Published in final edited form as:

Cardiol Young. 2010 December ; 20(6): 593–601. doi:10.1017/S1047951109990357.

Living at an altitude adversely affects exercise capacity in Fontan patients

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Abstract

Background—Data assessing the effect of altitude on Fontan haemodynamics are limited to experimental models and case reports. Both suggest a detrimental impact. This study describes exercise performance in patients with Fontan circulation and matched controls at a low altitude versus at sea level. We sought to assess the impact of increasing altitude on functional capacity in patients with Fontan palliation.

Methods—A retrospective review of 22 patients at low altitude (1602 metres) and 119 patients at sea level with Fontan circulation, as well as age-, gender-, and altitude-matched controls, underwent maximal cardiopulmonary exercise testing. Linear regression models were created to determine the influence of altitude on differences in exercise variables between Fontan patients and their matched controls.

Results—Peak oxygen consumption was 28.4 millilitres per kilogram per minute (72% predicted) for the sea-level cohort and 24.2 millilitres per kilogram per minute (63% predicted) for the moderate altitude cohort. The matched case–control differences for patients at moderate altitude were greater for peak oxygen consumption (–29% against –13%, $p = 0.04$), anaerobic threshold (–36% against –5%, $p = 0.001$), and oxygen pulse (–35% against –18%, $p = 0.007$) when compared with patients living at sea level. When compared to institution-matched controls, the same parameters fell by 3%, 8.9%, and 4.2%, respectively, for each increase of 1000 feet in residential altitude ($p = 0.03$, $p = 0.001$, and $p = 0.05$, respectively).

Conclusions—Patients with Fontan circulation at a higher altitude have impairment in aerobic capacity when compared with patients at sea level. Reduction in exercise capacity is associated with a reduction in stroke volume, likely related to increased pulmonary vascular resistance.

Keywords

Elevation; oxygen consumption; anaerobic threshold

Since 1971 the Fontan procedure has been routinely performed for the palliation of patients with single ventricle anatomy.¹ As the procedure results in passive systemic venous return into the pulmonary circulation, low pulmonary vascular resistance is essential.²

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The authors declare that they have no conflict of interest.

Pulmonary vascular resistance rises with increasing elevation gain³ secondary to the lower ambient oxygen concentration. Even a modest gain in altitude has been shown to negatively impact on immediate post-operative Fontan haemodynamics.⁴ The effect of altitude on long-term Fontan functional performance is unknown. Chronic exposure to lower ambient oxygen levels may adversely affect Fontan haemodynamics resulting in exercise intolerance, objective impairment in aerobic capacity, and subsequent development of earlier-onset cardiac failure. We sought to assess the effect of increasing altitude on exercise tolerance in patients who had undergone Fontan palliation.

Materials and methods

Patient population

This retrospective, matched case-control study enrolled all patients who underwent a Fontan procedure and subsequently completed a cardiopulmonary exercise test at one of two paediatric institutions: The Children's Hospital (Denver, Colorado, United States of America), elevation 1602 metres (5256 feet) and The Hospital for Sick Children (Toronto, Ontario, Canada), elevation 120 metres (394 feet). Fontan patients were matched by age, gender, and type of exercise protocol with institution-specific controls. Control patients underwent cardiopulmonary exercise testing to rule out arrhythmia or other cardiac pathology. In all instances, controls were deemed to have no evidence of cardiac or pulmonary pathology by history, examination, and cardiopulmonary stress testing. The study was approved by the research ethics boards at both institutions. Requirement for individual consent was waived for the retrospective data analysis.

Methodology

Patient charts were reviewed and demographic and cardiopulmonary exercise variables were recorded. Gender, age at exercise test, weight, height, body surface area, and body mass index were collected at the time of testing for all Fontan patients and their matched controls (Table 1). Underlying anatomy for Fontan patients, along with type of Fontan procedure, recent systolic function by echocardiography, Holter monitor results, and current medications were also recorded. Altitude at which the patients were living was established from the patient's zip code/postal code at the time of exercise testing.

