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Exercise capacity and cardiac allograft ischemic time in recent heart transplant recipients

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BACKGROUND: Prolonged ischemic times (IT) for transplant hearts transported under cold storage conditions are associated with an increased risk of mortality; however, the impact of IT on functional outcomes, such as exercise capacity (EC), is not fully understood. This prospective, observational cohort study aimed to determine the association between EC, a strong predictor for post-transplant survival, and relatively longer IT.

METHODS: Thirty heart transplant recipients were grouped dichotomously according to relatively longer (>180 minutes) or shorter (≤180 minutes) IT. A cardiopulmonary exercise test (CPET) was performed post-transplant upon cardiac rehabilitation admission, during which EC [peak volume of oxygen consumption (VO_2)] and CPET duration were measured and compared between groups.

RESULTS: This cohort was predominantly male (n = 22, 73%) with a median age of 57.5 years [Q1-Q3: 54.0-65.0]. Baseline demographics and characteristics were similar between groups aside from United Network for Organ Sharing listing status, in which patients listed as status 1 or 2 were more likely to have long IT. Twelve (40%) participants received a donor heart with long IT. Surprisingly, higher peak VO_2 was observed in those with long (15.0 ± 2.8) than short (13.1 ± 3.7) IT (p = 0.009). However, CPET duration was significantly shorter in recipients with a long IT (6.3 vs 7.7 minutes, p = 0.048) despite similar time since transplant, ratings of perceived exertion, protocol performed, and EC.

CONCLUSIONS: In this modest-sized cohort, EC was higher in heart transplant recipients with donor IT >180 minutes compared with those with IT ≤180 minutes. However, CPET duration was significantly shorter in those with relatively longer IT.

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Background

Reduced exercise capacity (EC) is a strong prognostic indicator of hospitalization risk[1] and poor long-term survival following orthotopic heart transplantation (OHT).[2] Although OHT comparatively improves EC for individuals with end-stage heart failure, surgical denervation of the donor heart following OHT leads to blunted heart rate (HR) variability and contributes to a significantly reduced EC compared to age-matched healthy counterparts.[3-8] Due to the role of EC in post-OHT survival, it is important to understand how other peritransplant variables impact EC to optimize postoperative functional outcomes.

Donor heart ischemic time (IT) has been linked to post-OHT mortality[9] and may impair EC in transplant recipients.[10] Over recent years, an increasing number of donor hearts with longer IT have been transplanted as a result of new donor organ allocation algorithms that aim to improve the accessibility of donor hearts for those with the greatest medical urgency. However, they have also resulted in a substantial increase in the distance traveled by donor organs (from procurement to transplant site) and, therefore, an increase in donor heart IT.[11-13] Much of the existing literature surrounding IT and OHT outcomes focuses on prolonged IT and post-transplant survival.[9,12,14-24] However, the overall impact of IT on EC is not fully understood.

Significant discrepancies exist in the literature regarding the impact of IT on EC in OHT recipients.[10,25,26] One study identified no relationship between IT and EC in OHT recipients over 1 year postoperatively,[25] while 1 describes a noticeable yet nonsignificant decrease in EC with increasing IT in a similar population.[26] Another study reported a significant decrease in EC with increasing IT in OHT recipients 2 months postoperatively[10]; however, that particular study had several limitations. First, OHT recipients were assessed 2 months postoperatively using the Bruce treadmill protocol,[27] known for its high aerobic demand in the first 3-minute stage and large increases in intensity with each progressive stage. This protocol may be poorly accommodated by heart transplant recipients given their chronotropically blunted responses to exercise attributable to surgical denervation and may incorrectly estimate EC.[28] Second, EC was assessed using *estimated* metabolic equivalent (METs) based on normative data for healthy populations with normal physiological responses to exercise. Direct metabolic assessment of expired gas exchange is the gold standard for the assessment of EC in individuals with cardiovascular disease or those with altered oxygen uptake kinetics and should be utilized when assessing EC in OHT recipients.[29] Lastly, OHT recipients may experience challenges when performing an exercise test on a treadmill, such as deconditioning,[30] and may require alternative modalities to safely assess EC. Health care professionals seeking to assess EC in OHT recipients must offer testing protocols and modalities appropriate for the individual OHT recipient.

An accurate understanding of the impact of donor heart IT on EC in early OHT recipients is essential to the optimal performance of donor hearts transplanted with prolonged IT. We sought to investigate the impact of donor IT on EC by utilizing cardiopulmonary exercise testing (CPET) and a testing protocol sensitive to the variable orthopedic and neurologic needs of patients following OHT.

Focusing exclusively on hearts transported using cold transport preservation media, we hypothesized that recipients of donor hearts with longer IT would demonstrate reduced EC in comparison with those who receive donor hearts with shorter IT.

Materials and methods

The protocol for this prospective, observational cohort study was approved by the institutional review board of Baylor Scott & White Research Institute. Participants provided written, informed consent before study procedures and were enrolled between January 2019 and June 2020. All consecutive eligible OHT recipients enrolling in a Phase 2 Cardiac Rehabilitation Program at Baylor Scott & White Heart and Vascular Hospital were given the opportunity to participate in the study until a cohort of 30 enrolled participants was accrued according to the institutional review board-approved cap (Figure 1). During this interval, all heart transplants at this center utilized donor hearts transported with nonbeating, cold cardioplegic transport with hearts donated after brain death. This study was conducted in accordance with the Declaration of Helsinki and complied with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement.

Eligibility criteria included hemodynamically stable adult (age 18-80 years) outpatients who had undergone OHT within 3 months of the study enrollment date and who survived to discharge with stamina sufficient to engage in outpatient cardiac rehabilitation. Excluded were patients with orthopedic, neurologic, or other limitations that precluded exercise testing on a treadmill or cycle ergometer; current inotropic therapy, those who required supplemental oxygen at rest or who had permanent tracheostomy; those discharged to a long-term acute care facility, skilled nursing facility, or with hospice care; inmates, pregnant women, and those who were unable to give consent (Figure 1).

