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ORIGINAL RESEARCH

Pulmonary artery size is associated with functional clinical status in the Fontan circulation

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ABSTRACT

Objective In the Fontan circulation, non-pulsatile pulmonary blood flow is suggested to negatively affect pulmonary artery growth. The pulmonary vasculature is regarded a key determinant of outcome after Fontan completion. We hypothesised that in Fontan patients pulmonary artery size correlates with follow-up and functional clinical status.

Methods This is a single-centre, cross-sectional cohort study. Thirty-nine paediatric and adult Fontan patients with a concomitant cardiac magnetic resonance (CMR) scan and a cardiopulmonary exercise test between 2012 and 2013 were included. CMR-derived left and right pulmonary artery cross-sectional areas were expressed as Nakata index. Functional status was defined as peak oxygen consumption (pVO_2) indexed for weight, as percentage of predicted (pred) and as New York Heart Association Functional Class (NYHA-FC).

Results Age at CMR was 18±7.2 years. Time since Fontan completion was 11.9±7.4 years. Nakata index was lower versus the reference values (238.6±78.5 vs 330±30 mm^2/m^2, p<0.001). Nakata index correlated negatively with age at CMR (r=−0.393, p=0.013) and time since Fontan completion (r=−0.341, p=0.034). pVO_2 was 27.9±8.9 mL/min/kg and pVO_2pred was 58.1%±14.1%. Nakata index correlated positively with pVO_2 (r=0.468, p=0.003) and pVO_2pred (r=0.353, p=0.028). Nakata index correlated negatively with NYHA-FC (r=−0.450, p=0.004). Nakata index was an independent predictor (β=0.359, p=0.007) for pVO_2 (adjusted R^2=0.442, with maximum heart rate and oxygen pulse at peak exercise).

Conclusions Pulmonary artery size expressed as Nakata index is a novel independent predictor for functional clinical status. Nakata index negatively correlated with follow-up duration, suggesting that chronic abnormal non-pulsatile pulmonary blood flow plays a role in lagging pulmonary arterial growth in the Fontan circulation.

INTRODUCTION

The Fontan circulation is the palliative option of choice for patients with a univentricular heart defect when biventricular repair is not possible. Although short-term outcomes after the Fontan procedure have improved over time, long-term prognosis is still unsatisfactory and is characterised by gradual failing of the Fontan circulation.[1] One of the non-physiological effects of the Fontan circulation is the introduction of non-pulsatile pulmonary arterial flow with a subphysiological pulmonary arterial pressure related to the absence of a subpulmonary ventricle. This abnormal pulmonary blood flow could negatively influence pulmonary artery (PA) growth and function in the Fontan circulation.

Studies focusing on the effect of pre-Fontan PA size on outcome after Fontan completion showed that pre-Fontan PA size had no effect on short-term and mid-term outcome after Fontan completion.[2 3] However, small PA size appeared to be a risk factor for reintervention.[4] Decreased PA size growth relative to body surface area during the first years after Fontan completion has been described by catheter angiography-based studies.[3 5 6] Longitudinal studies assessing post-Fontan PA size at long-term follow-up show conflicting results. One cardiac magnetic resonance (CMR)-based study suggested that PA size was normal and proportionate to body size at long-term follow-up.[7] In contrast, others showed that, although absolute PA diameter did increase over time, the normalised PA diameter decreased with age.[8 9]

There are limited data on the potential relationship between PA size and functional clinical status in Fontan patients. One study described that peak oxygen consumption (pVO_2) shortly after Fontan completion did not differ between paediatric patients with a preoperative Nakata index (the sum of the left and right PA cross-sectional area divided by the body surface area) below and above 250 mm^2/m^2.[3] Currently no CMR-based study has assessed the possible relationship between post-Fontan PA size expressed as Nakata index and functional clinical status in both paediatric and adult patients long term after Fontan completion. The objective of this study was to investigate whether PA size, assessed by CMR in patients long term after Fontan completion, is related to functional clinical status, defined as pVO_2 and New York Heart Association Functional Class (NYHA-FC). We hypothesised that PA size correlates positively with functional clinical status.

METHODS

Study population

It was a single-centre, cross-sectional cohort study. All Fontan patients >10 years followed at the University Medical Center Groningen, The Netherlands, undergo CMR and cardiopulmonary exercise test (CPET) as part of a standardised follow-up programme and were eligible for inclusion. Inclusion criteria consisted of a concomitant CMR and CPET performed between January 2012 and December 2013. Patients were excluded when CPET results were submaximal (respiratory

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exchange ratio (RER) <1.0) or not interpretable (eg, air leakage from mouthpiece) or absence of phase-contrast MRIs from both the left and right PAs.

