂	40 ± 6	62 ± 10	<0.001
O ₂ pulse, mL/beat	10 ± 3	12 ± 3	<0.001
Total Exercise Time, min	8 ± 3	9 ± 3	0.11
Peak Heart Rate, bpm	116 ± 17	125 ± 17	<0.001
Peak SBP, mmHg	149 ± 22	153 ± 22	0.18
Peak DBP, mmHg	81 ± 12	82 ± 11	0.71
Peak Respiratory Exchange Ratio	1.1 ± 0.1	1.1 ± 0.1	0.71
Hemoglobin at CPET, g/dL	13 ± 2	13 ± 2	0.23
Height, cm	176 ± 10	175 ± 10	0.35
Body Weight, kg	82 ± 19	88 ± 17	0.013
BMI at CPET, kg/m ²	26 ± 5	29 ± 5	<0.001
Beta Blocker Use at CPET	25 (21%)	20 (17%)	0.46
Acute Cellular Rejection, %	35 (29.7%)	35 (29.9%)	0.97
Post-Transplant LVEF, %	64 ± 12	66 ± 7	0.34

Values are mean ± standard deviation or number (proportion). Acronyms: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; DBP, diastolic blood pressure; SBP, systolic blood pressure; PVD, peripheral vascular disease; PVR, pulmonary vascular resistance; VCO₂, carbon dioxide output; VO₂, oxygen consumption.

3.2. Association of VO₂ Metrics with Post-Transplant Mortality

All metrics of post-transplant peak VO₂ were significantly associated with mortality in unadjusted and multivariable adjusted models, with a large effect size (Table 2). Estimates for the effect of different peak VO₂ metrics on mortality were only marginally different. In univariate models, each SD increase in %VO₂ (14%) was associated with a 34% decrease in mortality (HR 0.66, 95% CI 0.53 to 0.84, *p* = 0.001), equivalent to a 2.4% decrease in mortality per each %VO₂. After adjusting for demographics, comorbidities, and the time from transplant to CPET (i.e., Model 3)—each SD increase in %VO₂ was associated with a 32% decrease in mortality (HR 0.68, 95 CI 0.53 to 0.87, *p* < 0.002), equating to a 2.3% decrease in mortality per %VO₂. We analyzed the association between peak VO₂ and mortality using alternative weight indices, including unindexed estimates (absolute peak VO₂) and peak VO₂ indexed to total body mass (VO₂, body mass) or estimated lean mass (peak VO₂, lean). All of these had estimates comparable to that of the %VO₂ (Table 2). Lastly, we evaluated whether the observed association between %VO₂ and mortality was conditional on heart rate by looking at the association of O₂ pulse with mortality. The O₂ pulse, in which the absolute peak VO₂ is indexed to the peak heart rate, demonstrated an equally strong association with mortality as other peak VO₂ indices (Table 2). In unadjusted models, each SD increase in the O₂ pulse (3.0 mL O₂/beat) was associated with a 19% decrease in the hazard of mortality (HR 0.81, 95% CI 0.65 to 0.99, *p* = 0.043). After multivariable adjustment, the HR for O₂ pulse was 0.66 (95% CI 0.51 to 0.85, *p* = 0.002). Figure 3 displays the unadjusted Kaplan–Meier survival probability over time stratified by the median %VO₂ of 49%.

Table 2. Hazard Associated with each Standard Deviation Change in Peak VO₂.

	Model 1 Univariate		Model 2 Demographics		Model 3 Clinical Covariates	
	HR [§] (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Peak Oxygen Consumption						
Absolute Peak VO ₂ (SD ± 414 mL O ₂ /min)	0.75 (0.60, 0.93)	0.010	0.60 (0.46, 0.78)	0.000	0.62 (0.47, 0.81)	0.001
% Predicted Peak VO ₂ (SD ± 14%)	0.66 (0.53, 0.84)	0.001	0.63 (0.50, 0.81)	0.000	0.68 (0.53, 0.87)	0.002
Peak VO ₂ , body mass (SD ± 4 mL O ₂ /min/kg body mass)	0.69 (0.55, 0.87)	0.002	0.66 (0.52, 0.83)	0.000	0.72 (0.56, 0.91)	0.007
Peak VO ₂ , lean (SD ± 6 mL/min/kg lean mass)	0.62 (0.49, 0.78)	0.000	0.63 (0.50, 0.79)	0.000	0.68 (0.53, 0.86)	0.002
O ₂ Pulse (SD ± 3 mL O ₂ /beat)	0.81 (0.65, 0.99)	0.043	0.66 (0.52, 0.85)	0.001	0.66 (0.51, 0.85)	0.002