Exercise protocol

Cardiopulmonary exercise testing was performed on patients whose age and maturity allowed for compliance with testing instructions (generally at the age of 7 years and above). Routine data from these tests were analysed.⁵ Each patient underwent baseline spirometry followed by a progressive cardiopulmonary exercise test with continuous monitoring of 12-lead electrocardiogram, ventilation, oxygen saturation, gas exchange, and blood pressure. No patient had significant obstructive or restrictive lung disease on baseline spirometry, defined as 1-second forced expiratory volume, forced vital capacity or forced expiratory flow from 25–75% of vital capacity less than 70% predicted. The patients were encouraged to exercise to the point of exhaustion. Symptoms were recorded. Exercise testing was performed on a programmable ergometer, with respiratory data collected and analysed on a breath-by-breath basis and averaged for a 20-second period using a metabolic cart. Tests deemed suitable for analyses were those tests considered to reflect maximal effort based on an achieved respiratory quotient of greater than 1.0.⁶ The parameters of exercise performance such as peak oxygen consumption (millilitres per minute and millilitres per kilogram per minute), ventilatory anaerobic threshold (millilitres per kilogram per minute), ventilatory efficiency as measured by the rate of rise in ventilation per amount of expired carbon dioxide below the respiratory compensation point, oxygen pulse (millilitres per beat), defined as oxygen consumption divided by heart rate, resting and peak heart rate (beats per

minute), heart rate reserve (peak predicted heart rate of 210 minus age, minus peak heart rate attained), resting and peak systolic and diastolic blood pressures, oxygen saturation at rest and at peak exercise, and percentage of predicted peak oxygen consumption using previously established normal values were measured.⁵ Peak oxygen consumption was taken as the maximum oxygen consumption value obtained during the test. Anaerobic threshold was determined by using the “V-slope” method.⁶ The change in ventilation per amount of expired carbon dioxide was calculated from baseline up until the respiratory compensation point. This parameter is increased by abnormalities of pulmonary perfusion resulting in a ventilation–perfusion mismatch, and by systolic or diastolic ventricular dysfunction resulting in increased ventricular filling pressures.⁷ Oxygen pulse was measured and considered a surrogate measure of stroke volume, and arterio-venous oxygen difference and has been found to be a powerful predictor of outcome in adults with cardiac failure.^{8,9} Blood pressure was obtained every 2 minutes during exercise and recovery.

Statistical analysis

Data are presented as means with standard deviation, median with minimum and maximum and frequencies as appropriate. Demographic and medical differences between sea-level and altitude cohorts were assessed using unpaired *t*-tests with Satterthwaite correction as appropriate and Fisher’s exact tests (Table 2).

Fontan patients–control match

Fontan patients were matched with controls having neither cardiac structural defects nor restricted exercise capacity based on location, gender, and age. Fontan patients and controls were separately sorted by location and gender and then listed according to ascending age; position in their respective list determined the pairs. For the sea-level cohort, 119 matched pairs were created. For the higher altitude cohort, 22 matched pairs were created.

Fontan patient–control relative difference in exercise test results

For each exercise test result, the difference in score between Fontan patients and their control was divided by the result for the control patient. This value, the relative difference between the Fontan patient and his/her control, was used as the dependent variable in all regression models.

Selection of covariates

Variables potentially associated with the relative differences for each exercise test result between Fontan patients and their controls were sought from gender, diagnosis, dominant ventricle, transposition of the great arteries, type of Fontan surgery, ventricular function, pacemaker, medication, Holter results, age at exercise test, age at Fontan surgery, height, weight, body surface area, body mass index and control’s age at exercise test, body surface area, and body mass index through a bootstrap linear regression model (1000 samples). Variables or clusters of similar variables selected in 50% or more of the samples were considered important covariates. The procedure was repeated separately for all results and identified covariates were thereafter included in all regression models for this specific result.

Associations between Fontan patient–control relative difference and location

The association between relative Fontan–control differences on exercise test scores and patient’s location, adjusted for previously identified covariates, was tested in multivariable linear regression models (Table 3). Backward selection of variables (with the exception of patient location) was used to obtain the final model.

For each model, we reported the parameter estimate for patient location and standard error. The parameter estimate represents the estimated change in Fontan–control relative difference associated with patient location when accounting for covariates. In order to provide a more clinically relevant measure of the differences between Fontan patients living at sea level and those living at an altitude, the regression equations obtained above were solved and the test patients were created for each location. These calculated values represent the estimated average relative difference (adjusted for important covariates) between a Fontan patient and his/her matched control if he/she lives at sea level versus at altitude.