Patient characteristics

Patient characteristics were collected from medical records and included demographics, patient medical/surgical history and data from the standard clinical follow-up protocol for Fontan patients as described previously, including a 2 yearly CMR, CPET and lung function test (LFT).[10]

Cardiac magnetic resonance

All CMR studies were performed as described previously.[10] In short, a 1.5T system (Magnetom Avanto, Siemens, Germany) was used. No sedation was applied. The protocol included phase-contrast imaging of the ascending aorta, left and right PAs, and both venae cavae. Cardiac output (Qs) was defined as ascending aortic flow. Pulmonary flow (Qp) was defined as the sum of the left and right PA flow. Cardiac short-axis slides were performed to obtain ventricular volumes. Analysis was performed using QMass V.7.6 and QFlow V.5.6 (Medis, The Netherlands). The cross-sectional areas of the left and right PAs were segmented on multiple frames (typically 40) across the cardiac cycle, and minimal, maximal and mean areas were calculated and indexed for body surface area (BSA). The location of segmentation of the PAs was between the Fontan anastomosis and the first branching of the lobar arteries. PA pulsatility (ratio) was defined as the difference of the maximum and minimum area divided by the maximum area. The sum of the mean cross-sectional area of the left and right PAs was divided by BSA for calculation of CMR-derived Nakata index (mm^2/m^2).[11] CMR-derived Nakata index has been validated and used previously as an accurate non-invasive alternative to fluoroscopy-angiography.[9 12–14]

Cardiopulmonary exercise test

CPET was performed as described previously.[10] For children, a cycle ergometer with a ramp protocol was used with an increase of 15 or 20 Watt/min depending on their height. For adults, a treadmill with a Bruce or modified Bruce protocol was used. Oxygen saturation was continuously monitored by pulse oximetry. Oxygen uptake was measured using breath-by-breath analysis. The RER was the ratio between oxygen consumption uptake (VO2) and carbon dioxide production (VCO2) at peak exercise. Maximal effort during CPET was defined as an RER ≥1.0, and all patients with an RER <1.0 were excluded.[15 16] pVO_2 was calculated as the mean of the final 30 s of the test during peak exercise and was indexed for bodyweight. The pVO_2 as percentage of predicted was calculated using reference values.[15 17]

Pulmonary function test

Spirometry and diffusion capacity testing were performed according to the same protocol for all patients as described previously.[10] Percentage of predicted values for spirometry and diffusion capacity were calculated using reference values.[18 19] To measure lung volumes, a whole body plethysmography was used in children and the helium dilution test for adults. Percentage of predicted values for lung volumes was calculated from the corresponding reference values.[20 21]

Statistical analysis

Variables were tested for normality using visual inspection (histogram, Q-Q plot) and the Shapiro-Wilk test. Data are reported as mean±SD, unless reported otherwise. Pearson's or Spearman's correlation analysis was used to test for relationships between variables. Student's t-test was used to test between two groups. A paired t-test was used to test differences within patients. A one-sample t-test was used to test the difference in Nakata index between the Fontan group and the reference values.[11] Analysis of variance with post-hoc Bonferroni correction was used to test for differences between multiple groups. Univariable linear regression analyses were performed for pVO_2 (mL/min/kg) as outcome variable to identify potential variables for subsequent multiple linear regression analysis. The variables for univariable analysis were selected based on previous analyses from our group.[10]

Additional to these known variables, the Nakata index was tested. A selection of variables from the univariable regression results was made based on a p value <0.15 and those of clinical interest and relevance. These selected variables were used for subsequent multivariable linear regression analysis with a backwards-exclusion method. The multivariable linear regression model assumptions and integrity were tested. Heteroscedasticity and non-linearity were tested using a residuals scatterplot. Normality of the residuals was tested using a P-P plot and Shapiro-Wilk test. An outlier control was performed using Cook's distance (>1 considered significant). Collinearity was tested using the maximum variance inflation factor (VIF). SPSS V.22 statistical software was used. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Fifty-eight patients with a concomitant CPET and CMR were identified. Twelve were excluded because of incomplete CMR data, and seven were excluded due to uninterpretable CPET results (n=3 RER <1, and n=4 measurement errors). Final inclusion consisted of 39 patients. Age at CMR was 18±7.2 years. The median time between CMR and CPET examinations was 7 (0–56) days. Time between Fontan completion and CMR was 11.9±7.4 years. The baseline characteristics and the results from the clinical evaluation including CPET, LFT and CMR examinations are shown in table 1.

