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Original Article

New insights into the aspects of pulmonary diffusing capacity in Fontan patients

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Abstract *Background*: Patients with a functionally univentricular heart, palliated a.m. Fontan, consequently have non-pulsatile pulmonary blood flow and are known to have a reduced pulmonary diffusing capacity. However, the cause of this reduction remains unclear. We aimed to assess the possible determinants in the aetiology of a reduced diffusing capacity and also to assess whether it could be increased. Furthermore, we aimed to search for predictors of a reduced diffusing capacity. *Material and methods*: A total of 87 Fontan patients (mean age 16.3 ± 7.6 years) performed advanced pulmonary function tests and maximal cycle ergometer tests. A total of 10 Fontan patients and nine matched controls performed a supine pulmonary function test after a supine rest. *Results*: In the sitting pulmonary function test, the mean z-scores were: diffusing capacity, 2.38 ± 1.20; pulmonary capillary blood volume, 2.04 ± 0.80; and alveolar capillary membrane diffusing capacity, 0.14 ± 0.84. In the supine compared with the sitting pulmonary function test, the diffusing capacity increased by $51.7 \pm 11.9\%$ in the Fontan group and by $23.3 \pm 17.7\%$ in the control group ($p < 0.001$); moreover, the pulmonary capillary blood volume increased by $48.3 \pm 17.4\%$ in the Fontan group and by $20.2 \pm 13.9\%$ in the control group ($p = 0.001$). In a multiple linear regression analysis including the explanatory variables of surgical data and exercise data at rest and peak exercise, the resting cardiac index was an independent predictor of the diffusing capacity (regression coefficient: 0.18, $p < 0.001$). *Conclusions*: The pulmonary diffusing capacity was reduced in Fontan patients because of a reduced pulmonary capillary blood volume, whereas the alveolar capillary membrane diffusing capacity was preserved. The diffusing capacity was highly increasable in Fontan patients compared with controls, and the resting cardiac index was an independent predictor of the diffusing capacity.

Keywords: Fontan procedure; congenital heart disease; pulmonary diffusing capacity; exercise test

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In Fontan patients, the systemic and pulmonary circulations are coupled in series. the functionally single ventricle supplies pulsatile blood to the systemic circulation, whereas the pulmonary circulation is circulated with a non-pulsatile or severely attenuated pulsatile flow. before establishment of fontan circulation, pulmonary circulation may be subjected to either reduced or excessive blood flow depending on the diagnosis, and furthermore several sternotomies and thoracotomies have often been performed. thus, it is likely that the development of various pulmonary compartments and functioning of the lungs in fontan patients are affected by these conditions. few studies have described pulmonary function in fontan patients using advanced pulmonary testing with measurements of the diffusing

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capacity.[1–3] to date, all these studies have described a reduced diffusing capacity; however, the cause of this reduction remains unclear, and the potential of increasing it remains unestablished.

Studies on animal models have revealed that pulmonary capillaries are recruited during pulsatile flow[4,5] and that long-term non-pulsatile flow can lead to remodelling of the pulmonary vessels and increase in pulmonary vascular resistance.[6,7]

We aimed to assess the possible determinants in the aetiology of a reduced diffusing capacity in Fontan patients and in particular to distinguish between reduced alveolar capillary membrane diffusing capacities and reduced pulmonary capillary blood volumes. Furthermore, we aimed to examine whether the diffusing capacity, the pulmonary capillary blood volume, and the alveolar capillary membrane diffusing capacity would increase in the supine position in Fontan patients compared with a control group. Finally, we aimed to search for predictors of a reduced diffusing capacity in Fontan patients.

Materials and methods

Patients

A total of 136 Fontan patients were followed up at Rigshospitalet, Copenhagen. We excluded 30 patients aged 6 years or below as they were not expected to be able to perform a valid pulmonary function test. Furthermore, we excluded three patients because of neurological sequelae, and 16 patients refused to participate. The final group consisted of 87 patients (84.5%) out of the 103 eligible. None of them were on selective pulmonary vasodilators – prostacyclins, endothelin antagonists, or phosphodiesterase inhibitors. Of the 87 patients, 72 performed a cardiopulmonary exercise test. Of the 87 patients, 14 were considered too young/small to perform a valid exercise test, and one patient refused. The anatomical subtypes of Fontan patients were classified into six diagnostic categories: unbalanced atrioventricular septal defect, double-inlet left ventricle, hypoplastic left heart syndrome, pulmonary atresia and intact ventricular septum, tricuspid atresia, and "other Fontan".

