The unique clinical phenotype and exercise adaptation of Fontan patients with normal exercise capacity

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Background: Exercise limitation is almost universal among Fontan patients. Identifying unique clinical features in the small fraction of Fontan patients with normal exercise capacity (high capacity Fontan, HCF) provides potential to inform clinical strategies for those with low exercise capacity (usual Fontan, UF). **Methods:** We performed a retrospective chart review of all single ventricle patients palliated with a Fontan operation who underwent incremental cardiopulmonary exercise testing at Cincinnati Children's Hospital Medical Center from 2013-2018. Comparison was between patients with peak oxygen uptake (VO_2peak) < vs $\geq$80% predicted. **Results**: Twenty two of 112 patients were classified as HCF (68% female; 18±7 years). During incremental exercise, VO_2peak (86.1±6.1% vs 62±12.2 % predicted; $p<0.001$) was greater in HCF vs UF despite similar chronotropic impairment, resulting in a greater oxygen pulse in HCF. Pulmonary function, breathing reserve and V_E/VCO_2 slope were not different between groups. HCF were more likely to self-report exercise $\geq$4 days/week for at least 30 minutes (77% vs 10%, $p<0.001$), have normal systolic function (95% vs 74%, $p=0.003$), have fewer post-operative complications (8% vs 36%, $p=0.04$) and shorter post-Fontan length of stay (8±2.8 vs 12.4±0.9 days, $p=0.04$). **Conclusions**: Approximately 1 in 5 Fontan patients who undergo cardiopulmonary exercise testing have normal exercise capacity despite chronotropic impairment. This implies a better preserved stroke volume, perhaps due to greater muscle pump-mediated preload. Additionally, a complicated perioperative Fontan course is associated with eventual impaired functional capacity.

Electronic Table of Contents Summary:

Identifying unique features in Fontan patients with normal exercise capacity provides potential to inform clinical strategies for those in whom exercise capacity is limited. Approximately 1 in 5 Fontan patients have normal exercise capacity despite chronotropic impairment. This implies a better preserved stroke volume, perhaps due to greater muscle pump-mediated preload. Pulmonary function and ventilatory responses during exercise did not differ. Additionally, a complicated perioperative Fontan course is associated with eventual impaired functional capacity.

INTRODUCTION:

The Fontan operation provides excellent initial palliation for patients with univentricular circulations. Venous return from the body is surgically redirected into the pulmonary arteries without first passing into the single ventricle. In the process, it relieves cyanosis and reduces volume load of the single ventricle (1). Inherent to the hemodynamic characteristics of the Fontan procedure is a restriction in ventricular preload, especially during exercise, due to the lack of ventricular augmentation of pulmonary blood flow (2). This results in a near universal limitation of aerobic capacity (VO_2peak), with the majority of patients being below 80% predicted VO_2peak (3,4). Low aerobic capacity is an important marker of mortality and clinical morbidity in recent studies (5). Nevertheless, a small fraction of Fontan patients have normal aerobic capacity on cardiopulmonary exercise testing ($VO_{2peak} \geq 80\%$ predicted) (6). Very little is known about this group. Their clinical and physiological characteristics provide potential to better understand how more favorable hemodynamic responses may be harnessed in the therapeutic setting. We undertook this study to: [i] characterize the clinical phenotype of Fontan patients with normal exercise capacity; [ii] define differences in submaximal and maximal responses to incremental cardiopulmonary exercise testing between high capacity Fontan (HCF) and the usual Fontan (UF) population who manifest exercise limitation; and [iii] determine possible risk factors that can predict future impaired functional capacity, including how ventricular function affects exercise results in the UF group.

METHODS:

We performed a retrospective chart review of all single ventricle patients with Fontan palliation who underwent a cardiopulmonary exercise test (CPET) at Cincinnati Children's Hospital Medical Center from 2013-2018. HCF patients were defined on the basis of having normal VO_2peak (i.e. $\geq$80% predicted), and were compared with UF patients with low VO_2peak (i.e. <80% predicted) (7). Exclusion criteria included lack of a maximal effort exercise test and incomplete exercise data. Demographic data was obtained from chart review including age, sex, height, weight, medications, age at testing, age at Fontan, physical activity and New York Heart Association (NYHA) functional class. Patients were determined to be physically active by self-report of active engagement in organized sports, regular attendance at fitness classes or moderate to vigorous effort exercise $\geq$4 days a week for 30 minutes or more. Additionally, systemic ventricular systolic function and atrioventricular valve insufficiency was recorded from the echocardiogram report performed within six months of the CPET and was measured by two independent pediatric cardiologists. UF patients were further subdivide into having normal and abnormal ventricular systolic function to further examine the impact of ventricular function on the exercise responses in these more typical Fontan patients. Laboratory results from annual screening labs were recorded, including hemoglobin, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total serum protein, serum albumin, and gamma-glutamyl transferase (GGT). When available, Fontan surgical records and discharge summaries were reviewed and the pre-Fontan oxygen saturation, length of stay, time from Glenn to Fontan, total cardiopulmonary bypass time, weight and height and hospital discharge, and post-surgical complications (including complicated effusions, acquired heart block requiring pacemaker placement, wound infection, surgical revision, catheter based intervention prior to discharge and/or pancreatitis) were recorded.

