Relation of Fontan Baffle Stroke Volume to Fontan Failure and Lower Exercise Capacity in Patients With an Atriopulmonary Fontan

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Fontan failure remains a significant problem, especially in patients with an atriopulmonary Fontan. Fontan baffle volume change during the cardiac cycle (Fontan baffle stroke volume) may affect outcomes in Fontan circulation. Assuming that increased Fontan baffle stroke volume is associated with increased energy loss in the baffle, we hypothesized that higher baffle stroke volume is associated with worse exercise capacity and increased incidence of Fontan failure. Patients from 6 centers with an atriopulmonary or lateral tunnel Fontan operation were included if they had a cardiac magnetic resonance (CMR) study and an adequate cardiopulmonary exercise test. Fontan baffle stroke volume was defined as the difference between maximum and minimum Fontan baffle volumes. Fontan failure was defined as death, listing for transplantation, heart failure symptoms requiring medications, or peak VO_2 below 16 ml/kg/min. The study group consisted of 107 patients (median age 19 years, interquartile range, 14 to 29 years). Most patients (84%) had lateral tunnel procedure. During a median follow-up period of 6.8 [interquartile range: 3.2 to 8.8] years after the CMR, 25 (23%) patients had Fontan failure (7 deaths, 3 listed for transplantation, and 15 with heart failure symptoms). Predictors of Fontan failure on multivariable analysis were ventricular tachycardia, protein losing enteropathy, and additionally in atriopulmonary Fontan only, larger Fontan baffle stroke volume. Predictors of lower peak VO_2 on multivariable analysis were older age at CMR and additionally in atriopulmonary Fontan only, larger Fontan baffle stroke volume. In conclusion, larger Fontan baffle stroke volume was independently associated with lower peak VO_2 and Fontan failure in atriopulmonary Fontan. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:151−157)**

Despite the significant improvement in outcomes after the Fontan operation, many patients with Fontan circulation continue to have significant exercise impairment and develop Fontan failure (FF).[1-3] Cardiac MRI (CMR) has been shown to be a valuable tool to predict adverse outcomes in Fontan patients and offers important information on Fontan baffle anatomic details.[4,5] CMR can also provide measurements of the Fontan baffle volume changes during the cardiac cycle which may be associated with energy loss related to blood swirling and flow inefficiency. The difference between the maximal Fontan baffle volume and the minimal baffle volume (Fontan baffle stroke volume) may be an indicator for energy loss in the Fontan population.[6] Additionally, Fontan baffle stroke volume may relate to differences in pulmonary flow patterns that may contribute to long-term pulmonary vascular bed function, an important determinant of long-term outcomes.[7] Recent exercise CMR studies showed that energy loss in the Fontan baffle is associated with lower oxygen consumption at maximal exercise (peak VO_2) which is a measurement of exercise capacity.[8] Pulmonary vascular resistance is also another important determinant of peak VO_2 and plays an important role in the pathophysiology of FF in this patient population.[9] The associations of Fontan baffle stroke volume with peak VO_2 and FF are largely unknown.[10,11] Thus, the purpose of this study was to identify the impact of Fontan baffle stroke volume on peak VO_2 and clinical outcomes in patients after the Fontan operation. We hypothesized that higher Fontan baffle stroke volume is associated with lower peak VO_2 and development of FF.

Methods

This study was a multi-institutional retrospective study including patients from Boston Children's Hospital and a