The local ethics committee approved the study and all patients/guardians gave informed consent.

Examinations

The pulmonary function tests, measurement of the concentration of haemoglobin, and the exercise tests were performed on the same day.

Pulmonary function tests – sitting

Pulmonary function tests including assessment of static and dynamic volumes and capacities were performed during rest in the sitting position using Masterscreen PFT Pro (Viasys/Jäger; Wurzburg, Germany).

Spirometric variables

Forced vital capacities and forced expiratory volumes during the first second were determined as the highest of three measurements in accordance with the European Respiratory Society and American Thoracic Society guidelines.[8,9]

The single-breath diffusing capacity

The single-breath method, using a mixture containing 0.3% CO, 20% O_2, and 0.3% CH_4 balanced with N_2 (Linde/AGA, Munich, Germany), was used first. The pulmonary diffusing capacity for carbon monoxide was calculated after a 10-second breath hold. The diffusing capacity for carbon monoxide was corrected for the concentration of haemoglobin and alveolar volume. Subsequently, the single-breath method was performed using a mixture containing 0.3% CO, 20% O_2, and 12% He balanced with N_2 and mixed with a standard gas containing 400 ppm NO (Linde/AGA). Using both CO and NO in a simultaneous measurement allows the pulmonary capillary blood volume and alveolar capillary membrane diffusing capacity to be determined.[10] The rate of disappearance from alveolar gas was calculated after a 5-second breath hold. The alveolar capillary membrane diffusing capacity was calculated as the diffusing capacity for NO divided by 1.97.[10] All measurements were made in duplicate at 4-minute intervals in accordance with the European Respiratory Society and American Thoracic Society guidelines.

The test results were compared with the following reference data: spirometry at all ages according to the method described by Stanojevic et al[11]; the diffusing capacity corrected for haemoglobin concentrations, static lung volumes, pulmonary capillary blood volumes, and alveolar capillary membrane diffusing capacities for patients ≤ 18 years according to the method described by Zapletal et al[12]; and the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes for patients ≤ 18 years according to the method described by Stam et al[13]. In patients >18 years, the diffusing capacity and static lung volumes were expressed according to the method described by Cotes et al,[14] and the pulmonary capillary blood volumes and alveolar capillary membrane diffusing capacities were expressed according to the method described by Crapo et al[15].

Pulmonary function tests – supine

A subgroup of the patients was invited to undergo a supine pulmonary function test in order to test whether the diffusing capacity could be increased.

To minimise the selection bias, patients were eligible for this portion of the study only if they lived within a 10 km radius from the centre. A total of 19 patients were invited and 10 accepted. In these patients and in nine age-matched and sex-matched healthy controls – one control individual cancelled at the day of examination – all the pulmonary function tests were repeated in the supine position after a supine rest of 30 minutes.

Exercise protocol

A total of 72 patients underwent a symptom-limited cardiopulmonary exercise test using an electronically braked cycle ergometer in the upright position. Before the test, the stroke volume, cardiac output, and oxygen consumption at rest were estimated using the breath-by-breath inert gas rebreathing technique (Innocor™, Innovision, Odense, Denmark).[16] After a 3-minute warm-up without load, the workload was started at 25 W and increased by 25 W/2 minute. The heart rate and transcutaneous oxygen saturation were monitored continuously. Peak oxygen consumption was obtained using Innocor™ and was defined as the highest mean uptake of any 30-second interval during the exercise and the patient should achieve a respiratory exchange ratio above 1.0. Owing to the fact that the stroke volume and cardiac output were estimated from the pulmonary blood flow, the results of the stroke volume and cardiac output were not used in patients with an oxygen saturation at rest <90% because of the possibility of considerable shunting. The reference values for peak oxygen consumption were calculated for patients <18 years according to method described by Cooper and Weiler-Ravell[17] and for those ≥18 years according to the method described by Cooper and Storer.[18]