Altitude–sea-level Fontan patients match

As there are many factors potentially affecting Fontan patients' exercise capacity, a subgroup of Fontan patients from sea level were matched to Fontan patients from an altitude. Fontan patients were matched by gender, age, anatomy, transposition of the great arteries, type of Fontan connection, and age at Fontan surgery. All 22 Fontan patients from an altitude were successfully matched on all six criteria to sea-level Fontan patients.

Associations between Fontan patient–control relative difference and location restricted for matched Fontan patients

The analysis previously described was reported for a sub-analysis using the 22 sea-level Fontan patients (and their respective controls) that were matched to the 22 altitude patients (Table 4). In this sub-analysis, methodology – covariate selection, modelling, and solving of regression equations – was identical with the exception that covariate selection excluded factors on which Fontan patients were matched.

Effect of altitude on Fontan–control relative differences

A final sub-analysis replaced location, sea level or altitude, in regression models by altitude at which the patient lived in order to assess the change in Fontan–control relative difference for each increase of 1000 feet in altitude (Table 5). All statistical analyses were performed using SAS statistical software v9.1 (SAS Institute, Cary, North Carolina, United States of America).

Results

Enrollment and demographics

The study population consisted of a total of 282 patients, 238 (82%) from the sea-level institution (119 Fontan–control pairs) and 44 (18%) from the moderate altitude institution (22 Fontan–control pairs; Table 1). The Toronto patients were somewhat younger than the Denver patients at the time of the exercise test (mean 12 versus 15 years old, $p = 0.05$), but there were no other demographic differences.

Underlying anatomical diagnosis differed between the two institutional cohorts with tricuspid atresia being the most prevalent anatomy in the Denver cohort (73%) while the Toronto cohort was evenly split among a variety of anatomical diagnoses (Table 1). In the light of the differences in the underlying diagnoses, ventricular morphology was significantly different between the two patient cohorts. The type of Fontan connection, however, was similar between the two groups with the same percentage of patients undergoing extracardiac conduit, atriopulmonary connection and lateral tunnel connection (Table 1). Medical therapy did not differ between the two groups with the exception being that patients in the sea-level cohort were significantly more likely to be on angiotensin-converting enzyme inhibitors for the prevention of ventricular dysfunction (79% versus 36%, $p < 0.001$). This difference in medical therapy reflects different institutional practices, and at the dosages used, has been shown to have no significant impact on exercise blood

pressure or exercise performance.¹⁰ The patients' systolic function by echocardiography at the time of exercise test was similar between cohorts. The patients from the sea-level cohort lived at a mean altitude of 195.9 metres, while the other cohort lived at a mean altitude of 1478 metres.

As expected, the matched control patients from the sea-level cohort were younger at exercise testing than those from Denver (mean 13 versus 15 years old, $p = 0.02$). Both control groups were comparable in gender differences and body mass index.

Exercise test results

Raw exercise test results for all patients included in this study by patient centre (Toronto or Denver) and by physiology (Fontan or control) along with the paired differences by institutions are presented in Table 2. A total of 119 pairs were created for the sea-level cohort and 22 pairs were created for the moderate altitude cohort. The average difference in age between the Fontan patients and the matched control was a median of 0.2 years with no significant differences between institutions.

Fontan patients versus altitude-matched controls

Fontan patients from both institutions had significant impairment in most exercise test variables when compared to their institution-matched controls including reduced peak oxygen consumption and ventilatory anaerobic threshold (Table 2). Chronotropic incompetence has been previously reported in the Fontan patient,¹¹ and in keeping with this finding, we noted a reduced peak heart rate in both Fontan patient cohorts. Both Fontan groups had an impaired stroke volume (oxygen pulse) response to exercise, inefficient ventilation and a significant reduction in oxygen saturation at rest and with exertion. Despite the absence of clinically significant lung disease, Fontan patients maintained a higher respiratory rate at rest. In addition, the sea level Fontan cohort had a significantly higher respiratory rate with exercise compared with matched controls. This was not seen in the higher altitude cohort as tachypnea was present in both Fontan and control patients. Exercise at altitude is associated with a greater respiratory rate¹² and presumably a ceiling effect occurred wherein Fontan patients could not increase their respiratory rate to any greater degree due to the metabolic cost. Despite comparable respiratory rates, Fontan patients at altitude had much greater physiologic dead space when compared with altitude-matched controls (0.19 against 0.14; $p = 0.001$). This is thought to reflect abnormalities of ventilation-perfusion matching.⁷ At higher altitudes, hypoxia-induced pulmonary vasoconstriction further aggravates underlying ventilation-perfusion mismatch.