PA size and flow

The Nakata index was 238.6±78.5 mm^2/m^2, which was significantly lower (p<0.001) compared with the reference values (330±30 mm^2/m^2)[11] (see figure 1). There were no significant differences between the left and right PA areas: minimal area: 102.8 vs 106.3 mm^2/m^2 (p=0.764); maximal area: 132.4 vs 136.4 mm^2/m^2 (p=0.773); and mean area: 116.9 vs 121.8 mm^2/m^2 (p=0.706). There were no significant differences between the left and right pulmonary arterial pulsatility ratios: 0.23 vs 0.23 (p=0.844). The left PA flow was 1.1±0.4 L/min/m^2 and the right PA flow was 1.3±0.5 L/min/m^2. The left PA flow as percentage of the total PA flow was 47.6%±10.6%.

Relationships between Nakata index and functional clinical status

Nakata index correlated negatively with NYHA-FC (r=−0.450, p=0.004; see figure 2) and correlated positively with both pVO_2 indexed for weight (r=0.468, p=0.003) and pVO_2 as percentage of predicted (r=0.353, p=0.028; see figure 3).

Univariable and multivariable linear regression analyses for pVO_2

The results from the univariable regression analysis are shown in table 2. Seven variables were used for multivariable analysis:

Table 1 Baseline characteristics

Total (N=39)		
Female gender	18 (46.2)	
Diagnosis		
Tricuspid atresia	11 (28.2)	
Hypoplastic left heart syndrome	3 (7.7)	
DILV/DIRV	11 (28.2)	
Pulmonary atresia without VSD	5 (12.8)	
Atrioventricular septal defect	5 (12.8)	
Heterogeneous	4 (10.3)	
Morphological systemic left ventricle	32 (82.1)	
Previous interventions		
Banding main pulmonary artery*	13 (33.3)	
Atrioseptostomy (Rashkind)	7 (17.9)	
(Modified) Blalock-Taussig shunt†	15 (38.5)	
Superior cavopulmonary shunt (Glenn)	29 (74.4)	
Age at Fontan procedure (years)	6.0±3.6	
Type of Fontan		
APC	1 (2.6)	
TCPC-LT	20 (51.3)	
TCPC-ECC	18 (46.2)	
Fenestration present	19 (48.7)	
Clinical characteristics (n=39)		
Age (years)	18±7.2	
Body surface area (m^2)	1.65±0.3	
Body mass index (kg/m^2)	20.1±3.8	
SpO_2 in rest (%)	91.5±4.9	
NYHA-FC (I; II; III; IV as frequency)	20; 16; 3; 0	
CMR scan (n=39)		
Time between Fontan completion and CMR (years)	11.9±7.4	
Cardiac index (Qs) ($L/min/m^2$)	2.8±0.9	
Qp:Qs (ratio)	0.92±0.4	
Ejection fraction (%) (n=38)	55.0±8.0	
End-diastolic volume (mL/m^2) (n=38)	79.9±22.1	
CPET (n=39)		
Days between CPET and CMR (median, IQR)	7 (0–56)	
		(Predicted %)
Peak oxygen consumption (mL/min) Indexed for weight (mL/min/kg)	1481±511.3 27.9±8.9	(58.1±14.1) NA
O_2 pulse at peak exercise (mL/beat)	9.1±2.8	(44.2±15.2)
Maximum heart rate (beats/min)	163±23	(88±12.5)
Lung function test (n=37)		
FEV_1 (L)	3±0.9	(87.4±17.3)
FVC (L)	3.4±1.1	(87.9±15.2)
FEV_1/FVC (%)	86.8±6.6	(98.1±12.0)
Total lung capacity (L)	4.6±1.4	(91.5±14.7)
Peak expiratory flow (L/min)	6.5±2	(87.2±19.5)
Functional residual capacity (L)	2.1±0.8	(83.7±17.7)
Diffusion capacity test (n=34)		
DLCOc (mL/min/mm Hg)	5.9±2.2	(65.7±15.1)
DLCOc:alveolar volume (ratio)	1.4±0.2	(79.5±13.9)
Residual volume (L)	1.1±0.4	(95±24.7)

Data presented are mean±SD or as frequency (percentages) unless mentioned otherwise.
*No bilateral PA bandings were performed.
†No other systemic-to-pulmonary shunts (eg, Waterston/Potts/Sano) were performed.
APC, atriopulmonary connection; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; DILV/DIRV, double inlet left/right ventricle; DLCOc, diffusion capacity of the lungs for carbon monoxide corrected for haemoglobin; ECC, extracardiac conduit; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LT, lateral tunnel; NA, not applicable; NYHA-FC, New York Heart Association Functional Class; O_2, oxygen; PA, pulmonary artery; Qp:Qs, pulmonary flow:systemic flow; SpO_2, peripheral oxygen saturation; TCPC, total cavopulmonary connection; VSD, ventricular septal defect.