Statistical analysis

The results are expressed as mean and standard deviation of the z-scores and of the percentages predicted. In the Fontan and control groups, the intra-group and inter-group changes in the pulmonary function tests from the sitting to supine position were compared using paired and unpaired t-tests, respectively. The univariate and multiple linear regression analyses were performed with the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes as the dependent variable. The explanatory variables statistically significant in the univariate analyses were included in the multiple analysis. In the multiple analysis, backward elimination was used, removing a variable when $p > 0.1$. The variables were tested for collinearity before inclusion into the multiple analysis. The one-way analysis of variance was used for analysing the differences in diffusing capacities corrected for haemoglobin concentrations and alveolar volumes between the diagnostic categories. The unpaired t-test was used for analysing the differences between each of the following: the morphology of the systemic ventricle – left versus right; type of Fontan – lateral tunnel versus extracardiac conduit; type of stage 1 surgery – systemic to pulmonary artery shunt versus banding of the pulmonary artery; sex; and fenestration – patent versus closed/no fenestration. If a significant difference was found on using the t-test, adjustments for age and height were made using a multiple regression analysis.

Analyses were performed using STATA 11.0 (STATA Corp. LP, College Station, Texas).

Results

Study population

The diagnoses, demographic data, and clinical data from the Fontan group (n = 87) and the control group (n = 9) are summarised in Table 1. In the Fontan group, neonatal surgery was performed in 71 patients (82%) – systemic to pulmonary artery shunt, including the Norwood operation in 40 patients; banding of the pulmonary artery in 28 patients; and atrial septostomy in three patients. In five patients (6%), a patent fenestration was present.

Pulmonary function tests

The results of the pulmonary function tests are given in Table 2. The mean z-score of the diffusing capacity corrected for haemoglobin concentrations was -2.85 ± 1.26 and that corrected for both haemoglobin concentrations and alveolar volumes was -2.38 ± 1.20. We found a reduced pulmonary capillary blood volume (mean z-score -2.04 ± 0.80) and a normal alveolar capillary membrane diffusing capacity (mean z-score -0.14 ± 0.84). A total of 54 patients (62%) had a z-score of pulmonary capillary blood volume below -1.96, whereas only three patients (3%) had a z-score of alveolar capillary membrane diffusing capacity below -1.96. Expressed differently, the mean pulmonary capillary blood volume was $53 \pm 16.4\%$ of the expected value compared with a mean alveolar capillary membrane diffusing capacity of $97 \pm 20.9\%$ of the value expected. A reduced total lung capacity – forced expiratory volume during the first second/forced vital capacity – and an increased ratio were indicative of a restrictive physiology.

Supine pulmonary function tests

Changes in the results of the pulmonary function tests from the sitting to supine position are

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Table 1. Characteristics of the Fontan group and the control group.

	Fontan group			Control group
	PFT (sitting) (n = 87)	Exercise test (n = 72)	PFT (supine) (n = 10)	PFT (n = 9)
Age at examination (years)	16.3 (7.6)	17.2 (6.7)	19.1 (6.8)	20.5 (2.9)
Age at stage 1 surgery (years)	0.16 (0.23)	0.18 (0.25)	0.30 (0.49)	–
Age at stage 2 surgery (years)	3.5 (5.5)	3.5 (4.9)	4.1 (3.6)	–
Age at stage 3 surgery (years)	5.3 (6.0)	5.3 (5.8)	5.5 (3.4)	–
Sternotomies/thoracotomies (n)	3 (2–5)	3 (2–5)	3 (1–4)	0
Transcutaneous oxygen saturation (%)	95.1 (2.3)	95.2 (2.4)	95.3 (2.9)	98.7 (0.8)
Haemoglobin concentration (mmol/l)	9.1 (0.92)	9.3 (0.89)	9.3 (0.68)	8.9 (0.54)
Sex, n (%)				
Male	49 (56)	41 (57)	6 (60)	5 (56)
Systemic ventricle morphology, n (%)				
Right ventricle	32 (37)	26 (36)	3 (30)	0
Type of Fontan, n (%)				
RA–PA connection	4 (5)	4 (6)	1 (10)	–
Lateral tunnel	56 (64)	52 (72)	9 (90)	–
Extracardiac conduit	27 (31)	16 (22)	0	–
Functional classification, n (%)				
NYHA I	54 (62%)	42 (58)	9 (90)	9 (100)
NYHA II	31 (36)	28 (39)	1 (10)	0
NYHA III	2 (2)	2 (3)	0	0
Diagnostic category, n (%)				
AVSD	9 (10)	7 (10)	2 (20)	–
DILV	19 (22)	17 (24)	2 (20)	–
HLHS	8 (9)	6 (8)	1 (10)	–
Other Fontan	18 (21)	16 (22)	2 (20)	–
PA-IVS	8 (9)	6 (8)	0	–
TA	25 (29)	20 (28)	3 (30)	–

