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

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Key words: Fontan; exercise capacity; cardiopulmonary exercise testing; oxygen uptake; oxygen pulse; stroke volume.

32 **ABSTRACT: Abstract Word Count: 232**

33 **Background:** Exercise limitation is almost universal among Fontan patients. Identifying unique
34 clinical features in the small fraction of Fontan patients with normal exercise capacity (high
35 capacity Fontan, HCF) provides potential to inform clinical strategies for those with low exercise
36 capacity (usual Fontan, UF). **Methods:** We performed a retrospective chart review of all single
37 ventricle patients palliated with a Fontan operation who underwent incremental cardiopulmonary
38 exercise testing at Cincinnati Children's Hospital Medical Center from 2013-2018. Comparison
39 was between patients with peak oxygen uptake ($VO_2\text{peak}$) $<$ vs $\geq 80\%$ predicted. **Results:**
40 Twenty two of 112 patients were classified as HCF (68% female; 18 ± 7 years). During
41 incremental exercise, $VO_2\text{peak}$ ($86.1 \pm 6.1\%$ vs $62 \pm 12.2\%$ predicted; $p < 0.001$) was greater in
42 HCF vs UF despite similar chronotropic impairment, resulting in a greater oxygen pulse in HCF.
43 Pulmonary function, breathing reserve and V_E/VCO_2 slope were not different between groups.
44 HCF were more likely to self-report exercise ≥ 4 days/week for at least 30 minutes (77% vs 10%,
45 $p < 0.001$), have normal systolic function (95% vs 74%, $p = 0.003$), have fewer post-operative
46 complications (8% vs 36%, $p = 0.04$) and shorter post-Fontan length of stay (8 ± 2.8 vs 12.4 ± 0.9
47 days, $p = 0.04$). **Conclusions:** Approximately 1 in 5 Fontan patients who undergo
48 cardiopulmonary exercise testing have normal exercise capacity despite chronotropic
49 impairment. This implies a better preserved stroke volume, perhaps due to greater muscle pump-
50 mediated preload. Additionally, a complicated perioperative Fontan course is associated with
51 eventual impaired functional capacity.

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54 **Electronic Table of Contents Summary:**

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

62

63 **INTRODUCTION:**

64 The Fontan operation provides excellent initial palliation for patients with univentricular
65 circulations. Venous return from the body is surgically redirected into the pulmonary arteries
66 without first passing into the single ventricle. In the process, it relieves cyanosis and reduces
67 volume load of the single ventricle (1). Inherent to the hemodynamic characteristics of the
68 Fontan procedure is a restriction in ventricular preload, especially during exercise, due to the
69 lack of ventricular augmentation of pulmonary blood flow (2). This results in a near universal
70 limitation of aerobic capacity (VO_{2peak}), with the majority of patients being below 80%
71 predicted VO_{2peak} (3,4). Low aerobic capacity is an important marker of mortality and clinical
72 morbidity in recent studies (5). Nevertheless, a small fraction of Fontan patients have normal
73 aerobic capacity on cardiopulmonary exercise testing ($VO_{2peak} \geq 80\%$ predicted) (6). Very little
74 is known about this group. Their clinical and physiological characteristics provide potential to
75 better understand how more favorable hemodynamic responses may be harnessed in the

76 therapeutic setting. We undertook this study to: [i] characterize the clinical phenotype of Fontan
77 patients with normal exercise capacity; [ii] define differences in submaximal and maximal
78 responses to incremental cardiopulmonary exercise testing between high capacity Fontan (HCF)
79 and the usual Fontan (UF) population who manifest exercise limitation; and [iii] determine
80 possible risk factors that can predict future impaired functional capacity, including how
81 ventricular function affects exercise results in the UF group.

82 **METHODS:**

83 We performed a retrospective chart review of all single ventricle patients with Fontan
84 palliation who underwent a cardiopulmonary exercise test (CPET) at Cincinnati Children's
85 Hospital Medical Center from 2013-2018. HCF patients were defined on the basis of having
86 normal VO_2 peak (i.e. $\geq 80\%$ predicted), and were compared with UF patients with low VO_2 peak
87 (i.e. $< 80\%$ predicted) (7). Exclusion criteria included lack of a maximal effort exercise test and
88 incomplete exercise data. Demographic data was obtained from chart review including age, sex,
89 height, weight, medications, age at testing, age at Fontan, physical activity and New York Heart
90 Association (NYHA) functional class. Patients were determined to be physically active by self-
91 report of active engagement in organized sports, regular attendance at fitness classes or moderate
92 to vigorous effort exercise ≥ 4 days a week for 30 minutes or more. Additionally, systemic
93 ventricular systolic function and atrioventricular valve insufficiency was recorded from the
94 echocardiogram report performed within six months of the CPET and was measured by two
95 independent pediatric cardiologists. UF patients were further subdivide into having normal and
96 abnormal ventricular systolic function to further examine the impact of ventricular function on
97 the exercise responses in these more typical Fontan patients. Laboratory results from annual
98 screening labs were recorded, including hemoglobin, platelets, aspartate aminotransferase (AST),