Nakata index, gender, peripheral oxygen saturation (SpO_2) at rest, maximal heart rate, oxygen pulse at peak exercise, forced expiratory volume in 1 s (FEV_1) as % of predicted and indexed end-diastolic volume. Multivariable regression showed that Nakata index, maximum heart rate and oxygen pulse at peak exercise were independent predictors for pVO_2. This model including these three variables explained 44.2% of the variance of pVO_2 (see table 3). No significant interaction was present between these variables. The assumptions for the multivariable linear regression model were met. The residuals scatterplot showed no significant heteroscedasticity or non-linearity. The P-P plot and the Shapiro-Wilk test (p=0.182) showed normality of the residuals. Cook's distance did not show any significant outliers (max=0.154). There was no significant collinearity with a maximum VIF of 1.575.

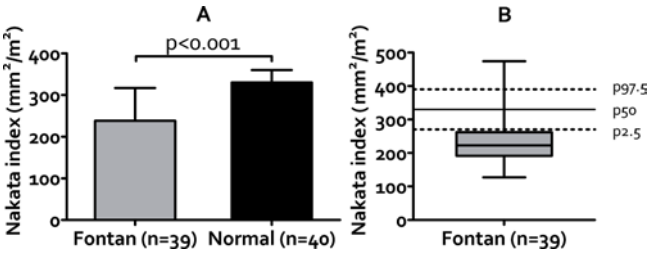

Figure 1 Nakata index. (A) Bar chart showing the difference (p<0.001) in Nakata index between the Fontan group (238.6±78.5 mm^2/m^2) and the reference values from healthy individuals (330±30 mm^2/m^2). Bars and whiskers represent mean and SD. (B) Boxplot showing Nakata index (238.6±78.5 mm^2/m^2) in the Fontan group (n=39). Reference values from healthy individuals (n=40) are shown as follows: the horizontal uninterrupted line represents mean (p50=330 mm^2/m^2), and the two horizontal interrupted lines represent the 95% CI (p2.5=270 mm^2/m^2; p97.5=390 mm^2/m^2).[11]

Relationships between Nakata index and baseline characteristics

Nakata index correlated negatively with both age at CMR (r=−0.393, p=0.013) and time since Fontan completion (r=−0.341, p=0.034) (see figure 4). Age at initial palliation (r=0.313, p=0.053), age at Glenn procedure (p=0.136) and age at Fontan completion (p=0.921) did not correlate with Nakata index. No significant differences in Nakata index between type of diagnosis were found. Nakata index was higher in patients (n=18) with an extracardiac conduit compared with patients (n=20) with a lateral tunnel (269.26±90.29 vs 214.21±57.44 mm^2/m^2, p=0.030). Nakata index was not different between patients with or without a fenestration (p=0.311). Nakata index was lower in patients with a history

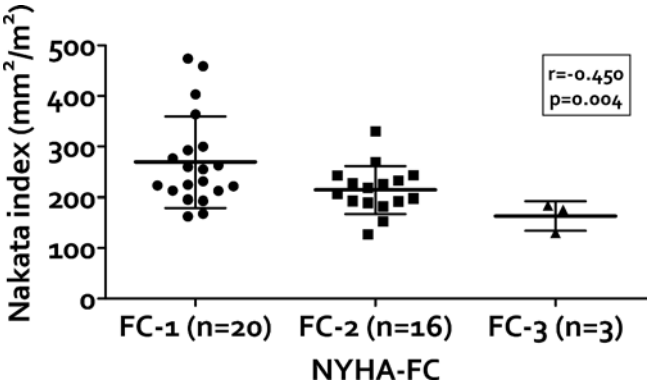

Figure 2 Nakata index and NYHA-FC. Dot plot showing the Nakata index for patients categorised by NYHA-FC. Nakata index correlates negatively with NYHA-FC. The horizontal lines with whiskers represent mean with SD. NYHA-FC, New York Heart Association Functional Class.