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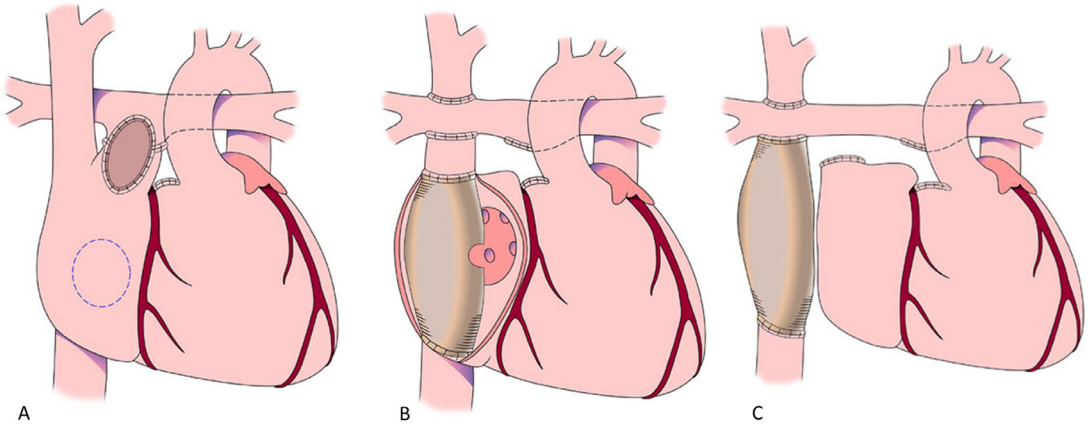

Figure 1. Illustration of different types of Fontan circulation. (A) Atriopulmonary Fontan. (B) Lateral tunnel Fontan. (C) Extracardiac conduit Fontan. Figures are used from the Boston Children's Multimedia library with permission.

Dutch network of 5 tertiary centers (Erasmus University Medical Center, Rotterdam; Academic Medical Center, Amsterdam; Leiden University Medical Center, Leiden; University Medical Center Utrecht, Utrecht; Radboud University Medical Center, Nijmegen). A database search identified all Fontan patients who, between January 1999 and July 2017, had a CMR study and cardiopulmonary exercise test (CPET) within 1 year of each other. Patients were included if Fontan baffle volume could be measured on CMR cine imaging and if they had an adequate exercise stress testing, defined as respiratory exchange ratio ≥1 or a heart rate ≥75% predicted. Patients were excluded if they had an extracardiac conduit type Fontan as the Fontan baffle volume change would be minimal in these patients. Figure 1 illustrates different types of Fontan operation. The institutional review board of the 6 centers approved this study.

CMR studies were performed with 1.5 Tesla scanners (Philips Healthcare, Best, the Netherlands and GE Medical Systems, Milwaukee, Wisconsin). If a patient had multiple eligible CMR and CPET studies, the study with the most complete data set and minimal time between CMR and CPET was used for analysis. The details of the CMR protocols used in our centers for assessment of patients after the Fontan operation have been published previously.[12–17] Briefly, ventricular assessment was performed by an electrocardiographically-gated, steady-state free precession cine CMR in vertical and horizontal ventricular long-axis planes, and a stack of slices in a ventricular short-axis plane or axial plane, encompassing the cardiac apex through the atria. Ventricular volumes were measured by manual tracing of endocardial and epicardial borders at end-diastole (maximal volume) and end-systole (minimal volume) as previously described.[5,14]

The Fontan baffle stroke volume was manually measured on steady-state free precession cine imaging in axial or short-axis planes (Figure 2). Fontan baffle geometries were defined from the inferior vena cava (just superior to the entrance of the hepatic veins) to immediately inferior to the level of the pulmonary arteries. The baffles were measured using the phase of the cardiac cycle with minimal and maximal volumes. To better account for differences in body size, Fontan baffle stroke volume, end diastolic volume (EDV), end systolic volume (ESV), Stroke volume (SV), and ventricular mass were indexed to body surface area (BSA) raised to the 1.3 power.[5,18] This method was selected based on studies showing that volumetric parameters are best adjusted to BSA raised to the 1.3 power.[18] In patients with axial cine imaging, circumferential strain measurements were obtained from the midportion of the Fontan baffle using feature tracking techniques. We did not perform strain analysis in patients who did not have an axial cine stack imaging. All analyses were performed using commercially available software (QMass, Medis Medical Imaging Systems, Leiden, the Netherlands) and (cmr^{42}, Circle Cardiovascular Imaging Inc., Calgary, Canada).