The selection of CPET protocol was determined by each participant's fall risk assessment conducted by a registered nurse as part of standard care upon entry into cardiac rehabilitation. Participants at risk for falls performed a ramped protocol[31] on a cycle ergometer (Monark 828E;

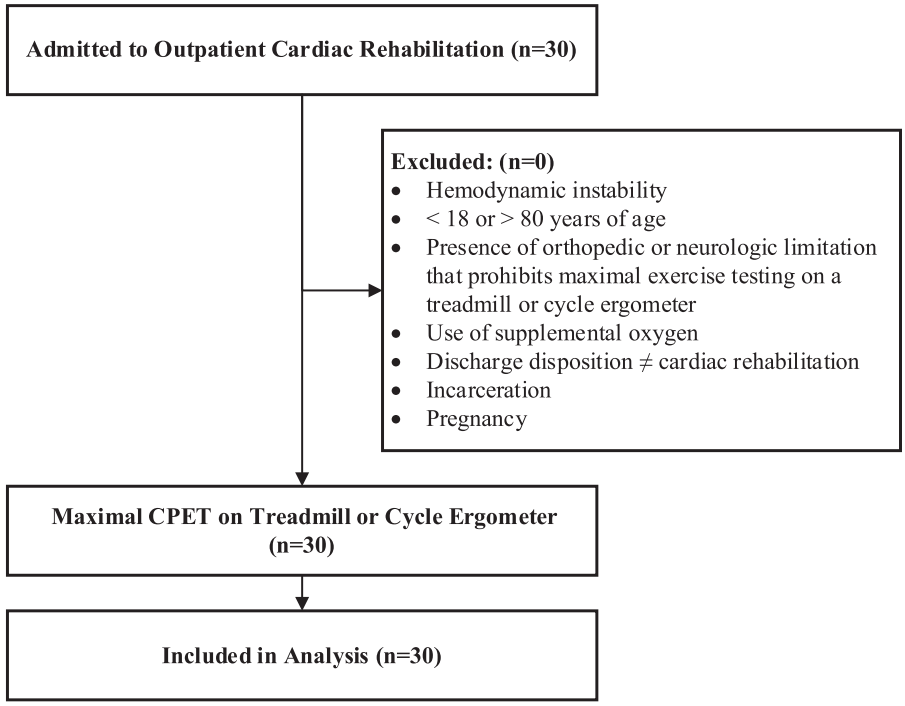

Figure 1 Flow diagram of study inclusion and exclusion methods. CPET, cardiopulmonary exercise test.

Monark Exercise, Vansbro, Sweden), in which the workload was increased by 10 W each minute until volitional fatigue or test termination criteria were met. Participants deemed not at risk for falls performed a Modified United States Airforce Aerospace Medicine[32] protocol on a motorized treadmill (TMX428CP Track Master, Full Vision, Inc., Newton, KS). These protocols were standard care in this department as they implemented relatively small increases in workload over time, which is preferred in clinical populations.[33] All participants were enrolled within 1 week of admission into cardiac rehabilitation, which was intended to minimize the training effect.

Upon entry to the testing facility, height and weight were measured and recorded in light clothing and footwear. A list of current medications was reviewed, and beta-blocker use or other antiarrhythmic use, if applicable, was recorded. Next, the participants completed a 5-minute seated rest period, after which auscultatory blood pressure (BP) was measured and recorded. A 3-lead electrocardiography (ECG) device (Quark C12x, COSMED, Concord, CA) was placed on the participant, and lead II was continually monitored for arrhythmias during rest, exercise, and recovery by telemetry competent staff. The participant was then fitted with metabolic equipment (7450 V2 Oro-nasal mask, Hans Rudolph, Inc., Shawnee, KS), and an adequate air seal was confirmed.

Participants were verbally educated to report their level of perceived exertion (Modified Borg Rating of Perceived Exertion [RPE][34]) and were asked to hold up the number of fingers corresponding with their current rating. All participants were instructed on testing procedures with a standardized script to perform the CPET until volitional fatigue and familiarized with the equipment. Participants were advised that no verbal or nonverbal encouragement or feedback would be provided by the study staff. The metabolic cart underwent appropriate warm-up and calibration according to manufacturer standards (Quark, COSMED, Rome, Italy) before CPET. If the participant was to perform the CPET on the cycle ergometer, the seat, the height, and the handlebars were adjusted for participant comfort while maintaining a slight bend in the knee at full leg extension. All CPET studies were performed within the cardiac rehabilitation department by a clinical exercise physiologist and registered nurse. BP, HR, and RPE were measured and recorded every 3 minutes.

After termination of the CPET, participants performed a seated cool-down period after which BP, HR, and RPE were measured and recorded. EC was determined using the final 30 seconds of breath-by-breath data recorded before terminating the test and anaerobic threshold (AT) was identified using the standard V-slope method. CPET termination criteria included (a) participant becoming symptomatic; (b) reporting increased pain; (c) participant request to terminate test; (d) dangerous arrhythmias observed on ECG; (e) unsafe drop in BP or increase to over 250/120 mm Hg; (f) participant report of "10" on RPE-CR-10 scale, indicating maximal effort, or (g) the clinical judgment of research staff to ensure the safety of the participant. CPET interpretation was performed blinded to donor IT. After completion of the study procedures and interpretation of the CPET, donor organ-specific data, including IT, were gathered through the United Network for Organ Sharing (UNOS) unique donor identification number and match run and cross-referenced with the corresponding printed CPET

report to allow for blinding of participant and research staff. Participants were neither informed of CPET outcomes nor donor IT.

Statistical analysis

The main exposure of this study was the duration of IT, which was dichotomized into longer and shorter IT using a prespecified cutoff of 180 minutes based on previous literature. There is no single universal definition of prolonged IT; however, 180 minutes is associated with worse outcomes following OHT[35] and was prespecified as it was utilized by Buendía-Fuentes et al,[10] in their previous work investigating IT and EC in OHT recipients. Furthermore, the intention was to study recipients transplanted with hearts within the range of routine donor IT encountered at our center to provide an accessible dichotomous range of donor IT (e.g., relatively shorter and longer times) rather than to study rare events at the extremes of donor IT (e.g., absolute shortest and longest).