Higher Peak VO₂ is associated with a decreased hazard of death or retransplantation. *Model 1*—unadjusted Cox proportional hazard model. *Model 2*—adjusted for age, race/ethnicity, sex, and days from transplant to CPET. *Model 3*—adjusted for Model 2 variables plus pulmonary vascular resistance, type 2 diabetes, ischemic cardiomyopathy, peripheral-vascular disease, chronic obstructive pulmonary disease, and hemoglobin. Hazard ratios (HR) are for a one standard deviation (SD) change in each metric. Acronyms: VO₂, oxygen consumption.

3.3. Predicting Post-Transplant Survival

We derived four models predicting survival at 1, 5, 10 and 15 years post-transplant as a function of post-transplant %VO₂ (Figure 4). From each model, we identified a %VO₂ cutoff below which the predicted survival to each timepoint was less than 80%. At 5 years post-transplant, 80% survival (95% CI 72 to 89%) was predicted by a %VO₂ below 29%. At 10 years, the 80% survival threshold (95% CI 74 to 87%) was predicted by a %VO₂ below 64%. Finally, at 15 years, 80% survival (95% CI 69 to 94%) was predicted by a %VO₂ below 88%. Only 5 patients in our sample died within the first year (2%), so no cutoff predicting 1-year survival less than 80% could be estimated.

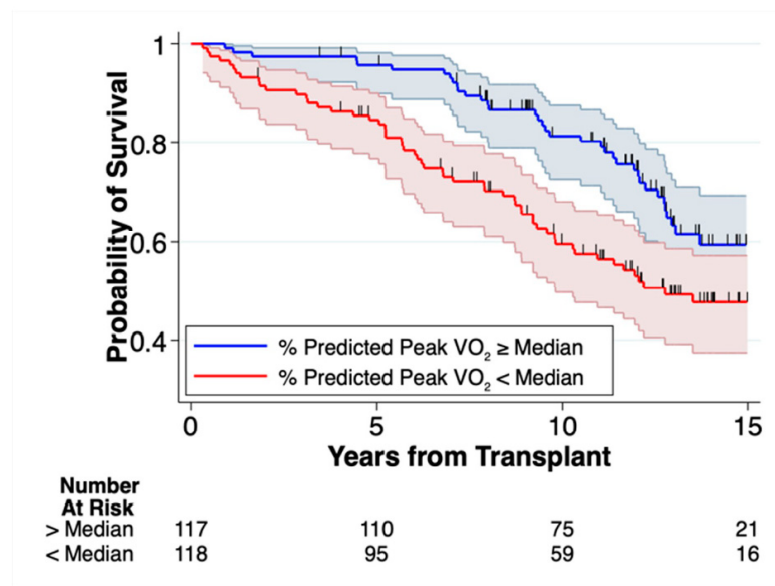


Figure 3. Kaplan–Meier Survival Estimates Stratified by Median % Predicted Peak VO₂. Patients with post-transplant % Predicted Peak VO₂ (%VO₂) below median had significantly lower long-term survival. The median %VO₂ was 49%. Vertical dash marks indicate censored events. Shaded areas represent the 95% Confidence Intervals.