Fontan patients at sea level and at moderate altitude

When comparing the raw exercise test variables between the two Fontan cohorts (Table 2), patients at an altitude had a significantly lower peak oxygen consumption, ventilatory anaerobic threshold, rest and peak oxygen saturation, and oxygen pulse. In addition, Fontan patients at an altitude had greater systolic and diastolic blood pressure at rest and with exertion. Rise in altitude is associated with increasing systemic vascular resistance¹³, which may adversely affect Fontan haemodynamics¹⁴ and may have accounted for the further compromise in stroke volume seen in the altitude cohort.

Control patients at sea level versus moderate altitude

Despite a comparable peak oxygen consumption and peak heart rate, healthy controls at altitude had earlier onset of anaerobiosis, presumably secondary to insufficient oxygen delivery to muscle cells to meet metabolic demand. In this regard, oxygen saturations were significantly lower at rest and with exercise when compared with healthy sea-level cohorts.

As noted in other populations residing at a higher altitude, these patients had greater systolic and diastolic blood pressure with exercise, and a greater respiratory rate with exercise.¹³ Tachypnea likely occurred secondary to greater lactate production in light of the earlier onset of anaerobiosis. These patients had an impaired rise in stroke volume with exercise, which may have occurred secondary to the greater increase in systemic vascular resistance seen at higher elevations.¹³

Comparison of Fontan–control-matched paired differences between Toronto and Denver

Comparisons of paired differences between Fontan patients and their respective controls across institutions, adjusted for covariates identified from bootstrap re-sampling (in most models body surface area and medication), are detailed in Table 3. Fontan patients followed at sea level were found to have peak oxygen consumption and ventilatory anaerobic threshold on average 13% and 5% lower than their matched controls, respectively. Fontan patients living at moderate altitude were found to have peak oxygen consumption and ventilatory anaerobic threshold on average 29% and 36% lower than their matched controls ($p = 0.04$ and 0.001 , respectively). Living at lower altitude was associated with peak oxygen pulse on average 18% lower than matched controls while higher altitude was associated with peak oxygen pulse on average 35% lower than matched controls ($p = 0.007$). Results for the sub-populations of Toronto/Denver Fontan patients matched for gender, age, anatomy, transposition of the great arteries, type of Fontan connection, and age at Fontan surgery are described in Table 4. No differences were found between the analysis for the entire cohort and the analysis for the Fontan-matched cohort indicating that observed differences between the two centres were not due to physiological differences resulting from Fontan type, anatomy, demographics, or patient age.

Effect of altitude on matched Fontan–control differences

When patient location was replaced by the altitude at which the patient resided, it was found, after adjustment for appropriate covariates, that altitude had a dose-dependent influence on a number of the exercise test results (Table 5). Peak oxygen consumption was lowered by 3% and ventilatory anaerobic threshold was lowered on average by 9% versus matched controls for each increase of 1000 feet in altitude ($p = 0.03$ and 0.001 respectively). Oxygen pulse had an average decrease of 4.2% relative to controls for each increase of 1000 feet in altitude ($p = 0.05$).

Discussion

Long-term survival following the Fontan procedure has greatly improved over the past several decades with most recent 10-year survival estimates of 85%.¹⁵ The impact of environmental elevation has historically not been considered when assessing patient suitability for Fontan palliation. While 30-day hospital mortality following Fontan palliation at altitude is comparable to sea level,¹⁶ long-term impact of altitude on outcome has not previously been addressed. Case reports have documented acute decompensation of sea-level Fontan patients travelling to moderate altitude¹⁷ but the clinical effect of chronic exposure to a hypoxic environment is unknown.

Exercise capacity in Fontan patients living near sea level has been well studied. Aerobic capacity at sea level is reduced in these patients. The source of functional impairment is a reduction in stroke volume, which may be due to impaired flow dynamics through the Fontan circuit, elevated pulmonary vascular resistance, impaired ventricular systolic contraction, and impaired diastolic relaxation.^{11,18–19} In addition, high altitude simulations have shown a further reduction in exercise performance in sea-level Fontan patients placed in a hypobaric chamber.²⁰

The unanswered question plaguing cardiologists practicing at higher elevations has been whether chronic exposure to altitude-related hypoxia has a detrimental impact on Fontan haemodynamics and if so, what is the magnitude of this effect? Should the Fontan procedure not be performed in patients residing above a certain altitude, and should patients with a “failing Fontan” be counselled to move to a lower altitude? It has been shown that young children with a Fontan circuit, living at moderate altitude, have impaired growth velocity.²¹ These data suggest that the alteration in haemodynamics occurring in a relatively hypoxic environment is not without clinical effect.

