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Age-specific determinants of reduced exercise capacity in youth after heart transplant: A longitudinal cohort study

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BACKGROUND: Although prior studies show that children have impaired exercise capacity after heart transplant, the age-specific determinants of this phenomenon are not well understood. We examine exercise capacity and its associations in school-age and adolescent youth post-heart transplant.
METHODS: This retrospective cohort study of heart transplant patients who completed a cardiopulmonary exercise test between 1999 and 2018 includes 332 tests on 104 patients younger than 18 years. Tests were stratified into those by school-aged children (5-11 years old) and adolescents (12-17). The primary outcome was peak oxygen consumption; secondary outcomes were anaerobic threshold and peak power production. Potential determinants included age at transplant, diagnosis, and laboratory and invasive hemodynamic measurements.
RESULTS: All exercise capacity outcomes for patients post-transplant regardless of age were significantly reduced compared to the predicted performance of age and sex-matched controls. Percent predicted median peak oxygen consumption (62.63, 95% confidence interval (CI) 59.18, 66.07), anaerobic threshold (66.52, 95%CI 62.24, 70.81), and peak power production (54.00, 95%CI 50.56, 57.44) were reduced. Younger age at transplant and a higher peak heart rate were independently associated with increased peak oxygen consumption across age groups. Elevated wedge pressure and brain natriuretic peptide predicted decreased exercise capacity in adolescents.

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CONCLUSIONS: Youth after heart transplant have significantly reduced exercise capacity. Younger age at transplant and higher peak heart rate predict increased exercise capacity throughout childhood. Indicators of congestion predict decreased exercise capacity in adolescents. These findings should encourage deeper attention to the relationship between exercise physiology and the social context of children after transplant.
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Background

Heart transplant (HT) remains the definitive therapy for children with refractory advanced heart failure. Post-HT survival has improved, and most children have normal systolic ventricular function after transplant.[1] However, studies have demonstrated that these patients have impaired exercise performance.[2-4] Moreover, the typical child with an HT participates in only 10% of the amount of daily physical activity recommended by the American Heart Association.[5] As exercise strongly contributes to cardiovascular and mental health,[6,7] and post-HT life is characterized by an increased cardiovascular risk profile and heightened risk for depression and anxiety, this is a major problem. Understanding and addressing this impaired exercise capacity has the potential to improve not only a child's survival, but also their functional capacity, social development, and overall well-being.

Prior studies on children after HT have found a reduction in exercise capacity.[2,3] However, this literature is marked by small sample sizes which preclude assessing potential determinants of exercise performance, and by limited data in a contemporary cohort. Given the developmental differences of school age children and adolescents, these determinants are likely age-specific. Although studies have shown that older age at transplant and increased time since transplant predict worse cardiopulmonary exercise test (CPET) performance, there is no literature on whether the predictive utility of other determinants of exercise capacity differ by age.[8] Addressing these knowledge gaps and developing a more refined understanding of the determinants of exercise performance in HT patients is a critical step in designing interventions to improve outcomes in this population.

Thus, the purpose of this study is to describe exercise capacity in a contemporary cohort of pediatric HT patients, to assess potential determinants of CPET performance, and to evaluate differences in those determinants between school-age and adolescent patients. We hypothesized that youth post-HT will demonstrate reduced exercise capacity compared to their peers and that adolescents will have reduced exercise performance relative to school-aged children regardless of HT timing.

Material and methods

Data source and study population

This single-center retrospective cohort study was conducted at a quaternary children's hospital in the northeast United States. All patients with an index HT were included who completed a maximal effort exercise test between 1999 and 2018 at an age less than 18 years old. A maximal effort test was stringently defined by a respiratory exchange ratio of > 1.20, the convention in our lab to minimize the possibility of type I error. At our institution, the standard of care is for all patients to receive annual CPET via a ramp protocol starting at 1-year post-HT regardless of age, if the child is developmentally able to complete a max effort test. It is our institution's practice to defer max effort CPET in all patients with known coronary artery vasculopathy or under active treatment for rejection, therefore these patients were excluded from the study cohort. It is our center's practice that all patients who can complete a test with cycle ergometry do so. For those patients unable to use the cycle (usually due to their height), treadmill testing was performed. Regardless of method, all CPETs include electrocardiogram, blood pressure, and oxygen saturation monitoring, in addition to metabolic testing. All tests are directly observed by a cardiologist with advanced training in exercise physiology who can stop the test if the patient demonstrates an inability to participate in testing, hemodynamic compromise, persistent complex ectopy, or ST-segment changes concerning for active ischemia. Chart abstraction of CPET and other variables was performed in 2022. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Main outcomes and measures