All patients underwent exercise testing on a stationary cycle ergometer (Lode Corival) using an incremental ramp protocol. The incremental rate was chosen based on the patient's body surface area (BSA) with a goal to reach intolerance in approximately 10 minutes. Cardiopulmonary responses to exercise were assessed breath-by-breath (Ultima CardiO2, MGC Diagnostics). Criteria for a maximal effort exercise test was if 2 of the following 3 criteria were met: respiratory exchange ratio (RER) >1.10; maximal heart rate greater $\geq$85% of the age predicted maximum (220 - age in years); or maximal Rating of Perceived Exertion >18 on a 6-20 scale (8). Predicted VO_2peak was calculated per Wasserman et al and Cooper et al (7, 9). In patients with a body mass index (BMI) < 18 and > 25, the underweight and overweight regression equations were used (7). Percent predicted peak power (in watts, W) was calculated using the prediction equation described by Wasserman et al (7). The chronotropic index (CI) was defined as the heart rate reserve (measured peak heart rate minus resting heart rate) divided by the difference between the predicted peak heart rate and the resting heart rate multiplied by 100; a CI >80% was identified as normal (10).

The anaerobic threshold (AT) was determined non-invasively using the modified V-slope method (11). Physiologic variables during submaximal exercise were then measured at 25% peak power and AT. 25% peak power was below AT for all participants.

As part of the exercise test, all patients underwent pulmonary function testing (PFT) using a metabolic cart (TrueMax 2400; Parvo Medics or Ultima CardiO2; Medgraphics). Each patient performed three tests with the best result used for analysis. Predicted FVC and FEV_1 were based on gender, age and height (12). Maximal voluntary ventilation (MVV) was calculated from FEV_1 x 40 (13). Breathing reserve was defined as follows: (MVV - maximum exercise ventilation)/MVV x 100 (7). Additionally, oxygen saturation by pulse oximetry (SpO_2) at rest and peak exercise were recorded from a forehead probe (Radical 7, Masimo).

Data are presented as mean ± standard deviation. Differences between HCF and UF groups various states of exercise were assessed using an unpaired t-test for normally distributed data and the Wilcoxon Signed-Rank Test for non-normally distributed data where appropriate. Univariate association between normally distributed variables was estimated using the Pearson correlation coefficient. A stepwise multivariable linear regression modeling procedure with 0.1 as the significance level for entry and 0.05 as the significance level for retention in the model was constructed to determine independent predictors of percent predicted VO_2peak. In addition, differences between UF patients with normal and abnormal systolic function as measured by echocardiogram were assessed using an unpaired t-test for normally distributed data and the Wilcoxon Signed-Rank Test for non-normally distributed data where appropriate. All p-values were two-tailed (where applicable) and differences and associations were considered significant when $p < 0.05$. Statistical analyses were performed using JMP®, Version 14 from SAS Institute Inc. (Cary, NC).

RESULTS:

A total of 130 Fontan patients underwent cardiopulmonary exercise testing from 2013-2018 with 112 completing a maximal effort test and included for analysis. A total of 22 patients achieving a VO_2peak >80% of predicted. These 22 patients comprised the HCF group. Baseline characteristics are shown (Table 1). HCF tended ($p=0.06$) to be more predominantly female than the UF group.

The HCF group comprised of the following anatomic diagnoses: tricuspid atresia (n=12, 54%), hypoplastic left heart syndrome (n=3, 14%), double inlet left ventricle (n=4, 18%), pulmonary atresia with intact ventricular septum (n=2, 9%), and double outlet right ventricle with pulmonary atresia (n=1, 5%). This distribution was not significantly different from the UF group: tricuspid atresia (n=35, 39%), hypoplastic left heart syndrome (n=29, 32%), double inlet left ventricle (n=11, 12%), pulmonary atresia with intact ventricular septum (n=7, 8%), double outlet right ventricle with pulmonary atresia (n=4, 5%), transposition of the great arteries with pulmonary stenosis (n=1, 2%), and unbalanced complete atrioventricular defect (n=1, 2%) (Table 1). The type of Fontan connection in the HCF group included extracardiac conduit (n=12, 54%), lateral tunnel (n=8, 36%), classic atriopulmonary connection (n=1, 5%) and unknown (n=1, 5%) (Table 1). Fontan surgical records and detailed discharge summaries following Fontan completion were available for 80 patients (73%). The HCF group had a shorter length of stay (8±2.8 vs 12.4±0.9 days, $p=0.04$), lower body mass index at hospital discharge (14.5±1.3 vs 15.9±2.1 kg/m^2, $p=0.01$) and fewer post-operative complications following the Fontan (8% vs 36%, $p=0.04$) than the UF group (Table 2).