Demographic and clinical data, including underlying diagnoses and type of single ventricle based on ventricular dominance, were abstracted from the medical records. The type of Fontan was classified as either a total cavopulmonary connection of the lateral tunnel type (LT) or atriopulmonary (AP). Additional parameters included age at Fontan and time from Fontan to CMR. Arrhythmia history was compiled by review of Holter monitors, electrocardiograms, electrophysiology catheterizations, and clinic notes. Other variables included a history of congestive heart failure requiring treatment (defined as New York Heart Association class II or greater), protein losing enteropathy (PLE), stroke, thrombus, or seizures. The definition of FF varies between studies.[19] Most studies define FF as either having symptomatic heart failure, significant exercise impairment, listing for transplantation, or death.[9,20] For our study, FF was defined as death, listing for transplantation, heart failure symptoms requiring medications, or peak VO_2 below 16 ml/kg/min. This peak VO_2 threshold was associated with increased mortality in Fontan patients in previous studies.[21]

CPET was performed using a calibrated cycle ergometer, and ramp or stepwise protocol.[22] For the ramp protocol the test starts with setting an initial work rate based on patient's BSA with linear increases every minute reaching a peak exercise after 10 minutes. For the stepwise protocol the intensity is increased every minute. Gas exchange at rest, during exercise, and during recovery was analyzed to determine peak VO_2.[23] Peak VO_2 was indexed to weight.[24] Seventy-two patients had ramp protocol while 35 had a stepwise protocol. Only studies with an adequate CPET were included for analysis.

The Student's *t* test or Mann-Whitney *U* test was used to compare 2 groups of continuous parametric or nonparametric variables, respectively. Fisher's exact test was used

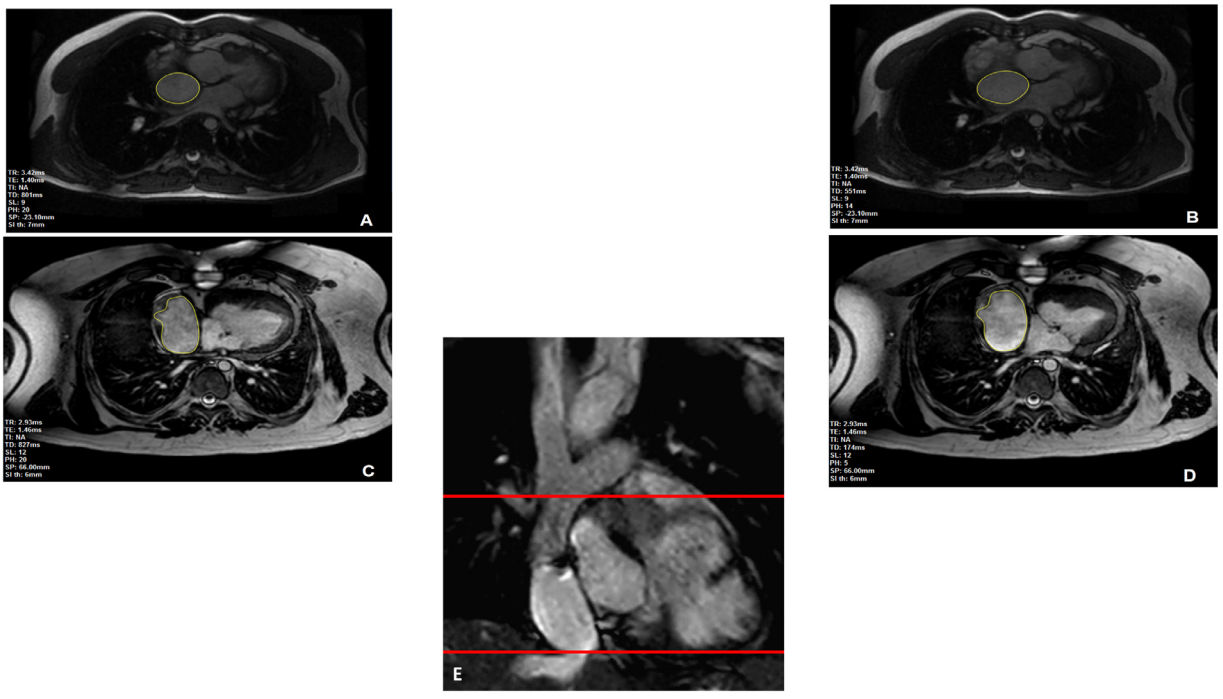

Figure 2. Fontan baffle stroke volume by Fontan anatomic type. (A) Minimum volume of lateral tunnel baffle. (B) Maximum volume of lateral tunnel baffle. (C) Minimum volume of atriopulmonary baffle. (D) Maximum volume of atriopulmonary baffle. (E) Contouring the Fontan baffle starting above the level of the hepatic veins to below the level of the branch pulmonary arteries.