The main outcome was the participant's EC, measured by peak volume of oxygen consumption (VO_2), which was dichotomized into lower and higher EC using a prespecified cutoff of 14 ml O_2/kg/min. A prespecified sensitivity analysis was performed using a dichotomous cutoff of 12 ml O_2/kg/min.[36] These 2 cutoffs were selected as they represent the standard thresholds below which transplant is most typically justified in an ambulatory, non–inodilator-dependent participant (14 ml O_2/kg/min for pretransplant patients without current beta-blocker use and 12 ml O_2/kg/min with beta-blocker use). Secondary CPET variables analyzed included exercise modality (cycle ergometer or treadmill), CPET duration, peak HR, peak power output (W) for participants completing the CPET using the cycle ergometer, and peak RPE.

To assess for confounding variables that may differ between IT groups, several donor, recipient, and post-transplant allograft function characteristics were compared between groups (Table 1). Donor-specific variables included age, sex, cause of death, hepatitis C viremia status, as well as warm, cold, and total IT. Recipient variables included serum creatinine as a measure of organ function, length of stay in intensive care (pretransplant, post-transplant, and total days), left ventricular ejection fraction (LVEF) as a measure of graft function, serum hemoglobin before CPET to assess for anemia, presence of left ventricular assist device or temporary mechanical circulatory support before OHT, UNOS listing status at the time of OHT, and standard right heart catheterization parameters (cardiac index [CI], cardiac output [CO], pulmonary artery [PA] systolic, PA diastolic, and PA mean pressures, pulmonary capillary wedge [PCW] pressure, pulmonary vascular resistance [PVR], right atrial [RA] mean pressure, and systemic vascular resistance [SVR]) were collected using the report from the first postoperative heart catheterization performed 6 weeks after transplant. Data are reported as percentages or counts for categorical variables and compared between participants with shorter and longer IT times using a Fisher's Exact Test; medians and interquartile range (IQR: Q1, Q3) for continuous variables were calculated and compared using *t*-tests or Wilcoxon rank sum tests. An additional descriptive analysis was performed to explore the impact of primary graft dysfunction after OHT, rejection, cytomegalovirus (CMV) viremia, and donor-specific antigens (DSA), where applicable, on EC and CPET duration.

Analysis of covariance on EC as a continuous variable was used to adjust for potential confounding variables that were potentially significant ($p < 0.05$) in the univariable comparison of IT groups; no adjustment for multiple comparisons was made. To identify associations with high EC (≥14 ml O_2/kg/min), univariable and multivariable logistic regressions were implemented selecting IT as a continuous variable instead of dichotomized above and below 180 minutes. Continuous IT provided more precise estimates for the odds ratio (narrower 95%CI) and was not limited by small cell counts (< 5) as was the case with dichotomized IT. Multivariable model selection was performed using lasso selection followed by backward stepwise selection, minimizing the misclassification error in the first step and maximizing the model Akaike information criteria in the second step. All variables with $p < 0.20$ from the univariable analysis (IT, age, UNOS listing status, exercise protocol, AT, PA systolic, and thermodilution CI), as well as CPET duration, were entered for selection. All analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was assessed 2-sided at a level of 0.05.

Results

The sample was predominantly non-Hispanic, White, and male with a median [IQR] recipient age of 57.5 years [54.0-65.0]. Donors were predominantly male ($n = 18$, 60%) and mean donor age was 36.0 ± 13.4 years. CPET was performed at a median of 29.5 [21.5, 35] days post-transplant. Of 30 OHT recipients, 12 (40%) received a donor heart with long IT. Patients with long IT were more likely to have a UNOS listing status of 1 or 2, but all other recipient and donor demographics and characteristics were similar between IT groups (Table 1).

CPET characteristics and outcomes are reported in Table 2. Thirteen participants were deemed at risk for falls and subsequently performed the cycle ergometer protocol, while the remaining 17 performed the treadmill protocol. Of those who performed the cycle ergometer protocol, 9 (69%) and 4 (31%) recipients had short and long IT, respectively, compared to 9 (53%) and 8 (47%) who performed the treadmill protocol. Two participants reported beta-blocker use, and 1 participant reported the use of another antiarrhythmic medication at the time of testing. Although we had anticipated performing a separate analysis using ≥12 ml O_2/kg/min as the threshold for high EC in participants using beta blockers based on previous literature,[36] both participants receiving beta-blockade had an EC ≥14 ml O_2/kg/min and were therefore not analyzed separately. A larger proportion of the long IT group tested with

Table 1 Demographics and Characteristics of Heart Transplant Recipients and Donors