The primary outcome for this study was peak oxygen consumption (PVO2) (ml/min). Secondary outcomes included oxygen consumption at the anaerobic threshold (AT) (ml/min), a measurement of submaximal aerobic exercise determined by analysis of respiratory gas exchange where the subject switched from aerobic to anaerobic metabolism, and peak power production (PW) (W) at maximum exertion. Given the strong dependence of these values on patient age and sex, we modeled them as percent predicted by age and sex, using previously published normative values as the reference.[9] Patient age at CPET was the primary exposure and stratifying variable of interest. We stratified each CPET into two groups, those performed by school-aged children (5-11 years old) and adolescents (12-17) based on an a priori developmental framework.[10] Participants could be included in both groups over the course of the study. Potential determinants of exercise performance were determined beforehand by a literature review and spanned both patient characteristics and clinical values.[2-5] These variables included sex, age at transplant, diagnosis (congenital heart disease (CHD) vs cardiomyopathy), body mass index (BMI), diastolic dysfunction (brain natriuretic peptide (BNP) and pulmonary

capillary wedge pressure (PCWP)), invasive cardiac index (ICI), peak heart rate (PHR), and resting heart rate (RHR). Time since transplant was not included due to its collinearity with age at transplant and patient age which leads to well-documented model identification problems.[11] As the distribution of BMI varies by age and sex, we transformed BMI into an age- and sex-corrected Z score.[9] For laboratory and diagnostic catheterization data, we abstracted data from the most recent value prior to the CPET within 1 year. Catheterization data were obtained from routine annual surveillance catheterizations or more frequently in the setting of clinical concern.

Statistical analysis

Descriptive statistics were first calculated. Missing data were handled using joint multiple imputation to create 100 imputed data sets which were combined according to Rubin's rules.[12-14] Multiple imputation methods combine results from many plausible data sets to account for the uncertainty created by missingness[15-17] and are routinely applied to limit bias from missing data. Imputation models included sex, age at HT, diagnosis, and age at CPET. PW was only measurable in participants who could perform cycle ergometry and thus could not be justifiably imputed for those using a treadmill. Given multiple exercise tests per participant, we used linear mixed models to allow for the inclusion of both patient and exercise test-level variables, which improves not only study power but also internal validity.[18] We first ran intercept-only models to estimate deviation from baseline (i.e., 100% predicted values). Next, we regressed each outcome on patient age to assess for differences in exercise capacity. Finally, we stratified the sample by patient age and ran two models for each potential determinant individually to maximize power. The first model was unadjusted, the second model was adjusted by patient age at transplant and diagnosis. We did not directly test for effect modification by age, as power limitations would lead to an elevated false negative rate.[19] The significance threshold was specified prior to analyses at $\alpha = 0.05$. Statistical analyses were performed in R version 4.1.1, using the *tidyverse, lme4*, and *jomo* packages.[12,20-22]

Results

Demographics and clinical characteristics

There were 489 potentially eligible CPETs on 120 patients. Of these tests, 148 tests were submaximal or missing all outcome data, and 9 tests were performed by participants who did not meet inclusion criteria. Patient factors that lead to CPET termination included trouble tolerating the mouthpiece ($n = 3$), presyncope ($n = 1$), dyspnea ($n = 1$), and limited cooperation ($n = 1$). Thus, the final sample consisted of 332 CPETs on 104 patients who received their index HT from 1990 to 2016. The cohort was 51% female and 59% white. The median age of transplant was at 7.8 years of age (Interquartile Range (IQR) 2.3-13.4). In terms of indication for HT, 40% of patients received a transplant in the setting of CHD, with 60% of patients receiving a transplant for cardiomyopathy, myocarditis, or other acquired heart disease, including Kawasaki disease ($n = 1$) and ventricular dysfunction of undetermined etiology ($n = 3$). The youngest participant to complete a CPET was 5 years of age. Participants completed a median of 3 CPETs (IQR 2-6) over a median of 2.7 years (IQR 0.9-6.0). The total number of participants included in each age group over the course of the study was 49 participants in the school-age group and 86 in the adolescent group. The majority of the CPET's were conducted on a bicycle (69%) with the rest occurring on treadmill (31%) at a median age of 13.8 years old (IQR 11.4-16.2). There was a large amount of missing data on the following variables: PW (31%), BNP (33%), ICI (46%), PCWP (46%)[16] (Table 1).

