



ORIGINAL RESEARCH

# End-Organ Function and Exercise Performance in Patients With Fontan Circulation: What Characterizes the High Performers?

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**BACKGROUND:** The physiologic hallmarks of the Fontan circulation—chronically elevated central venous pressures and low cardiac output—have significant effects not only on cardiovascular status but also impact other organ systems. Exercise capacity is limited in many and declines with age, accelerating in adolescence, but with wide variability. We explore the relationship between exercise performance and end-organ function in outpatient subjects with a Fontan circulation.

**METHODS AND RESULTS:** This is a cross-sectional analysis of subject end-organ characterization from our outpatient Fontan circulation clinic with peak oxygen consumption (peak  $\text{Vo}_2$ ) at cardiopulmonary exercise testing as the primary outcome. We perform linear regression to assess associations between clinical characteristics and peak  $\text{Vo}_2$  as well as the magnitude of the association of clinical characteristics with peak  $\text{Vo}_2$ . Of 265 subjects age 12.8 (9.5–16.4) years, there is a negative correlation between age and peak  $\text{Vo}_2$  ( $-0.49$ ,  $P<0.001$ ). Of those undergoing ramp cycle exercise testing, 34% perform above 80% predicted peak  $\text{Vo}_2$ . Variables positively associated with peak  $\text{Vo}_2$  and their effect size include vitamin D sufficiency ( $+3.00$ ,  $P=0.020$ ) and absolute lymphocyte count ( $+0.23$ ,  $P=0.005$ ). Status as overweight/obese ( $-3.91$ ,  $P=0.003$ ) and hemoglobin ( $-0.77$ ,  $P=0.003$ ) are negatively associated. Neither ventricular morphology, timing of Fontan palliation, nor Fontan circulation type affect peak  $\text{Vo}_2$ .

**CONCLUSIONS:** Higher peak  $\text{Vo}_2$  in those with a Fontan circulation is associated with younger age, vitamin D sufficiency, absence of overweight/obese, lower hemoglobin, and a healthier hepatic profile. Whether exercise training or other initiatives can modify organ characteristics in those with a Fontan circulation is worthy of exploration.

**Key Words:** congenital heart disease ■ exercise testing ■ Fontan procedure ■ single ventricle

Strategies of care for those born with single ventricle congenital heart disease culminates in the channeling of systemic venous return directly to the pulmonary circulation without ventricular thrust, a state known as the Fontan circulation.<sup>1</sup> Implementation of this surgical approach currently allows for long-term outcomes with survival ranging from 75% to 80% at up to 25 years of age.<sup>2,3</sup> The physiologic hallmarks of the Fontan circulation—chronically elevated central

venous pressure and low cardiac output—have significant effects not only on cardiovascular status but also potentially impact other organ systems. Hepatic, endocrine, renal, and lymphatic systems can all be negatively affected, with variable degrees of dysfunction reported.<sup>4</sup> It is well recognized that overall, as a group, in patients with a Fontan circulation, exercise capacity is limited and declines with age. This decline accelerates in the adolescent years.<sup>5–10</sup>

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## CLINICAL PERSPECTIVE

### What Is New?

- In young subjects with a Fontan circulation, exercise capacity as measured by cardiopulmonary exercise testing is associated with the health of multiple noncardiovascular end-organ systems in which progressive decline and dysfunction is common in this population.

### What Are the Clinical Implications?

- Because end-organ health is associated with exercise performance, it is reasonable to consider that increasing exercise capacity through measures such as training, modification of lifestyle, and nutrition enhancement may improve end-organ health and thus improve overall wellness in individuals with Fontan circulation.
- Our study identifies elements of organ function associated with exercise capacity that may be useful to consider as we strive to develop a condition-specific “composite score of wellness” formula for our patients with Fontan circulation that may aid in characterizing clinical status and predict future outcomes.

## Nonstandard Abbreviations and Acronyms

<b>ALC</b>	absolute lymphocyte count
<b>CPET</b>	cardiopulmonary exercise testing
<b>GGT</b>	gamma glutamyl transferase
<b>Peak <math>\dot{V}O_2</math></b>	peak oxygen consumption

Diminished exercise capacity, as measured by peak oxygen consumption (peak  $\dot{V}O_2$ ), portends prognosis and predicts both increased morbidity and risk of hospitalization, with a nearly doubled hazard of mortality or transplant for every 10% decline in peak  $\dot{V}O_2$ .<sup>11–14</sup>

Despite these findings, there is an impressively wide spectrum of exercise capacity in individuals with Fontan circulation. Attention is deservedly focused on understanding the mechanisms underlying what limits exercise capacity; however, few studies have investigated characteristics in patients with single ventricle and Fontan circulation who perform at normal or supranormal exercise capacity.<sup>15,16</sup> Furthermore, there are few data on any associations between end-organ function and exercise capacity. Exploration of the complex interplay between end-organ functionality and exercise capacity may provide insight into improved understanding of the pathophysiology of the Fontan

circulation and perhaps offer clues into ways to best preserve organ function, overall health, and wellness. In this study, we look to identify clinical characteristics and end-organ parameters associated with higher exercise performance in patients with Fontan circulation.