Variable	Total ($n = 30$)	Short IT ($n = 18$)	Long IT ($n = 12$)	p
Recipient				
Recipient age (years)	57.5 [54.0, 65.0]	60 [55.2, 66.8]	56 [52.5, 61]	0.18
Recipient sex, male	21 (73%)	13 (72%)	9 (75%)	1.00
Ethnicity, Hispanic	4 (13%)	3 (17%)	1 (8%)	0.63
Race, African American	5 (17%)	4 (22%)	1 (8%)	0.62
Height (m)	1.7 (0.1)	1.7 (0.1)	1.8 (0.1)	0.41
Weight (kg)	79.3 (18.5)	78.7 (19)	80.2 (18.4)	0.83
BMI (kg/m^2)	26.0 (5.1)	26.1 (4.8)	25.9 (5.6)	0.95
Prior LVAD	4 (13%)	3 (17%)	1 (8%)	0.63
Prior tMCS				0.37
None	22 (73%)	15 (83%)	7 (58%)	
Axillary IABP	1 (3%)	0 (0%)	1 (8%)	
Axillary Impella	5 (17%)	2 (11%)	3 (25%)	
VA ECMO	2 (7%)	1 (6%)	1 (8%)	
UNOS listing status				0.03
1	2 (7%)	1 (6%)	1 (8%)	
2	7 (23%)	2 (11%)	5 (42%)	
3	9 (30%)	5 (28%)	4 (33%)	
4	10 (56%)	10 (56%)	1 (8%)	
5	0 (0%)	0 (0%)	0 (0%)	
6	1 (3%)	0 (0%)	1 (8%)	
Beta-blocker Use	2 (7%)	1 (6%)	1 (8%)	1.00
Antiarrhythmic use	1 (3%)	1 (6%)	0 (0%)	1.00
Postoperative day	29.5 [21.5, 35]	30.5 [21.5, 36.2]	29.5 [26.2, 35]	0.78
Increased fall risk	13 (43%)	9 (50%)	4 (33%)	0.60
Serum creatinine (mg/dl)	1.3 (0.3)	1.3 (0.4)	1.3 (0.2)	0.83
Pre-OHT ICU LOS (days)[a]	0 [0, 6.75]	0 [0, 1.5]	4.5 [0,8]	0.19
Post-OHT ICU LOS (days)	4 [3, 6.75]	3 [3,4]	5 [3.75, 8.25]	0.08
Total ICU LOS (days)	7 [3,12]	4 [3,11]	10 [6.5, 16.3]	0.09
Hemoglobin (g/dl)	11.9 (1.35)	11.6 (1.28)	12.4 (1.33)	0.54
LVEF (%)	60 (7.57)	60.5 (6.95)	60.3 (8.77)	0.73
PA mean (mm Hg)	19 [16.2, 24.5]	19.5 [17.2, 23]	19 [14.8, 25]	0.77
PA dystolic (mm Hg)	29.5 [26,34]	30.8 (8.7)	30.1 (7.7)	0.81
PA diastolic (mm Hg)	11 [9,17]	12 [9.2, 16.5]	10 [8, 20.2]	0.42
PCW mean (mm Hg)	9 [7.2, 14.5]	10.8 (5.5)	11.2 (6.4)	0.88
PVR (dsc-5)	125 [101,197]	133 [95,197]	119 [105,173]	0.60
PVR (Wood units)	1.6 [1.3, 2.5]	1.7 [1.2, 2.5]	1.5 [1.3, 2.2]	0.60
RA mean (mm Hg)	6.5 [5.3, 10]	6.5 [5,9]	7 [6,10]	0.49
SVR (dsc-5)	1360 [1138,1523]	1360 [1111,1523]	1291 [1139,1470]	0.98
SVR (Wood units)	17 [14,19]	17 [14,19]	16 [14,18]	0.98
CI (Td) (liter/min/m^2)	2.8 (0.6)	2.8 (0.6)	2.8 (0.6)	0.78
CO (Td) (liter/min)	5.4 (1.1)	5.2 (0.9)	5.6 (1.4)	0.46
CI (estimated Fick) (liter/min/m^2)	3.0 (0.7)	3.1 (0.7)	2.9 (0.6)	0.26
CO (estimated Fick) (liter/min)	6.1 [4.9, 6.4]	6.1 [4.9, 6.7]	6 [5.3, 6.2]	0.43
Donor				
Donor age (years)	36.0 (13.4)	34.9 (13.5)	37.8 (13.7)	0.58
Donor sex, male	18 (60%)	9 (50%)	9 (75%)	0.26
Donor cause of death				0.67
Anoxia	12 (40%)	6 (33%)	6 (50%)	
CVA/ICH	7 (23%)	5 (28%)	2 (17%)	
CNS disease related	2 (7%)	2 (11%)	0 (0%)	
Trauma	9 (30%)	5 (28%)	4 (33%)	
Hepatitis C NAT positive	1 (3%)	0 (0%)	1 (8%)	0.40

(*continued on next page*)

Table 1 (*Continued*)

Variable	Total ($n = 30$)	Short IT ($n = 18$)	Long IT ($n = 12$)	p
Warm ischemic time (minutes)	45 (10)	45 (9)	44 (11)	0.82
Cold ischemic time (minutes)	123 (74)	69 (22)	204 (42)	< .001[a]
Total ischemic time (minutes)	167 (72)	114 (24)	248 (35)	< 0.001[a]

Abbreviations: BMI, body mass index; CI, cardiac index; CNS, central nervous system; CO, cardiac output; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; ICH, intracerebral hemorrhage; ICU, intensive care; IQR, interquartile range; IT, ischemic time; Long IT, ischemic time was greater than 180 minutes; LOS, length of stay; LVAD, Left ventricular assist device; LVEF, left ventricular ejection fraction; NAT, Nucleic Acid Amplification Testing; OHT, orthotopic heart transplantation; PA, pulmonary artery pressure; PCW, pulmonary capillary wedge pressure; PVR, peripheral vascular resistance; RA, right atrial; Short IT, ischemic time was less than 180 minutes; SVR, systemic vascular resistance; Td, thermodilution; tMCS, temporary mechanical circulatory support; UNOS, United Network of Organ Sharing; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

Variable summaries are provided as mean (± standard deviation) or median [IQR: quartiles] if skewed for ordinal and continuous variables. Categorical variables are summarized as absolute counts (%).

[a]Data may be left-skewed, but no overt difference was noted in outcomes.

a high EC (83% vs 28%, $p = 0.009$). As a continuous variable, the mean EC for the short and long IT groups was 13.1 ± 3.7 ml O_2/kg/min and 15.0 ± 2.8 ml O_2/kg/min, respectively ($p = 0.13$). This remained comparable adjusting for CPET duration as well as comparing IT groups within each exercise protocol (Figure 2). CPET duration was significantly shorter in recipients with a long IT (6.3 vs 7.7 minutes, $p = 0.048$, Figure 3A) despite similar duration from OHT to time of CPET, RPE, protocol performed, and EC. This difference was driven by participants who performed the treadmill protocol, where CPET duration was shorter in long IT relative to short IT recipients (mean 5.9 vs 7.6 minutes, $p = 0.038$, Figure 3B); whereas the duration was comparable among those completing the cycle ergometer protocol (long vs short IT: 7.3 vs 7.8 minutes, $p = 0.64$, Figure 3C).