Post-transplant exercise capacity

All exercise capacity outcomes were significantly reduced compared to the predicted performance of age- and sex-matched controls before and after adjustment. Median PVO2 (62.63, 95% confidence interval (CI) 59.18, 66.07; b_0 69.09, 95%CI 62.79, 75.38), AT (66.52, 95%CI 62.24, 70.81; b_0 74.60, 95%CI 66.66, 82.54), and PW (54.00, 95%CI 50.56, 57.44; b_0 61.41, 95%CI 54.27, 68.56) were affected similarly (Table 2). When considering the effect of age, adolescents demonstrated small, insignificant increases in PVO2 (b 0.20, 95%CI −3.26, 3.66, ab 1.01, 95%CI −2.48, 4.51) and AT (b 0.79, 95%CI −4.96, 6.54; ab 2.73, 95%CI −3.13, 8.59), but a decrease in PW (b −3.43, 95%CI −5.9, −0.95; ab −3.14, 95%CI −5.63, −0.64) compared to children ages 5 to 11 (Table 3).

Determinants of CPET performance

In evaluating clinical factors associated with exercise performance, younger age at HT ($ab_{adolescent}$ −0.99, 95%CI −1.58, −0.41; $ab_{school-age}$ −2.46, 95%CI −4.21, −0.70) and a higher PHR (ab_a 0.26, 95%CI 0.16, 0.35; ab_s 0.33, 95%CI 0.11, 0.55) were independently associated with increased PVO2 in both school-aged children and adolescents. A higher BMI was associated with decreased exercise performance in both age groups prior to adjustment, but only in adolescents after confounding adjustment (ab_a −5.17, 95%CI −6.99, −3.35; ab_s −3.67, 95%CI −7.71, 0.37). Given the documented J-shaped curve of BMI effects, we also performed a sensitivity analysis in which we excluded underweight participants, defined as those who had a BMI less than 2 standard deviations below the mean.[23] In this analysis, we now found BMI predicted decreased exercise performance in both age groups even after adjustment (ab_a −5.94, 95%CI −8.1, −3.78; ab_s −7.01, 95%CI −11.67, −2.35). Diagnosis had no effect on exercise capacity. In adolescence, female sex (b_a 8.20, 95%CI 1.47, 14.94) was associated with higher PVO2, though this effect was not significant in adjusted analysis. Adolescents also demonstrated worse exercise capacity with both an elevated BNP

Table 1 Descriptive Statistics of Participants

Variable	Overall (*n* 104)	School-age children (*n* 49)	Adolescents (*n* 86)	*p*
Age at HT median (IQR)	7.77 (2.31, 13.35)	2.59 (0.84, 6.17)	9.97 (3.32, 14.19)	< 0.001
Sex *n* (%)				
Female	51 (49.0)	30 (61.2)	40 (46.5)	0.143
Male	53 (51.0)	19 (38.8)	46 (53.5)	
Race *n* (%)				
Asian	1 (1.0)	1 (2.0)	1 (1.2)	0.908
Black or African American	31 (29.8)	16 (32.7)	24 (27.9)	
Unknown/not reported	11 (10.6)	4 (8.2)	8 (9.3)	
White	61 (58.7)	28 (57.1)	53 (61.6)	
Ethnicity *n* (%)				
Hispanic or Latino	9 (8.7)	5 (10.2)	6 (7.0)	0.053
Not Hispanic or Latino	82 (60.7)	35 (71.4)	47 (54.7)	
Unknown/not reported	42 (31.1)	9 (18.4)	33 (38.4)	
Diagnosis *n* (%)				
CHD	42 (40.4)	25 (51.0)	29 (33.7)	0.073
CM/MC/AHD	62 (59.6)	24 (49.0)	57 (66.3)	

Abbreviations: CHD, congenital heart disease; CM/MC/AHD, cardiomyopathy, myocarditis, acquired heart disease; HT, heart transplant.