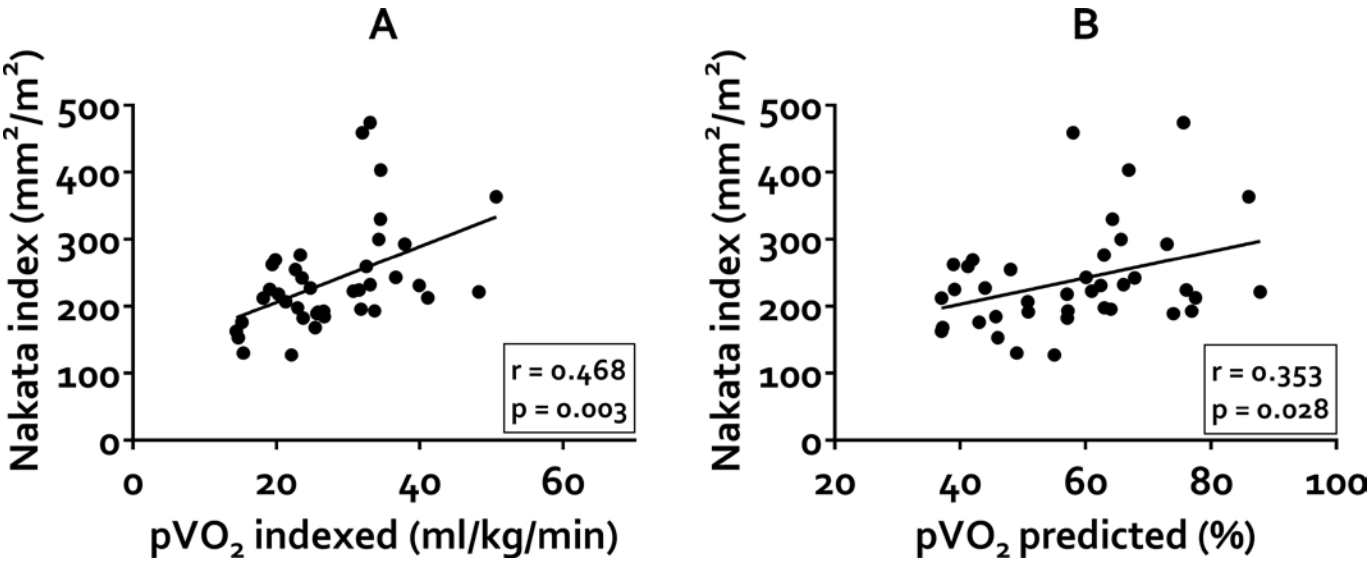

Figure 3 Nakata index and pVO_2. Scatterplot showing the relationship between Nakata index and pVO_2. Nakata index correlates positively with both pVO_2 indexed for weight (A) and as percentage of predicted (B). pVO2, peak oxygen consumption.

Table 2 Univariable regression analysis for peak oxygen consumption (mL/min/kg)

Variable	r	P value
Pulmonary artery		
Nakata index (mm^2/m^2)	**0.468**	**0.003**
Pulmonary flow distribution (left PA flow/total PA flow as %)	0.153	0.354
Baseline		
Gender (male/female)	**0.419**	**0.008**
Height at CPET (cm)	−0.231	0.157
Age at Fontan completion (years)	−0.080	0.629
Type of Fontan (APC vs TCPC)	0.276	0.089
Systemic ventricle (left/right)	−0.052	0.753
Hb (g/L)	−0.243	0.142
SpO_2 at rest (%)	**0.600**	**<0.001**
Cardiopulmonary exercise test		
Max heart rate (beats/min)	**0.466**	**0.003**
O_2 pulse at peak (mL/beat)	**0.380**	**0.017**
Lung function test		
FVC (L)	−0.039	0.816
FVC (% of predicted)	0.163	0.334
FEV_1 (L)	0.048	0.776
FEV_1 (% of predicted)	**0.254**	**0.124**
RV/TLC %	0.028	0.869
FEV_1/FVC %	0.213	0.205
Cardiac magnetic resonance		
EDV indexed (mL/m^2)	**0.532**	**0.001**
ESV indexed (mL/m^2)	0.444	0.005
Ejection fraction (%)	−0.051	0.763
Cardiac output indexed ($L/min/m^2$)	0.429	0.007

Variables depicted in bold were selected for multivariable regression analysis.
APC, atriopulmonary connection; CPET, cardiopulmonary exercise test; EDV, end-diastolic volume; ESV, end-systolic volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Hb, haemoglobin; O_2, oxygen; PA, pulmonary artery; RV, residual volume; SpO_2, peripheral oxygen saturation; TCPC, total cavopulmonary connection; TLC, total lung capacity.

of initial central PA banding or systemic-to-pulmonary shunt (ie, Blalock-Taussig shunt) compared with patients without these interventions (p=0.045). Nakata index between patients with a previous central PA banding (219.5±41.8) versus those with a previous systemic-to-pulmonary shunt (213.5±49.8) did not differ (p=0.732). The number of performed thoracotomies correlated negatively with Nakata index (r=−0.475, p=0.002), whereas the number of sternotomies and the total number of thoracic procedures showed no correlation (p=0.277 and p=0.318, respectively).