## METHODS

The authors declare that all supporting data are available within the article.

We performed a single-center retrospective analysis of subjects with a Fontan circulation evaluated at the Children’s Hospital of Philadelphia’s Single Ventricle Survivorship Program, between the years 2011 and 2018. Permission for data collection and analysis is included under Institutional Review Board approval for the Children’s Hospital of Philadelphia’s Cardiac Center Single Ventricle—Fontan Registry (CHOP IRB 12-009791). The requirement for subjects to provide informed consent was waived. This clinic, now known as the Fontan Rehabilitation, Wellness, Activity and Resilience Development program, was created to provide multidisciplinary evaluation and surveillance services at regular intervals to patients with a Fontan circulation, as proposed in a consensus statement.<sup>4</sup> All study subjects were ambulatory and outpatient at the time of evaluation.

Subjects were included in the study if, at their most recent visit, they completed cardiopulmonary exercise testing (CPET) and underwent a comprehensive end-organ surveillance evaluation, an evaluation that is intended to reflect measurable areas of potential vulnerability in patients with a Fontan circulation. Patient cardiac anatomy, medical and surgical history, medications, vital signs and anthropometric measures, blood laboratory data, abdominal ultrasound, and CPET peak  $\dot{V}O_2$  data were collected cross-sectionally at their most recent Single Ventricle Survivorship Program visit. Estimated glomerular filtration rate (eGFR) was calculated for subjects using the updated bedside Schwartz formula.<sup>17</sup> CPET was performed according to standard protocols.<sup>6</sup> Subjects who underwent ramp cycle protocols were asked to exercise to maximal volition (respiratory exchange ratio >1.10) using an electronically braked cycle ergometer. The protocol consists of 3 minutes of pedaling in an unloaded state followed by a ramp increase in work rate (W) to maximal exercise. The steepness of the ramp protocol was determined by subject weight in kilograms and designed to achieve predicted peak work rate in 10 to 12 minutes of cycling time. Subjects who did not meet the height requirements for cycle ergometry (height >130 cm) were exercised using a graded treadmill protocol. This consisted of 3 minutes of walking followed by

incremental increases in speed and grade every 1 minute until maximal exercise is reached. Metabolic and ventilatory data, including minute oxygen consumption, were obtained throughout the exercise study and for the first 2 minutes of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics V29, Yorba Linda, CA). For subjects who underwent ramp cycle testing, peak  $\text{Vo}_2$  data were converted to percent predicted peak  $\text{Vo}_2$  based on age and sex.<sup>18</sup> High performers were defined as individuals performing  $\geq 80\%$  predicted peak  $\text{Vo}_2$ .

## Statistical Analysis

Student *t* test for continuous variables and  $\chi^2$  test for categorical variables was used to compare clinical characteristics and end-organ parameters between high performers and those performing below 80% predicted peak  $\text{Vo}_2$ . Pearson correlation coefficient was used to measure the correlation between age and peak  $\text{Vo}_2$ . Univariate linear regression model was used to study the association between independent clinical characteristic variables and the outcome peak  $\text{Vo}_2$ . The magnitude of the association between clinical characteristics and exercise capacity was calculated and reported as an effect size of absolute change in peak  $\text{Vo}_2$ . Among the continuous variables, several were re-scaled to allow for interpretation of a clinically meaningful effect size: absolute lymphocyte count (ALC) and platelet count values were divided by 100, and brain natriuretic peptide, 25-OH vitamin D, intact parathyroid hormone, eGFR, and gamma-glutamyl transferase (GGT) values were divided by 10. For clinical characteristics expected to have a significant correlation with age (extracardiac conduit Fontan, liver span size), a linear regression model with age as an additional independent variable was performed. To assess the effect of liver span size when accounting for the effect of body mass, additional linear regression models with weight or body mass index (BMI) percentile as additional independent variables were performed. We also conducted a multivariable regression analysis to examine the adjusted association between clinical characteristics and the outcome peak  $\text{Vo}_2$ . To select variables for the multivariable regression, we examined the correlation between each pair of clinical characteristics that had  $P < 0.1$  in the univariate analysis and calculated the variance inflation factor to quantify multicollinearity among variables. Among highly correlated variables, we chose variables based on their clinical importance and the primary research interest of this study. Multivariable regression models including and excluding age as a variable were performed. The final model included vitamin D sufficiency, platelet count, ALC, hemoglobin, sex, and

obesity. Age was not included in the final model because of collinearity with other variables, with the study objective to evaluate the association between exercise performance and end-organ function variables that may prove to be modifiable. In the univariate analysis, we used Bonferroni approach to adjust for multiple comparisons. A  $P < 0.0025$  was considered as statistical significance at the nominal level of 0.05. All statistical analysis was performed in R version 3.6.0.