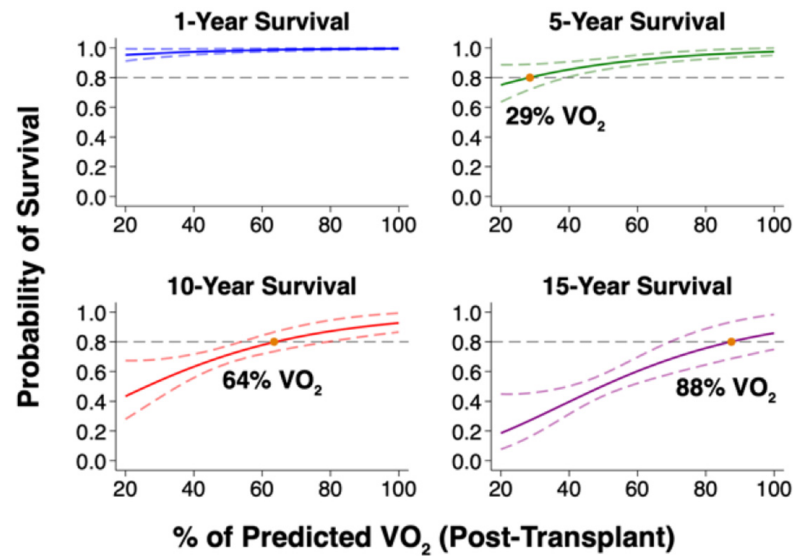


Figure 4. Predicted Survival Free from Re-transplantation based on Post-Transplant % Predicted Peak VO₂. Post-Transplant % Predicted Peak VO₂ predicts long-term survival. Plots based on unadjusted flexible parametric survival models, displaying mean survival (solid lines) along with upper and lower 95% confidence intervals (dashed lines). Acronyms: VO₂, oxygen consumption.

4. Discussion

An association between pre-transplant peak VO₂ and mortality in ambulatory heart failure was first established over two decades ago [1], and numerous studies have corroborated this association across multiple populations [2,19,20]. In this retrospective cohort analysis, we evaluated whether lower peak VO₂ in the early *post-transplant* period is associated with long-term post-transplant mortality. Our major findings were that: (1) diminished post-transplant peak VO₂ was strongly associated with mortality over nearly two decades of follow-up and (2) this association was independent of parameters known to directly

influence VO_2 , such as hemoglobin, sex, heart rate, body mass, and the number of days from transplant to CPET.

The etiology of diminished peak VO_2 is multifactorial, involving cardiac and extracardiac parameters. Only some of these will respond directly to improved cardiac function, while some deficits are likely to remain, explaining why several studies have shown little improvement in peak VO_2 after heart transplant or mechanical circulatory support [6,8]. In our analysis, we attempted to differentiate whether the association between diminished peak VO_2 and mortality post-transplant was inherent to peak VO_2 or instead confounded by several common comorbidities. In the fully adjusted model, each SD (14%) increase in % VO_2 remained associated with a 32% decrease in the hazard of mortality (HR 0.68, 95 CI 0.53 to 0.87, $p = 0.002$). This effect size is in accordance with another single-center study out of Norway that analyzed transplants from the decade prior [21], confirming the generalizability of this association across time and institution. Moreover, we showed that this effect was independent of several additional extracardiac factors such as COPD, diabetes, peripheral vascular disease, and pulmonary vascular resistance.

These latter comorbidities, though not severe enough to preclude transplant in the first place, could still significantly confound the relationship between VO_2 and mortality. Instead, their adjustment had negligible effect. Similarly, the association between VO_2 and mortality was independent of post-transplant factors that can significantly impact the peak VO_2 or mortality, including body mass, LVEF, hemoglobin, creatinine, a history of acute cellular or antibody mediated rejection, the number of days from transplant to CPET, and immunosuppressive regimen. Additionally, the O_2 pulse—which indexes the peak VO_2 to peak heart rate—was strongly associated with mortality in all multivariable models. This confirms that the association was not conditional on heart rate response, which can be diminished post-transplant secondary to sympathetic denervation. Based on the strong association between peak VO_2 and survival, higher % VO_2 predicted a greater probability of survival each year post-transplant. Using 80% survival probability as a target, this threshold was predicted at 5, 10 and 15 years by increasing % VO_2 cutoffs of 29%, 64%, and 88%, respectively. If externally validated, this metric could provide a useful prognostic screening tool for the early post-transplant period.