Relationships between Nakata index and pulmonary function

Nakata index correlated positively with pulmonary perfusion and pulmonary respiratory function parameters, as depicted in table 4. Nakata index did not correlate with desaturation during CPET, defined as the difference between SpO_2 at rest and at peak exercise (p=0.206, n=33).

DISCUSSION

This study showed that that PA size expressed as CMR-derived Nakata index is lower in Fontan patients compared with the normal reference values. Nakata index correlated negatively with both age and time since Fontan completion. Nakata index at follow-up correlated negatively with NYHA-FC and positively with pVO_2. Moreover, multivariate regression analysis showed that Nakata index at follow-up was an independent predictor for functional clinical status defined as pVO_2. Additionally, Nakata

Table 3 Multivariable regression model for predictors of pVO_2 (mL/min/kg)

Variable	Standardised beta coefficient	P value	R^2	Adjusted R^2
Nakata index (mm^2/m^2)	0.358	0.007	0.486	0.442
Maximum heart rate (beats/min)	0.386	0.004		
O_2 pulse at peak exercise (mL/beat)	0.363	0.005		

O_2, oxygen; pVO_2, peak oxygen consumption.

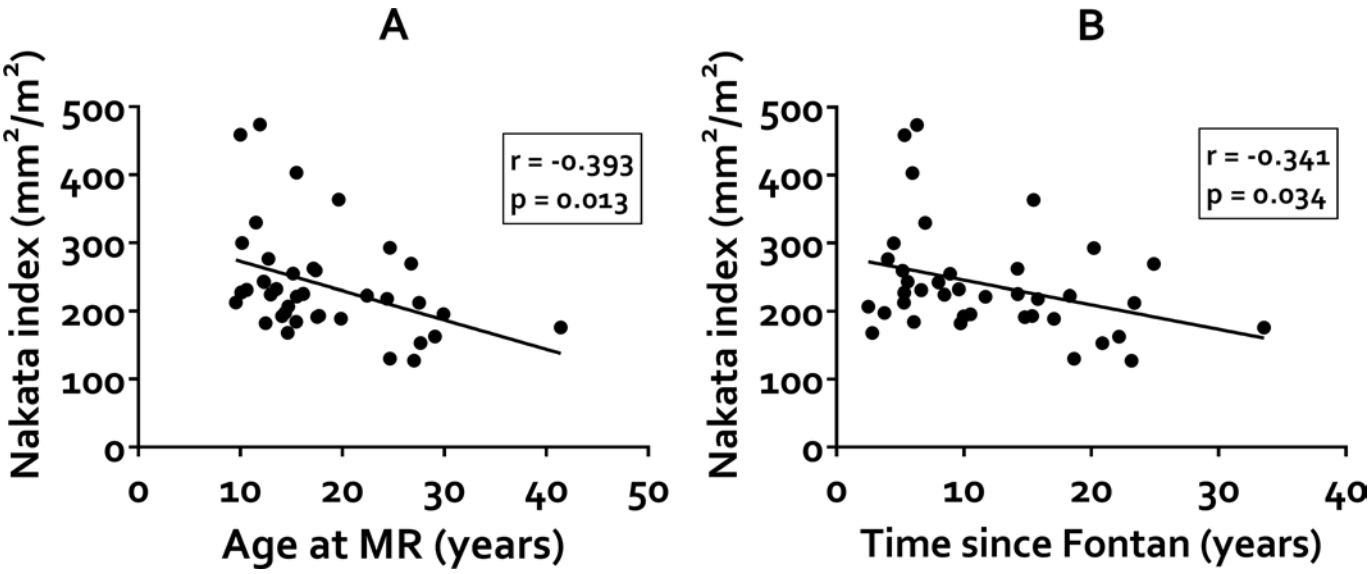

Figure 4 Nakata index and follow-up duration. Scatterplot showing the relationship between Nakata index and follow-up duration. Nakata index correlates negatively with both age at MRI (A) and time since Fontan completion (B).

index was associated with pulmonary perfusion and pulmonary respiratory function parameters.