AVSD = atrioventricular septal defect; DILV = double-inlet left ventricle; HLHS = hypoplastic left heart syndrome; NYHA = New York Heart Association; PA-IVS = pulmonary atresia and intact ventricular septum; PFT = pulmonary function test; RA–PA = Right atrium–pulmonary artery; Stage 1 surgery = palliative neonatal operation, e.g. systemic to pulmonary artery shunt or banding of the pulmonary artery; Stage 2 surgery = Glenn anastomosis; Stage 3 surgery = Fontan-type operation; TA = tricuspid atresia

The Fontan group performed a sitting and a supine pulmonary function test and an exercise test. The control group performed a sitting and a supine pulmonary function test. Continuous data are expressed as mean (standard deviation). Discrete data are expressed as median (95% confidence interval)

Table 2. Results of the pulmonary function test (n = 87) and exercise test (n = 72) in Fontan patients.

	Z-score	Percentage predicted
FEV1 (L)	−0.73 (1.23)	91.4 (14.4)
FVC (L)	−0.94 (1.27)	89.5 (14.0)
FEV_1/FVC (%)	0.30 (1.08)	101.3 (7.6)
DLCOc (mmol/min/kPa)	−2.85 (1.26)	61.0 (13.7)
DLCOc/VA (mmol/min/kPa/L)	−2.38 (1.20)	70.3 (14.5)
Dm (mmol/min/kPa)	−0.14 (0.84)	97.0 (20.9)
Vc (ml)	−2.04 (0.80)	53.3 (16.4)
VA (L)	−1.76 (0.89)	76.2 (12.0)
FRC (L)	0.17 (1.72)	100.8 (25.3)
ERV (L)	−0.09 (2.23)	95.4 (41.4)
RV (L)	0.24 (1.07)	108.0 (31.4)
TLC (L)	−0.74 (1.46)	90.7 (12.1)
VC (L)	−0.71 (1.64)	93.7 (15.2)
VIN (L)	−1.46 (1.28)	83.7 (13.9)
$VO_{2\ peak}$ (ml/kg/min)		60.8 (13.2)

DLCOc = diffusing capacity for carbon monoxide corrected for haemoglobin; DLCOc/VA = diffusing capacity for carbon monoxide corrected for haemoglobin and alveolar volume; Dm = alveolar capillary membrane diffusing capacity; ERV = expiratory reserve volume; FEV1 = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; VA = alveolar volume; Vc = pulmonary capillary blood volume; VC = vital capacity; VIN = volume of inspired gas; $VO_{2\ peak}$ = peak oxygen consumption

Results are expressed as mean (standard deviation)

Table 3. Change in the pulmonary function tests from the sitting to supine position in Fontan patients and controls.

	Percentage change from sitting to supine				
	Fontan group	Intragroup difference (p-value)	Control group	Intragroup difference (p-value)	Intergroup difference (p-value)
SpO_2 (%)	1.2 (0.9)	0.006	0.6 (0.7)	0.06	0.09
FEV_1 (L)	−14.9 (5.2)	<0.001	−15.2 (6.8)	0.002	0.94
FVC (L)	−12.9 (3.7)	<0.001	−13.1 (5.2)	<0.001	0.94
DLCOc (mmol/min/kPa)	41.4 (9.7)	<0.001	13.6 (14.0)	0.03	<0.001
DLCOc/VA (mmol/min/kPa/L)	51.7 (11.9)	<0.001	23.3 (17.7)	0.003	<0.001
Dm (mmol/min/kPa)	14.1 (6.3)	<0.001	6.6 (4.0)	0.001	0.008
Vc (ml)	48.3 (17.4)	<0.001	20.2 (13.9)	0.008	0.001