99 alanine aminotransferase (ALT), total serum protein, serum albumin, and gamma-glutamyl
100 transferase (GGT). When available, Fontan surgical records and discharge summaries were
101 reviewed and the pre-Fontan oxygen saturation, length of stay, time from Glenn to Fontan, total
102 cardiopulmonary bypass time, weight and height and hospital discharge, and post-surgical
103 complications (including complicated effusions, acquired heart block requiring pacemaker
104 placement, wound infection, surgical revision, catheter based intervention prior to discharge
105 and/or pancreatitis) were recorded.

106 All patients underwent exercise testing on a stationary cycle ergometer (Lode Corival)
107 using an incremental ramp protocol. The incremental rate was chosen based on the patient's
108 body surface area (BSA) with a goal to reach intolerance in approximately 10 minutes.
109 Cardiopulmonary responses to exercise were assessed breath-by-breath (Ultima Cardio2, MGC
110 Diagnostics). Criteria for a maximal effort exercise test was if 2 of the following 3 criteria were
111 met: respiratory exchange ratio (RER) >1.10; maximal heart rate greater \geq 85% of the age
112 predicted maximum (220 - age in years); or maximal Rating of Perceived Exertion >18 on a 6-20
113 scale (8). Predicted VO_2 peak was calculated per Wasserman et al and Cooper et al (7, 9). In
114 patients with a body mass index (BMI) < 18 and > 25, the underweight and overweight
115 regression equations were used (7). Percent predicted peak power (in watts, W) was calculated
116 using the prediction equation described by Wasserman et al (7). The chronotropic index (CI)
117 was defined as the heart rate reserve (measured peak heart rate minus resting heart rate) divided
118 by the difference between the predicted peak heart rate and the resting heart rate multiplied by
119 100; a CI >80% was identified as normal (10).

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

123 As part of the exercise test, all patients underwent pulmonary function testing (PFT)
124 using a metabolic cart (TrueMax 2400; Parvo Medics or Ultima CardiO2; Medgraphics). Each
125 patient performed three tests with the best result used for analysis. Predicted FVC and FEV₁
126 were based on gender, age and height (12). Maximal voluntary ventilation (MVV) was
127 calculated from FEV₁ x 40 (13). Breathing reserve was defined as follows: (MVV - maximum
128 exercise ventilation)/MVV x 100 (7). Additionally, oxygen saturation by pulse oximetry (SpO₂)
129 at rest and peak exercise were recorded from a forehead probe (Radical 7, Masimo).

130 Data are presented as mean ± standard deviation. Differences between HCF and UF
131 groups various states of exercise were assessed using an unpaired t-test for normally distributed
132 data and the Wilcoxon Signed-Rank Test for non-normally distributed data where appropriate.
133 Univariate association between normally distributed variables was estimated using the Pearson
134 correlation coefficient. A stepwise multivariable linear regression modeling procedure with 0.1
135 as the significance level for entry and 0.05 as the significance level for retention in the model
136 was constructed to determine independent predictors of percent predicted VO₂peak. In addition,
137 differences between UF patients with normal and abnormal systolic function as measured by
138 echocardiogram were assessed using an unpaired t-test for normally distributed data and the
139 Wilcoxon Signed-Rank Test for non-normally distributed data where appropriate. All p-values
140 were two-tailed (where applicable) and differences and associations were considered significant
141 when p < 0.05. Statistical analyses were performed using JMP®, Version 14 from SAS Institute
142 Inc. (Cary, NC).

143 **RESULTS:**

144 A total of 130 Fontan patients underwent cardiopulmonary exercise testing from 2013-
145 2018 with 112 completing a maximal effort test and included for analysis. A total of 22 patients
146 achieving a VO_2 peak $>80\%$ of predicted. These 22 patients comprised the HCF group. Baseline
147 characteristics are shown (Table 1). HCF tended ($p=0.06$) to be more predominantly female than
148 the UF group.