for categorical variables. Univariate association between normally distributed variables was estimated using the Pearson correlation coefficient. A multivariable linear regression modeling procedure with 0.1 as the significance level for entry and 0.05 as the significance level to remain in the model was constructed to determine independent predictors of peak VO_2. A multivariable logistic regression model with 0.1 as the significance level for entry and 0.05 as the significance level to remain in the model was constructed to identify the independent factors associated with FF. To study the interaction between Fontan baffle stroke volume and Fontan type, an interaction term was used in the multivariable models. All p values were 2-tailed, and differences and associations were considered significant when $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 24.0, Armonk, New York) and JMP (version 12, SAS Institute Inc., Cary, North Carolina).

Results

There were 107 patients in the study cohort who met the inclusion criteria. The mean age at CMR was 21.3 ± 9.9 years and the mean time since Fontan was 16.0 ± 6.9 years. Most patients (84%) had LT Fontan procedure while 16% had AP Fontan. Other characteristics of the study cohort are shown in Table 1. The Fontan baffle stroke volume was significantly larger in patients with an AP Fontan compared with LT Fontan (10 ± 6 vs 3 ± 2 ml/$BSA^{1.3}$, $p < 0.001$; Figure 3).

The median follow-up period was 6.8 (3.2 to 8.8) years after the CMR. A total of 25 (23%) of patients met the composite end point of FF (7 deaths, 3 listed for transplantation, 15 had heart failure symptoms requiring medications or peak VO_2 < 16 ml/kg/min). Patients with FF had significantly higher Fontan baffle stroke volume (6 ± 6 vs 3 ± 3 ml/$BSA^{1.3}$; $p = 0.02$; Figure 4). Tables 1 and 2 report the univariate analysis for parameters of patients with and without FF.

Predictors of FF by univariate analysis are summarized in Table 3. On multivariable analysis, ventricular tachycardia, PLE, and Fontan baffle stroke volume in AP Fontan (but not in LT Fontan) were significantly associated with FF (Table 3).

The mean peak VO_2 for our Fontan cohort was 26 ± 8 ml/kg/min. The univariate predictors of lower peak VO_2 were summarized in Table 4. On multivariable analysis, only older age at CMR and Fontan baffle stroke volume in AP Fontan (but not in LT Fontan) were associated with a lower peak VO_2 (Table 4).

Strain measurements were completed in 63 patients. Midventricular Fontan baffle circumferential strain measurements were weakly correlated with Fontan baffle stroke volume ($r = 0.35$, $p = 0.004$) and did not correlate with FF or peak VO_2.

Discussion

This study found that Fontan baffle stroke volume was higher in AP Fontan compared with LT Fontan and was independently associated with worse exercise capacity and FF in AP Fontan. Other predictors of FF included ventricular tachycardia and PLE whereas older age at CMR, a surrogate for older age and longer time since Fontan, was the only other predictor of lower peak VO_2. This study introduces Fontan baffle stroke volume as a novel, potentially clinically important parameter, especially in AP Fontan patients.