Fifteen participants (50%) tested with high EC. Univariable logistic regression was used to evaluate associations with high EC (Figure 4). Counter to expectations, each 30-minute increase in IT, evaluated as a continuous measure, was associated with a 40% increase in the odds of achieving a high EC (odds ratio 1.8, 95%CI: 1.2-2.8, $p = 0.006$). Performing the treadmill protocol (odds ratio 8, 95%CI: 1.5-42, $p = 0.014$) as well as increases in AT (odds ratio 1.7, 95%CI: 1.09-2.7, $p = 0.019$) and thermodilution CI (odds ratio 6.7, 95%CI: 1.2-36.6, $p = 0.029$) were also associated with an increased odds of achieving high EC. The association remained following adjustment for exercise protocol, thermodilution CI, and CPET duration in a multivariable analysis, with every 30-minute increase in IT being associated with a 1.11 (95%CI: 1.05, 1.17) times increase in the odds of having a high EC ($p = 0.002$).

The results of our exploratory descriptive analysis (Figures S1-S8) demonstrate that of 30 participants, 1 (3%) had evidence of primary graft dysfunction following transplant that recovered before CPET, 1 (3%) had pre-existing graft dysfunction from the donor, and 4 other patients (13%) had mildly reduced LVEF (between 40% and 50%) reported on the most temporally proximate echocardiogram before CPET, but none had LVEF < 40%. The EC and CPET duration of patients with primary or pre-existing graft dysfunction or reduced LVEF relative to the

Table 2 Cardiopulmonary Exercise Test Outcomes of Orthotopic Heart Transplant Recipients With Long and Short Cardiac Allograft Ischemic Time

Variable	Total ($n = 30$)	Short IT ($n = 18$)	Long IT ($n = 12$)	p
Modality				0.60
Cycle ergometer	13 (43%)	9 (50%)	4 (33%)	
Treadmill	17 (57%)	9 (50%)	8 (67%)	
Exercise capacity				
Peak VO_2 (ml O_2/kg/min)	13.9 (3.4)	13.1 (3.7)	15.0 (2.8)	0.13
Peak VO_2 ≥14 (ml O_2/kg/min)	15 (50%)	5 (28%)	10 (83%)	0.009*
Metabolic equivalents	3.9 (1)	3.7 (1.1)	4.3 (0.8)	0.13
Test duration (minutes)	7.2 (2.1)	7.7 (2.3)	6.3 (1.4)	0.048*
Peak heart rate (bpm)	118 (22)	115 (21)	122 (23)	0.43
Peak power (cycle ergometer Watts)	50 [50,70]	50 [50,70]	55 [50,65]	0.87
Rating of perceived exertion (0-10)	9.5 [7.3, 10]	9 [6.2, 10]	9.5 [8.8, 10]	0.47
Anaerobic threshold (ml/kg/min)	9.5 (2.4)	9.4 (2.5)	9.7 (2.5)	0.78

Abbreviations: IQR, interquartile range; IT, ischemic time; Long IT, ischemic time was > 180 minutes; Short IT, ischemic time ≤180 minutes; VO_2; volume of oxygen consumption.

Variables are reported by long vs short ischemic times. Variable summaries are provided as mean (± standard deviation) or median [IQR: quartiles] if skewed for ordinal and continuous variables. Categorical variables are summarized as absolute counts (%). P values marked with an asterisk (*) are significant at the 0.05 level.