149 The HCF group comprised of the following anatomic diagnoses: tricuspid atresia ($n=12$,
150 54%), hypoplastic left heart syndrome ($n=3$, 14%), double inlet left ventricle ($n=4$, 18%),
151 pulmonary atresia with intact ventricular septum ($n=2$, 9%), and double outlet right ventricle
152 with pulmonary atresia ($n=1$, 5%). This distribution was not significantly different from the UF
153 group: tricuspid atresia ($n=35$, 39%), hypoplastic left heart syndrome ($n=29$, 32%), double inlet
154 left ventricle ($n=11$, 12%), pulmonary atresia with intact ventricular septum ($n=7$, 8%), double
155 outlet right ventricle with pulmonary atresia ($n=4$, 5%), transposition of the great arteries with
156 pulmonary stenosis ($n=1$, 2%), and unbalanced complete atrioventricular defect ($n=1$, 2%)
157 (Table 1). The type of Fontan connection in the HCF group included extracardiac conduit ($n=12$,
158 54%), lateral tunnel ($n=8$, 36%), classic atriopulmonary connection ($n=1$, 5%) and unknown
159 ($n=1$, 5%) (Table 1). Fontan surgical records and detailed discharge summaries following
160 Fontan completion were available for 80 patients (73%). The HCF group had a shorter length of
161 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
162 15.9 ± 2.1 kg/m^2 , $p=0.01$) and fewer post-operative complications following the Fontan (8% vs
163 36% , $p=0.04$) than the UF group (Table 2).

164 Laboratory findings near the time of the CPET were not significantly different between
165 groups (Table 2). Four (18%) HCF patients had evidence of Fontan associated liver disease as

166 they had splenomegaly, thrombocytopenia and hepatic nodules on imaging as opposed to 33
167 (37%) of UF (p=0.08). There was one patient death and one listed for transplant during the study
168 period, both in the UF group. In the HCF group, 1 patient had a pacemaker/ICD compared to 6
169 patients in the UF group.

170 In this cohort, 102 patients had an echocardiogram at the time of their CPET (Table 2).
171 Among HCF, only 1/21 (4.5%) had had ventricular systolic dysfunction classified as mild or
172 greater, as opposed to 21/81 (26.0%) in the UF group (p=0.03). There was no significant
173 difference between the degree of systemic atrioventricular valve regurgitation between the
174 groups. Pulmonary function data were available (i.e. good effort given during the test and
175 complete data available) for 95 patients (19 HCF, 76 UF), and there were no significant
176 differences between HCF and UF in the measures evaluated (Table 2). HCF patients tended to
177 have a lower VE/VCO₂ slope (32.1±4.4 vs 34.9±7.3, p=0.1). 17 of the 22 HCF patients self-
178 reported their functional capacity as active including regular performance of running, weight
179 lifting, cycling, dance or swimming as opposed to 9 of the 88 UF patients (p<0.00001). There
180 was no significant difference in the NYHA functional class between groups.

181 At 25% peak power HCF patients had lower heart rate (47.4±6.9 vs 50.9±6.6 %
182 predicted, p=0.03), yet greater VO₂ (34.3±10.5 vs 26.7±6 % predicted VO₂peak, p<0.0001).
183 Heart rate at AT was not different between HCF and UF, yet % predicted VO₂peak remained
184 substantially higher in the HCF group (Table 3; Figure 1). At peak exercise, there remained only
185 a significant difference between the groups in % predicted VO₂peak (Figure 2), which resulted in
186 a normal to above normal O₂Pulse in the HCF group compared to a low O₂Pulse in the UF group
187 (Table 4). To determine whether differences at 25% peak power were associated with the greater
188 absolute power achieved in HCF patients, we evaluated responses at the same absolute power in

189 both groups (40 W). Four UF patients were removed from this analysis because 40W was above
190 AT. In HCF at 40 W, VO_2 (39.9 ± 12.2 vs 32.4 ± 10.4 % predicted VO_{2peak} , $p=0.004$) remained
191 significantly greater, without a significant difference in HR (52.1 ± 9 vs 54.2 ± 8 % predicted,
192 $p=0.29$).

193 We also compared normal ($n=60$) and abnormal ($n=21$) ventricular systolic function on
194 echocardiogram within the UF group. At 25% peak power, there was no significant difference in
195 the VO_2 , heart rate or O_2Pulse between UF with normal vs abnormal systolic function. At AT,
196 heart rate was significantly greater in UF with normal vs abnormal systolic function (67.7 ± 11 vs
197 61.7 ± 11.3 % predicted, $p=0.04$) (Figure 3). This difference was maintained at peak exercise
198 (84.3 ± 9.2 vs 73.3 ± 15.6 % predicted, $p<0.005$). VO_{2peak} was also less in UF with systolic
199 dysfunction (63.7 ± 11 vs 56 ± 14.3 % predicted, $p=0.02$) (Figure 3).