Table 1
Demographic and clinical characteristics of the study cohort

Variable	All patients (n = 107)	Fontan failure		p Value
		Yes (n = 25)	No (n = 82)	
Age at cardiac MRI (years)	21.3 ± 9.9	26.9 ± 10.1	19.5 ± 9.37	0.002
Time since Fontan (years)	16.0 ± 6.9	19.7 ± 6.6	14.9 ± 6.5	0.002
Time between cardiac MRI and exercise test (months)	2.2 ± 6.1	4.0 ± 8.0	1.6 ± 3.8	0.22
Body surface area at CMR (m^2)	1.6 ± 0.4	1.7 ± 0.3	1.6 ± 0.4	0.16
Cardiac diagnosis				0.43
Tricuspid atresia	16 (15%)	6 (24%)	10 (12%)	
Double-inlet left ventricle	27 (25%)	4 (16%)	23 (28%)	
Hypoplastic left heart syndrome	16 (15%)	3 (12%)	13 (16%)	
Unbalanced atrioventricular canal	9 (8%)	4 (16%)	5 (6%)	
Double-outlet right ventricle	17 (16)	4 (16%)	13 (16%)	
Complex 2 ventricle	7 (7%)	2 (8%)	5 (6%)	
Hypoplastic tricuspid valve/right ventricle	5 (5%)	2 (8%)	3 (4%)	
Pulmonary atresia/intact ventricular septum	5 (5%)	0 (0)	5 (6%)	
Mitral atresia	5 (5%)	0 (0%)	5 (6%)	
Heterotaxy	8 (8%)	3 (12%)	5 (6%)	0.38
Dominant ventricular morphology				0.5
Left ventricle	48 (45%)	13 (52%)	35 (43%)	
Right ventricle	40 (37%)	7 (28%)	33 (40%)	
2 ventricles	19 (18%)	5 (20%)	14 (27%)	
Fontan type				0.004
Lateral tunnel Fontan	90 (84%)	16 (64%)	74 (90%)	
Atriopulmonary Fontan	17 (16%)	9 (36%)	8 (10%)	
Ventricular tachycardia	3 (3%)	3 (12%)	0 (0%)	0.001
Protein losing enteropathy	3 (3%)	3 (12%)	0 (0%)	0.001

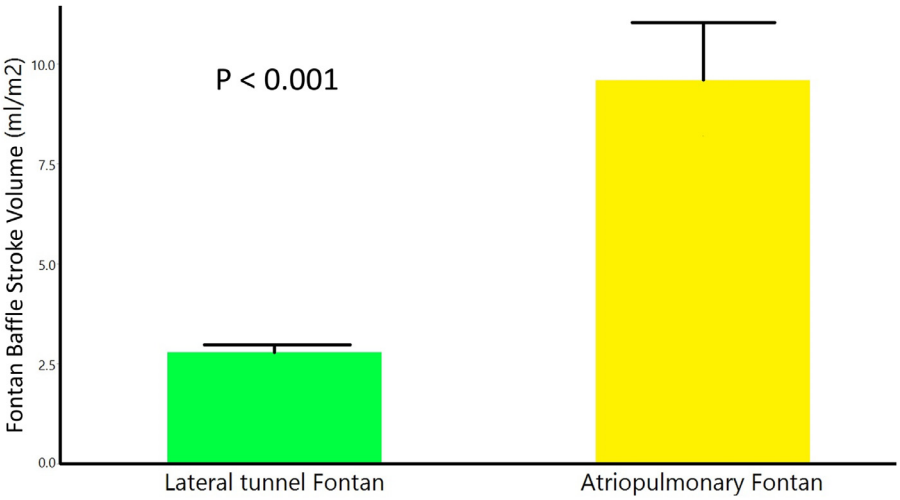

Figure 3. Fontan baffle stroke volume by Fontan anatomic type. Results are presented as means and standard errors.

As with previous studies, we found significant exercise impairment in Fontan patients.[25,26] Many other determinants of reduced exercise capacity have been reported in the literature including chronotropic impairment, diastolic dysfunction, and power loss in the Fontan circulation.[11,27] Noncardiac factors such as age, muscle mass, and conditioning are also probably important determinants.[11,27] In addition to confirming the association of age with exercise capacity, our study found that Fontan baffle stroke volume is another independent factor that adversely affects exercise capacity in the AP Fontan population. We speculate that Fontan baffle stroke volume is a surrogate for energy loss in the AP Fontan circulation. Previous studies have demonstrated the association of energy loss exercise intolerance in Fontan patients.[28–30] While calculation of energy loss may be a more sophisticated parameter, it is not readily available in clinical practice because it requires applying flow dynamics simulations to MRI datasets.[31] In contrast, Fontan baffle stroke volume is easily measured and can be done retrospectively on standard cine imaging.