Diminished peak VO_2 that is unrelated to cardiac dysfunction or major comorbidities may indicate impaired skeletal muscle function, consistent with the “muscle hypothesis” in chronic heart failure [22]. Even in a healthy population, diminished exercise capacity is associated with increased mortality [23]; even more so in a heart failure population with deranged skeletal muscle oxidative capacity. Inadequate skeletal muscle oxidative capacity during exercise appears as a common element in multiple heart failure phenotypes, including heart failure with either reduced or preserved ejection fraction [24]. In chronic heart failure, this may be related to reduced O_2 diffusion or deficiencies in mitochondrial density and efficiency [25], and these deficiencies post-transplant may be a holdover from the pre-transplant period. This is corroborated by the observation that lower pre-transplant peak VO_2 predicts lower post-transplant peak VO_2 [8], although skeletal muscle oxidative capacity could also worsen post-transplant secondary to chronic exposure to steroids and calcineurin inhibitors or prolonged hospitalizations [25]. Furthermore, it may be possible to detect reduced skeletal muscle oxidative capacity via a decline in the arteriovenous oxygen difference, implying decreased extraction and utilization of oxygen. Thus, it is notable that mortality in this study was strongly associated with decreased O_2 pulse, which in addition to correlating with stroke volume also provides an indirect measure of the arteriovenous oxygen difference [26].

5. Limitations of Our Study

This study is retrospective in nature, which increases the possibility for misclassification bias using variables measured for clinical intent. In particular, peak VO_2 were determined via a 10 s average rather than 30 s, which may overestimate peak VO_2 (although this was measured in similar fashion for all subjects). As a single center study

with a predominantly white population, generalizability to other sites may be reduced. In this study, most patients did not have pre-transplant CPET to analyze the prognostic importance of the change in parameters from pre- to post-transplant—this is a topic of future interest. Selection bias likely exists in the ability to perform a CPET, per se, thus estimates of association with mortality in the CPET population likely underestimate mortality in the overall heart transplant population that includes patients who were unable to perform CPET. Some covariate data were missing in this study, but no variables had greater than 15% missingness, and we were able to minimize bias through multiple imputation of missing datapoints.

6. Conclusions

Post-transplant peak VO_2 during maximal exercise is strongly associated with long-term post-transplant survival. The independent association between peak VO_2 metrics and mortality was independent of several important confounders and factors that contribute directly to VO_2 . We observed an association between O_2 pulse and mortality, suggesting that diminished post-transplant skeletal muscle oxidative capacity is a link between decreased peak VO_2 and survival. High-intensity exercise conditioning after transplant can safely augment peak VO_2 [27], but future studies are needed to evaluate whether improved peak VO_2 would lead to improved survival. If so, more aggressive cardiopulmonary rehabilitation post-transplant would be warranted, with peak VO_2 as an objective target.

Author Contributions: Conceptualization, T.C.H. and E.Y.B.; Formal analysis, T.C.H.; Data curation, T.C.H., Y.Z., R.S.Z., M.V.G. and M.M.; Writing—original draft, T.C.H.; Writing—review & editing, Y.Z., R.S.Z., M.V.G., M.M., R.C.M., J.A.M., M.S.T., J.W.W., P.A., M.A.A., L.R.G., R.S.Z., P.Z. and E.Y.B.; Supervision, E.Y.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the University of Pennsylvania.

Informed Consent Statement: Ethical review and approval were waived for this study. This is a retrospective study of preexisting clinical data and a signed informed consent document is not feasible, as many patients are no longer available to obtain authorization for use or disclosure of protected health information (PHI). Furthermore, a consent form will increase the risk of potential harm from a breach of confidentiality by becoming a “link” stored to identify the subject.

Data Availability Statement: The data that support the findings are available on request from the first author, T.C.H.

Conflicts of Interest: The authors declare no conflict of interest. All investigators are affiliated with the University of Pennsylvania, which has received clinical research support from Abbott and Medtronic. M.A.A. is on the advisory board for FineHeart and has a consulting relationship with Abbott. P.Z. has consulted for Vyair. E.Y.B. has received additional research support from Impulse Dynamics to the University of Pennsylvania.