Laboratory findings near the time of the CPET were not significantly different between groups (Table 2). Four (18%) HCF patients had evidence of Fontan associated liver disease as they had splenomegaly, thrombocytopenia and hepatic nodules on imaging as opposed to 33 (37%) of UF ($p=0.08$). There was one patient death and one listed for transplant during the study period, both in the UF group. In the HCF group, 1 patient had a pacemaker/ICD compared to 6 patients in the UF group.

In this cohort, 102 patients had an echocardiogram at the time of their CPET (Table 2). Among HCF, only 1/21 (4.5%) had had ventricular systolic dysfunction classified as mild or greater, as opposed to 21/81 (26.0%) in the UF group ($p=0.03$). There was no significant difference between the degree of systemic atrioventricular valve regurgitation between the groups. Pulmonary function data were available (i.e. good effort given during the test and complete data available) for 95 patients (19 HCF, 76 UF), and there were no significant differences between HCF and UF in the measures evaluated (Table 2). HCF patients tended to have a lower VE/VCO_2 slope (32.1±4.4 vs 34.9±7.3, $p=0.1$). 17 of the 22 HCF patients self-reported their functional capacity as active including regular performance of running, weight lifting, cycling, dance or swimming as opposed to 9 of the 88 UF patients ($p<0.00001$). There was no significant difference in the NYHA functional class between groups.

At 25% peak power HCF patients had lower heart rate (47.4±6.9 vs 50.9±6.6 % predicted, $p=0.03$), yet greater VO_2 (34.3±10.5 vs 26.7±6 % predicted VO_2peak, $p<0.0001$). Heart rate at AT was not different between HCF and UF, yet % predicted VO_2peak remained substantially higher in the HCF group (Table 3; Figure 1). At peak exercise, there remained only a significant difference between the groups in % predicted VO_2peak (Figure 2), which resulted in a normal to above normal O_2Pulse in the HCF group compared to a low O_2Pulse in the UF group (Table 4). To determine whether differences at 25% peak power were associated with the greater absolute power achieved in HCF patients, we evaluated responses at the same absolute power in both groups (40 W). Four UF patients were removed from this analysis because 40W was above AT. In HCF at 40 W, VO_2 (39.9±12.2 vs 32.4±10.4 % predicted VO_2peak, p=0.004) remained significantly greater, without a significant difference in HR (52.1±9 vs 54.2±8 % predicted, p=0.29).

We also compared normal (n=60) and abnormal (n=21) ventricular systolic function on echocardiogram within the UF group. At 25% peak power, there was no significant difference in the VO_2, heart rate or O_2Pulse between UF with normal vs abnormal systolic function. At AT, heart rate was significantly greater in UF with normal vs abnormal systolic function (67.7±11 vs 61.7±11.3 % predicted, p=0.04) (Figure 3). This difference was maintained at peak exercise (84.3±9.2 vs 73.3±15.6 % predicted, p<0.005). VO_2peak was also less in UF with systolic dysfunction (63.7±11 vs 56±14.3 % predicted, p=0.02) (Figure 3).

On univariate analysis, echocardiographic ventricular systolic function at time of CPET, a self-reported active lifestyle, length of stay following Fontan completion, and post-operative complications were associated with % predicted VO_2peak (Table 5). On multivariable analysis, a self-reported active lifestyle and ventricular systolic function at time of CPET were associated with % predicted VO_2peak (Table 5).

DISCUSSION:

Functional capacity, as assessed by exercise testing, is usually severely limited in Fontan patients. The physiological mechanisms of this limitation includes inadequate preload augmentation to the single ventricle (14), inadequate heart rate reserve (15), and poor conditioning with relative skeletal muscle weakness (16). Poor exercise performance is associated with acute cardiovascular decompensation, need for heart transplantation, and early mortality (17). There is evidence however that a few Fontan patients achieve normal exercise performance (6). The most notable study looking at high-performing Fontan patients involved 14 patients all of which had $\geq$ 80% predicted peak VO_2 on CPET and without comparison to Fontan patients with poor exercise capacity (6). Their characteristics however remain poorly understood despite the obvious potential lessons that can be learned from their exercise responses.

This study examined the exercise adaptation of high capacity Fontan patients during ramp incremental cycle ergometer exercise up to the limit of tolerance. We found that 1 in 5 Fontan patients who undergo cardiopulmonary exercise testing have normal exercise capacity for their age, gender, and body habitus. Such high functioning Fontan patients tend to lead physically more active lifestyles, but do not differ in baseline spirometry or the ventilatory response to exercise. While there was a statistically significant difference between the groups in baseline SpO_2 prior to CPET, this is likely not clinically significant as both groups were normal.