The energy loss in the AP Fontan has been demonstrated in animal studies and in vitro models, and was the theoretical

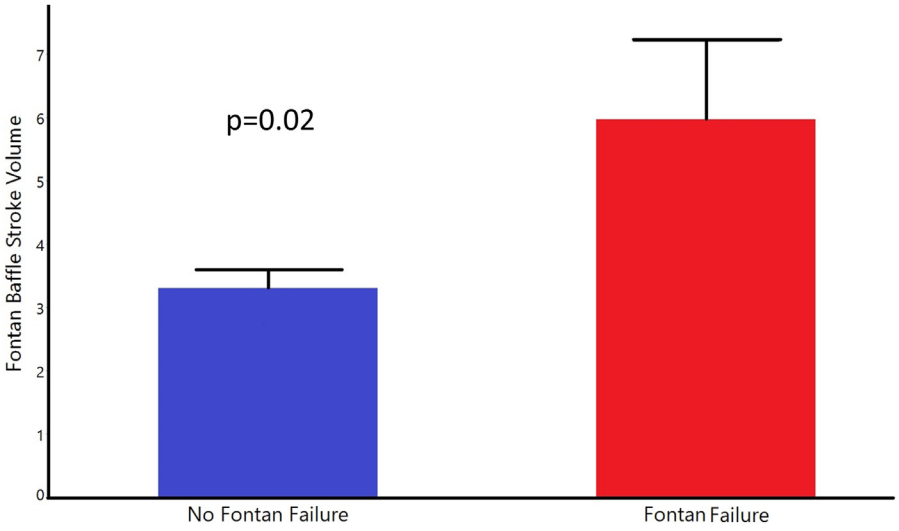

Figure 4. Fontan baffle stroke volume in patients with and without Fontan failure. Results are presented as means and standard errors.

Table 2
CMR measurements in patients with and without Fontan failure

Variable	All patients (n = 107)	Fontan failure		p Value
		Yes (n = 25)	No (n = 82)	
Ventricular end-diastolic volume (ml/BSA$^{1.3}$)	88 ± 26	92 ± 28	87 ± 25	0.38
Ventricular end-systolic volume (ml/BSA$^{1.3}$)	44 ± 16	45 ± 20	43 ± 15	0.53
Indexed ventricular stroke volume (ml/BSA$^{1.3}$)	50 ± 18	54 ± 16	49 ± 18	0.16
Ventricular mass-to-volume ratio (gram/ml)	0.55 ± 0.19	0.53 ± 0.20	0.58 ± 0.18	0.13
Indexed ventricular mass (gram/BSA$^{1.3}$)	60.0 ± 14.8	59.6 ± 21.6	60.7 ± 15.1	0.83
Ventricular ejection fraction (%)	51 ± 9	52 ± 11	50 ± 9	0.57
Fontan baffle maximum volume (ml/ BSA$^{1.3}$)	32 ± 27	51 ± 46	26 ± 15	0.01
Fontan baffle minimum volume (ml/ BSA$^{1.3}$)	29 ± 24	45 ± 39	24 ± 13	0.01
Fontan baffle stroke volume (ml/ BSA$^{1.3}$)	4 ± 4	5 ± 5	3 ± 3	0.02

Abbreviations: BSA = Body surface area; ml = milliliters.