In this study, we have shown the impact of altitude on exercise capacity in both healthy children and children with a Fontan circuit. Fontan patients experience a disproportionate degree of exercise impairment when living at higher altitude. The aetiology of the impairment appears to be due to reduction in stroke volume. Reduction in stroke volume leads to inadequate oxygen delivery to the muscles therefore requiring anaerobic metabolism at lower workloads. Our model showed a direct correlation between increased altitude and decreased oxygen pulse. Because pulmonary blood flow is not driven by the ventricle in the Fontan patient, but rather, occurs by passive flow, a limited increase in pulmonary blood flow occurs with exercise.²² As altitude increases, pulmonary vascular resistance rises, further compromising oxygen delivery, ventilation–perfusion matching, and forward flow. The situation is further aggravated by the increase in sympathetic tone that accompanies elevation gain. The rise in systemic vascular resistance that ensues further hinders cardiac output.

Exercise capacity, in particular peak oxygen consumption and oxygen pulse, has been shown to be a strong correlate of clinical outcome in many different populations.²³ While there is insufficient long-term data on patients with Fontan palliation living at higher altitude, the extent of exercise impairment seen on intermediate follow-up does not bode well for long-term prognosis.

This study is subject to several limitations. As the study was retrospective in nature, it was not possible to control for all potentially confounding variables. This was taken into account when the statistical analysis was performed. Clinical practice in Denver has been, in part, dictated by the fact that Fontan patients have increased long-term morbidity at altitude. Thus, patient numbers are relatively small in the higher altitude cohort. Historically, patients with hypoplastic left cardiac syndrome more frequently underwent orthotopic cardiac transplantation in Denver, accounting for some of the difference in patient numbers and ventricular morphology. While the elevation of Denver (1602 metres) qualifies as only low altitude by altitude medicine standards, it is the highest centre in North America where the Fontan procedure is routinely performed. Results may have been more conclusive if patients were drawn from higher altitude. Controls were taken from a group of patients with cardiac symptoms and this may not reflect the general population. However, oxygen consumption in this group was near normal. If the oxygen consumption in this group were artefactually reduced, it would only lessen the discrepancy between this group and the Fontan group.

In summary, exercise capacity is impaired in Fontan patients when compared with matched controls. A further reduction in exercise capacity is seen in Fontan patients living at higher elevations. For every 305 metres (1000 feet) rise in elevation gain, there is a significant fall in stroke volume resulting in a significant decline in peak oxygen consumption.

In Denver and other centres located well above sea-level, patients are cautioned as to the detrimental effect of altitude on Fontan function. They are encouraged to avoid travel to surrounding areas of higher altitude. In the face of clinical deterioration, families are counselled to consider relocation to a city at sea level.

Acknowledgments

The authors thank the Pediatric Heart Network for their review and support of this manuscript. This study is supported by the National Institutes of Health (McCrindle U01 HL068288).

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Table 1

Subject demographics and medical history.

Fontan physiology	Toronto (119 patients)	Denver (22 patients)	p
Gender (female; %)	45/119 (38)	6/22 (27)	0.47
Altitude (feet)	643 ± 202	4850 ± 1216	<0.001
Age at exercise test (years)	12 ± 3	15 ± 6	0.05
Weight (kg)	43 ± 18	47 ± 17	0.31
Height (cm)	147 ± 18	153 ± 19	0.16
Body surface area (m ²)	1.3 ± 0.3	1.4 ± 0.3	0.21
Body mass index (kg/m ²)	19 ± 4.0	19 ± 3	0.69
Age at Fontan surgery (years)	4 ± 2	4 ± 3	0.44
Diagnosis			
Tricuspid atresia (%)	28/119 (24)	16/22 (73)	<0.001
Double inlet left ventricle (%)	24/119 (20)	2/22 (9)	<0.001
Pulmonary atresia (%)	28/119 (24)	3/22 (14)	<0.001
Hypoplastic left cardiac syndrome (%)	16/119 (13)	1/22 (4)	<0.001
Other (%)	23/119 (19)	0/22 (0)	<0.001
Dominant ventricle			
Left (%)	76/119 (64)	21/22 (96)	0.002
Right (%)	40/119 (34)	1/22 (4)	0.004
Neither (%)	3/119 (2)	0/22 (0)	1.00
Transposed great arteries (%)	14/119 (12)	5/22 (23)	0.18
Fontan connection			
Atriopulmonary connection (%)	30/119 (25)	7/22 (32)	0.60
Lateral tunnel (%)	43/119 (37)	7/22 (32)	0.81
Extracardiac conduit (%)	43/119 (36)	8/22 (36)	1.00
Bjork modification (%)	3/119 (2)	0/22 (0)	1.00
Reduced systolic ventricular function (%)	22/119 (18)	3/22 (14)	0.77
Atrioventricular valve regurgitation			
None (%)	25/116 (22)	5/22 (23)	1.00
Trace (%)	34/116 (29)	9/22 (41)	0.32