We did not find any significant difference in body habitus, gender, systemic right vs. left ventricle, or NYHA functional class between HCF and UF patients. Instead, profound differences were demonstrated in gas exchange patterns at submaximal and peak exercise. In HCF, VO_2 was greater from early to peak exercise, with no difference between groups in the degree of mild chronotropic impairment. This resulted in a greater O_2Pulse in HCF throughout exercise by allowing more time for ventricular filling at slower heart rates as expected based on the Starling mechanism. This is somewhat expected when making a comparison between fit and less fit individuals. This O_2Pulse pattern implies greater stroke volume augmentation and/or peripheral O_2 extraction in the fit Fontan phenotype. However, greater stroke volume is the more likely mechanism given that fractional O_2 extraction is relatively invariant among patients when normalized to % VO_2peak (7) or in total cavopulmonary connection circulations (19). In circulations with a subpulmonary pump, exercise adaptation is facilitated through the effect of the muscle and respiratory pumps augmenting ventricular preload (18). In patients with a Fontan circulation, stroke volume, chronotropy and cardiac augmentation is blunted throughout exercise, beginning at unloaded exercise. We could not demonstrate differences in ventilatory responses or ventilatory efficiency, emphasizing the potential role of the skeletal muscle pump (particularly lower limb muscle mass and strength) in enhancing the exercise response in the HCF group. In addition, the workload during different stages of exercise closely mirrored the oxygen consumption, as expected in comparing fit and less fit individuals.

Shafer et al. demonstrated early blunting of SV augmentation in Fontan patients, but showed that cardiac output can still be increased through the greater heart rate response and increased preload achieved through the skeletal and respiratory muscle pumps (18). Recent work has demonstrated a close correlation between thigh cross-sectional area and relative VO_2peak in Fontan patients (20). It is unclear whether impaired cardiac function in Fontan patients contributes to an under-muscled phenotype, e.g. by impaired nutritive flow and slower oxygenation kinetics during development (21). Nevertheless, it is clear that the muscle strength responds well to exercise training in Fontan patients (in both respiratory and ambulatory muscles) (22), suggesting that physical activity and exercise training are an important target to help maintain physical function and aerobic capacity. This is further supported by self-reported active lifestyle being independently associated with VO_2peak on multivariable analysis.

While describing the exercise adaptation patterns of HCF patients is important in understanding the physiology during exercise in these patients, we also attempted to determine risk factors earlier in life that could explain why certain Fontan patients were able to have more normal exercise capacity. While there were no differences between anatomic or surgical phenotype, we found significant differences between the groups in length of stay following Fontan completion, post-Fontan complications and body mass index at hospital discharge. Additionally, there was a statistically significant correlation between VO_2peak and post-Fontan complications and length of stay following Fontan. This can imply that a difficult postoperative course following the Fontan negatively affects future functional capacity. This is in keeping with previous research demonstrating length of stay as a strong risk factor for worse late outcomes (23). While length of stay was not shown to be associated with VO_2peak on multivariable analysis, this may be a reflection of the overall small numbers in this study.

Ventricular systolic function at the time of CPET appears to be associated with functional capacity. For one, systolic dysfunction was less common in the HCF compared to the UF group. When further stratified, the UF patients with worse systolic function had a significantly lower heart rate response and lower VO_2peak, compared to those UF patients with normal systolic function. On multivariable analysis, ventricular systolic function at the time of exercise testing was associated with VO_2peak. This is the opposite of previously reported findings, yet this is a somewhat intuitive finding which stresses the importance of a healthy myocardium in achieving a high aerobic capacity (24).

We found no significant differences in GGT between the HCF and UF groups. GGT is one of the earliest markers of Fontan associated liver disease and increases primarily in response to congestion (25). Our findings suggest that the physically active and aerobically fit HCF patients had no greater degree of systemic congestion than UF. This is reassuring in that it suggests the physiologic adaptation required for greater physical activity and physical fitness does not necessarily increase the burden of hepatic disease as we and others have previously suggested (26-27). Indeed, the tendency for a lower incidence of liver abnormality in the HCF group is consistent with the protective effect of aerobic fitness and/or activity on liver and inflammatory function, as demonstrated in preclinical studies (28). This study therefore has important implications in highlighting the potential positive role that exercise rehabilitation geared towards skeletal muscle strength improvement may play in cardiovascular functioning during submaximal exercise in Fontan patients.

