Cardiology in the Young

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Impaired lung function in children and adolescents with Fontan circulation may improve after endurance training

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Original Article

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Abstract

Objectives: The objective of this research was to study lung function, physical capacity, and effect of endurance training in children and adolescents after Fontan palliation compared with healthy matched controls. *Methods:* Fontan patients (n = 30) and healthy matched control patients (n = 25) performed dynamic and static spirometry, and pulmonary diffusing capacity and maximal oxygen uptake tests, before and after a 12-week endurance training programme and at follow-up after 1 year. *Results:* Fontan patients had a restrictive lung pattern, reduced pulmonary diffusing capacity (4.27 ± 1.16 versus 6.61 ± 1.88 mmol/kPa/minute, $p < 0.001$), and a reduced maximal oxygen uptake (35.0 ± 5.1 versus 43.7 ± 8.4 ml/minute/kg, $p < 0.001$) compared with controls. Patients had air trapping with a higher portion of residual volume of total lung capacity compared with controls (26 ± 6 versus 22 ± 5%, $p < 0.05$). Vital capacity increased for patients, from 2.80 ± 0.97 to 2.91 ± 0.95 L, $p < 0.05$, but not for controls after endurance training. The difference in diffusing capacity between patients and controls appeared to be greater with increasing age. *Conclusions:* Fontan patients have a restrictive lung pattern, reduced pulmonary diffusing capacity, and reduced maximal oxygen uptake compared with healthy controls. Endurance training may improve vital capacity in Fontan patients. The normal increase in pulmonary diffusing capacity with age and growth was reduced in Fontan patients, which is concerning. Apart from general health effects, exercise may improve lung function in young Fontan patients and should be encouraged.

Children born with univentricular hearts undergo stepwise palliative surgery to a Fontan circulation – that is a single subsystemic ventricle without a subpulmonary ventricle and thereby a passive venous return to the pulmonary circulation.[1–4] The non-pulsatile pulmonary blood flow in Fontan patients may cause vascular changes, and furthermore lung development may be limited by early and repeated surgical interventions. Children with a Fontan circulation have reduced exercise capacity[5–9] and a lower quality of life[10–14] than healthy children. Several studies have shown that physical training can improve exercise tolerance in Fontan patients[15–17] and that the effects can be long-lasting.[18] Training effects have also been shown to improve peripheral muscular function in children with CHD.[19] A few studies have reported that children after Fontan palliation have abnormal spirometry with low forced vital capacity and that this was associated with reduced exercise capacity.[20] Children who have undergone Fontan palliation have also been shown to have reduced pulmonary diffusing capacity,[21–24] but the reason for this has not been fully understood. To our knowledge, there is no published study that includes complete static and dynamic spirometry and measurement of pulmonary diffusing capacity and exercise capacity before and after an endurance training programme in this patient group compared with a healthy matched control group.

Our aim was to study whether lung function was correlated with exercise capacity and maximal oxygen uptake and whether lung function could be improved through endurance training in children after Fontan palliation compared with healthy matched controls.

Material

Children with Fontan palliation born between 1990 and 2005 in the Stockholm region, n = 53, were considered for inclusion in the study. Exclusion of 23 patients was made after hospital charts had been reviewed or the patients had declined participation. Exclusions were owing to neurodevelopmental disorder (n = 5), heart transplant (n = 2), acute myocarditis (n = 1), being under investigation for further surgery (n = 1), muscle weakness (n = 1), having moved to another geographical region (n = 2), or short stature – below 125 cm (n = 1). The number of

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families who declined participation was ten. Each patient and their parents were asked to suggest a healthy peer of the same age and gender to serve as a healthy control.

Methods

Lung function

Spirometry, including measurements of static and dynamic volumes and flows, was performed using body plethysmography (V-max®; Vyaire Medical, Mettawa, Illinois, United States of America) with the patient at rest in the sitting position. An N_2 gas wash-out study was also performed, where the individual inhaled 100% oxygen and then washed it out with air to a N_2 concentration of 1/40; subsequently, functional residual capacity was calculated. Single-breath diffusing capacity was measured with carbon monoxide. After inhalation of a test gas with a defined concentration of carbon monoxide, the individual held his/her breath for 8–10 seconds, while carbon monoxide diffused over the alveolar membrane. Then, the individual exhaled, carbon monoxide concentration was measured, and the diffusing capacity was calculated. All tests were performed at least twice for each patient and control or until similar values were achieved.