200 On univariate analysis, echocardiographic ventricular systolic function at time of CPET,
201 a self-reported active lifestyle, length of stay following Fontan completion, and post-operative
202 complications were associated with % predicted VO_{2peak} (Table 5). On multivariable analysis,
203 a self-reported active lifestyle and ventricular systolic function at time of CPET were associated
204 with % predicted VO_{2peak} (Table 5).

205 **DISCUSSION:**

206 Functional capacity, as assessed by exercise testing, is usually severely limited in Fontan
207 patients. The physiological mechanisms of this limitation includes inadequate preload
208 augmentation to the single ventricle (14), inadequate heart rate reserve (15), and poor
209 conditioning with relative skeletal muscle weakness (16). Poor exercise performance is
210 associated with acute cardiovascular decompensation, need for heart transplantation, and early

211 mortality (17). There is evidence however that a few Fontan patients achieve normal exercise
212 performance (6). The most notable study looking at high-performing Fontan patients involved
213 14 patients all of which had $\geq 80\%$ predicted peak VO_2 on CPET and without comparison to
214 Fontan patients with poor exercise capacity (6). Their characteristics however remain poorly
215 understood despite the obvious potential lessons that can be learned from their exercise
216 responses.

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

224 We did not find any significant difference in body habitus, gender, systemic right vs. left
225 ventricle, or NYHA functional class between HCF and UF patients. Instead, profound
226 differences were demonstrated in gas exchange patterns at submaximal and peak exercise. In
227 HCF, VO_2 was greater from early to peak exercise, with no difference between groups in the
228 degree of mild chronotropic impairment. This resulted in a greater O_2 Pulse in HCF throughout
229 exercise by allowing more time for ventricular filling at slower heart rates as expected based on
230 the Starling mechanism. This is somewhat expected when making a comparison between fit and
231 less fit individuals. This O_2 Pulse pattern implies greater stroke volume augmentation and/or
232 peripheral O_2 extraction in the fit Fontan phenotype. However, greater stroke volume is the
233 more likely mechanism given that fractional O_2 extraction is relatively invariant among patients

234 when normalized to % VO_2peak (7) or in total cavopulmonary connection circulations (19). In
235 circulations with a subpulmonary pump, exercise adaptation is facilitated through the effect of
236 the muscle and respiratory pumps augmenting ventricular preload (18). In patients with a Fontan
237 circulation, stroke volume, chronotropy and cardiac augmentation is blunted throughout exercise,
238 beginning at unloaded exercise. We could not demonstrate differences in ventilatory responses
239 or ventilatory efficiency, emphasizing the potential role of the skeletal muscle pump (particularly
240 lower limb muscle mass and strength) in enhancing the exercise response in the HCF group. In
241 addition, the workload during different stages of exercise closely mirrored the oxygen
242 consumption, as expected in comparing fit and less fit individuals.

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

254 While describing the exercise adaptation patterns of HCF patients is important in
255 understanding the physiology during exercise in these patients, we also attempted to determine
256 risk factors earlier in life that could explain why certain Fontan patients were able to have more

257 normal exercise capacity. While there were no differences between anatomic or surgical
258 phenotype, we found significant differences between the groups in length of stay following
259 Fontan completion, post-Fontan complications and body mass index at hospital discharge.
260 Additionally, there was a statistically significant correlation between VO_2 peak and post-Fontan
261 complications and length of stay following Fontan. This can imply that a difficult postoperative
262 course following the Fontan negatively affects future functional capacity. This is in keeping
263 with previous research demonstrating length of stay as a strong risk factor for worse late
264 outcomes (23). While length of stay was not shown to be associated with VO_2 peak on
265 multivariable analysis, this may be a reflection of the overall small numbers in this study.

266 Ventricular systolic function at the time of CPET appears to be associated with functional
267 capacity. For one, systolic dysfunction was less common in the HCF compared to the UF group.
268 When further stratified, the UF patients with worse systolic function had a significantly lower
269 heart rate response and lower VO_2 peak, compared to those UF patients with normal systolic
270 function. On multivariable analysis, ventricular systolic function at the time of exercise testing
271 was associated with VO_2 peak. This is the opposite of previously reported findings, yet this is a
272 somewhat intuitive finding which stresses the importance of a healthy myocardium in achieving
273 a high aerobic capacity (24).