There were several limitations to this study. This was a retrospective observational study over an extended period of time. The active study group was composed of only 22 patients, which is a relatively small number and limited the sensitivity to detect significant differences among variables between the groups. In addition, activity was self-reported by patients and noted in chart review, which while helpful in showing the health perception of Fontan patients is not as effective as objective measures of daily physical activity such as activity monitors. Addition study using validated surveys and activity monitors should be performed examining the exercise habits of Fontan patients. We did not directly measure stroke volume or cardiac output during exercise, and we did not specifically investigate arterio-venous O_2 concentration differences to identify the role of skeletal muscle O_2 extraction. In this study we also did not endeavor to define differences between the Fontan circulation and normal subjects during submaximal exercise, and we refer the reader to previous studies for that comparison (18-19). Lastly, the determination of ventilatory anaerobic threshold by V-slope is subjective with significant reviewer variability and its clinical use may be limited for these reasons (29).

In conclusion, almost one fifth of Fontan patients can achieve a normal aerobic capacity on a cardiopulmonary exercise test. These HCF patients tended to have a shorter, less complicated immediate postoperative course, implying that difficulties during the post-Fontan period have long-lasting, detrimental effects on cardiorespiratory fitness. These patients also tend to have normal ventricular systolic function, highlighting the importance of myocardial health in maximizing aerobic capacity. In addition, we observed a significantly greater O_2Pulse during submaximal exercise in HCF patients suggesting better preserved SV in this high capacity group. Finally, HCF patients self-reported greater habitual physical activity, which may be due to better exercise tolerance or, more intriguingly, it may be that regular exercise training increases cardiorespiratory fitness, as demonstrated in Fontan rehabilitation studies. Overall, these data imply that stronger skeletal and respiratory muscle pump function may increase pre-load and SV, allowing normal aerobic capacity in these patients. These findings highlight the importance of preserving the mechanisms that allows for stroke volume augmentation throughout the Fontan patient's lifetime.

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FIGURE LEGENDS:

Figure 1: A comparison of the VO_2, heart rate, O_2Pulse, and V_E/VCO_2 slope between the high capacity (orange) and usual (purple) Fontan patients during incremental exercise. HCF (high capacity Fontan), UF (usual Fontan), VO_2 (oxygen uptake), % Pred (percent predicted), O_2Pulse (oxygen pulse), V_E/VCO_2 (ventilatory equivalent for CO_2 output), AT (anaerobic threshold).

Figure 2: Parallel plot demonstrating the progression of percent predicted of VO_2peak during different stages of exercise in individual patients.

Figure 3: Differences at peak exercise between VO_2, O_2Pulse, and heart rate between the high capacity Fontans (orange), usual Fontan with normal systolic function (purple) and usual Fontans with abnormal systolic function (blue). VO_2 (oxygen uptake), O_2Pulse (oxygen pulse), AT (anaerobic threshold).

Table 1

	HCF	**UF**	**p-value**
Number (n)	22	88	
Female Sex (%)	68%	45%	0.06
Age at CPET (yrs)	18.1±6.6	17.3±6.0	0.60
Age at Fontan (yrs)	3.6±1.6	4.0±1.8	0.46
Time from Fontan completion to CPET (yrs)	14.7±6.7	13.6±6	0.49
Height (cm)	159±15	162±10	0.50
Weight (kg)	53.2±18.4	60.7±18.6	0.13
BSA (m^2)	1.52±0.30	1.64±0.30	0.26
Anatomic diagnosis	Tricuspid atresia 54% HLHS 14% Double inlet left ventricle 18% PA/IVS 9% DORV/PA 5%	Tricuspid atresia 39% HLHS 32% Double inlet left ventricle 12% PA/IVS 8% DORV/PA 5% TGA/pulmonary stenosis 2% Unbalanced CAVC 2%	N.S.
Fontan subtype	EC 54% LT 36% AP 5%	EC 68% LT 26% AP 2%	N.S.

	NA 5%	NA 4%	
Systemic LV	77%	63%	0.19
Predominant rhythm	Sinus 84% Ectopic atrial 16%	Sinus 96% Ectopic atrial 4%	0.06
NYHA Class	I 79% II 21%	I 71% II 23% III 1% Unknown 5%	0.35
Active lifestyle	77%	10%	<0.00001
Cardiac medication	ACE inhibitor 42% B-blocker 9% Spironolactone 4% None 58%	ACE inhibitor 59% B-blocker 8% Spironolactone 10% Diuretic 13% Digoxin 3% None 34%	N.S.
Anticoagulation	Aspirin 80% Warfarin 10% None 10%	Aspirin 77% Warfarin 20% None 3%	N.S.
Fontan LOS (days)	8.1±2.8	12.4±8.9	0.04
Pre-Fontan SpO_2 (%)	80.9±4.3	81.4±4.1	0.40
Post-operative complications (%)	8%	36%	0.04

Cardiopulmonary bypass time (min)	91.8±17.5	99.8±30.9	0.20
Time from Glenn to Fontan (yrs)	3.1±1.5	3.2±1.8	0.50
Height at hospital discharge (cm)	97.9±12.1	97.7±10.7	0.90
Weight at hospital discharge (kg)	13.9±3.6	15.3±5.3	0.30
BMI at hospital discharge (kg/m^2)	14.5±1.3	15.9±2.1	0.01