## RESULTS

### Overall Cohort Characteristics and Association With End-Organ Parameters

A total of 421 subjects were seen in the Fontan Rehabilitation, Wellness, and Resilience Development clinic during the study period. Of 334 subjects who attempted exercise testing, 265 achieved maximal exercise testing and met inclusion criteria for analysis. Of these, 163 subjects completed exercise testing per the ramp cycle protocol and 102 subjects completed graded treadmill protocol exercise testing. Table 1 summarizes key demographic and clinical characteristics of the 265 subjects in the study cohort. Subjects range in age from 5.5 to 48 years, with a median of 12.8 years; 37% are female, and 16% are overweight or obese. Most of the group comprises individuals with a dominant right ventricular morphology of their single ventricle, 32 (12%) have heterotaxy syndrome, and 81% received a fenestration at the time of their Fontan surgery. Three subjects died subsequent to evaluation. Protein-losing enteropathy (active or controlled under treatment) is present in 22 (8%) and plastic bronchitis in 6 (2%) subjects. Brain natriuretic peptide levels are within normal range of  $< 100$  pg/mL in the vast majority; however, it is  $> 250$  pg/mL in 2 subjects (1%). Hypoalbuminemia defined as albumin  $< 3.5$  g/dL is present in 17 subjects (6%). GGT levels are abnormally above the upper level of normal for age and sex, as per the Children's Hospital of Philadelphia's core laboratory reference ranges, in 223 subjects (94%). As for other markers of end-organ function, 74 subjects (28%) have calculated eGFR  $< 90$  mL/min per  $1.73$  m<sup>2</sup>, 84 subjects (32%) have platelet counts below the lower level of normal for age and sex, and 48 subjects (19%) have ALCs less than the lower level of normal for age and sex. Two-hundred-one subjects (81%) demonstrate vitamin D sufficiency (defined as 25-OH vitamin D  $> 20$  ng/mL).

The distribution of absolute peak  $\text{Vo}_2$  values by age for the entire study cohort is displayed in the Figure. The median peak  $\text{Vo}_2$  is 32.6 mL/kg per minute. There is a significant negative correlation

**Table 1. Key Demographic and Clinical Characteristics of the Study Cohort**

	All Subjects (N=265)
Age at FORWARD visit, y	12.8 (9.5–16.4)
Female	97 (37%)
Right heart morphology of single ventricle	164 (62%)
Hypoplastic left heart syndrome	125 (47%)
Extra cardiac conduit Fontan	148 (56%)
Age at Fontan palliation, y	2.6 (2.0–3.4)
Fenestrated Fontan	197 (81%)
Number of cardiovascular medications	2 (1–3)
Protein losing enteropathy	22 (8%)
Plastic bronchitis	6 (2%)
Pulse oximetry (%)	94 (91–95)
Body mass index percentile (%)*	44 (17–72)
Overweight/obese†	38 (16%)
Brain natriuretic peptide, pg/mL	19 (10–34)
International normalized ratio	1.20 (1.15–1.26)
Gamma glutamyl transferase, U/L	50 (36–75)
Albumin, g/dL	4.6 (4.3–4.9)
Liver span size, cm‡	13.9 (12.6–15.4)
eGFR, mL/min per 1.73 m <sup>2§</sup>	105 (89–118)
Platelet count, K/ $\mu$ L	223 (173–275)
Hemoglobin, g/dL	14.9 (14.1–16)
Absolute lymphocyte count, K/ $\mu$ L	1440 (1111–1825)
Calcium, mg/dL	9.6 (9.3–9.9)
25-OH vitamin D, ng/mL	30 (22–38)
Vitamin D sufficiency	201 (81%)
Intact parathyroid hormone, pg/mL	49 (33–76)

Categorical variables labeled with number (%). Continuous variables labeled with median and interquartile range (25%–75%). eGFR indicates estimated glomerular filtration rate; and FORWARD indicates Fontan Rehabilitation, Wellness, and Resilience Development.

\*Body mass index percentile excludes subjects >20 years of age.

†Overweight/obese defined as body mass index percentile  $\geq$ 85th percentile for age and sex.

‡Liver span size as measured on abdominal ultrasound.

§Calculated by bedside Schwartz formula:  $0.413 \times \text{height (cm)} / \text{creatinine (mg/dL)}$ .

||Defined as 25-OH vitamin D  $\geq$ 20 ng/mL.

between peak  $\text{Vo}_2$  and age, with a Pearson correlation of  $-0.49$ ,  $P < 0.001$ .

### Characteristics of High Performers and Association With End-Organ Parameters

When stratifying the cohort between individuals performing above (high performer) and below 80 percent predicted peak  $\text{Vo}_2$ , 34% of subjects perform above 80%. Higher performers exhibit a distinct profile as they are significantly younger, more likely female, and have end-organ parameters that demonstrate higher eGFR, vitamin D sufficiency, and lower GGT. Higher performers trend toward lower hemoglobin, higher platelet count, and higher ALCs (Table 2).