PA size over time

Although this was a cross-sectional study and individual changes in PA size over time were not assessed, we did find that age and time since Fontan completion were negatively correlated with Nakata index. These findings are consistent with longitudinal studies reporting a decrease in PA size proportional to BSA over time,[3 8 9] which is in contrast to normal individuals in whom Nakata index increases during growth.[22] The lower Nakata indices over time after Fontan completion could be explained as a consequence of the subphysiological pressure and non-pulsatile flow in the PAs in these patients. One could argue that the non-pulsatile, low-pressure flow is a negative stimulus for PA growth, where the results of the current study indicate that this has adverse effects on functional clinical status.

Table 4 Univariate correlations between Nakata index and pulmonary function parameters

	r	P value
SpO_2 at rest (%)	0.416	0.014
SpO_2 at peak exercise (%) (n=33)	0.473	0.005
Pulmonary flow (L/min/m²)	0.584	<0.001
FEV_1 as % of predicted	0.532	0.001
FVC as % of predicted	0.472	0.003
FEV1/FVC as % of predicted	0.385	0.019
PEF as % of predicted	0.396	0.015
TLC as % of predicted	0.585	<0.001
RV as % of predicted	0.405	0.013
DLCOc as % of predicted	0.437	0.010
FRC as % of predicted	0.447	0.006

DLCOc, diffusion capacity of the lungs for carbon monoxide corrected for haemoglobin; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; PEF, peak expiratory flow; r, correlation coefficient; RV, residual volume; SpO_2, peripheral oxygen saturation; TLC, total lung capacity.

Pulmonary arterial function and functional clinical status

Exercise capacity (ie, pVO_2) is determined by multiple factors, including lung function, cardiac function, peripheral skeletal muscles and metabolism. In the normal population, pVO_2 declines with age. In Fontan patients the absolute pVO_2 is lower, but the decline with age is similar as in the normal population. In other words, in the regression equation of this relationship, the intercept but not the slope alters. As shown previously, time since Fontan does not correlate with pVO_2 (when adjusted for the normal decline of pVO_2 over time).[10] Considering that we were assessing independent clinical relevant predictors specifically for Fontan patients, we choose a priori not to include age (or time since Fontan) as a candidate variable for the multivariable model.

This study shows that additional to the known determinants of exercise capacity, in Fontan patients PA size is a novel factor independently associated with exercise capacity. To our knowledge, this has not been reported previously in Fontan patients. Nevertheless, a comparable observation has recently been made in patients after arterial switch surgery for transposition of the great arteries.[23] Although these findings concerned the main PA (MPA) area and a reduced MPA size was most likely to be related to previous surgical interventions, this also showed to be an independent predictor for exercise capacity.[23]

Additionally to our findings concerning Nakata index, the relationship between other pulmonary arterial parameters and exercise capacity has been studied. Recently Alsaied *et al*[24] reported that (mal)distribution of pulmonary blood flow (MPBF) in Fontan patients was independently associated with exercise capacity, whereas no correlation could be demonstrated between asymmetry of the left and right PA branch cross-sectional area and exercise capacity. In contrast, we did not find an association between pulmonary blood flow (mal)distribution and exercise capacity (table 2). This discrepancy might be explained by a larger proportion of patients with hypoplastic left heart syndrome (HLHS) in the study cohort of Alsaied *et al*[24]. In that study MPBF correlated with a diagnosis of HLHS, and in almost all (94%) patients with MPBF this was based on left pulmonary artery (LPA) compression, which is thought to occur frequently in Fontan patients with HLHS due to abnormal aortic dimensions.

Furthermore it is likely that (the lack of) pulmonary distensibility also plays a role in Fontan patients, as it is known from healthy individuals that a more distensible pulmonary circulation predicts a higher pVO_2.[25] Fontan patients are likely to have a limited distensibility due to both proximal (due to surgical anastomoses) and peripheral (due to adverse pulmonary vascular remodelling) stiffening of the PAs over time.[25–27] This adverse pulmonary remodelling is thought to be the result of chronic non-pulsatile flow combined with low PA pressure variability during exercise.