System calibrations were made in accordance with the manufacturer's specifications once a day, using a known volume and a known pressure in the box for static and dynamic volumes and capacities. N_2 ventilation calibration was made with two defined reference gases (O_2 and CO_2) and ambient air. Calibration of diffusing capacity system was made before every test with a standardised test gas. Swedish reference values[25–27] were used for lung function tests.

Cardiopulmonary exercise testing

The patients performed symptom-limited exercise tests using a stationary, calibrated upright cycle ergometer (Monark Ergomedic 839E; Monark Exercise AB, Vansbro, Sweden) with a continuous increase in load, connected to a testing system (GE CASE Exercise testing system; Davis Medical Electronics Inc., Vista, California, United States of America). Start load and continuous increment of load during the test were chosen individually, on the basis of self-reported physical capacity and activity in order for each individual to reach exhaustion within approximately 10 minutes. Body mass (kg) and height (m) were measured before the test. Echocardiography was performed on all individuals before the test in order to detect signs of thrombosis, intracardiac shunting, or significant valvular incompetence. The children were instructed to maintain a constant pedalling rate of 60 rpm and were actively encouraged throughout the test. Standard 12-lead electrocardiogram, blood pressure, and pulse oximetry were monitored before, during, and for 10 minutes after the test. Blood pressure was measured with cuff and radial artery Doppler signals during the test.

Breath-by-breath analyses of metabolic variables (V-max®), including oxygen consumption and respiratory parameters, were performed continuously through the use of a mouth-piece and a nose clip. The patients and control patients were encouraged throughout the test to perform and continue until maximal exhaustion. Maximal oxygen uptake data were obtained by averaging oxygen consumption in the last 20 seconds of each test and correcting for each individual's weight in kilogram (maximal oxygen uptake, ml/minute/kg). The mass flow meter was calibrated with a fixed volume and the gas analyser with two reference gases before every test.

Endurance training programme and 1-year follow-up

Each Fontan patient and control patient, together with at least one parent, was interviewed about their organised physical exercise during an average school week. Duration in minutes was stated and average perceived intensity was estimated using the Borg scale, which is a method by which a patient can quantify self-perceived exercise effort on a scale from six to 20.[28] An individualised endurance training programme was designed for each patient based on this history, the results of the ergometer and oxygen uptake tests, time of year, and available sports and instructors near school or home. The contract was to include 2×45 minutes of extra instructor-led endurance training every week for 12 consecutive weeks, with maintained baseline activities such as physical education in school and other sports. The endurance training programmes included sports such as running, jogging, skiing, cycling, riding, swimming, dancing, football, and so on. The purpose of the training programme was to increase endurance training at a submaximal level with the aim to increase load gradually during the training programme. Type of activity, duration, and intensity (Borg scale) were reported in a logbook and analysed by the study leaders together with the study patients and a parent. Duration and intensity of the training were recorded as weekly average during the training period.

Lung function tests and cardiopulmonary exercise testing were repeated after the 12-week endurance training programme and again after 1 year, without further encouragement regarding extra exercise from the study leaders, as described previously.[6]

Statistical analysis

The statistical analyses between the groups were performed using t-tests and χ^2 tests as appropriate. Repeated-measures ANOVA was carried out to perform analyses over time. A multiple stepwise regression analysis was performed with maximal oxygen uptake as the dependent variable, and gender, having a heart defect, age, length, weight, forced vital capacity, forced expiratory volume at the end of the 1st second (FEV1.0), vital capacity, total lung capacity , residual volume, and pulmonary diffusing capacity as independent variables. Statistical significance was set at $p < 0.05$. The statistical programme used was Statistica 12 (StatSoft Inc., Tulsa, Oakland, United States of America).

Results

After parental consent and child assent, the study group comprised 30 patients with Fontan circulation and 25 healthy control patients. In total, 17 patients brought a peer each to serve as a healthy control patient. The remaining 13 patients did not want to, or could not, bring a control patient. For the patients who could not bring a peer, we recruited eight age- and gender-matched controls – independent controls – among families and friends of the hospital staff.

The patient group comprised 14 girls and 16 boys. The control group comprised 12 girls and 13 boys. Mean age in years was 14.2 ± 3.2 for patients and 13.6 ± 3.5 for controls, $p = 0.49$. Median age in years was 13.4 for patients and 12.7 for controls. Weight and height did not differ significantly between patients and controls. Body mass index was $18.3 \pm 2.2\ kg/m^2$ for patients

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Table 1. Characteristics of patients and controls.