Single variable regression of the association of changes in clinical characteristics and peak  $\text{Vo}_2$  listed in order of greatest positive to greatest negative effect is shown in Table 3. Significant greatest positive effects include vitamin D sufficiency, extracardiac conduit type of Fontan palliation, platelet count, ALC, and eGFR. Absolute vitamin D and calcium levels have a nearly significant positive effect on peak  $\text{Vo}_2$ . Significant greatest negative effects include status as overweight or obese and number of cardiovascular medications. Hemoglobin and GGT values trend toward negative association with peak  $\text{Vo}_2$ .

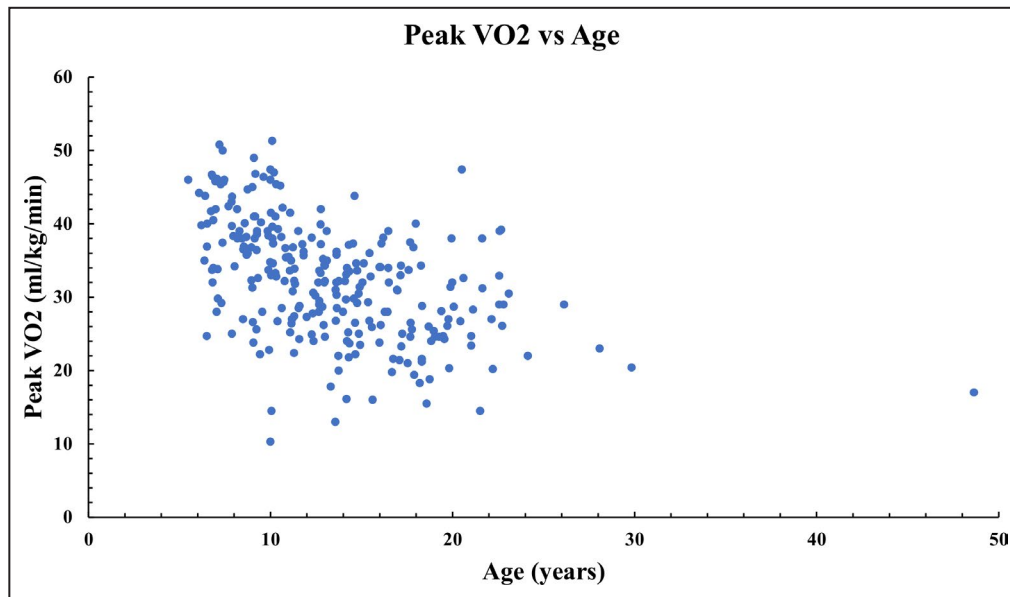
Liver span size as measured by abdominal ultrasound demonstrates significant negative association with peak  $\text{Vo}_2$  ( $-0.82$ ,  $P < 0.001$ ). Because liver span size may be confounded by age and body mass, additional linear regressions were performed adjusting for age, BMI percentile, or weight. With such indexing to age and body size, no significant effect was seen between liver span and peak  $\text{Vo}_2$ . An additional independent variable expected to have a significant correlation with age is the extracardiac conduit type of Fontan, as this type of Fontan surgery was performed with greater frequency in our younger population. A multivariable linear regression model with age as an additional independent variable eliminated the statistically significant positive association with peak  $\text{Vo}_2$  related to undergoing extracardiac conduit type of Fontan. Of note, age at Fontan surgery, underlying morphology of the single ventricle, protein-losing enteropathy or plastic bronchitis, and brain natriuretic peptide levels do not demonstrate a significant effect on peak  $\text{Vo}_2$ .

### Multivariate Analysis of Parameters Associated With Exercise Performance

Results of multivariate linear regressions are demonstrated in Table 4. Including age in the model yields a very strong negative association between age and exercise performance. Obesity is also significantly negatively associated. Multivariate linear regression excluding age shows vitamin D sufficiency and ALCs have a significant positive relationship with peak  $\text{Vo}_2$ , and hemoglobin level and status as overweight or obese have a significant negative relationship with peak  $\text{Vo}_2$ . Platelet count has a nearly significant positive relationship with peak  $\text{Vo}_2$ . Inclusion of GGT and eGFR in the model did not demonstrate statistical significance.

## DISCUSSION

In this study we explore the relationship between the status of cardiovascular wellness as gauged by CPET-measured peak  $\text{Vo}_2$  and clinical characteristics of



**Figure 1. Distribution of peak oxygen consumption (peak  $V_{O_2}$ ) and age.**

This figure demonstrates the cross-sectional distribution of all 265 study subjects' peak  $V_{O_2}$  performance and age in years. The figure demonstrates a significant downward slope in exercise performance with age, with a significant negative correlation between peak  $V_{O_2}$  and age (Pearson correlation  $-0.49$ ,  $P < 0.001$ ).

end-organ function as measured by laboratory values, in a large cohort of outpatients with a Fontan circulation. Younger age, vitamin D sufficiency, absence of overweight or obese status, lower hemoglobin, higher ALC, and a healthier hepatic profile are associated with higher exercise performance on CPET. Anatomic morphology of the single ventricle, timing of Fontan palliation, and type of Fontan are not significantly associated with exercise performance.