DLCOc = diffusing capacity for carbon monoxide corrected for haemoglobin; DLCOc/VA = diffusing capacity for carbon monoxide corrected for haemoglobin and alveolar volume; Dm = alveolar capillary membrane diffusing capacity; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; SpO_2 = transcutaneous oxygen saturation; Vc = pulmonary capillary blood volume

Intra-group and inter-group differences from the sitting to supine position were compared using paired and unpaired t test, respectively

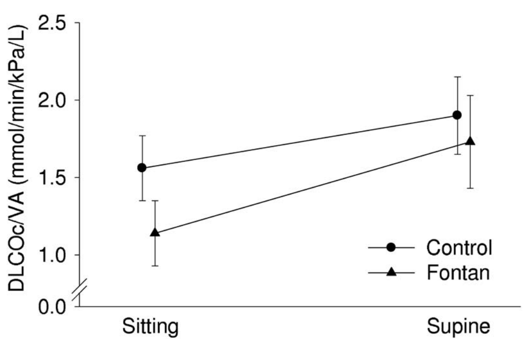

Figure 1.
Change in the pulmonary diffusing capacity for carbon monoxide corrected for haemoglobin concentrations and alveolar volumes (DLCOc/VA) from the sitting to the supine position in Fontan patients and healthy controls.

summarised in Table 3. In the sitting position, all individuals in the control group except one demonstrated results within the normal reference range. After a supine rest, the diffusing capacity corrected for haemoglobin concentrations increased by 41.4 ± 9.7% in the Fontan group compared with 13.6 ± 14.0% in the control group ($p < 0.001$). The diffusing capacity corrected for haemoglobin concentrations and alveolar volumes increased by 51.7 ± 11.9% in the Fontan group compared with 23.3 ± 17.7% in the control group ($p < 0.001$; Fig 1). The increase in the diffusing capacity was mainly caused by an increase in the pulmonary capillary blood volume (48.3 ± 17.4% in the Fontan group compared with 20.2 ± 13.9% in the control group, $p = 0.001$). However, the alveolar capillary membrane diffusing capacity also increased (14.1 ± 6.3% in the Fontan group and 6.6 ± 4.0% in the control group, $p = 0.008$). The degree of reduction in spirometry parameters was equal in both groups. In both groups, the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes, pulmonary capillary blood volumes, and alveolar capillary membrane diffusing capacities increased significantly from the sitting to supine position.

Exercise test

All patients achieved a respiratory exchange ratio of above 1.0. Of the patients, two had oxygen saturation at rest <90%, and the results of their stroke volumes and cardiac outputs were not used. The mean peak oxygen consumption was 60.8 ± 13.2% of that expected (Table 2). The mean peak oxygen consumption corrected for body weight was 27.4 ± 6.1 ml/kg/minute. The mean maximum heart rate was 81.9 ± 9.1% of that expected, and oxygen saturation decreased from a mean of 95.2 ± 2.4% at rest to 86.8 ± 8.0% at maximum work. The mean systolic blood pressure changed from 118 ± 13.8 mmHg at rest to 158 ± 25.8 mmHg at maximum work. The mean stroke volume index at rest – stroke volume per body surface area – was 34.0 ± 11.6 ml/m^2; the mean cardiac index at rest – cardiac output per body surface area – was 2.69 ± 0.78 $l/min/m^2$; and the mean oxygen consumption at rest was 3.5 ± 1.9 ml/kg/min.

Predictors of diffusing capacity corrected for haemoglobin concentrations and alveolar volumes

Table 4 displays the results of the univariate and multiple regression analyses of the potential predictors of diffusing capacities corrected for haemoglobin concentrations and alveolar volumes. In the multiple analysis, the cardiac index at rest

Table 4. DLCOc/VA from the univariate and multiple linear regression analyses as the dependent variable.