Table 2 Descriptive Statistics of CPET

Variable	CPETs overall (*n* 332)	CPETs in school-age children (*n* 98)	CPETs in adolescents (*n* 234)
CPET mode *n* (%)			
Bike	229 (69)	40 (41)	189 (81)
Treadmill	103 (31)	58 (59)	45 (19)
Peak HR (bpm, median [IQR])	171.00 [151.00, 184.00]	174.00 [160.00, 184.00]	169.00 [149.25, 181.75]
Resting HR (bpm, median [IQR])	100.50 [88.00, 113.00]	102.00 [91.00, 113.75]	100.00 [87.00, 112.00]
PVO2 (ml, median [IQR])	2,000.09 [1,625.18, 2,601.08]	1361.46 [1,158.01, 1,570.07]	2,040.01 [1,967.33, 2,880.80]
PVO2%P (median [IQR])	69.01 [56.52, 83.06]	82.09 [60.15, 94.51]	65.89 [54.90, 76.60]
AT (ml, median [IQR])	863.88 [658.78, 1,046.89]	658.17 [504.90, 776.72]	944.02 [756.36, 1,080.38]
AT%P (median [IQR])	70.57 [56.80, 87.92]	80.09 [60.54, 104.05]	68.72 [56.49, 82.43]
Power (W, median [IQR])	100.00 [76.00, 122.00]	74.50 [68.50, 86.75]	108.00 [83.00, 127.00]
Power%P (median [IQR])	56.92 [46.80, 67.57]	61.39 [54.61, 78.60]	55.90 [45.81, 64.04]

AT, anaerobic threshold; CPET, cardiopulmonary exercise test; PVO2, peak oxygen consumption.
%P: Percent of predicted value by age and sex.

(ab_a −2.28 95%CI −4.37, −0.18) and higher PCWP (ab_a −0.78, 95%CI −1.46, −0.1). Turning to AT and PW, we noted similar trends in the effects of age at transplant, BMI, and PHR, although not all coefficients remained significant after adjustment (Tables 4, 5, 6)

Discussion

This single-center cohort study of the largest known sample of CPET of youth after HT demonstrated significant deficits in exercise capacity. Age at transplant and PHR predicted

Table 3 Percent Predicted Exercise Capacity in Post-HT Children Compared to Typical Children and Between Age Cohorts

	% Predicted performance [95% CI]		Adolescent % predicted – school age % predicted [95% CI]	
Variable	Unadjusted	Adjusted	Unadjusted	Adjusted
PVO2	62.63 [59.18, 66.07][a]	69.09 [62.79, 75.38][a]	0.20 [−3.26, 3.66]	1.01 [−2.48, 4.51]
AT	66.52 [62.24, 70.81][a]	74.6 [66.66, 82.54][a]	0.79 [−4.96, 6.54]	2.73 [−3.13, 8.59]
Peak power	54 [50.56, 57.44][a]	61.41 [54.27, 68.56][a]	−5.12 [−8.03, −2.21][a]	−4.73 [−7.66, −1.79][a]

Abbreviations: AT, anaerobic threshold; CI, confidence interval; HT, heart transplant; PVO2, peak oxygen consumption.
[a]$p < 0.05$. For % predicted performance, H_0:β100%; for adolescent % predicted – school age % predicted, H_0:β0. Adjusted estimates were obtained through a linear mixed model that included age at transplant and diagnosis (CHD vs CM/MC/AHD).

Table 4 Linear Mixed Model Estimates (*b*) of PVO2 Regressed on Clinical Variables and Personal Characteristics