In our study cohort, >30% of the subjects undergoing ramp cycle CPET performed at a peak  $V_{O_2}$  >80% predicted for age. Although physiologically challenged with the absence of a subpulmonary ventricle, individuals with Fontan circulation exhibit wide variability in their exercise capacities with reassurance that a significant subset appear to perform very well. As a comparison, in studies assessing “Super-Fontans” or “High-Capacity Fontans,” defined as individuals achieving >80% of predicted peak  $V_{O_2}$ , high-achieving performance was seen in 11% and 19% of subjects, respectively.<sup>15,16</sup> Differences in patient phenotype, particularly the older ages of the subjects in each of these studies, may explain their lower prevalence of higher exercise performance. Clearly there is a subset of individuals with Fontan circulation who perform at a high level, but what defines and characterizes this group? Can a deeper analysis of overall health status offer insights into their uniqueness?

We found a significant negative correlation between peak  $V_{O_2}$  and age, with a steep decline particularly

notable in adolescence, supporting several prior studies.<sup>5–10</sup> When including age in our multivariable regression analysis model, the strength of the association with exercise performance is dominant and only obesity is additionally of significance. This speaks to the sobering reality that age, or simply the time elapsed with having a Fontan circulation, may be the strongest factor influencing exercise performance, perhaps suggesting unmitigated decline of capacity with passage of time. Because age is nonmodifiable, we performed an additional regression model excluding age to identify additional variables that may be related to exercise capacity. We discover that, besides age, other variables appear to be of importance. We hypothesize a complex interplay and possible association between healthier end-organ systems and increased exercise capacity. Using laboratory values to reflect hepatic, hematologic, renal, and musculoskeletal health, we found that healthier end-organ function in each of these systems is associated with increased exercise performance.

In regard to musculoskeletal health, vitamin D sufficiency demonstrates the strongest positive association with exercise performance. Vitamin D deficiency in patients with Fontan circulation is associated with lower-leg lean mass z-scores and sarcopenia, which negatively influences exercise capacity.<sup>19,20</sup> Vitamin D stores are known to reflect musculoskeletal health and physical activity levels in children and adolescents.<sup>21</sup> The identified positive association between vitamin D

**Table 2. Key Demographic and Clinical Demographics in Subjects Undergoing Cycle Ramp Protocol, With Statistical Analysis Between Cohorts Stratified Above and Below 80% Predicted Peak  $\text{Vo}_2$** 

	Peak $\text{Vo}_2$ $\geq 80\%$ (N=56)	Peak $\text{Vo}_2$ $< 80\%$ (N=107)	P Value
Age at FORWARD visit, y	12.3 (10.3–13.7)	16.0 (14.2–18.8)	$<0.001^*$
Female	28 (50%)	30 (28%)	0.005
Right heart morphology of single ventricle	33 (59%)	62 (58%)	0.904
Extra cardiac conduit Fontan	35 (63%)	50 (48%)	0.072
Age at Fontan palliation, y	2.7 (2.0–3.6)	2.1 (1.8–3.1)	0.568
Number of cardiovascular medications	2 (1–2)	2 (1.5–3)	0.002 <sup>†</sup>
Protein losing enteropathy or plastic bronchitis	4 (7%)	11 (10%)	0.510
Pulse oximetry (%)	94 (91–96)	94 (91–95)	0.487
Body mass index percentile (%) <sup>‡</sup>	54 (16–75)	44 (16–72)	0.637
Overweight/obese <sup>§</sup>	9 (17%)	16 (17%)	0.987
Brain natriuretic peptide, pg/mL	18 (5–26)	20 (10–38)	0.157
International normalized ratio	1.17 (1.13–1.26)	1.22 (1.16–1.26)	0.491
Gamma glutamyl transferase, U/L	51 (42–65)	56 (40–90)	0.002 <sup>†</sup>
Albumin, g/dL	4.7 (4.5–4.9)	4.7 (4.5–4.9)	0.567
Liver span size, cm <sup>  </sup>	13.9 (12.7–15.1)	15.2 (14.2–16.3)	0.147
eGFR, mL/min per 1.73 m <sup>2¶</sup>	111 (97–121)	98 (85–111)	0.0006 <sup>†</sup>
Platelet count, K/ $\mu$ L	227 (187–260)	182 (150–251)	0.014
Hemoglobin, g/dL	14.7 (14.2–15.5)	15.4 (14.4–16.4)	0.012
Absolute lymphocyte count, K/ $\mu$ L	1560 (1266–1883)	1220 (965–1625)	0.151
Vitamin D sufficiency <sup>#</sup>	49 (92%)	70 (69%)	0.001 <sup>†</sup>
Calcium, mg/dL	9.6 (9.4–9.8)	9.6 (9.3–9.9)	0.590
25-OH vitamin D, ng/mL	31 (23–40)	25 (18–36)	0.134
Intact parathyroid hormone, pg/mL	46 (34–74)	52 (37–83)	0.190

Categorical variables labeled with number (%). Continuous variables labeled with median (25%–75%). Univariate analysis performed with Student *t* test for continuous variables and  $\chi^2$  analysis for categorical variables. eGFR indicates estimated glomerular filtration rate; FORWARD, Fontan Rehabilitation, Wellness, and Resilience Development; and  $\text{Vo}_2$ , oxygen consumption.