	Univariate			Multiple		
	β	SE	p-value	β	SE	p-value
Demography						
Age at examination (years)	−0.017	0.004	<0.001			ns
Height (cm)	−0.008	0.002	<0.001			ns
Age at stage 1 surgery (years)	−0.228	0.171	0.188			
Age at stage 2 surgery (years)	−0.011	0.006	0.067			
Age at stage 3 surgery (years)	−0.009	0.006	0.124			
Sternotomies/thoracotomies (n)	0.007	0.034	0.829			
NYHA functional class	−0.001	0.030	0.967			
Rest						
Oxygen saturation (%)	0.015	0.014	0.290			
Heart rate (min^{-1})	0.005	0.002	0.045	0.005	0.002	0.021
Systolic blood pressure (mmHg)	−0.001	0.002	0.99			
Stroke volume index (ml/m^2)	0.006	0.003	0.050			ns
Cardiac index (L/m^2)	0.163	0.040	<0.001	0.176	0.039	<0.001
$VO_{2\ rest}$ (ml/kg/min)	0.037	0.018	0.052			
Maximum work						
Oxygen saturation (%)	0.004	0.005	0.479			
Heart rate (min^{-1})	0.005	0.002	0.008			ns
Systolic blood pressure (mmHg)	−0.002	0.001	0.119			
VE/VCO_2 slope	−0.003	0.002	0.112			
$VO_{2\ peak}$ (ml/kg/min)	0.013	0.005	0.014			ns

DLCOc/VA = diffusing capacity for carbon monoxide corrected for haemoglobin and alveolar volume; β = regression coefficient; ns = not significant; NYHA = New York Heart Association; p = p-value; SE = standard error; Stage 1 surgery = Palliative neonatal operation, e.g. systemic to pulmonary artery shunt or banding of the pulmonary artery; Stage 2 surgery = Glenn anastomosis, Stage 3 surgery = Fontan-type operation; VE/VCO_2 slope = ventilatory equivalent ratio for carbon dioxide; VO2 = oxygen consumption
In the multiple analysis backward elimination was used, removing a variable when $p > 0.1$. Adjusted R-square in the multivariable model was 0.34

was a significant predictor (regression coefficient 0.18, $p < 0.001$). Furthermore, the heart rate at rest remained statistically significant after adjustment (regression coefficient 0.005; $p = 0.02$). The peak oxygen consumption, stroke volume index, and maximum heart rate could not be used as predictors after adjustment. A highly significant difference in the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes was found between the types of stage 3 surgery (lateral tunnel; 1.22 mmol/min/kPa/l versus extracardiac conduit; 1.52 mmol/min/kPa/l; $p < 0.001$). The difference remained statistically significant after adjustment for age and height ($p = 0.006$). There was no difference in the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes between the six diagnostic categories of Fontan ($p = 0.18$), between the morphologies of the systemic ventricle ($p = 0.71$), between the sex ($p = 0.08$), between the status of fenestration ($p = 0.32$), or between the type of neonatal surgery ($p = 0.08$).

Discussion

We found a marked reduction in the pulmonary diffusing capacity, similar to that observed in previous studies evaluating the pulmonary function of Fontan patients.[1–3] In addition, the present study assessed the possible determinants in the aetiology of the reduction and found a reduced pulmonary capillary blood volume and a normal alveolar capillary membrane diffusing capacity. However, compared with the control group, the diffusing capacity increased significantly in Fontan patients in the supine position compared with that in the sitting position, mainly because of an increase in the pulmonary capillary blood volume. Furthermore, we found that both the cardiac index and heart rate at rest were independent predictors of the diffusing capacity.

We used diffusing capacities corrected for haemoglobin concentrations and alveolar volumes instead of diffusing capacities corrected for haemoglobin concentrations only when evaluating the diffusing capacity. Our results indicated a restrictive physiology in Fontan patients, which is in agreement with previous findings.[3] In patients with decreased total lung capacity, a decreased diffusing capacity corrected for haemoglobin concentrations is at least partly due to the lower lung volume.[13] We preferred to compare the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes of these patients at their actual decreased total lung capacity because it is a better method to grade a diffusion disorder.[13]

Furthermore, we chose to analyse the results of the diffusing capacity in one common group of Fontan patients rather than dividing the group into children and adults. It seemed reasonable as we found a mean z-score of the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes of −2.38, which is similar to the results reported in Fontan children by Matthews et al (mean z-score; −2.19).[1] In the latter study, a mean z-score of the diffusing capacity corrected for haemoglobin concentrations was −2.88, whereas Larsson et al[2] reported a z-score for the diffusing capacity corrected for haemoglobin concentrations of −3.1 in Fontan children and adults. We found a similar z-score of −2.85 for the diffusing capacity corrected for haemoglobin concentrations in children and adults.