	Unadjusted *b* [95%CI]		Adjusted *b* [95%CI]	
Variable	School-age children	Adolescents	School-age children	Adolescents
Age at HT	−2.29 [−4.03, −0.56][a]	−0.90 [−1.48, −0.31][a]	−2.46 [−4.21, −0.70][a]	−0.99 [−1.58, −0.41][a]
Sex				
Male				
Female	3.57 [−8.22, 15.35]	8.2 [1.47, 14.94][a]	1.79 [−9.35, 12.93]	4.31 [−2.74, 11.36]
Diagnosis				
CHD				
CM/MC/AHD	1.43 [−10.09, 12.96]	3.96 [−3.42, 11.33]	1.9 [−8.76, 12.56]	5.55 [−1.45, 12.54]
Age at CPET	−0.86 [−3.11, 1.38]	0.33 [−0.52, 1.18]	−0.58 [−2.82, 1.66]	0.61 [−0.25, 1.48]
BMI	−4.45 [−8.47, −0.44][a]	−5.48 [−7.35, −3.61][a]	−3.67 [−7.71, 0.37][b]	−5.17 [−6.99, −3.35][a,b]
BNP (log)	−3.1 [−7.15, 0.95]	−2.28 [−4.38, −0.18][a]	−2.97 [−7.02, 1.07]	−2.28 [−4.37, −0.18][a]
Peak HR	0.38 [0.16, 0.60][a]	0.27 [0.18, 0.37][a]	0.33 [0.11, 0.55][a]	0.26 [0.16, 0.35][a]
Resting HR	0.09 [−0.11, 0.28]	−0.09 [−0.20, 0.02]	0.05 [−0.14, 0.25]	−0.07 [−0.18, 0.04]
Cardiac index	3.01 [−2.60, 8.63]	1.21 [−1.16, 3.57]	2.66 [−3.08, 8.39]	1.11 [−1.24, 3.46]
Wedge pressure	−0.57 [−1.75, 0.62]	−0.81 [−1.49, −0.14][a]	−0.39 [−1.59, 0.81]	−0.78 [−1.46, −0.10][a]

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, confidence interval; CM/MC/AHD, cardiomyopathy, myocarditis, acquired heart disease; CPET, cardiopulmonary exercise test; HT, heart transplant; PVO2, peak oxygen consumption.
[a]$p < 0.05$.
[b]$p < 0.05$ in BMI sensitivity analysis excluding participants with BMI z score < −2. Adjusted models included age at HT and diagnosis.

Table 5 Linear Mixed Model Estimates (*b*) of Anaerobic Threshold Regressed on Clinical Variables and Personal Characteristics

	Unadjusted *b* [95%CI]		Adjusted *b* [95%CI]	
Variable	School-age children	Adolescents	School-age children	Adolescents
Age at HT	−3.99 [−6.15, −1.84][a]	-0.91 [−1.60, −0.23][a]	−4.34 [−6.41, −2.28][a]	−1 [−1.67, −0.33][a]
Sex				
Male				
Female	4.23 [−10.78, 19.24]	6.25 [−1.42, 13.91]	0.98 [−11.74, 13.69]	2.09 [−5.96, 10.14]
Diagnosis				
CHD				
CM/MC/AHD	1.61 [−13.14, 16.36]	3.89 [−4.43, 12.21]	2.36 [−9.88, 14.6]	5.36 [−2.61, 13.33]
Age at CPET	−2.55 [−6.46, 1.36]	−1 [−2.33, 0.33]	−2.03 [−5.78, 1.71]	−0.55 [−1.94, 0.84]
BMI	−3.64 [−9.47, 2.18]	−4.84 [−7.26, −2.41][a]	−1.73 [−7.19, 3.73]	−4.55 [−6.90, −2.21][a,b]
BNP (log)	−6.63 [−12.9, −0.36][a]	−1.75 [−4.82, 1.32]	−5.65 [−11.54, 0.24]	−1.66 [−4.63, 1.31]
Peak HR	0.33 [−0.02, 0.68]	0.25 [0.12, 0.38][a]	0.16 [−0.18, 0.51]	0.22 [0.09, 0.35][a]
Resting HR	0.14 [−0.18, 0.46]	−0.09 [−0.25, 0.07]	0.04 [−0.25, 0.33]	−0.05 [−0.21, 0.11]
Cardiac index	0.6 [−8.37, 9.57]	3.13 [−0.58, 6.83]	−0.03 [−8.73, 8.68]	3.05 [−0.69, 6.78]
Wedge pressure	−1.73 [−3.68, 0.22]	−0.76 [−1.75, 0.23]	−1.37 [−3.24, 0.49]	−0.69 [−1.68, 0.29]

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, confidence interval; CM/MC/AHD, cardiomyopathy, myocarditis, acquired heart disease; CPET, cardiopulmonary exercise test; HT, heart transplant.
[a]$p < 0.05$.
[b]$p < 0.05$ in BMI sensitivity analysis excluding participants with BMI z score < −2. Adjusted models included age at HT and diagnosis.

exercise capacity across outcome metric and age group. BNP, PCWP, and BMI predicted exercise performance in adolescent patients.