\*Signifies  $P < 0.00004$  (0.001/24).

<sup>†</sup>Signifies  $P < 0.0021$  (0.05/24).

<sup>‡</sup>Body mass index percentile excludes subjects  $\geq 20$  years of age.

<sup>§</sup>Overweight/obese defined as body mass index percentile  $\geq 85$ th percentile for age and sex.

<sup>||</sup>Liver span size as measured on abdominal ultrasound.

<sup>¶</sup>Calculated by bedside Schwartz formula:  $0.413 \times \text{height (cm)} / \text{creatinine (mg/dL)}$ .

<sup>#</sup>Defined as 25-OH vitamin D  $\geq 20$  ng/mL.

**Table 3. Single Variable Regression of Impact of Changes in Clinical Characteristics on Peak  $\text{Vo}_2$** 

	Effect Size <sup>*</sup>	P Value
Vitamin D sufficiency	4.48	$<0.001^{\dagger}$
Extracardiac conduit Fontan	3.14	0.001 <sup>†</sup>
Platelet count, K/ $\mu$ L <sup>§</sup>	2.32	$<0.001^{\dagger}$
Calcium, mg/dL	2.05	0.029
25-OH vitamin D, ng/mL <sup>  </sup>	0.97	0.005
eGFR, mL/min per 1.73 m <sup>2  ¶</sup>	0.63	0.002 <sup>†</sup>
Absolute lymphocyte count, K/ $\mu$ L <sup>§</sup>	0.28	$<0.001^{\dagger}$
Pulse oximetry, %	0.26	0.030
Body mass index percentile, % <sup>‡</sup>	−0.05	0.004
Brain natriuretic peptide, pg/mL <sup>  </sup>	−0.16	0.135
Gamma-glutamyl transferase, U/L <sup>  </sup>	−0.23	0.037
Intact parathyroid hormone, pg/mL <sup>  </sup>	−0.24	0.059
Hemoglobin, g/dL	−0.84	0.009
Number of cardiovascular medications	−1.45	$<0.001^{\dagger}$
Female	−1.81	0.072
Protein-losing enteropathy or plastic bronchitis	−1.85	0.240
Overweight/obese <sup>#</sup>	−5.16	$<0.001^{**}$

eGFR indicates estimated glomerular filtration rate; and  $\text{Vo}_2$ , oxygen consumption.

\*Absolute change in peak  $\text{Vo}_2$  for an increase of 1 for continuous variables or for a value of 1 for dichotomous variables.

<sup>†</sup>Signifies  $P < 0.0005$  (0.01/20).

<sup>‡</sup>Signifies  $P < 0.0025$  (0.05/20).

<sup>§</sup>Re-scaled by dividing variable by 100 for clinically meaningful effect size.

<sup>||</sup>Re-scaled by dividing variable by 10 for clinically meaningful effect size.

<sup>¶</sup>Calculated by bedside Schwartz formula:  $0.413 \times \text{height (cm)} / \text{creatinine (mg/dL)}$ .

<sup>#</sup>Excludes analysis for subjects  $\geq 20$  years of age or with protein-losing enteropathy.

\*\*Signifies  $P < 0.0025$  (0.05/20).

sufficiency and peak  $\text{Vo}_2$  in individuals with a Fontan circulation suggests that maintenance of regular physical activity may beget improved maximal exercise capacity. Vitamin D sufficiency might be protective against sarcopenia in patients with a Fontan circulation and vitamin D supplementation and/or maintenance of frequent exercise activity at a younger age may have a long-lasting beneficial role.

We found overweight or obese subjects to have a significant decreased peak  $\text{Vo}_2$  compared with subjects with BMI less than the 85th percentile. Higher BMI z-score is associated with decreased exercise performance in children and adolescents with Fontan circulation.<sup>22</sup> Patients with Fontan circulation, like many children with complex congenital heart disease, are likely to have their activity levels restricted by their cardiologist, associated with decreased weekly exercise activity levels and increased BMI.<sup>23</sup> This finding further supports the implication that, specifically for the child with Fontan circulation, regular physical activity may beget improved maximal exercise capacity.

**Table 4. Multivariate Linear Regressions of Association Between Clinical Characteristics and Peak  $\text{Vo}_2$ , With Age Included and Excluded in the Model**

	Age Included		Age Excluded	
	Effect Size*	P Value	Effect Size*	P Value
Vitamin D sufficiency	1.47	0.142	3.00	0.020 <sup>†</sup>
Platelet count $\text{K}/\mu\text{L}$ <sup>‡</sup>	0.20	0.844	1.24	0.055
Absolute lymphocyte count, $\text{K}/\mu\text{L}$ <sup>‡</sup>	1.24	0.216	0.23	0.005 <sup>§</sup>
Hemoglobin, g/dL	-0.70	0.485	-0.77	0.014 <sup>†</sup>
Female	-1.89	0.061	-1.73	0.076
Overweight/obese	-3.12	0.002 <sup>§</sup>	-3.91	0.003 <sup>§</sup>
Age, y	-6.91	<0.001 <sup>  </sup>	...	...