	Patients	Controls	p
Number, n	30	25	
Male/female, n	16/14	13/12	0.92
Age (years)	14.2 ± 3.2 (8.9–20.4)	13.6 ± 3.5 (8.9–19.0)	0.49
Weight (kg)	43.9 ± 11.8 (24.0–62.0)	49.1 ± 16 (28.0–89.0)	0.17
Height (m)	1.53 ± 0.14 (1.28–1.78)	1.57 ± 0.16 (1.32–1.86)	0.29
BMI (kg/m^2)	18.3 ± 2.2 (14.6–24.2)	19.2 ± 3.3 (15.3–27.2)	0.22
Cardiac diagnosis	20 hypoplastic RV		
	9 hypoplastic LV		
	1 unbalanced AVSD		

AVSD = atrio-ventricular septal defect; BMI = body mass index; RV = right ventricle; LV = left ventricle.
Values are presented as mean ± 1 SD (min–max).

and 19.2 ± 3.3 kg/m^2 for controls, p = 0.22; see Table 1. Growth during the study period of 1 year was similar for patients and controls when analysing length and weight. Fontan circulation was completed at a median age of 2.4 (1.1–6.4) years, all with a synthetic extracardiac conduit and without any fenestrations. Pacemakers with epicardial leads were present in three patients owing to sinus node dysfunction. All patients were on anti-coagulation treatment with aspirin (n = 28) or warfarin (n = 2). Enalapril or captopril was prescribed for 19 patients.

Baseline before training programme

Self-reported exercise in minutes/week was lower for patients than for controls before the training programme: 113.5 ± 66.1 minutes/week versus 227.6 ± 147.2 minutes/week, p < 0.001. Average intensity on the Borg scale for all activities was significantly lower for patients than for controls (13.0 ± 2.1 versus 14.3 ± 1.9, p < 0.05), as described previously.[11]

Lung function

Results from lung tests at baseline are presented in Table 2. At baseline, forced vital capacity and forced expiratory volume at the end of the 1st second in absolute values showed tendencies to be lower, and percent of predicted was significantly lower for patients than for controls.

Vital capacity in absolute values showed a tendency to be lower, and percent of predicted was significantly lower for patients than for controls. Total lung capacity, functional residual capacity in plethysmograph and measured with nitrogen wash-out , and residual volume were similar in patients and controls. As a measure of air trapping, functional residual capacity measured with nitrogen wash-out was subtracted from functional residual capacity in plethysmograph, using mean values for the three visits, in patients and controls (0.03 ± 0.31 versus −0.13 ± 0.23 L, p = 0.07). Another measure of air trapping is increased portion of residual volume in relation to total lung capacity, and patients had significantly higher portion of residual volume in relation to total lung capacity than controls (26 ± 6 versus 22 ± 5%, p < 0.05).

Diffusing capacity for carbon monoxide was lower for patients compared with controls (4.27 ± 1.16 versus 6.61 ± 1.88 mmol/kPa/minute, p < 0.001). The slope of the regression line between age and diffusing capacity for carbon monoxide was different between patients and controls (p < 0.05) (Fig 1). The lung clearance index was similar in patients and controls.

Cardiopulmonary exercise testing

Start load was set lower for patients compared with controls (0.67 ± 0.12 versus 0.79 ± 0.15 watts/kg, p < 0.05). Increase of load during the test was similar in patients and controls (0.24 ± 0.07 versus 0.27 ± 0.06 watts/minute/kg, p = 0.07). Test duration was shorter for patients than for controls (7.0 ± 1.9 versus 8.2 ± 1.8 minutes, p < 0.05). Respiratory ratios at maximal oxygen uptake were >1 for both patients and controls, but significantly lower for the patient group (1.05 ± 0.08 versus 1.11 ± 0.08, p < 0.01), as described earlier.[6] Borg score at maximal oxygen uptake was similar in patients and controls (18.0 ± 1.2 versus 18.2 ± 0.8, p = 0.64).