Abbreviations

CPET	cardiopulmonary exercise test
HFrEF	heart failure with reduced ejection fraction
Peak VO_2	peak oxygen consumption
Peak VO_2 , body mass	peak oxygen consumption indexed to total body mass
Peak VO_2 , lean	peak oxygen consumption indexed to estimated lean body mass
RER	respiratory exchange ratio
% VO_2	percent of predicted peak oxygen consumption
VT	ventilatory threshold

References

1. Mancini, D.M.; Eisen, H.; Kussmaul, W.; Mull, R.; Edmonds, L.H.; Wilson, J.R. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* **1991**, *83*, 778–786. [[CrossRef](#)] [[PubMed](#)]
2. Elmariah, S.; Goldberg, L.R.; Allen, M.T.; Kao, A. Effects of Gender on Peak Oxygen Consumption and the Timing of Cardiac Transplantation. *J. Am. Coll. Cardiol.* **2006**, *47*, 2237–2242. [[CrossRef](#)] [[PubMed](#)]
3. Metra, M.; Ponikowski, P.; Dickstein, K.; McMurray, J.J.V.; Gavazzi, A.; Bergh, C.-H.; Fraser, A.G.; Jaarsma, T.; Pitsis, A.; Mohacsi, P.; et al. Heart Failure Association of the European Society of Cardiology. Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2007**, *9*, 684–694. [[CrossRef](#)] [[PubMed](#)]
4. Weber, K.T.; Kinasevitz, G.T.; Janicki, J.S.; Fishman, A.P. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* **1982**, *65*, 1213–1223. [[CrossRef](#)]
5. Wilson, J.R.; Rayos, G.; Yeoh, T.K.; Gothard, P. Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. *J. Am. Coll. Cardiol.* **1995**, *26*, 429–435. [[CrossRef](#)]
6. Borrelli, E.; Pogliaghi, S.; Molinello, A.; Diciolla, F.; Maccherini, M.; Grassi, B. Serial Assessment of Peak VO₂ and VO₂ Kinetics Early after Heart Transplantation. *Med. Sci. Sports Exerc.* **2003**, *35*, 1798–1804. [[CrossRef](#)]
7. Carter, R.; Al-Rawas, O.A.; Stevenson, A.; Mcdonagh, T.; Stevenson, R.D. Exercise responses following heart transplantation: 5 year follow-up. *Scott. Med. J.* **2006**, *51*, 6–14. [[CrossRef](#)]
8. Williams, T.J.; Mckenna, M.J. Exercise Limitation Following Transplantation. *Compr. Physiol.* **2012**, *2*, 1937–1979.
9. Myers, J.; Kaminsky, L.A.; Lima, R.; Christle, J.W.; Ashley, E.; Arena, R. A Reference Equation for Normal Standards for VO₂ Max: Analysis from the Fitness Registry and the Importance of Exercise National Database (FRIEND Registry). *Prog. Cardiovasc. Dis.* **2017**, *60*, 21–29. [[CrossRef](#)]
10. Malhotra, R.; Bakken, K.; D’Elia, E.; Lewis, G.D. Cardiopulmonary Exercise Testing in Heart Failure. *J. Am. Coll. Cardiol. HF* **2016**, *4*, 607–616. [[CrossRef](#)]
11. Lee, D.H.; Keum, N.; Hu, F.B.; Orav, E.J.; Rimm, E.B.; Sun, Q.; Willett, W.C.; Giovannucci, E.L. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999–2006. *Br. J. Nutr.* **2017**, *118*, 858–866. [[CrossRef](#)] [[PubMed](#)]
12. Fleg, J.L.; Pina, I.L.; Balady, G.J.; Chaitman, B.R.; Flether, B.; Lavie, C.; Limacher, M.C.; Stein, R.A.; Williams, M.; Bazzarre, T. Assessment of functional capacity in clinical and research applications: An advisory from the committee on exercise, rehabilitation, and prevention, council on clinical cardiology, American Heart Association. *Circ. Lippincott Williams Wilkins* **2000**, *102*, 1591–1597. [[CrossRef](#)] [[PubMed](#)]
13. Mezzani, A.; Corrà, U.; Bosimini, E.; Giordano, A.; Giannuzzi, P. Contribution of peak respiratory exchange ratio to peak VO₂ prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. *Am. Heart J.* **2003**, *145*, 1102–1107. [[CrossRef](#)]