Table 1: Baseline demographics and clinical characteristics of HCF and UF patients at time of exercise test. HCF (high capacity Fontan), UF (usual Fontan), CPET (cardiopulmonary exercise test), yrs (years), BSA (body surface area), cm (centimeters), kg (kilograms), m^2 (meters squared), BMI (body mass index), LV (left ventricle), HLHS (hypoplastic left heart syndrome), PA (pulmonary atresia), IVS (intact ventricular septum), DORV (double outlet right ventricle), TGA (transposition of the great arteries), CAVC (complete atrioventricular canal defect), EC (extracardiac), LT (lateral tunnel), AP (atriopulmonary), NA (unknown), NYHA (New York Heart Association), LOS (length of stay), min (minutes).

	HCF	HCF n	UF	UF n	Normal Values	p-value
Echocardiogram results						
Abnormal ventricular function	1 (mild)	/21	15 (mild), 5 (mod), 1 (sev)	/81		0.03
Mod-sev AV valve insufficiency	2	/21	12	/80		0.52
PFT results						
FVC (% pred)	77.1±15	/19	79.3±15.4	/76	>80	0.59
FEV_1 (% pred)	76.4±15.6	/19	77.1±17.3	/76	>80	0.87
FEV_1/FVC (% pred)	99.9±7.1	/19	96.5±9.8	/76	>80	0.19
Breathing reserve (%)	39.7±10.6	/19	44.8±16.3	/76	>20	0.20
Laboratory results						
Hemoglobin (gm/dL)	16±1.4	/19	15.5±1.6	/65	13-16	0.21
Platelets (K/mcl)	198.3±58.5	/19	191.4±71.9	/65	135-466	0.54
Albumin (gm/dL)	4.4±0.4	/19	4.2±0.6	/64	3.3-4.8	0.22
AST (u/L)	27.2±21.1	/19	27.4±10.7	/69	10-36	0.10
ALT (u/L)	36.9±25.4	/19	39±18	/69	12-49	0.28
Total Protein (mg/dL)	7.5±1.1	/19	7.5±1.4	/62	0.1-11	0.75
GGT (u/L)	62.4±39.7	/16	84.4±55.3	/31	5-55	0.06

Table 2: Resting echocardiographic, spirometric and laboratory results in HCF and UF patients.

HCF (high capacity Fontan), UF (usual Fontan), n (number), Mod (moderate), sev (severe), AV (atrioventricular), FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), % pred (percent predicted), AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (gamma-glutamyl transferase).

	25% peak power			Anaerobic threshold		
	HCF	**UF**	**p-value**	**HCF**	**UF**	**p-value**
HR (min^{-1})	95.7±14.1	103.3±14.5	0.03	138±21	134.5±23.7	0.410
HR (% pred peak)	47.4±6.9	50.9±6.6	0.03	68.3±10	66.3±11	0.350
SBP (mm Hg)	126.8±16.8	130±13.7	0.19	145±23.7	143.7±17.8	0.930
VO_2 (% pred of VO_2peak)	34.3±10.5	26.7±5.9	<0.0001	61.8±9.6	46.8±12	<0.0001
Indexed VO_2 ($ml.kg.min^{-1}$)	12.1±3.1	10.5±2.3	0.006	21.9±18.6	18.6±0.6	0.008
O_2Pulse (% pred of maximum O_2Pulse)	71.3±16.2	53.4±13.5	<0.0001	91.6±16.2	71±16.9	<0.0001
Power output (% pred of peak power)	31.5±10.5	29.2±10.2	0.35	65.5±15.9	42.1±17.8	<0.0001
V_E ($L.min^{-1}$)	17.3±4.0	18.5±4.3	0.23	34.0±7.6	33.2±9.2	0.630
RR (min^{-1})	28.5±11	28.6±7.3	0.43	35.9±11.5	36.6±11	0.780
V_T (L)	7.8±2.8	8.4±2.9	0.48	12.8±5.1	11.8±4.4	0.450
SpO_2 (%)	95.6±2.7	93.6±4	0.03	94.5±4.8	92.7±4.2	0.020
V_E/VCO_2	36.1±6.2	35.3±6.1	0.45	30±5.8	32.5±7.9	0.090

Table 3: Submaximal cardiopulmonary exercise test responses between the high capacity Fontan (HCF) and usual Fontan (UF) patients at 25% peak power and anaerobic threshold. HCF (high capacity Fontan), UF (usual Fontan), RER (respiratory exchange ratio), VO_2 (oxygen uptake), % pred (percent predicted), O_2Pulse (oxygen pulse), V_E (minute ventilation), RR (respiratory rate),

SpO_2 (oxygen saturation by pulse oximetry), SBP (systolic blood pressure), HR (heart rate), V_T (tidal volume), V_E/VCO_2 (ventilatory equivalent), AT (anaerobic threshold).