The finding of persistently diminished exercise capacity in HT patients in this large, heterogenous, contemporary cohort corroborates prior literature and highlights an area which deserves increased clinical attention—improving the modifiable cardiovascular risk profile of HT patients. HT patients have been shown to have elevated levels of triglycerides, low-density lipoprotein cholesterol, obesity, hypertension, and diabetes mellitus which contribute to coronary graft vasculopathy and chronic kidney disease, two of the primary drivers of long-term morbidity and mortality.[24-28] Increasing physical activity leads to improvements in these biomarkers. However, our results suggest that children after HT have poor exercise capacity, potentially limiting their ability to modify their cardiovascular risk. While several recent studies have aimed to improve exercise capacity in these patients,[29] further work is clearly needed to develop interventions which are effective, sustainable, and accessible.

Our study demonstrates that children who are transplanted earlier in life have improved, if not close to normal, exercise capacity. Focusing first on biological factors, graft

Table 6 Linear Mixed Model Estimates (*b*) of Peak Power Regressed on Clinical Variables and Personal Characteristics

	Unadjusted *b*[95%CI]		Adjusted *b* [95%CI]	
Variable	School-age children	Adolescents	School-age children	Adolescents
Age at HT	−1.82 [−3.50, −0.14][a]	−0.60 [−1.22, 0.02]	−1.64 [−3.36, 0.08]	−0.65 [−1.28, −0.03][a]
Sex				
Male				
Female	2.19 [−11.52, 15.91]	3.57 [−3.40, 10.54]	2.97 [−9.42, 15.37]	0.60 [−7.03, 8.22]
Diagnosis				
CHD				
CM/MC/AHD	−10.43 [−22.50, 1.63]	1.59 [−6.03, 9.21]	−8.07 [−19.71, 3.58]	2.67 [−4.85, 10.19]
Age at CPET	−3.05 [−5.76, −0.35][a]	0.33 [−0.35, 1.02]	−3.40 [−6.11, −0.69][a]	0.47 [−0.23, 1.16]
BMI	−4.30 [−8.05, −0.55][a]	−3.87 [−5.5, −2.24][a]	−2.93 [−6.89, 1.03][b]	−3.73 [−5.36, −2.09][a,b]
BNP (log)	0.43 [−3.66, 4.52]	−0.62 [−2.27, 1.03]	1.28 [−2.85, 5.41]	−0.63 [−2.28, 1.03]
Peak HR	0.19 [−0.01, 0.39]	0.17 [0.09, 0.25][a]	0.19 [−0.01, 0.38]	0.17 [0.09, 0.25][a]
Resting HR	−0.24 [−0.67, 0.19]	−0.07 [−0.15, 0.02]	−0.14 [−0.56, 0.28]	−0.06 [−0.15, 0.03]
Cardiac index	2.39 [−2.24, 7.03]	−0.03 [−1.75, 1.70]	2.54 [−1.99, 7.07]	−0.04 [−1.77, 1.69]
Wedge pressure	0.14 [−0.93, 1.20]	−0.29 [−0.83, 0.26]	0.32 [−0.73, 1.37]	−0.27 [−0.82, 0.27]

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, confidence interval; CM/MC/AHD, cardiomyopathy, myocarditis, acquired heart disease; CPET, cardiopulmonary exercise test; HT, heart transplant.

[a] $p < 0.05$.

[b] $p < 0.05$ in BMI sensitivity analysis excluding participants with BMI z score < −2. Adjusted models included age at HT and diagnosis.

function, and comorbidity burden may play a role. Children transplanted earlier in life have increased transplant-free survival,[30] rejection-free survival, and time to coronary artery vasculopathy. Although the effect of rejection is less clear, coronary artery vasculopathy has been associated with decreased exercise capacity.[31-34] Furthermore, those who are transplanted later may have incurred a greater extracardiac comorbidity burden which limits their physical abilities.[35,36] For instance, in a cohort of pediatric Fontan patients with circulatory failure, 69% had a poor New York Heart Association functional status of 3 or 4, 25% had liver dysfunction, and 10% had renal dysfunction.[35] Turning to psychosocial factors, children who grow up with heart disease may face activity restrictions, further limiting their exposure and engagement with exercise.[37] In contrast, those who are transplanted at a younger may have the opportunity to make physical activity a habit as children. A history of exercise has been shown to be protective in adults,[38] and this behavioral hypothesis is further strengthened by our finding that timing of transplant, rather than diagnosis, is predictive of exercise capacity. In sum, these results suggest that strategies to increase activity levels in HT patients should take their pretransplant course into account and support the utility of modeling HT recovery within a developmental framework.