At rest, heart rate was similar in patients and controls: 83 ± 15 versus 82 ± 12 beats per minute, p = 0.80. All had sinus rhythm during the tests. Systolic blood pressure was also similar in patients and controls at rest: 111 ± 9 versus 114 ± 9 mmHg, p = 0.14. However, oxygen saturation at rest was significantly lower in patients than in controls (95 ± 3 versus 98 ± 1%, p < 0.001). At maximal effort, patients had significantly lower heart rate (167 ± 20 versus 191 ± 10 beats per minute, p < 0.001, systolic blood pressure (146 ± 14 versus 161 ± 16 mmHg, p < 0.001), and oxygen saturation (91 ± 4 versus 98 ± 1%, p < 0.001) than controls.

Patients and controls had similar respiratory rate (49 ± 7 versus 48.5 ± 10 breaths/minute, p = 0.86) and minute-ventilation (63.4 ± 19.8 versus 72.7 ± 27.8 L/minute, p = 0.16) at maximal effort. Maximum work-load was lower for patients than for controls: 2.3 ± 0.4 versus 3.0 ± 0.7 watts/kg, p < 0.001. Maximal oxygen uptake was also lower for patients than for controls – 35.0 ± 5.1 versus 43.7 ± 8.4 ml/minute/kg, p < 0.001 – as reported previously.[6] Ventilatory equivalent for carbon dioxide (ventilatory equivalent/ventlatory equivalent for carbon dioxide) at maximal effort was significantly higher for patients than for controls; see Table 3.

After endurance training programme and 1-year follow-up

One patient did not fulfil the training period of 12 weeks. One patient and two control patients did not come back for the 1-year follow-up visit.

Both patients and controls reported an increase of exercise/week after the training programme to 168.3 ± 92.7 minutes/week for patients and 296.4 ± 185.3 minutes/week for controls. At follow-up after 1 year, patients reported a decreased amount of exercise comparable with that before starting the training programme (122.3 ± 89.7 minutes/week), whereas controls reported a maintained amount of exercise as after the training programme (312.3 ± 225.6 minutes/week). After training, patients reported a significant increase in average intensity on the Borg scale for all activities (14.0 ± 2.0), whereas controls reported similar average intensity (14.6 ± 1.4). At follow-up after 1 year, patients (11.9 ± 5.4) and controls (14.1 ± 3.8) reported average intensity for all activities similar to after the training programme, as described previously.[6]

Forced vital capacity, forced expiratory volume at the end of the 1st second, vital capacity, diffusing capacity for carbon monoxide, and lung clearance index were analysed for the three separate visits and are presented in Table 3. Forced vital capacity did not increase significantly after training for patients (p = 0.21)

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Table 2. Results from lung function tests at baseline.

	Patients	Controls	p	Valid patients, n	Valid controls, n
Dynamic spirometry					
FVC, L	2.68 ± 0.94	3.20 ± 1.02	0.055	30	25
FVC, % ref	86 ± 17	97 ± 13	0.010	30	25
FEV1.0, L	2.35 ± 0.68	2.79 ± 0.96	0.054	30	25
FEV1.0, % ref	84 ± 13	90 ± 12	0.052	30	25
FEV1.0/FVC, %	90 ± 7	87 ± 7	0.154	30	25
FEF50%, L/second	3.60 ± 0.92	3.93 ± 1.58	0.339	30	25
FEF50%, % ref	99 ± 20	97 ± 24	0.693	30	25
FEF75%, L/second	1.83 ± 0.58	1.99 ± 1.03	0.482	30	25
FEF75%, % ref	97 ± 27	91 ± 32	0.497	30	25
Static spirometry					
VC, L	2.80 ± 0.97	3.37 ± 1.12	0.051	29	25
VC, % ref	87 ± 15	97 ± 11	0.006	29	25
TLC, L	3.81 ± 1.24	4.41 ± 1.65	0.142	27	25
TLC, % ref	99 ± 15	104 ± 11	0.176	27	25
FRCPL, L	1.84 ± 0.70	1.97 ± 0.68	0.522	27	25
FRCPL, % ref	111 ± 23	106 ± 21	0.482	27	25
FRCN2, L	1.78 ± 0.59	2.01 ± 0.72	0.193	29	25
FRCN2, % ref	102 ± 19	109 ± 22	0.249	29	25
RV, L	1.06 ± 0.44	1.10 ± 0.59	0.785	27	25
RV, % ref	167 ± 57	151 ± 55	0.315	27	25
Pulmonary diffusing capacity					
DLCO, mmol/kPa/minute	4.27 ± 1.16	6.61 ± 1.88	< 0.001	29	25
DLCO, % ref	60 ± 11	87 ± 10	< 0.001	29	25
LCI	5.93 ± 0.95	5.72 ± 0.59	0.339	30	25