It has previously been speculated that the function of the alveolar capillary membrane in Fontan patients may be affected by the non-pulsatile flow. However, our results indicate that the function is preserved. As an explanation for the reduced diffusing capacity, we found a mean pulmonary capillary blood volume of only 53% of the reference values. Reduced pulmonary perfusion in Fontan patients compared with controls has previously been shown.[19] In a recent study by Wang et al,[20] pulmonary perfusion was reported in 43 Fontan patients palliated with an extracardiac conduit who were examined at 1 month and 5 years after the Fontan operation. The total pulmonary perfusion did not change significantly between the two examinations, whereas perfusion of the lower lung segment compared with the upper lung segment and that of the posterior segment of the lower lobe significantly increased in the latter examination. This finding may be explained by the pulmonary vascular bed being exposed to the flow without a pre-pulmonary pump as the driving force leading to a gravity-dependent distribution of the pulmonary blood. Supporting this theory, we found a highly significant increase in the pulmonary capillary blood volume in Fontan patients from the sitting to supine position compared with a control group. Matsushita et al[21] performed pulmonary ventilation–perfusion distribution in Fontan patients in the sitting and supine position and reported a significant increase in the ratio of upper lung versus lower lung segment perfusion from the sitting to supine position. Therefore, the increased diffusing capacity observed in Fontan patients in the supine position is potentially due to the increased pulmonary capillary blood volume, mainly because of increased perfusion of the upper lung segments. Consequently, in controls with a pumping right ventricle and pulsatile pulmonary blood flow, the blood volume in the sitting position is already "near normally" distributed and therefore increases in the same manner as seen in Fontan patients. Furthermore, the alveolar capillary membrane diffusing capacity increased significantly in Fontan patients in a supine position compared with the control group. Gas is exchanged only through the part of the alveolar membrane, which is in contact with capillaries filled with blood. Therefore, the increase in the alveolar capillary membrane diffusing capacity might potentially be explained by the increase in the pulmonary capillary blood volume.