Fontan physiology	Toronto (119 patients)	Denver (22 patients)	p
Mild (%)	47/116 (40)	6/22 (27)	0.34
Moderate (%)	10/116 (9)	2/22 (9)	1.00
Atrial tachycardia on Holter (%)	10/119 (8)	4/22 (18)	0.24
Other arrhythmia on Holter (%)	7/119 (6)	2/22 (9)	0.63
Pacemaker (%)	9/119 (8)	3/22 (14)	0.40
Medication			
ACE inhibitors (%)	66/84 (79)	8/22 (36)	<0.001
Anti-thrombotic/aspirin (%)	25/84 (30)	10/22 (45)	0.21
Anti-arrhythmic (%)	17/84 (20)	7/22 (32)	0.27
β -Blockers (%)	5/84 (6)	1/22 (5)	1.00
Diuretics (%)	6/84 (7)	0/22 (0)	0.34
Calcium channels blockers (%)	0/84 (0)	1/22 (5)	0.21
Controls			
Gender (female; %)	45/119 (38)	6/22 (27)	0.63
Age at exercise test (years)	13 $\pm$ 3	15 $\pm$ 5	0.02
Weight (kg)	53 $\pm$ 18	49 $\pm$ 17	0.38
Height (cm)	159 $\pm$ 17	160 $\pm$ 20	0.74
Body surface area (m ²)	1.5 $\pm$ 0.3	1.5 $\pm$ 0.4	0.82
Body mass index (kg/m ²)	21 $\pm$ 5	19 $\pm$ 3	0.15

ACE = angiotensin converting enzyme

Table 2

Exercise test results comparing Fontan patients and controls between institutions.

Exercise test result	Toronto (119 pairs)			Denver (22 pairs)		Fontans		Controls	
	Fontan	Control	p	Fontan	Control	p	p	p	p
Peak VO ₂ (ml/kg/min)	28.4 ± 6.4	5.9 ± 9.4	<0.001	24.2 ± 5.1	36.7 ± 4.0	<0.001	0.005	0.005	0.97
VAT (ml/kg/min)	25.2 ± 6.1	29.3 ± 7.9	<0.001	14.7 ± 3.6	25.5 ± 4.6	<0.001	<0.001	<0.001	0.02
Peak systolic BP (mmHg)	135 ± 18	150 ± 22	<0.001	155 ± 33	172 ± 30	0.07	<0.001	<0.001	0.001
Peak diastolic BP (mmHg)	64 ± 8	62 ± 7	0.03	86 ± 21	79 ± 15	0.21	<0.001	<0.001	<0.001
Peak HR (bpm)	159 ± 22	181 ± 19	<0.001	164 ± 23	190 ± 10	<0.001	0.29	0.04	0.04
O ₂ pulse (VO ₂ /HR)	8.1 ± 3.4	10.9 ± 4.4	<0.001	6.8 ± 2.0	9.9 ± 3.5	<0.001	0.02	0.001	0.001
ΔVE/ΔVCO ₂	42.3 ± 11.0	31.9 ± 8.3	<0.001	42.1 ± 4.8	33.0 ± 4.5	<0.001	0.89	0.13	0.13
O ₂ saturation at rest (%)	96 ± 3	100 ± 1	<0.001	94 ± 3.0	98 ± 2.0	<0.001	0.01	0.001	0.001
O ₂ saturation at peak (%)	93 ± 5	99 ± 4	<0.001	88 ± 7.0	95 ± 3.0	0.001	0.001	0.001	0.001
Respiratory rate at rest	22 ± 7	19 ± 6	0.001	20 ± 6.0	17 ± 5.0	0.05	0.13	0.24	0.24
Respiratory rate at peak	54 ± 12	49 ± 10	0.003	53 ± 11	53 ± 13	0.94	0.83	0.006	0.006
Percentage of VO ₂ max	72 ± 20	91 ± 30	<0.0001	63 ± 26	92 ± 22	<0.0001	<0.0001	NS	NS