DLCO = diffusing capacity for carbon monoxide; FEF50% = forced expiratory flow at 50% of FVC exhaled; FEF75% = forced expiratory flow at 75% of FVC exhaled; FEV1.0 = forced expiratory volume at the end of the 1st second; FRCN2 = functional residual capacity, N_2 wash-out; FRCPL = functional residual capacity, plethysmography; FVC = forced vital capacity; LCI = lung clearance index; RV = residual volume; TLC = total lung capacity; VC = vital capacity; % ref = percentage of normal reference values (see Methods section).
Values are presented as mean ± 1 SD.

or controls (p = 0.20). At follow-up after 1 year, forced vital capacity had increased significantly for both groups (p < 0.001). Forced expiratory volume at the end of the 1st second did not increase significantly after training for patients (p = 0.57) or controls (p = 0.98). At follow-up after 1 year, forced expiratory volume at the end of the 1st second had increased significantly for both patients (p < 0.01) and controls (p < 0.001). Vital capacity increased significantly after training for patients, from 2.80 ± 0.97 to 2.91 ± 0.95 L, p < 0.05, but not for controls (p = 0.22). At follow-up after 1 year, vital capacity had increased significantly for patients (p < 0.01) and controls (p < 0.001) (Fig 2). Diffusing capacity for carbon monoxide did not change significantly after training for patients (p = 0.79) or controls (p = 0.11). At follow-up after 1 year, diffusing capacity for carbon monoxide had not changed significantly from after training for patients (p = 0.18), but had increased significantly for controls (p < 0.01). Lung clearance index did not change significantly after training or at the 1-year follow-up for patients or controls.

Maximal oxygen uptake increased significantly after training for controls, from 43.7 ± 8.4 to 45.7 ± 9.4 ml/minute/kg, p < 0.05. In the patient group, however, maximal oxygen uptake did not increase after training (p = 0.95). Each group had similar maximal oxygen uptake at follow-up after 1 year as after training. Ventilatory equivalent for carbon dioxide at maximal effort did not change for patients or controls after the training programme but increased significantly at follow-up after 1 year for patients (p < 0.05) but not for controls (p = 0.63) (Table 3).

Multiple regression model

In a multiple stepwise regression model, the only significant independent positive predictors of maximal oxygen uptake were

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pulmonary diffusing capacity ($p < 0.001$) and weight ($p < 0.001$). Adjusted R^2 in this model was 0.82, and thus pulmonary diffusing capacity and the patient's weight explain 82% of the variation in maximal oxygen uptake in our model. Having a heart defect was not significantly correlated with maximal oxygen uptake when adjusting for pulmonary diffusing capacity ($p = 0.11$).

Discussion

A Fontan circulation, lacking a subpulmonary pumping ventricle, creates a continuous non-pulsatile pulmonary blood flow.[2,3,29]

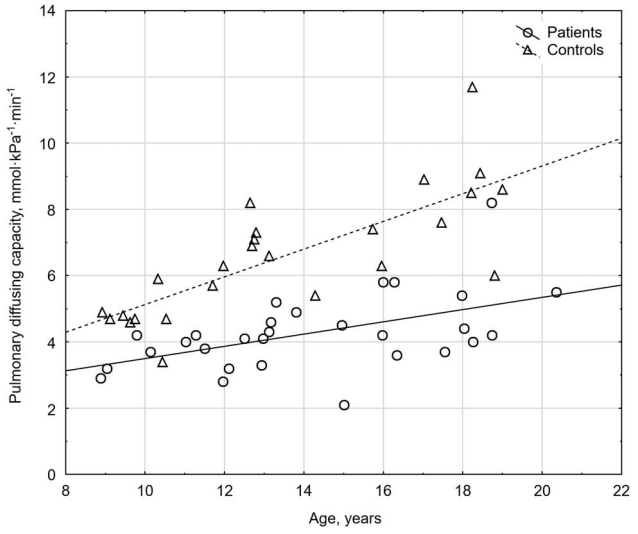

Figure 1. Pulmonary diffusing capacity in mmol/kPa/minute versus age in years in Fontan patients ($y = 1.65 + 0.18 \times x$; $r = 0.51$; $p < 0.01$; $r^2 = 0.26$) and controls ($y = 0.94 + 0.42 \times x$; $r = 0.77$; $p < 0.001$; $r^2 = 0.60$).