14. O’Connor, C.M.; Whellan, D.J.; Lee, K.L.; Keteyian, S.J.; Cooper, L.S.; Ellis, S.J.; Leifer, E.S.; Kraus, W.E.; Kitzman, D.W.; Blumenthal, J.A.; et al. Efficacy and safety of exercise training in patients with chronic heart failure HF-ACTION randomized controlled trial. *J. Am. Med. Assoc.* **2009**, *301*, 1439–1450. [[CrossRef](#)] [[PubMed](#)]
15. Whellan, D.J.; O’Connor, C.M.; Lee, K.L.; Keteyian, S.J.; Cooper, L.S.; Ellis, S.J.; Leifer, E.S.; Kraus, W.E.; Kitzman, D.W.; Blumenthal, J.A.; et al. Heart Failure and a Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION): Design and rationale. *Am. Heart J.* **2007**, *153*, 201–211. [[CrossRef](#)]
16. Cox, D.R.; Oakes, D. *Analysis of Survival Data. Analysis of Survival Data*; CRC Press: Boca Raton, FL, USA, 2018; pp. 1–201.
17. Schoenfeld, D. Partial Residuals for The Proportional Hazards Regression Model. *Biometrika* **1982**, *69*, 239. [[CrossRef](#)]
18. Royston, P.; Parmar, M.K.B. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat. Med.* **2002**, *21*, 2175–2197. [[CrossRef](#)]
19. Elmariah, S.; Goldberg, L.R.; Allen, M.T.; Kao, A. The Effects of Race on Peak Oxygen Consumption and Survival in Patients with Systolic Dysfunction. *J. Card. Fail* **2010**, *16*, 332–339. [[CrossRef](#)]
20. Menachem, J.N.; Reza, N.; Mazurek, J.A.; Burstein, D.; Birati, E.Y.; Fox, A.; Kim, Y.Y.; Molina, M.; Partington, S.L.; Tanna, M.; et al. Cardiopulmonary Exercise Testing—A Valuable Tool, Not Gatekeeper When Referring Patients with Adult Congenital Heart Disease for Transplant Evaluation. *World J. Pediatr. Congenit. Heart Surg.* **2019**, *10*, 286–291. [[CrossRef](#)]
21. Yardley, M.; Havik, O.E.; Grov, I.; Relbo, A.; Gullestad, L.; Nytrøen, K. Peak oxygen uptake and self-reported physical health are strong predictors of long-term survival after heart transplantation. *Clin. Transplant.* **2016**, *30*, 161–169. [[CrossRef](#)]
22. Coats, A.J.S. The “Muscle Hypothesis” of chronic heart failure. *J. Mol. Cell. Cardiol.* **1996**, *28*, 2255–2262. [[CrossRef](#)] [[PubMed](#)]
23. Myers, J.; Prakash, M.; Froelicher, V.; Do, D.; Partington, S.; Atwood, J.E. Exercise capacity and mortality among men referred for exercise testing. *N. Engl. J. Med.* **2002**, *346*, 793–801. [[CrossRef](#)] [[PubMed](#)]
24. Weiss, K.; Schär, M.; Panjrath, G.S.; Zhang, Y.; Sharma, K.; Bottomley, P.A.; Golozar, A.; Steinberg, A.; Gerstenblith, G.; Russell, S.D.; et al. Fatigability, Exercise Intolerance, and Abnormal Skeletal Muscle Energetics in Heart Failure. *Circ. Heart Fail.* **2017**, *10*, e004129. [[CrossRef](#)] [[PubMed](#)]

25. Houstis, N.E.; Eisman, A.S.; Pappagianopoulos, P.P.; Wooster, L.; Bailey, C.S.; Wagner, P.D.; Lewis, G.D. Exercise intolerance in heart failure with preserved ejection fraction: Diagnosing and ranking Its causes using personalized O₂ pathway analysis. *Circulation* **2018**, *137*, 148–161. [[CrossRef](#)]
26. Gmada, N.; Al-Hadabi, B.; Haj Sassi, R.; Abdel Samia, B.; Bouhlef, E. Relationship between oxygen pulse and arteriovenous oxygen difference in healthy subjects: Effect of exercise intensity. *Sci. Sports* **2019**, *34*, e297–e306. [[CrossRef](#)]
27. Nytrøen, K.; Rolid, K.; Andreassen, A.K.; Yardley, M.; Gude, E.; Dahle, D.O.; Bjørkelund, E.; Relbo Authen, A.; Grov, I.; Philip Wigh, J.; et al. Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia: One-Year Follow-Up of the HITTS Randomized, Controlled Study. *Circulation* **2019**, *139*, 2198–2211. [[CrossRef](#)]

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