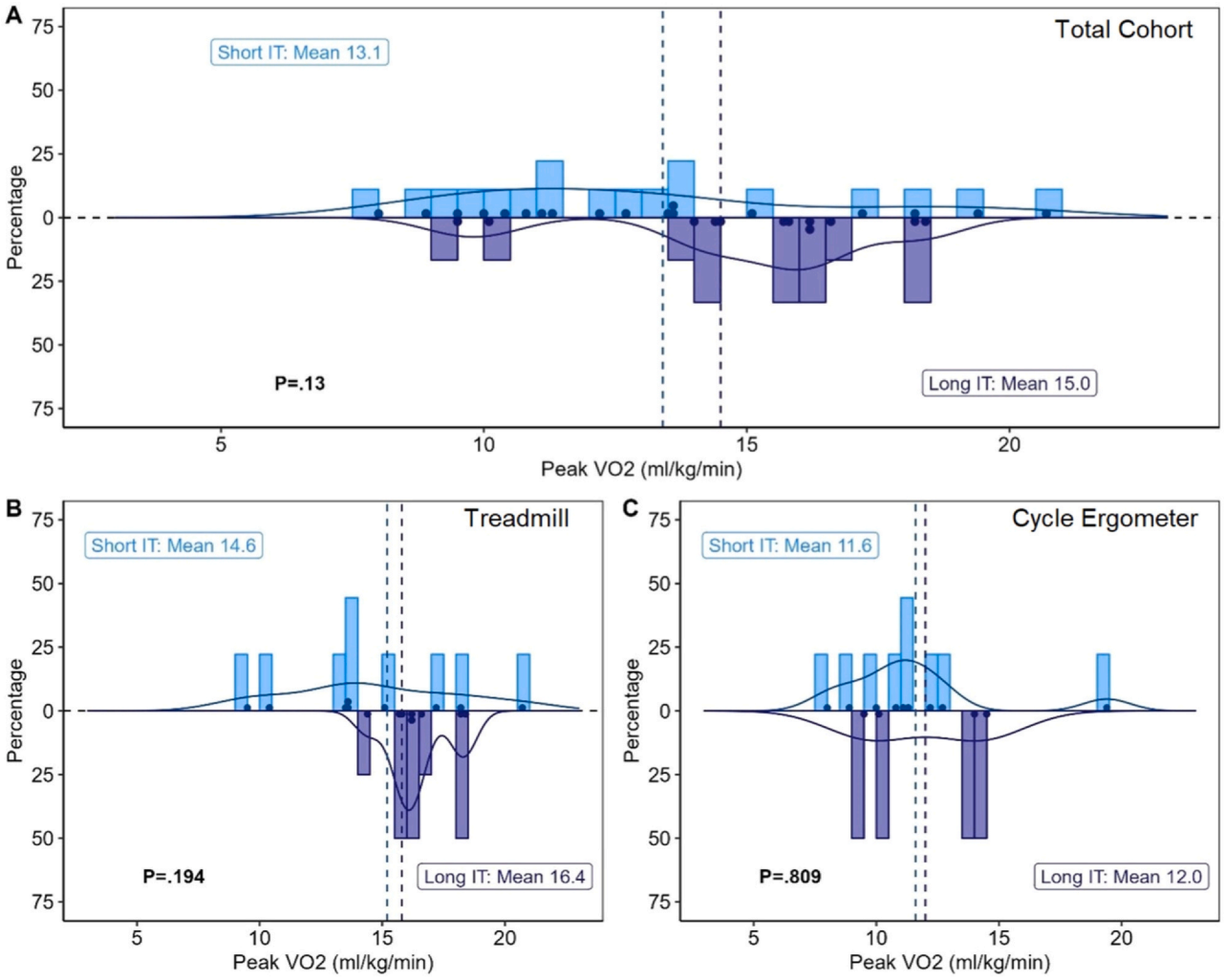

Figure 2 Histogram (bars) and density (line) estimates of the distribution of exercise capacity measured as peak VO_2 (ml/kg/min) comparing shorter (≤180 minutes, top of each panel [blue]) vs longer (> 180 minutes, bottom of each panel [purple]) ischemic times in (A) the overall sample, (B) participants who performed the treadmill protocol, and (C) participants who performed the cycle ergometer protocol. Each histogram bar represents the percentage of peak VO_2 observed within 0.5 ml/kg/min increment bins starting at 0 ml/kg/min. The density line is a smoothed representation of the histogram. Each dot represents a single observation. IT, ischemic time; VO_2, volume of oxygen consumption.

sample are identified graphically in Figures S1 and S2. Although these numbers are too small to analyze separately, it is notable that the recipient of the heart from a donor with a pretransplant mildly decreased LVEF exercised for an above-average time. Two (7%) had potential rejection following OHT (> 1R or > pAMR0); 1 for whom antibody-mediated rejection (AMR) was identified the day after CPET and for whom resolution was achieved conservatively with oral steroids, and 1 diagnosed and treated successfully for AMR [0R pAMR1(H+)] following postoperative day 9 endomyocardial biopsy with LVEF stably 50% by discharge and subsequent CPET and quiescent endomyocardial biopsy (1R pAMR0) 2 days following CPET. EC and duration of patients with AMR relative to the sample are displayed in Figures S3 and S4, respectively (see Supplementary Digital Content). No invasive CMV disease occurred during the interval from transplant through CPET. The individual EC and duration for patients with transiently detectable CMV viremia during the study period are displayed in Figures S5 and S6, respectively. Of the 30 patients, CMV was not detected in 26 (86%) despite standard care surveillance with at least weekly or biweekly quantitative polymerase chain reaction assay during this interval. Four participants had detectible CMV in the timeframe from transplant to CPET, including 2 of whom had CMV below the lower limit of quantification and the remaining 2 had minor elevations that did not rise to the transplant center's standard care threshold of 1,000 copies/ml, for which the transplant center would treat or change prophylaxis. Last, 20 patients (67%) did not have DSAs, and the remaining 10 (33%) are identified in Figures S7 (EC) and S8 (exercise duration).