Fontan patients can experience long-term cardiopulmonary complications, including heart failure.[4] Children and adolescents with Fontan circulation have reduced exercise capacity[5–9] caused by impaired heart and/or lung function.[20–23] Reduced lung volumes and capacities, restrictive ventilatory pattern, and impairment of the diffusing capacity may contribute to sub-optimal exercise performance in this patient group.[30]

Our study shows that children who have undergone Fontan palliation have a tendency towards reduced forced vital capacity, forced expiratory volume at the end of the 1st second, and vital capacity. Thus, they have a tendency towards a restrictive lung pattern. We also present data showing that Fontan patients have a significantly reduced pulmonary diffusing capacity compared with healthy controls. Moreover, our results show that Fontan patients may have trapping of air with a higher ratio of residual volume in relation to total lung capacity and a tendency towards greater difference between functional residual capacity in plethysmograph and functional residual capacity measured with nitrogen wash-out, compared with controls. After endurance training, vital capacity increased significantly for patients, but not for controls (Fig 2). Diffusing capacity for carbon monoxide did not increase after training in patients or controls, but at the follow-up after 1 year it had increased for controls, but not for patients. Thus, it seems as if the normal increase of diffusing capacity with age and growth is reduced in Fontan patients (Fig 1). This could reflect an abnormal development of diffusing capacity with growth in Fontan patients but a progressive pulmonary vasculopathy, unrelated to growth, cannot be ruled out.

Possible effects of Fontan palliation on lung function

Turquetto et al[30] have also reported that Fontan patients have reduced forced vital capacity, forced expiratory volume at the end of the 1st second, and pulmonary diffusing capacity when

Table 3. Results after endurance training and at 1-year follow-up.

	Baseline			After training 12 Weeks			1-year follow-up		
	Patients	Controls	p	Patients	Controls	p	Patients	Controls	p
Number, n	30	25		29	25		28	23	
Female/male, n	14/16	12/13	0.92	13/16	12/13	0.82	12/16	11/12	0.72
Age (years)	14.2 ± 3.2	13.6 ± 3.5	0.50	14.5 ± 3.2	13.9 ± 3.5	0.53	15.1 ± 3.2	14.6 ± 3.4	0.60
Weight (kg)	43.9 ± 11.8	49.1 ± 16.0	0.17	45.4 ± 12.1	50.7 ± 16.0	0.17	47.6 ± 12.4	51.9 ± 14.5	0.26
Height (m)	1.53 ± 0.14	1.58 ± 0.16	0.29	1.54 ± 0.14	1.59 ± 0.16	0.26	1.57 ± 0.14	1.62 ± 0.15	0.29
FVC (L)	2.68 ± 0.94	3.20 ± 1.02	0.06	2.74 ± 0.90	3.26 ± 0.98	0.05	2.94 ± 0.89	3.37 ± 0.92	0.10
FEV1.0 (L)	2.35 ± 0.68	2.79 ± 0.96	0.05	2.38 ± 0.68	2.79 ± 0.91	0.07	2.56 ± 0.70	2.90 ± 0.86	0.13
VC (L)	2.80 ± 0.97	3.37 ± 1.12	0.05	2.91 ± 0.95	3.43 ± 1.06	0.07	3.08 ± 0.95	3.56 ± 0.98	0.08
DLCO (mmol/kPa/minute)	4.271.16	6.61 ± 1.88	< 0.001	4.33 ± 1.37	6.35 ± 1.89	< 0.001	4.64 ± 1.49	6.89 ± 1.96	< 0.001
LCI	5.93 ± 0.95	5.72 ± 0.59	0.34	5.84 ± 0.83	5.70 ± 0.58	0.50	5.87 ± 1.03	5.90 ± 0.51	0.92
RER	1.05 ± 0.08	1.11 ± 0.08	< 0.01	1.07 ± 0.05	1.11 ± 0.08	< 0.05	1.08 ± 0.08	1.12 ± 0.08	0.12
$\dot{V}O_{2max}$ (ml/minute/kg)	35.0 ± 5.1	43.7 ± 8.4	< 0.001	35.6 ± 6.3	45.7 ± 9.4	< 0.001	35.2 ± 5.9	45.8 ± 9.9	< 0.001
VE/VCO2	39.0 ± 4.3	30.8 ± 3.6	< 0.001	39.2 ± 4.6	31.3 ± 3.6	< 0.001	40.8 ± 5.3	31.6 ± 3.9	< 0.001