As noted in prior work, we found that chronotropic ability is an important factor in post-HT exercise capacity. The inability of a denervated heart to mount a normal rate response to exercise inherently limits maximal cardiac output and PVO2. Although this limitation has traditionally been regarded as nonmodifiable, there is evidence that reinnervation may occur in up to 70% of patients with HT.[39] Furthermore, there are data that endurance training mitigates the negative effects of post-HT chronotropic incompetency in adult HT patients.[40] If a similar effect was identified in children post-HT, we could improve the effectiveness of pediatric cardiac rehabilitation programs.

Importantly, indicators of congestion, specifically PCWP and BNP, were associated with decreased PVO2 in adolescence, reinforcing the importance of diastolic function in exercise performance after HT. This finding has been seen in prior studies of pediatric HT patients.[5] Given the chronotropic impairment seen after transplant, an increased stroke volume is necessary to meet the cardiac demand of peak exercise. In those with diastolic dysfunction, this compensatory physiologic mechanism cannot be achieved. This finding not only helps develop an adequate mechanistic understanding of impaired exercise tolerance, but also raises the possibility of future therapeutic targets. A recent trial of adults with heart failure with preserved ejection fraction demonstrated improved clinical outcomes in those on the sodium-glucose cotransporter-2 inhibitor empagliflozin compared to placebo.[41] Whether this benefit would apply to transplanted hearts is unknown, however this possibility may be worth considering in future studies.

The significant but limited association between BMI and exercise capacity highlights the need to encourage physical activity for reasons beyond weight management. It is tempting to interpret this result as evidence that clinicians should focus on weight management to increase exercise capacity. However, our study found a small effect, as a decrease of an entire standard deviation predicts only an improvement of 5% PVO2. The directionality of this relationship is also unclear, and overall health, socioeconomic status, or social support may confound the association between BMI and exercise capacity.[37] This limited effect size is consistent with studies of BMI and physical activity participation. A systematic review of organized sport in children found that BMI and physical activity engagement are associated weakly, if at all.[42,43] The nonlinearity seen in

the effect is also unsurprising but concerning. Children after HT may be underweight for a number of reasons, including prior CHD or opportunistic infections. The low exercise capacity of underweight children seen in our study underscores the reality that encouraging weight loss is not free from risk. Overweight children may develop an eating disorder as they seek weight loss, and malnutrition in youth with CHD is associated with increased morbidity.[44,45] Rossano et al found that underweight children at transplant demonstrated worse graft survival compared to typical weight children, but that overweight children demonstrated similar survival.[46] Taken together, focusing on weight management may not be the best way to increase exercise capacity. Rather, this result supports centering physical activity interventions on functional benefits. Improved functional status is correlated with better quality of life in children with heart failure.[47] Qualitative studies also found that CHD patients note that their reduced physical activity and stamina cause significant distress.[48] As exercise capacity is weakly associated with BMI and more relevant to patient quality of life, clinicians should frame activity interventions in the context of patient priorities rather than just weight management.

This study has several limitations given the constraints inherent in studying this population. The observational and retrospective nature of the study may threaten its internal validity. Although our sample size is large relative to other studies, it remains too small for more complex confounding adjustment. As only sufficiently healthy patients could participate in CPETs, survivorship and wellness bias may also affect our inferences. Treadmill tests would be expected to show a higher PVO2 than those performed on bicycles, but the difference in modalities is not enough to explain the differences we saw in our cohorts. The significant missing data on several key variables may result in selection bias even with multiple imputation. Finally, residual confounding may exist given the numerous factors that may drive both exercise capacity and recovery after HT.

Conclusions

Our large sample and use of developmentally grounded mixed models allowed us to detect and to characterize decreased exercise capacity among children after HT. The findings of this examination should encourage deeper clinical attention to physical activity in pediatric HT and development of exercise interventions which account for the complex relationships between physiology and the social context in which children develop. As these children experience worse cardiovascular health outcomes, regular monitoring of exercise capacity and its antecedents should be incorporated into routine post-transplant care.

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Author contributions

All of the authors participated in the completion of this manuscript.

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