Table 3
Predictors of Fontan failure

Predictor	Odds ratio or parameter estimate ± SE	p Value
Univariate analysis		
Peak VO_2 (ml/kg/min) (n = 107)	−0.12 ± 0.04*	0.001
Protein losing enteropathy (n = 107)	21.9 ± 200.0†	0.01
Fontan type (atriopulmonary) (n = 107)	5.2 ± 1.7†	0.004
Ventricular arrhythmia (n = 107)	21.9 ± 200.0†	0.01
History of stroke (n = 107)	3.8 ± 1.3†	0.02
Age at CMR (year) (n = 107)	0.07 ± 0.02*	0.002
Time since Fontan (year) (n = 107)	0.11 ± 0.03*	0.002
Fontan baffle volume change (ml/m^2) (n = 107)	0.17 ± 0.07*	0.01
Multivariable analysis (n = 107)		
Ventricular arrhythmia	10.2 ± 3.6†	0.004
Protein losing enteropathy	10.2 ± 3.5†	0.004
Fontan baffle volume change in atriopulmonary Fontan using an interaction term (stroke volume * Fontan anatomic type)	0.22 ± 0.10*	0.02

* Parameter estimate ± standard error.
† Odds ratio for Fontan failure.

Table 4
Predictors of exercise capacity

Predictor	Parameter estimate ± SE	p Value
Univariate analysis		
Fontan Type (atriopulmonary) (n = 107)	−9.19 ± 1.31	<0.001
Systemic right ventricle (n = 107)	−7.60 ± 1.87	<0.001
History of seizures (n = 107)	−3.87 ± 1.48	0.020
History of stroke (n = 107)	−5.65 ± 1.72	0.003
Age at CMR (year) (n = 107)	−0.45 ± 0.06	<0.001
Time since Fontan (year) (n = 107)	−0.58 ± 0.10	<0.001
Fontan baffle volume change (ml/m^2) (n = 107)	−0.49 ± 0.20	0.010
Mass to volume ratio (gm/ml) (n = 107)	−6.06 ± 2.41	0.010
End diastolic volume (ml/m^2) (n = 107)	−0.05 ± 0.02	0.030
Multivariable analysis (n = 107)		
Age at MRI	−0.34 ± 0.07	<0.001
Fontan baffle volume change in atriopulmonary Fontan using an interaction term (stroke volume * Fontan anatomic type)	−0.60 ± 0.21	0.009