DLCO = diffusing capacity for carbon monoxide; FEV1.0 = forced expiratory volume at the end of the 1st second; FVC = forced vital capacity; LCI = lung clearance index; RER = respiratory exchange ratio; VC = vital capacity; VE/VCO_2 = ventlatory equivalent for carbon dioxide; $\dot{V}O_{2max}$ = maximal oxygen uptake.
Values presented as mean ± 1 SD.

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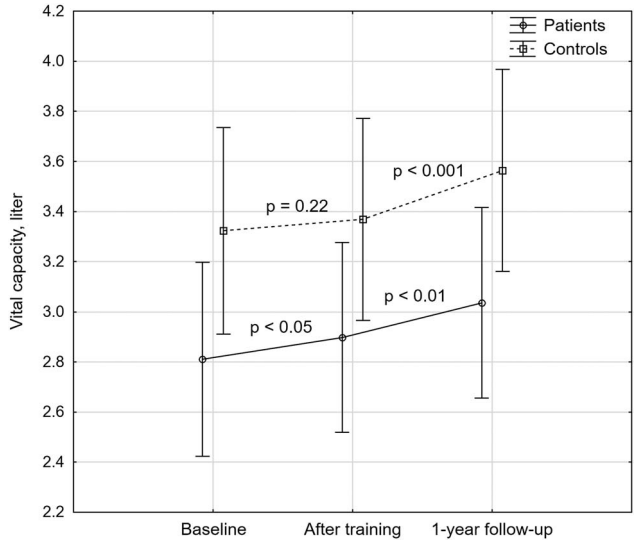

Figure 2. Vital capacity in litres at baseline, after endurance training for 12 weeks, and at follow-up after 1 year for patients and controls.

compared with healthy controls and that there was a strong correlation between peak oxygen uptake and lung function. These results are in line with our findings regarding lung function, pulmonary diffusing capacity, and association with maximal oxygen uptake. A multicentre study by Opotowsky et al[20] showed a reduced forced vital capacity in Fontan patients, and this was associated with impaired exercise capacity. They speculated that factors such as surgical interventions and chest wall abnormalities might negatively affect lung function, including forced vital capacity, by affecting the chest wall mechanically and thereby affecting lung growth. However, that study did not include healthy controls or an exercise training intervention.

Matthews et al[23] also found a markedly reduced pulmonary diffusing capacity and suggested that this might be caused by the abnormal circulation through the lungs. The constant flow and pressure in the pulmonary vasculature might cause thickening of the alveolar capillary membrane with decreased diffusing capacity as a result. Idorn et al[21] have shown that diffusing capacity in Fontan patients is associated with pulmonary capillary blood volume and diffusing capacity was found to be increased in the supine position, when pulmonary capillary blood volume increases. One could reason that if the non-pulsatile flow in the pulmonary vasculature results in a smaller blood volume in the pulmonary arteries, then this could limit the diffusion capacity. Yin et al[31] have shown a redistribution of pulmonary blood flow after Fontan palliation, and this could also explain a reduced pulmonary diffusing capacity in these patients. Mettauer et al[32] described a restrictive lung pattern and reduced diffusing capacity in adults with chronic heart failure compared with healthy controls. They stated that the reduced diffusing capacity in patients with chronic heart failure was owing to permanent alteration of the alveolar capillary membrane and that it is related to the duration and severity of heart failure, and not reversible after heart transplantation.

Trapping of air in our patient group can be explained by repeated surgical procedures with restricted lung physiology as a result, leading to non-ventilated lung sections peripherally. Earlier studies[23,24] have also shown that these patients have signs of trapped gas. Ohuchi et al[24] speculate that reduced mechanical mobility of the lungs owing to surgical interventions results in air trapping and possibly also limits exercise capacity. One could speculate that the non-pulsatile pulmonary blood flow can cause air trapping by reduced expiratory gas transport in small airways.