Table 4

	Units	**High Capacity Fontan (HCF)**	**Usual Fontan (UF)**	**Normal Values**	**p-value**
Peak RER		1.19±0.14	1.18±0.10	>1.10	0.730
Incremental exercise test duration	min	8.7±1.1	8.1±1.4	8-10	0.060
Peak power (% pred)	%	93.1±12.8	66.9±17.9	>80	<0.0001
VO_2peak (% pred)	%	86.1±6.1	61.5±12.2	>80	<0.0001
VO_2peak	$ml.kg.min^{-1}$	30.6±4.8	24.2±5.8	Variable	<0.0001
Peak O_2Pulse (% pred)	%	103.9±9.2	76.8±18.2	>80	<0.0001
Baseline SpO_2	%	97.6±1.8	96.0±2.2	>90	0.001
Peak SpO_2	%	94.9±2.7	93.4±4.1	>90	0.130
SBP	mm Hg	154.1±25.9	157.3±20.2	Variable	0.540
Peak HR	min^{-1}	168.1±13.9	165.4±25	Variable	0.780
Peak HR (% pred)	%	83.3±6.5	81.5±11.6	>85	0.880
Chronotropic index	%	74.3±9.0	69.8±19.1	>80	0.610
$\Delta V_E/\Delta VCO_2$		32.1±4.4	34.9±7.3	Variable	0.100
Peak V_E	$L.min^{-1}$	59.9±20.2	57.6±20.9	Variable	0.630
Peak RR	min^{-1}	48.6±8.9	49.4±11.6	<60	0.750

Table 4: Cardiopulmonary exercise test responses between the high capacity Fontan (HCF) and usual Fontan (UF) patients at peak exercise. HCF (high capacity Fontan), UF (usual Fontan), RER (respiratory exchange ratio), VO_2 (oxygen uptake), % pred (percent predicted), O_2Pulse (oxygen pulse), SpO_2 (oxygen saturation by pulse oximetry), SBP (systolic blood pressure), HR (heart rate), V_E/VCO_2 (ventilatory efficiency), V_E (minute ventilation), RR (respiratory rate).

Univariate analysis	R value	P value
Active lifestyle	0.45	<0.0001
Pre-CPET systolic function	0.29	0.004
Post-operative complications	-0.25	0.030
BMI at hospital discharge	-0.25	0.030
Fontan LOS	-0.22	0.040
Cardiopulmonary bypass time	-0.16	0.190
Weight at hospital discharge	-0.13	0.300
Age at CPET	-0.05	0.600
Time from Glenn to Fontan	-0.01	0.900
Height at hospital discharge	0.003	0.900
Multivariable analysis	**Standardized β coefficient (parameter estimates)**	**P value**
Active lifestyle	0.24 (9.5±4.6)	0.040
Pre-CPET systolic function	-0.20 (-7.4±3.6)	0.040
BMI at hospital discharge	-0.20 (-1.7±0.9)	0.070
Post-operative complications	-0.03 (-1.1±4.9)	0.800
Fontan LOS	-0.02 (-0.03±0.2)	0.900

Table 5: Results of the univariate and multivariable analysis for percent predicted of VO_2peak. VO_2 (oxygen uptake), CPET (cardiopulmonary exercise test), BMI (body mass index), LOS (length of stay).