AT = anaerobic threshold; BP = blood pressure; HR = heart rate; O₂ pulse = VO₂/HR; VCO₂ = production of CO₂; VE = minute ventilation; VO₂ = oxygen consumption

p-values were obtained by paired t-tests; p-values provided for differences between patients and institution-matched controls as well as p-values for comparison between Fontan patients at sea level versus altitude and for comparison between controls at sea level versus altitude

Table 3

Comparison of Fontan-control-matched paired differences adjusted for selected covariates (entire cohort).

	R ² (%)	PE (s.e.)	p	Mean relative difference versus control (95% CI)	
				Toronto (%)	Denver (%)
VO ₂ max (ml/kg/min)	19	0.164 (0.076)	0.04	-13 (-39 to 15)	-29 (-41 to -17)
VAT (ml/kg/min)	24	0.319 (0.090)	0.001	-5 (-35 to 26)	-36 (-49 to -24)
Resting HR (bpm)	19	-0.104 (0.067)	0.12	-20 (-37 to 77)	-30 (-13 to 77)
Peak HR (bpm)	9	0.039 (0.044)	0.38	-21 (-45 to 4)	-25 (-41 to -8)
Systolic BP at rest (mmHg)	12	-0.055 (0.034)	0.11	-4 (-15 to 6)	3 (-2 to 8)
Diastolic BP at rest (mmHg)	17	-0.141 (0.048)	0.004	-8 (-24 to 7)	6 (-0.2 to 12)
Peak systolic BP (mmHg)	9	0.039 (0.035)	0.26	-8 (-19 to 4)	-11 (-16 to -7)
Peak diastolic BP (mmHg)	4	-0.110 (0.052)	0.04	-6 (-15 to 4)	3 (-16 to 23)
O ₂ saturation at rest (%)	5	0.006 (0.009)	0.48	-5 (-9 to -1)	-5 (-8 to -3)
O ₂ saturation at peak (%)	<1	0.009 (0.017)	0.60	-6 (-12 to 0.4)	-7 (-10 to -4)
RR at rest	<1	-0.055 (0.128)	0.67	-6 (-21 to 72)	31 (9 to 53)
RR at peak	15	0.068 (0.073)	0.36	50 (0.3 to 100)	44 (8 to 79)
O ₂ pulse (VO ₂ /HR)	40	0.166 (0.062)	0.007	-18 (-33 to -3)	-35 (-37 to -32)
ΔVE/ΔVCO ₂	1	0.116 (0.115)	0.31	42 (0.1 to 83)	30 (11 to 49)
Percentage of predicted VO ₂ max	-0	-0.177 (0.743)	0.02	-15 (-29 to 0)	-33 (-47 to -18)

ΔVE/ΔVCO₂ = change in ventilation per amount of expired carbon dioxide; AT = anaerobic threshold; BP = blood pressure; HR = heart rate; O₂ pulse = VO₂/HR; RR = respiratory rate; VE = minute ventilation; VO₂ = oxygen consumption

Relative differences between Fontan patients and their respective controls (in percentage) were modelled against patient location. Given is the R² of the model, the parameter estimate with standard error, and p-value for the variable "location". Regression equations were solved to obtain a mean relative difference between Fontan patients and their respective controls for each geographic location

Table 4

Comparison of Fontan-control-matched paired differences adjusted for selected covariates (matched Fontans only).