Nakata index and respiratory function

Pulmonary function test results did not reveal significantly impaired lung function, except for a reduced pulmonary diffusion capacity (diffusion capacity of the lungs for carbon monoxide corrected for haemoglobin (DLCOc)). It has been described that DLCOc is reduced in Fontan patients,[28] and our findings are consistent in that regard. The aetiology of reduced DLCOc in Fontan patients is unknown and is likely multifactorial. In this study, DLCOc was relatively higher when correcting for alveolar volumes, suggesting that lower lung volumes (ie, total lung capacity (TLC)) contribute at least partly to the decreased DLCOc, although TLC was not significantly impaired in our cohort. Interestingly, a previous study suggested that reduced mean capillary blood volume was partly responsible for reduced diffusion capacity in Fontan patients, showing that DLCOc increased when the patient changed from sitting to supine position due to increased mean capillary blood volume.[28] The authors explained this by the gravity-dependent pulmonary flow present in the Fontan circulation. We now show that Nakata index correlates positively with DLCOc. It is possible that MPA branches also contribute to decreased pulmonary perfusion and a lower capillary blood volume. It is difficult to discern whether the MPA branches are responsible for reduced diffusion capacity alone or together with adverse remodelled peripheral pulmonary vessels, and whether a low Nakata index is a surrogate marker for the total pulmonary vasculature. Additionally the existence of (subclinical) pulmonary emboli and plastic bronchitis has been proposed to be responsible for decreased DLCOc.

Nakata index was correlated with several spirometry parameters (table 4). We can only speculate on the nature of this relation; decreased FEV_1 and forced vital capacity in Fontan patients may be associated with multiple previous thoracic surgeries. These procedures might also affect PA size. Additionally, limited ventilatory function in Fontan patients may adversely affect pulmonary blood flow. Such limitation might be associated with further impairment of PA growth.

Oxygen saturations both at rest and during peak exercise correlated positively with Nakata index. This might be explained by the speculation that a lower Nakata index is associated with increased central venous pressures and increased pulmonary vascular resistance, leading to more right-to-left shunting (eg, increased systemic venous-to-pulmonary venous collateral flow, and/or fenestration flow) causing desaturation.

Clinical implications

Throughout the years a well-developed pulmonary vascular tree has been considered to be an important factor in order to opt for a Fontan palliation. Our results emphasise the importance of initial optimisation of the PA branch areas pre-Fontan stage (eg, consideration of additional antegrade pulmonary flow) and during the Fontan procedure (eg, optimal Fontan conduit anastomosis). However, our results show that PA size is lower in older Fontan patients, suggesting that PA size is decreasing over time and that it has significant impact on exercise capacity later in life. Therefore it may be of additional value to optimise maintenance of the pulmonary vasculature after Fontan completion by routinely screening for anatomical abnormalities in the PAs during follow-up of Fontan patients and accurately address flow-reducing and growth-reducing lesions, for instance with catheter interventions. This should especially be considered in patients with symptoms of Fontan failure and reduced exercise capacity without good explanations. Furthermore, the use of pulmonary vasodilator therapies has been advocated in Fontan patients. However its effects on modulation of the pulmonary vasculature and on clinical performance in Fontan patients are currently insufficiently investigated.

Limitations

This study has limitations inherent to a cross-sectional study design, which does not allow for assessment of causal relationships. Patients with contraindications for MRI such as an implanted pacemaker could not be included, leading to a potential selection bias. Different CPET techniques were used for adults (treadmill) and children (bicycle), and pVO_2 from bicycle tests are suggested to be 5%–10% lower.[29] However the pVO_2 results were indexed to predicted reference values based on the corresponding technique of testing and were therefore considered comparable.

CONCLUSIONS

This study identified PA size expressed as CMR-derived Nakata index as a novel independent predictor for functional clinical status. Nakata index is correlated negatively with time since Fontan completion, suggesting that chronic abnormal non-pulsatile pulmonary blood flow plays a role in lagging pulmonary arterial growth in the Fontan circulation.

Key messages

What is already known on this subject?

- In the Fontan circulation, non-pulsatile pulmonary flow is suggested to negatively affect pulmonary artery growth.
- The pulmonary vasculature is regarded a key determinant of outcome after Fontan completion.
- However there are limited data on the potential relationship between pulmonary artery size and functional clinical status in Fontan patients.

What might this study add?

- This study showed that pulmonary artery size expressed as Nakata index is a novel independent predictor for functional clinical status, and Nakata index correlated negatively with follow-up duration.

How might this impact on clinical practice?

- These findings emphasise the importance of initial optimisation of the pulmonary arteries.
- Moreover, this study implicates that it may be of additional clinical value to optimise maintenance of the pulmonary vasculature during follow-up after Fontan completion, and this could be done by routinely screening for anatomical abnormalities in the pulmonary arteries during follow-up and accurately addressing flow-reducing and growth-reducing lesions.

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