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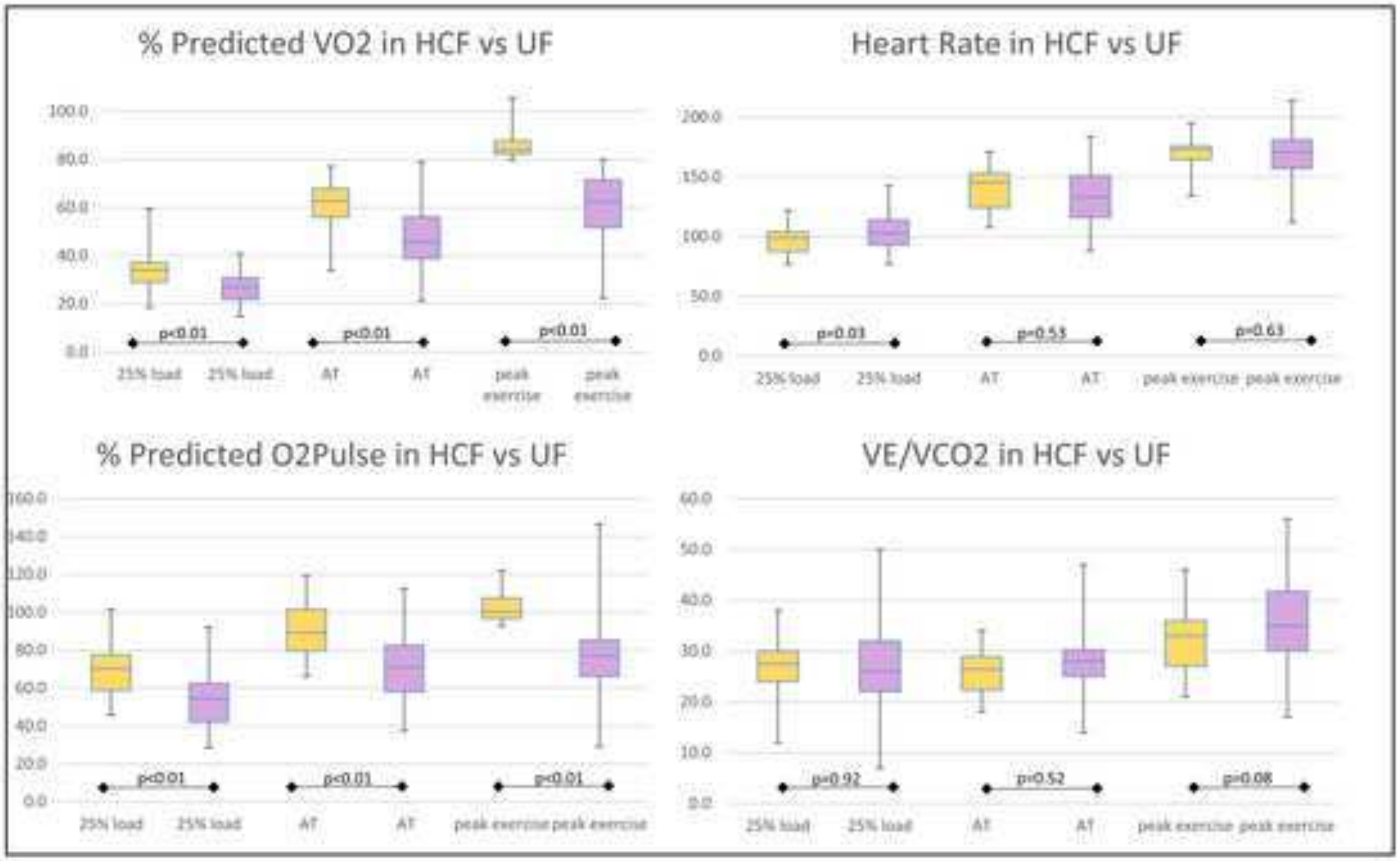

Figure 2

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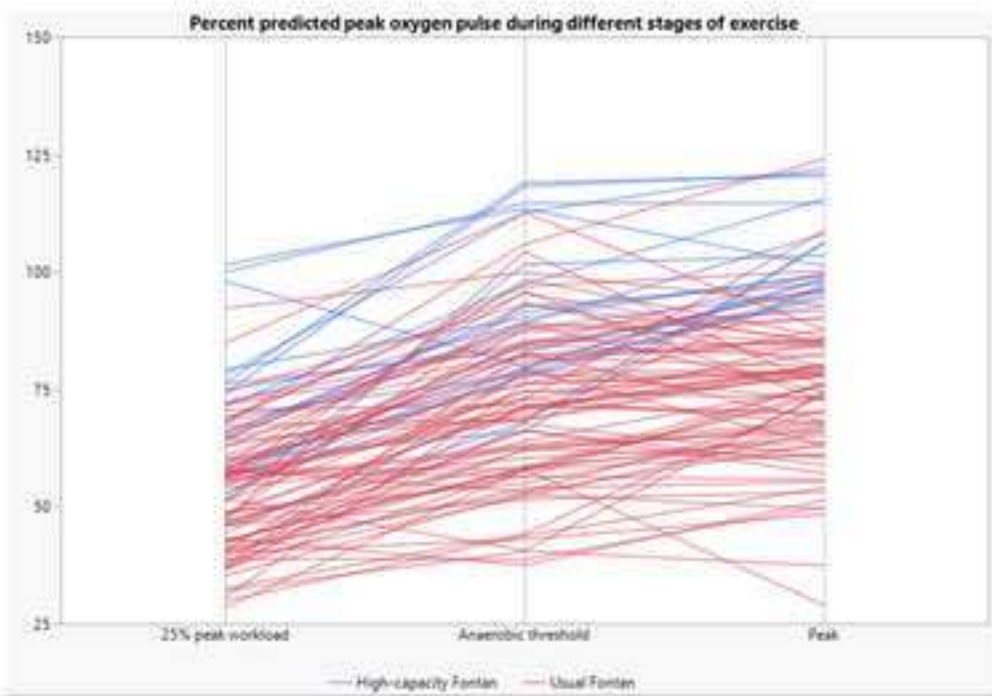

Figure 3

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