274 We found no significant differences in GGT between the HCF and UF groups. GGT is
275 one of the earliest markers of Fontan associated liver disease and increases primarily in response
276 to congestion (25). Our findings suggest that the physically active and aerobically fit HCF
277 patients had no greater degree of systemic congestion than UF. This is reassuring in that it
278 suggests the physiologic adaptation required for greater physical activity and physical fitness
279 does not necessarily increase the burden of hepatic disease as we and others have previously

280 suggested (26-27). Indeed, the tendency for a lower incidence of liver abnormality in the HCF
281 group is consistent with the protective effect of aerobic fitness and/or activity on liver and
282 inflammatory function, as demonstrated in preclinical studies (28). This study therefore has
283 important implications in highlighting the potential positive role that exercise rehabilitation
284 geared towards skeletal muscle strength improvement may play in cardiovascular functioning
285 during submaximal exercise in Fontan patients.

286 There were several limitations to this study. This was a retrospective observational study
287 over an extended period of time. The active study group was composed of only 22 patients,
288 which is a relatively small number and limited the sensitivity to detect significant differences
289 among variables between the groups. In addition, activity was self-reported by patients and
290 noted in chart review, which while helpful in showing the health perception of Fontan patients is
291 not as effective as objective measures of daily physical activity such as activity monitors.
292 Addition study using validated surveys and activity monitors should be performed examining the
293 exercise habits of Fontan patients. We did not directly measure stroke volume or cardiac output
294 during exercise, and we did not specifically investigate arterio-venous O₂ concentration
295 differences to identify the role of skeletal muscle O₂ extraction. In this study we also did not
296 endeavor to define differences between the Fontan circulation and normal subjects during
297 submaximal exercise, and we refer the reader to previous studies for that comparison (18-19).
298 Lastly, the determination of ventilatory anaerobic threshold by V-slope is subjective with
299 significant reviewer variability and its clinical use may be limited for these reasons (29).

300 In conclusion, almost one fifth of Fontan patients can achieve a normal aerobic capacity
301 on a cardiopulmonary exercise test. These HCF patients tended to have a shorter, less
302 complicated immediate postoperative course, implying that difficulties during the post-Fontan

303 period have long-lasting, detrimental effects on cardiorespiratory fitness. These patients also
304 tend to have normal ventricular systolic function, highlighting the importance of myocardial
305 health in maximizing aerobic capacity. In addition, we observed a significantly greater O₂Pulse
306 during submaximal exercise in HCF patients suggesting better preserved SV in this high capacity
307 group. Finally, HCF patients self-reported greater habitual physical activity, which may be due
308 to better exercise tolerance or, more intriguingly, it may be that regular exercise training
309 increases cardiorespiratory fitness, as demonstrated in Fontan rehabilitation studies. Overall,
310 these data imply that stronger skeletal and respiratory muscle pump function may increase pre-
311 load and SV, allowing normal aerobic capacity in these patients. These findings highlight the
312 importance of preserving the mechanisms that allows for stroke volume augmentation
313 throughout the Fontan patient's lifetime.

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408 **FIGURE LEGENDS:**

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

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

416

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

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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), m² (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), FEV₁ (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 ₂ peak)	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 ₂ Pulse (% pred of maximum O ₂ Pulse)	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), VO₂ (oxygen uptake), % pred (percent predicted), O₂Pulse (oxygen pulse), V_E (minute ventilation), RR (respiratory rate),

SpO₂ (oxygen saturation by pulse oximetry), SBP (systolic blood pressure), HR (heart rate), V_T (tidal volume), V_E/VCO₂ (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 ₂ peak (% pred)	%	86.1±6.1	61.5±12.2	>80	<0.0001
VO ₂ peak	ml.kg.min ⁻¹	30.6±4.8	24.2±5.8	Variable	<0.0001
Peak O ₂ Pulse (% 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
ΔV _E /ΔVCO 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_2 Pulse (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 \pm 4.6)	0.040
Pre-CPET systolic function	-0.20 (-7.4 \pm 3.6)	0.040
BMI at hospital discharge	-0.20 (-1.7 \pm 0.9)	0.070
Post-operative complications	-0.03 (-1.1 \pm 4.9)	0.800
Fontan LOS	-0.02 (-0.03 \pm 0.2)	0.900

Table 5: Results of the univariate and multivariable analysis for percent predicted of VO₂peak.

VO₂ (oxygen uptake), CPET (cardiopulmonary exercise test), BMI (body mass index), LOS (length of stay).