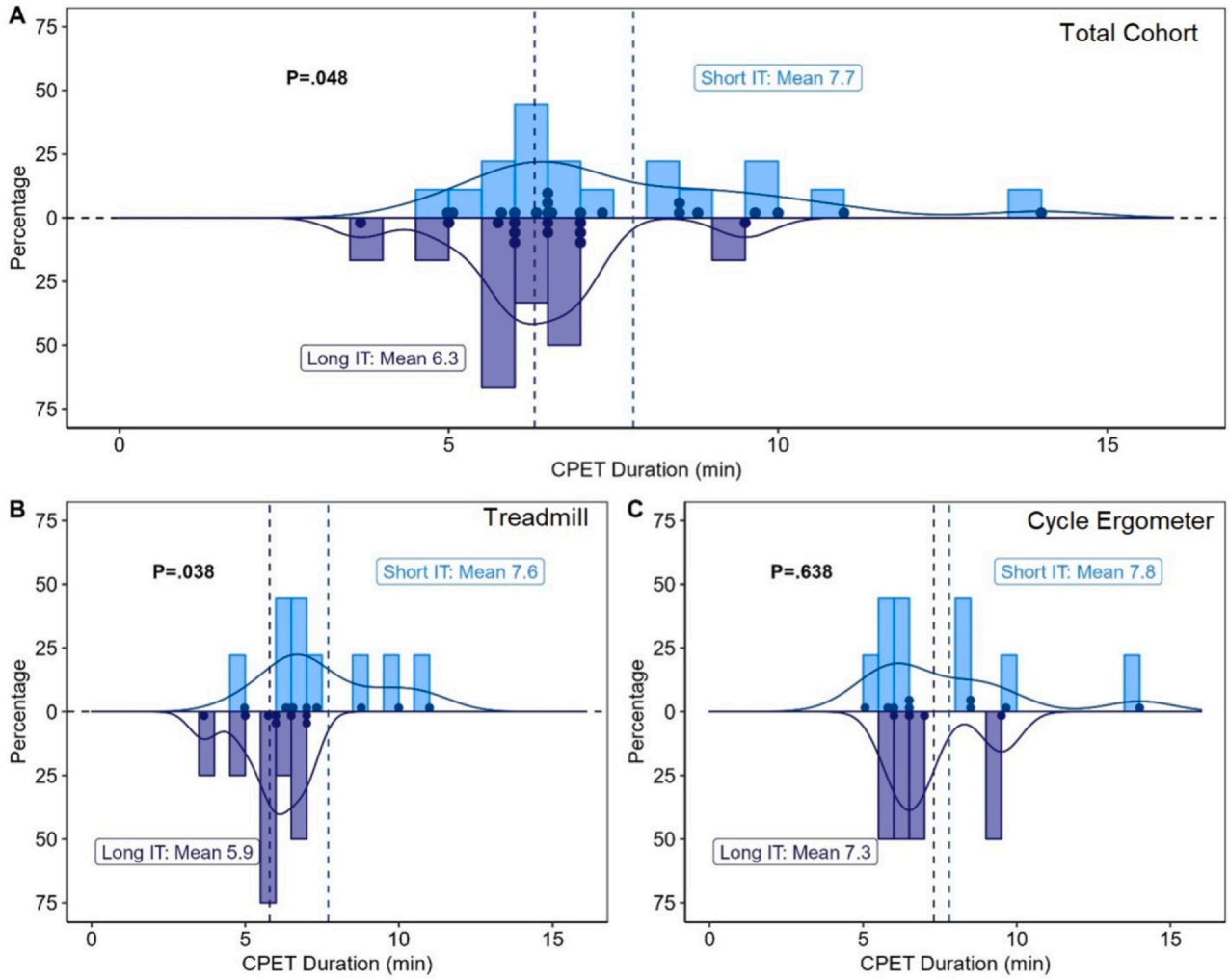

Figure 3 Histogram (bars) and density (line) estimates of the distribution of cardiopulmonary exercise test duration comparing shorter (≤180 minutes, top of each panel [blue]) vs longer (> 180 minutes, bottom of each panel [purple]) ischemic times in (A) the overall sample, (B) participants who performed the treadmill protocol, and (C) participants who performed the cycle ergometer protocol. Each histogram bar represents the percentage of CPET durations observed within 30-second increment bins starting at 0 minute. The density line is a smoothed representation of the histogram. Each dot represents a single observation. CPET, cardiopulmonary exercise test; IT, ischemic time.

Discussion

In this study, we aimed to describe the impact, if any, that longer IT (> 180 minutes) had on the EC of OHT recipients within the first 3 postoperative months. In a sample of 30 OHT recipients who survived to discharge with stamina sufficient to engage in outpatient cardiac rehabilitation, EC was not significantly reduced when IT was greater than 180 minutes. Contrary and paradoxical to our hypothesis, EC was significantly higher in the long IT group. In a multivariable model, each 30-minute increase in IT was associated with a significant increase in the odds of having a high EC (defined as peak VO_2 > 14 ml O_2/kg/min).

Interestingly, CPET duration was significantly shorter in the long IT group despite higher EC as determined by peak VO_2. Specifically, the test duration was significantly shorter in the long IT group who performed the treadmill protocol, while the duration was slightly shorter in the long IT group tested on the cycle ergometer. We postulate this difference may be attributed to peripheral muscular deconditioning, which may be more evident during treadmill testing due to the large amount of active, contributing muscle mass required for upright walking, although it may be due to more complex reasons or chance (type I error). No significant differences were observed in intensive care length-of-stay to suggest 1 group had experienced hospital-acquired functional decline more than the other, and similarly, no significant differences in hemoglobin at the time of CPET were observed between patients with long and short IT to suggest anemia as a cause for this difference (Table 1). Our additional descriptive analysis did not show any relationship between rejection, graft function, infection, or DSAs with EC or duration as well. Future research is needed to identify the effect of CPET modality and protocol on