In the multiple regression analysis, the cardiac index at rest was a highly significant predictor of the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes. The cardiac index is determined by the stroke volume, heart rate, and body surface area. The stroke volume is mainly determined by the preload, afterload, and systolic and diastolic ventricular functions. However, of the available variables contributing to the cardiac index, only heart rate at rest predicted the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes in the multiple regression analysis. Though speaking against the theory that the resting heart rate is the main determinant of cardiac index in Fontan patients, Barber et al[22] reported that atrial pacing at different rates at rest showed no change in the cardiac output because of the proportional decrease in the stroke volume. Nevertheless, the exact principle behind the cardiac index acting as an independent predictor of the diffusing capacity remains unclear. In Fontan circulation, the systemic vascular and pulmonary vascular beds are connected in series without the presence of a pre-pulmonary pump to provide additional forward flow through the lungs. Therefore, a low pulmonary vascular resistance is of crucial importance to provide sufficient preload to the systemic ventricle in Fontan circulation. This preload appears to be the most important determinant for cardiac output in Fontan patients[23] and even a mild increase of pulmonary vascular resistance has been shown to significantly decrease the cardiac output.[24] It could be hypothesised that an increased pulmonary vascular resistance could reduce the pulmonary capillary blood volume, particularly in the upper lung segments, and thereby reduce the diffusing capacity. Increased pulmonary vascular resistance is observed in many Fontan patients.[25] The underlying mechanism is unclear and is likely to be multi-factorial. In Fontan physiology, blood flow through the pulmonary arteries is completely or almost completely non-pulsatile and largely driven by systemic venous pressure and negative intrathoracic pressure during inspiration.[26] In animal studies, the pulsatile pulmonary blood flow plays an important role in the reduction of pulmonary vascular resistance by passive capillary recruitment.[4,5] Pulsatile flow is an important factor in regulating the shear-mediated and stress-mediated release of a number of endothelium-derived vasoactive molecules, including nitric oxide, and lowering of pulmonary vascular resistance.[25,26] Our results showed that the diffusing capacity may be increased to a great extent in Fontan patients in the supine position, most probably because of a gravity-dependent increase in the pulmonary blood flow. Whether the increase is due to opening of non-perfused capillaries or dilatation of perfused capillaries remains unclear; however, it shows that pulmonary vessels in Fontan patients are subject to manipulation. This finding is supported by a study by Khambadkone et al,[25] who administered inhaled nitric oxide to Fontan patients and observed a fall in the pulmonary vascular resistance. Whether administration of pulmonary vasodilators results in an increased diffusing capacity needs to be determined. Giardini et al[27] reported a significant increase in the peak oxygen consumption after administration of a single dose of sildenafil in Fontan patients. Goldberg et al[28] reported a significantly improved ventilatory efficiency during peak and submaximal exercise but no significant improvement in the peak oxygen consumption after 6 weeks of oral sildenafil treatment in Fontan patients. Whether the improvements found in the two studies were results of an increased cardiac output due to an increased preload and/or increased pulmonary diffusing capacity remains unknown. However, Goldstein et al[29] performed supine and sitting exercise tests in Fontan patients and reported a similar peak oxygen consumption or oxygen pulse – a surrogate for pulmonary stroke volume – in the two positions. This, together with our results of increased diffusing capacities in the supine position, indicates that a reduced diffusing capacity is not a limiting factor of peak oxygen consumption in Fontan patients. Supporting this theory, the peak oxygen consumption was not an independent predictor of the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes in the present study. It was previously reported that the pulmonary diffusing capacity increases during and immediately after exercise in healthy individuals.[30] It would be interesting to observe whether Fontan patients recruit areas of the pulmonary vascular bed during exercise. An area of interest of future studies could be to perform both sitting and supine exercise tests, measure the diffusing capacity in the immediate post-exercise period, and compare the results with those of a control group.

Interestingly, the diffusing capacity corrected for haemoglobin concentrations and alveolar volumes was significantly higher in patients palliated with an extracardiac conduit compared with those palliated with a lateral tunnel, even after adjustment for age. The possible explanations for this finding could be that an extracardiac conduit maximises laminar blood flow, as conduit irregularities and associated turbulences are reduced because of the more uniform calibre and circular geometry compared with the lateral tunnel.[31] To our knowledge, data comparing pulmonary blood flow through the lateral tunnel and the extracardiac conduit have not been published. The reason for our finding warrants further research.

Limitations

We compared data from our patients with data from other demographic regions, thereby potentially introducing bias. Furthermore, the supine pulmonary function test was performed only in 10 of the 87 Fontan patients. These 10 patients were older compared with the 87 patients, and almost all of them (90%) had a lateral tunnel. Therefore, the supine tests should be repeated in more patients in order to draw final conclusions.

Future perspectives

As emphasised, the potential explanations for the reduced diffusing capacity in Fontan patients may include the univentricular physiology without a pre-pulmonary pump, the non-pulsatile pulmonary flow, and the elevated pulmonary vascular resistance. Currently, in development, a cavopulmonary mechanical assist device designed to provide pulsatile forward flow to the pulmonary arteries, thereby converting the univentricular Fontan circulation to a "biventricular Fontan", could potentially improve the diffusing capacity and relieve several other Fontan-related complications.[32]

Conclusions

In conclusion, we found a marked reduction in the diffusing capacity in Fontan patients. On assessing the aetiology of this reduction, we found reduced pulmonary capillary blood volumes; however, the function of the alveolar capillary membrane appeared normal. Furthermore, we showed that the diffusing capacity was highly increasable in Fontan patients compared with a control group, mainly because of an increase in the pulmonary capillary blood volume. The cardiac index at rest was an independent predictor of the diffusing capacity in Fontan patients, and the diffusing capacity was significantly higher in patients palliated with an extracardiac conduit compared with those palliated with a lateral tunnel.

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Conflicts of interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Danish Society of Good Clinical Practice and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the local ethics committee "Region Hovedstaden" (Protocol: H-C-2009-039). All patients/guardians gave informed consent.

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