	R ² (%)	PE (s.e.)	p	Mean relative difference versus control (95% CI)	
				Toronto (%)	Denver (%)
Peak VO ₂ (ml/kg/min)	18	0.184 (0.066)	0.005	-14 (-35 to 7)	-33 (-41 to -24)
VAT (ml/kg/min)	38	0.543 (0.132)	<0.001	15 (-26 to 56)	-39 (-55 to -24)
Rest HR	19	-0.231 (0.080)	0.004	-16 (-42 to 9)	8 (-3 to 17)
Peak HR	<1	-0.005 (0.048)	0.91	-14 (-29 to 1)	-13 (-19 to -7)
Rest systolic BP (mmHg)	28	-0.118 (0.045)	0.008	-18 (-38 to 2)	8 (0 to 16)
Rest diastolic BP (mmHg)	32	-0.258 (0.063)	<0.001	-9 (-21 to 3)	3 (-0 to 6)
Peak systolic BP (mmHg)	6	-0.022 (0.058)	0.71	-12 (-30 to 7)	-10 (-17 to -3)
Peak diastolic BP (mmHg)	<1	-0.148 (0.097)	0.13	-1 (-31 to 31)	14 (2 to 26)
O ₂ saturation at rest (%)	12	0.001 (0.013)	0.95	-3 (-11 to 6)	-3 (-9 to 3)
O ₂ saturation at peak (%)	<1	0.004 (0.034)	0.91	-7 (-17 to 4)	-7 (-11 to -3)
Respiratory rate at rest	5	-0.259 (0.218)	0.24	5 (-61 to 71)	31 (8 to 54)
Respiratory rate at peak	<1	0.019 (0.100)	0.85	6 (-26 to 37)	4 (-8 to 16)
O ₂ pulse (VO ₂ /HR)	52	0.331 (0.084)	<0.001	4 (-19 to 28)	-29 (-35 to -22)
ΔVE/ΔVCO ₂	3	0.111 (0.111)	0.32	41 (9 to 74)	30 (19 to 41)
Percentage of predicted VO ₂ max	20	-0.150 (0.061)	0.02	-18 (-30 to -6)	-33 (-45 to -21)

BP = blood pressure; VAT = anaerobic threshold; VE = minute ventilation; HR = heart rate; VO₂ = oxygen consumption; O₂ pulse = VO₂/HR; VCO₂ = production of CO₂; ΔVE/ΔVCO₂ = rate of rise in ventilation per amount of expired carbon dioxide

Analysis restricted to Fontan patients from Toronto and Denver matched on gender, age at exercise tests, diagnosis, type of Fontan connection, and age at Fontan and their matched controls (n = 44 pairs). Relative differences between Fontan patients and their respective controls (in percentage) were modelled against patient location. Given is the R² of the model, the parameter estimate with standard error, and p-value for the variable "location". Regression equations were solved to obtain a mean relative difference between Fontan patients and their respective controls for each geographic location

Table 5

Effect of altitude on matched Fontan–control relative differences.

	Relative difference per 1000 feet elevation (%)	p
Peak VO ₂ (ml/kg/min)	−3 (−6 to 0)	0.03
VAT (ml/kg/min)	−9 (−14 to −4)	0.001
Rest HR	4 (1 to 7)	0.03
Peak HR	0 (−2 to 1)	0.67
Rest systolic BP (mmHg)	3 (0 to 6)	0.04
Rest diastolic BP (mmHg)	2 (0 to 3)	0.08
Peak systolic BP (mmHg)	0 (−2 to 3)	0.98
Peak diastolic BP (mmHg)	1 (−3 to 5)	0.54
O ₂ saturation at rest (%)	0 (−1 to 0)	0.42
O ₂ saturation at peak (%)	0 (−1 to 1)	0.97
VE at rest (l/min)	3 (−3 to 9)	0.30
VE at peak (l/min)	−5 (−9 to 0)	0.04
Respiratory rate at rest	6 (−2 to 13)	0.13
Respiratory rate at peak	0 (−3 to 4)	0.92
O ₂ pulse (VO ₂ /HR)	−4 (−8 to −1)	0.02
Δ VE/ Δ VCO ₂	−1 (−5 to 3)	0.56
Percentage of predicted VO ₂ max	−6 (−9 to −3)	0.03

Δ VE/ Δ VCO₂ = rate of rise in ventilation per amount of expired carbon dioxide; BP = blood pressure; HR = heart rate; O₂ pulse = VO₂/HR; VAT = anaerobic threshold; VE = minute ventilation; VO₂ = oxygen consumption

Relative differences between Fontan patients and their respective controls (in percentage) were modelled against patient living at altitude. Given is the change in exercise test results relative to matched control per 1000 feet increase in elevation adjusted for important covariates