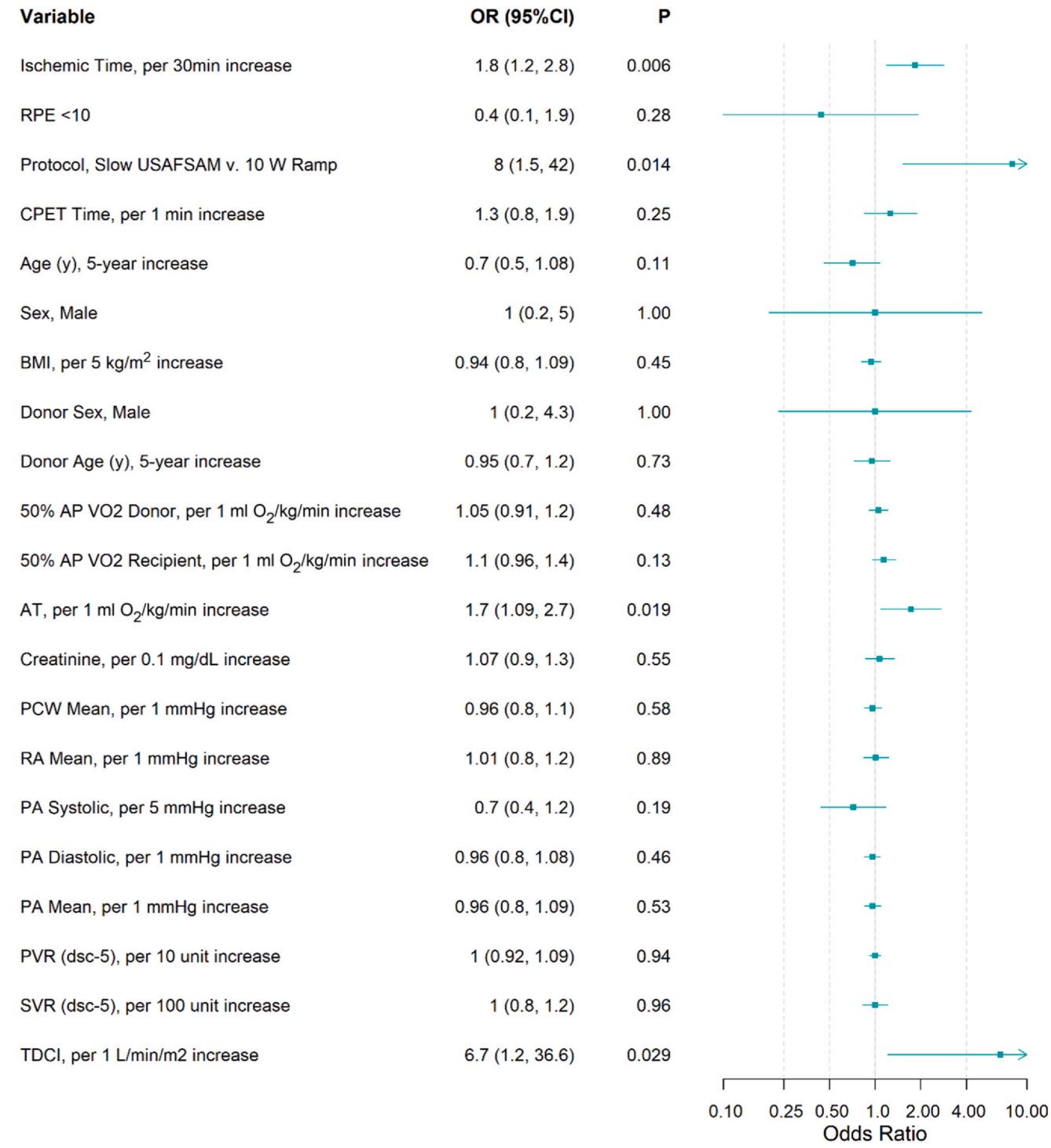

Figure 4 Forest plot of odds ratios from logistic regression analysis on high exercise capacity. AP, age-predicted max; AT, anaerobic threshold; BMI, body mass index; CPET, cardiopulmonary exercise test; PCW, pulmonary capillary wedge pressure; PA, pulmonary artery pressure; RPE, rate of perceived exertion; PVR, peripheral vascular resistance; RA, right atrial pressure; SVR, systemic vascular resistance; TDCI, cardiac index by thermodilution; USAFSAM, United States Airforce School of Aeronautic Medicine; VO_2, volume of oxygen consumption; W, Watts.

functional outcomes in the months following OHT, although such an investigation will be confounded by the training effect from cardiac rehabilitation. To avoid training effects, the current study utilized a CPET protocol upon initial phase 2 (outpatient) cardiac rehabilitation.

In the current study, EC was lower relative to age-predicted maximum in both the short and long IT groups, which is consistent with previous literature describing impaired EC in recent OHT recipients.[3,6] In comparison to previous literature, we observed much lower EC outcomes in our sample, which may be a result of the relatively short time interval (median 29.5 days) from OHT to CPET, donor or recipient age, and training effect in other studies. Several studies reporting higher EC in OHT recipients describe

significantly younger recipients[10,37] who performed the CPET months to years following OHT,[2,3,26] which allows for substantial recovery time, patient accommodation to transplant-related blunted chronotropic response to exercise, and a significant training effect following completion of cardiac rehabilitation.[38-40]

The results of the present study contrast with previous work by Buendía-Fuentes et al,[10] in which authors reported a significant negative association between IT and EC, reporting the majority of their sample had an imputed EC exceeding 4.5 METs. The discordant results may be partially due to the modality and protocol chosen to test and evaluate OHT recipients. More critically, EC was indirectly estimated in that study using METs imputed from performance during a Bruce treadmill protocol,[27,28] which is a suboptimal method of measuring EC in this population due to the likelihood of overestimating EC. Additionally, the estimation of EC based on normative data derived from healthy populations is not representative of OHT recipients due to an abnormal chronotropic response to exercise from myocardial denervation.[3,6,8,38] Since breath-by-breath gas analysis and an individualized CPET modality were used in the present study, the results in our current report more accurately reflect the EC of early OHT recipients and serve as a more credible, objective basis from which to compare the association of IT with EC.[29]

Although the results of the present study provide valuable insight into the relationship between donor IT and the ability of the transplanted heart to do work within the first 3 months immediately following surgery, the sample size ($n = 30$) is modest. During the 18 months of enrollment, our facility increasingly stabilized transplant recipient candidates with temporary mechanical circulatory support devices, allowing the most critical patients to survive until transplant, which resulted in additional orthopedic and neurologic limitations precluding some transplant recipients from participating in this study. Nevertheless, this study provides core data informing an unmet need for further exercise physiology research in the cardiac transplant population. To detect differences in the proportion of patients with high EC (defined as a dichotomous endpoint with peak $VO_2 > 14$ ml O_2/kg/min), the study is underpowered with a posthoc power of 60% to detect a difference between long and short IT times based on the observed difference of 42% (at a 5% significance level). However, the present sample size is sufficient to detect a clinically meaningful difference of one MET (3.5 ± 3.0 ml O_2/kg/min of peak VO_2) between groups with at least 85% power when analyzed as a continuous endpoint.

The investigation into the effect extended prolonged IT has on EC after OHT could be strengthened by a larger sample, across multiple transplant centers, with a longitudinal analysis to account for the effect of IT on long-term functional allograft recovery. Additionally, the development of an exercise protocol with normative data to estimate EC in postoperative OHT recipients is needed. A lag in impactful circulating catecholamine concentrations observed during exercise onset in OHT recipients may warrant a protocol with longer stages to reduce early fatigue. Due to the variation of the results in the literature surrounding the impact of increasing IT on the immediate and long-term allograft function following OHT, further investigation is warranted exploring the impact of longer IT among heart transplant recipients transplanted using hearts transported with a nonbeating cold preservation technique.

Our study also had key strengths; specifically, this study is the first, to our knowledge, to provide objective measures of EC via metabolic testing at the discrete time of entry into cardiac rehabilitation. This cohort represented heart transplantation exclusively from conventional donation after brain death, with the use of standard cardioplegia and cold preservation transport. No *ex vivo* organ transport systems were utilized. The study terminated new patient enrollment in April 2020, following the declaration of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) public health emergency in the United States, and despite its modest sample size, it represented one of the largest studies on this patient population. We hope our report will serve as a foundational reference on which others may build to expand our understanding of functional capacity following OHT.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R.L.G. reports a relationship with CareDx Inc. that includes grant funding, with Alnylam Pharmaceuticals Inc. that includes advisory board membership, consulting, and speaking and lecture fees., and with Pfizer Inc. that includes speaking and lecture fees. R.L.G. serves on the Legislative Affairs Committee of the American Society of Transplant Surgeons (2023-2026). The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Study concept: K.B., A.A.A.E., C.C., R.L.G. Study design: K.B., J.V., A.A.A.E., C.C., R.L.G. Literature search: K.B., J.V., J.F., A.A.A.E., C.C., R.L.G. Data acquisition: K.B., J.V., R.L.G. Data analysis: K.B., J.V., J.F., A.A.A.E., C.C., R.L.G. Manuscript preparation: K.B., J.V., J.F., A.A.A.E.,

C.C., R.L.G. Manuscript editing: K.B., J.V., J.F., A.A.A.E., C.C., R.L.G. All authors read and approved the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100115.

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