Effects of endurance training

The endurance training programmes were individually designed for each child based on the patient's history of physical exercise, practised sports, and results from exercise tests. The purpose was to choose an exercise form that the child would want to continue with after the end of the study. Sutherland et al[16] have reported that Fontan patients can improve exercise tolerance and they recommended that exercise programmes for Fontan patients should be at least 2 months with at least twice-weekly training sessions. With those recommendations in mind, training programmes were designed with duration of 3 months and with twice-weekly training sessions.

Our results also show that vital capacity increased significantly after training for patients, but not for controls. Forced vital capacity and forced expiratory volume at the end of the 1st second did not increase after training for patients or controls. At follow-up after 1 year, forced vital capacity, forced expiratory volume at the end of the 1st second, and vital capacity had all increased for both patients and controls, possibly because of growth and older age. Exercise training might have a positive effect on lung function in Fontan patients, as vital capacity increased for the patients, but not for the controls. More research is needed to clarify this. An increase in vital capacity for the patients can be explained by an improved chest musculature and movement. Laohachai et al[33] have demonstrated that respiratory muscle training can improve respiratory muscle strength, give more efficient ventilation during exercise, and also increase resting cardiac output in Fontan patients. They propose that exercise training might give these patients better exercise tolerance and reduced long-term morbidity and mortality. These findings are in line with our results and support the notion that exercise training might improve chest musculature and therefore also vital capacity in our patient group. Familiarisation with lung function testing has to be taken into consideration when repeating tests. However, all tests were performed in a similar manner for patients and controls, and improvement of vital capacity could only be seen in the patient group. The clinical importance of a small but significant increase of vital capacity in the patient group is unclear. In a recent published paper[6], quality of life increased after this endurance training programme, both reported by the Fontan patients and their parents. It is of course difficult to conclude which measured improvement of heart function and/or lung function that is the main explanation for improved health-related quality of life after training. The important message is that Fontan patients should be encouraged to participate in physical activities from early in life in order to improve physical performance and lung function. This could then give better possibilities for Fontan patients to engage in and enjoy physical activities and sports together with healthy peers.

In the multiple regression model, independent positive predictors for maximal oxygen uptake were diffusing capacity for carbon monoxide and the patient's weight. This has been described earlier in healthy individuals with varying cardiorespiratory fitness by Zavorsky and Smoliga.[34] They found that individuals with a higher cardiopulmonary fitness also had a higher pulmonary diffusing capacity and those with a lower cardiopulmonary fitness had a lower pulmonary diffusing

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capacity. Thus, Fontan patients have a significantly reduced diffusing capacity compared with controls, and do not show the same increase in diffusing capacity with age and growth as controls. This may affect their maximal oxygen uptake and physical performance. Early palliative procedures to optimise pulmonary blood flow, and the timing and type of Fontan operation, are important factors for cardiopulmonary circulation later in life. Crucially, they can also help optimise lung growth and prevent permanent lung damage, which would otherwise probably affect physical performance and daily life throughout childhood, adolescence, and adulthood.

Limitations

The number of patients was limited by the size of our Fontan cohort. One could speculate as to whether the patients who chose to participate represented a group with more favourable outcomes than the patients who chose not to participate. The self-selection of control patients can be questioned, but we felt it was important to compare lung function and exercise capacity in peers who the patients are likely to compare themselves with. Moreover, endurance training programmes with longer duration and higher weekly frequency could have given other results. The purpose of individually designed training programmes was to support compliance during the study and improve chances for continued exercise after the study. Different training programmes and for longer periods may give more marked or different effects, and thus more studies are needed to present the full effects of endurance training of Fontan patients. Familiarisation with lung function and exercise testing is important to consider when repeating tests. However, patients and controls performed identical tests with same intervals permitting comparisons between the groups to be made.

Conclusions

Young Fontan patients have restrictive lung patterns and signs of air trapping. They also have a reduced pulmonary diffusing capacity and the normal increase of diffusing capacity with age appears to differ from that of healthy controls. Exercise capacity is reduced, but endurance training seems to improve vital capacity in this patient group, possibly because of an improvement of chest musculature and movement. Lung function and pulmonary diffusing capacity seem to be associated with maximal oxygen uptake. Further research is needed to more fully understand the mechanisms and find explanations for the impaired lung function and abnormal pulmonary diffusing capacity in this patient group, which are both of great concern. However, endurance training may improve lung function in young Fontan patients and should be encouraged.

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Conflicts of Interest. None.

Ethical Standards. The study was approved by the Ethical Review Board at Karolinska Institutet (DNR 2010/84-31/4), Stockholm.

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