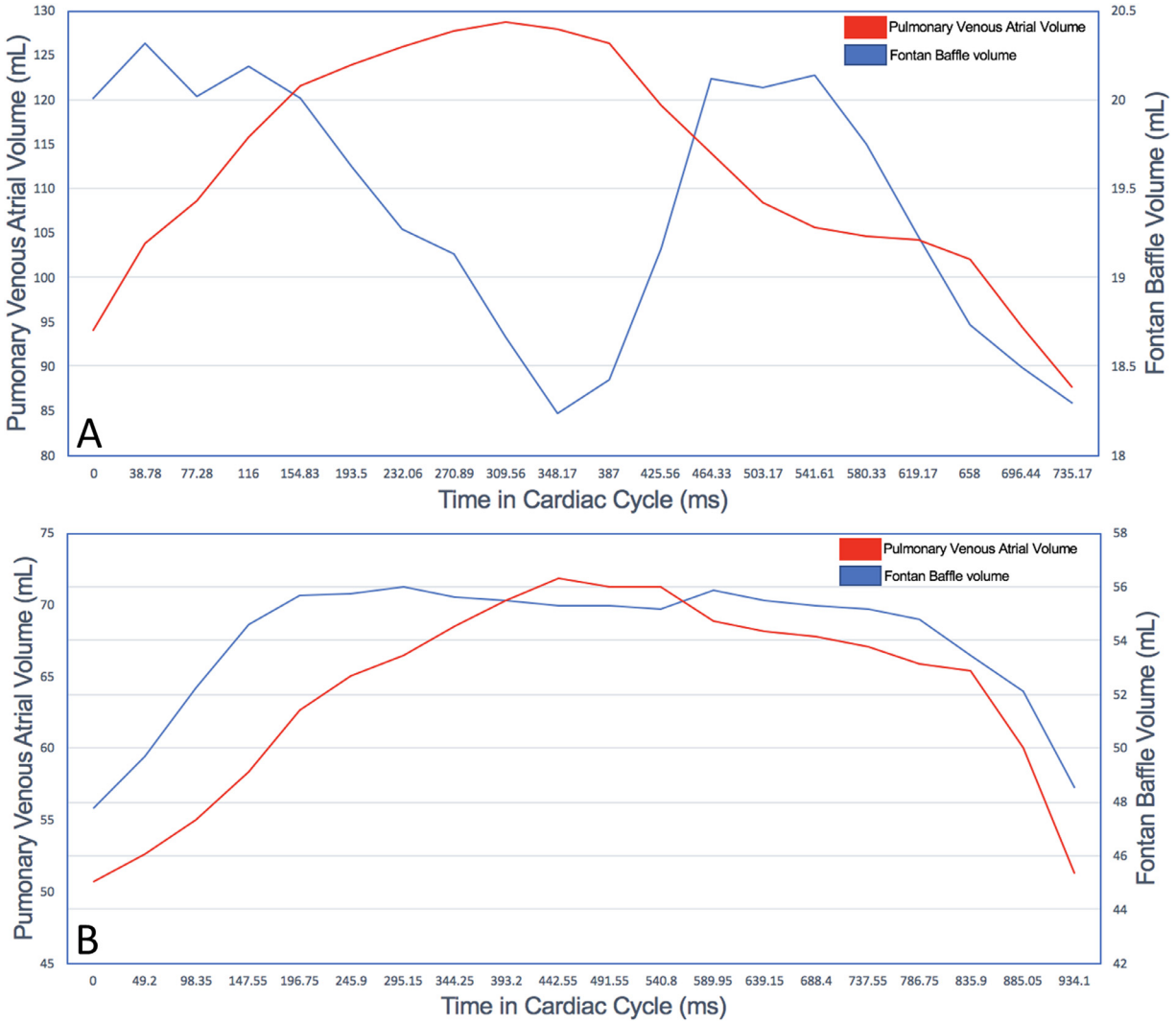

Figure 5. The change of the Fontan baffle stroke volume and the pulmonary venous atrium over the cardiac cycle. (A) Synergistic movement of the Fontan baffle and pulmonary venous atrium in one patient with lateral tunnel Fontan. (B) No synergistic movement of the Fontan baffle and pulmonary venous atrium in atriopulmonary Fontan.

basis for implementing LT Fontan.[32–34] Significant energy loss in AP Fontan is due to atrial dilation and change in volume during the cardiac cycle which may represent an "energy sink" with swirling of blood and little impetus for forward flow.[32–34] This loss may result in diminished ability to increase pulmonary blood flow and ventricular stroke volume with exercise in the AP Fontan compared with the LT Fontan.[35] Following similar reasoning, one might expect LT Fontan patients with greater Fontan stroke volume to be at greater risk for negative outcomes; however, this was not the case in our study. We speculate that could be due to the interaction between the pulmonary venous atrium and the Fontan baffle in LT Fontan. The baffle becomes smaller when the pulmonary venous atrium fills and larger when it empties. This pattern may create synergy between the atrium and the Fontan baffle in LT Fontan. This is shown in Figure 5 in which we see synergistic movement of the Fontan baffle and pulmonary venous atrium in LT Fontan while we do not see similar pattern in AP Fontan.

Baffle peak circumferential strain was associated with volumetric changes of the Fontan baffle although it was not associated with exercise capacity or with FF. This could be related to the small number of patients who we were able to obtain strain measurements for since many patients did not have axial cine stack imaging.

The study has some limitations. Similar to many CMR studies, there is a risk for selection bias as patients with pacemakers and defibrillators could not be evaluated while sicker patients could be overrepresented because they are more likely to have a CMR. Also, about 20% of patients had major artifact on their CMR images and many were excluded due to inability to contour the Fontan baffle. Furthermore, this study included only patients with an adequate CPET, which limited the sample size and may have introduced selection bias toward patients with higher functional status. Finally, we did not have catheterization pressure measurements on most of our patients and thus correlations with pulmonary vascular resistance could not be performed.

In conclusion, in patients after the AP Fontan operation, Fontan baffle stroke volume was independently associated with FF and lower exercise capacity. This study identifies

Fontan baffle stroke volume as a novel parameter and potentially important risk factor in AP Fontan patients.

Disclosures

The authors have no conflicts of interest to disclose.

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