$\text{Vo}_2$  indicates oxygen consumption.

\*Absolute change in peak  $\text{Vo}_2$  for an increase of 1 for continuous variables or for a value of 1 for dichotomous variables.

<sup>†</sup>Signifies  $P < 0.05$ .

<sup>‡</sup>Re-scaled by dividing variable by 100 for clinically meaningful effect size.

<sup>§</sup>Signifies  $P < 0.01$ .

<sup>||</sup>Signifies  $P < 0.001$ .

We found a higher lymphocyte count associated with better exercise capacity. Lymphopenia is seen in patients with Fontan circulation<sup>24</sup> and is presumably related to lymphatic congestion and low levels of chronic enteric lymph loss. Lower lymphocyte levels may reflect a greater degree of lymphatic and venous congestion and may be a surrogate for relatively sub-optimal hemodynamics, manifested as limitations in exercise capacity.

Subjects with a higher hemoglobin level have an associated significant decreased peak  $\text{Vo}_2$ . Higher hemoglobin levels among subjects within our overall cohort, for which there is an elevated median hemoglobin of 14.9 mg/dL, likely reflect a reactive polycythemia to mild cyanosis. Reactive polycythemia may indicate sustained, relatively lower oxyhemoglobin saturations and, despite an attempt at physiological compensation, may reflect limitations to oxygen-carrying capacity that influence peak exercise capacity in these individuals. In support of this theory, resting oxyhemoglobin saturations trend toward a positive relationship with peak  $\text{Vo}_2$  in our univariate analysis. In contrast, previous research has demonstrated a positive correlation between peak  $\text{Vo}_2$  and hemoglobin in a cohort of 115 6-to-20 year-old subjects with a Fontan circulation.<sup>10</sup> More detailed study incorporating the fundamental causes of lower oxygen saturation such as fenestration patency versus venous collaterals or intrapulmonary shunting, as well as improved understandings of iron absorption and individual capacity for red blood cell production, will provide a clearer picture on the value of hemoglobin level as a parameter of wellness or unwellness in the Fontan circulation.

As for hepatic end-organ health, we found that subjects with higher platelet counts perform at higher associated peak  $\text{Vo}_2$  on univariate analysis and have a trend toward higher associated peak  $\text{Vo}_2$  on multivariate

analysis. Subjects with lower GGT values trend toward higher associated peak  $\text{Vo}_2$ . Fontan-associated liver disease, attributed to elevated central venous pressures and increased hepatic congestion, may be characterized serologically by elevated GGT and decreased platelet counts.<sup>25-27</sup> Our data suggest that subjects with higher exercise performance may exhibit more favorable hemodynamic conditions, perhaps a lower central venous pressure and thus decreased hepatic congestion, than their lower-performing peers.

Though not significant in multivariate regression, univariate analysis demonstrates an association between higher glomerular filtration rate and exercise capacity as measured by peak  $\text{Vo}_2$ . Renal dysfunction in the Fontan circulation is attributed to decreased kidney perfusion as a result of low cardiac output inherent to the Fontan circulation, in addition to multiple lifetime exposures to renal toxicities (prolonged cyanosis, cardiopulmonary bypass runs, nephrotoxic medications, and intravenous contrast).<sup>4</sup> In patients with Fontan circulation, low stroke volume index at maximal exercise is proposed as the most important factor limiting exercise capacity.<sup>28</sup> Higher glomerular filtration rate likely reflects a better hemodynamic status in the individual. Though the bedside Schwartz formula is a good surrogate measure of glomerular filtration rate in a study population such as ours mostly comprising individuals below the age of 18 years, the lack of statistical significance between peak  $\text{Vo}_2$  and eGFR on multivariate analysis may be because creatinine, used in the calculation, is known to be a late marker of renal dysfunction in individuals with a Fontan circulation.<sup>29</sup> Cystatin C levels may be more sensitive in childhood and thus is the preferred tool to use as surveillance for renal performance.<sup>4</sup>

Are these findings fixed or is there a possibility for modification? It is plausible to presume that enhancing

exercise capacity in individuals with a Fontan circulation at younger ages might also influence and modify end-organ functionality. Investigators have demonstrated that high-intensity resistance training and inspiratory muscle training can have significant effects on cardiac output and exercise capacity,<sup>30,31</sup> whereas aerobic exercise training has not demonstrated similar lasting effects in this patient population.<sup>32,33</sup> Weekly sports participation and exercise more than 4 days per week has been demonstrated to be associated with increased exercise capacity on exercise testing.<sup>16,34</sup> Medication treatment with phosphodiesterase type 5 inhibition has recently been demonstrated to improve submaximal measures of exercise performance.<sup>35</sup> These types of interventions may augment exercise capacity, which could reciprocally influence end-organ functionality and, based on our findings of associations, is deserving of further investigation. Alternatively, it is possible that these findings of organ dysfunction are fixed, and that there is an underlying heterogeneity in organ functional capacity in individuals who have undergone the Fontan palliation. Heterogeneity in the Fontan population may be related to factors such as an inherent “resilience” or the underlying genetics and prenatal environment, among others, variables that might limit or benefit an individual’s potential for exercise capacity as well as end-organ function.

An important limitation of our study data is that peak  $\text{Vo}_2$  was measured via graded treadmill protocol in about 40% and ramp cycle protocol in about 60% of subjects. Ideally, all subjects would have exercise tests in accordance with one protocol; however, the relatively young age span of our cohort was prohibitive. To address this, we performed a subanalysis of only ramp cycle protocol subjects for analysis of the high performers (>80% predicted peak  $\text{Vo}_2$  versus <80%, Table 2) but analyzed the influence of organ functionality on exercise performance using absolute peak  $\text{Vo}_2$  for the entire cohort (Tables 3 and 4), with similar trends in associations for the subgroup and overall noted. An additional limitation is the cross-sectional nature of the data derived from a single center. Longitudinal data would more accurately describe the trajectory of exercise performance as individual patients transition from childhood through adolescence and into adulthood. In addition, the selection of peak  $\text{Vo}_2$  as the primary outcome is a limitation in the study, as this variable does not reflect the most common type of day-to-day activity undertaken by subjects. Additional exercise parameters may be useful to study, including  $\text{Vo}_2$  at anaerobic threshold and work rate at peak exercise. Nevertheless, we selected peak  $\text{Vo}_2$  because it is a measurement frequently used in the literature and is commonly associated with morbidity and mortality in patients with a Fontan circulation. Additional

parameters that we did not assess but would be of value to analyze in future study include self-reported activity level and sports participation, as well as imaging measures of ventricular and atrioventricular valve performance. Lastly, there is selection bias, because the 265 study subjects are derived from a larger cohort of patients seen in the Fontan Rehabilitation, Wellness, and Resilience Development clinic during this time period. Of the 156 subjects who did not undergo interpretable CPET studies, a subset was physically and/or cognitively unable to complete CPET and may represent a patient population with a greater degree of cardiovascular dysfunction and end-organ morbidity. Others who were excluded were too young to participate in CPET, which may provide for further age-related bias. Our findings thus apply towards a selected, healthier population, but do likely reflect a majority of relatively young Fontan circulation individuals within the community who appear well, are outpatients, and visit their healthcare providers 1 to 2 times per year for surveillance.

Our study findings lay the groundwork for further exploration. Future prospective longitudinal assessments with larger cohorts of patients with Fontan circulation could further assess the efficacy of interventions such as cardiopulmonary rehabilitation, lower-extremity leg muscle mass strengthening, and medication management as modalities for improving cardiopulmonary exercise testing performance. Importantly, we anticipate our findings will aid in developing a condition-specific “composite score of wellness” for patients with a Fontan circulation. The parameters we evaluated reflect measurable areas of potential vulnerability in patients with a Fontan circulation. We identify clinical characteristics and important elements of end-organ function that are strongly associated with exercise capacity, as well as elements not associated. We do not know or expect that any specific improvement in one or a group of variables will lead to an increase or decrease in exercise performance; rather, we are demonstrating the magnitude of association of a specific end-organ variable with a measure of cardiovascular wellness, that of exercise. In understanding the strength of the association with exercise performance, we have laid the foundations for identifying variables to include in development of such a Fontan circulation wellness score. Age, overweight/obesity status, vitamin D sufficiency, platelet count, lymphocyte count, hemoglobin, and eGFR are candidate elements to include in the development of such a wellness prediction model, while ventricular morphology is not. Future endeavors would be to develop a model using these elements, among others, and to apply the model prospectively to determine utility to predict outcome measures (ie, transplant-free survival and quality of life).



## CONCLUSIONS

In a cohort of 265 subjects with a Fontan circulation, younger age, vitamin D sufficiency, absence of overweight or obese status, lower hemoglobin and laboratory values reflecting higher lymphocyte counts and a healthier hepatic profile are associated with higher performance on cardiopulmonary exercise testing. Anatomic morphology of the single ventricle, timing of Fontan palliation, and type of Fontan surgery do not have a significant association with peak  $\dot{V}O_2$ . Our study identifies important elements of organ function associated with exercise capacity that may be useful to consider as we attempt to develop a condition-specific “composite score of wellness” formula for our patients with Fontan circulation, which could then be tested to predict future outcomes. For healthcare providers caring for patients with a Fontan circulation, our data suggest that exercise capacity is associated with the health of multiple end-organ systems in which natural progressive decline and dysfunction is common. Whether exercise training at younger ages or other initiatives can modify organ dysfunction is worthy of future exploration.

## ARTICLE INFORMATION

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