Hemodynamics of Fontan Failure

The Role of Pulmonary Vascular Disease

BACKGROUND: Nonpulsatile pulmonary blood flow in Fontan circulation results in pulmonary vascular disease, but the potential relationships between pulmonary vascular resistance index (PVRI) and Fontan failure have not been studied. The objective was to determine whether the absence of subpulmonary ventricle in the Fontan circulation would make patients more vulnerable to even low-level elevations in PVRI, and when coupled with low cardiac index, this would identify patients at increased risk of Fontan failure.

METHODS AND RESULTS: Two hundred sixty-one adult Fontan patients underwent cardiac catheterization; age 26±3 years, men 146 (56%), atriopulmonary Fontan 144 (55%). Patients were divided into 2 groups: those with high PVRI (>2 WU·m^2) and low cardiac index <2.5 L min^{-1} m^{-2} (group 1, n=70, 30%), and those with normal PVRI and normal cardiac index (group 2, n=182, 70%). Fontan failure was defined by the composite of all-cause mortality, listing for heart transplantation, or initiation of palliative care. There were 68 (26%) cases of Fontan failure during a mean follow-up of 8.6±2.4 years. When compared with group 2, freedom from Fontan failure was significantly lower in group 1: 66% versus 89% at 5 years. The combination of high PVRI and low cardiac index was an independent risk factor for Fontan failure (hazard ratio, 1.84; 95% confidence interval, 1.09–2.85).

CONCLUSIONS: When coupled with low cardiac index, even mild elevations in PVRI identify patients at high risk of Fontan failure. This suggests that pulmonary vascular disease is a key mechanism underlying Fontan failure and supports further studies to understand the pathophysiology and target treatments to pulmonary vascular tone in this population.

Alexander C. Egbe, MBBS, MPH
Heidi M. Connolly, MD
William R. Miranda, MD
Naser M. Ammash, MD
Donald J. Hagler, MD
Gruschen R. Veldtman, MD
Barry A. Borlaug, MD

Correspondence to: Barry A. Borlaug, MD, Mayo Clinic and Foundation, 200 First St SW, Rochester, MN 55905. E-mail borlaug.barry@mayo.edu

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WHAT IS NEW?

- The combination of high pulmonary vascular resistance and low cardiac output is the hemodynamic phenotype of patients who are at the highest risk for Fontan failure.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Because patients with high pulmonary vascular resistance and low cardiac output represent a high-risk subgroup, these patients should be considered for a trial of pulmonary vasodilator therapy and early referral to an accredited adult congenital heart disease center for evaluation and possible transplant consideration to reduce mortality.

Congenital heart disease is an important and understudied cause of heart failure.[1] Patients lacking an effective subpulmonary ventricle constitute an important group among the broader population of patients with adult congenital heart disease.[1] The Fontan operation is an effective palliation for children with single ventricle anatomy, but is associated with high morbidity and mortality in the adult years.[2–4] Although the Fontan procedure addresses the hemodynamic limitations associated with the single ventricle anatomy, it creates a unique circulatory milieu, characterized by nonpulsatile lung perfusion, systemic venous hypertension, and low cardiac output.[5] These hemodynamic derangements may contribute to the excess morbidity and mortality in this population, but the mechanisms are poorly understood.[5–8]

Chronic, nonpulsatile pulmonary blood flow in the Fontan circulation may cause pulmonary endothelial dysfunction, but the potential role of pulmonary vascular disease on the pathogenesis of Fontan failure has not been studied.[9,10] Indeed, identification of pulmonary vascular disease in the Fontan physiology is challenging because elevated pulmonary vascular resistance index (PVRI) is often masked by the low cardiac output state that is common in this population.[5,11] We hypothesized that because there is no subpulmonary ventricle in the Fontan circulation, even low-level increases in PVRI would greatly impede blood flow, and that when this was coupled with low cardiac output, patients would be at increased risk for the development of Fontan failure. To test this hypothesis, we examined clinical outcomes among Fontan patients with low output and elevated PVRI undergoing clinically indicated cardiac catheterization at our institution over a 25-year period.

METHODS

Patient Selection

This was a retrospective review of adult Fontan patients (>18 years) followed at the Mayo Clinic Adult Congenital Heart Disease program. We identified all patients who underwent cardiac catheterization for clinical indications from January 1, 1990, through December 31, 2015 (Figure I in the Data Supplement). The Mayo Clinic Institutional Review Board approved this study and waived informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Invasive and Clinical Data Acquisition

Medical records were reviewed in detail including clinical notes, echocardiograms, magnetic resonance imaging, cardiopulmonary exercise tests, and surgical notes. Fontan-associated diseases were defined as in previous studies[6,12] and include protein-losing enteropathy (elevated stool α-1 antitrypsin concentration >54 mg/dL with decreased serum albumin <3.5 g/dL and accompanying symptoms); cirrhosis (liver stiffness >5.0 kPa by magnetic resonance elastography or stage 4 fibrosis on histology); and heart failure hospitalization (admission for worsening heart failure signs and symptoms requiring intravenous diuretics).

All cardiac catheterization procedures were reviewed, and invasive hemodynamic data were analyzed. In patients undergoing >1 cardiac catheterization in adulthood, we retrieved the data from the first cardiac catheterization. Fontan (central venous) pressures, pulmonary artery pressures, pulmonary capillary wedge pressures, and systemic ventricular end-diastolic pressures were recorded at end expiration.

Cardiac output was determined by the Fick technique using assumed O_2 consumption and directly measured O_2 contents in the pulmonary artery and systemic circulations.[13] Cardiac index was calculated by the quotient of cardiac output and body surface area. PVRI was calculated by (mean pulmonary artery pressure)/cardiac index. Systemic vascular resistance index was calculated by (mean systemic arterial pressure–Fontan pressure)/cardiac index. Plasma volume at the time of catheterization was estimated by: (1–hematocrit) (a+[b weight in kg]), where a=1530 in men and 864 in women, and b=41 in men and 47.9 in women.[14]

Study Hypotheses and End Points

The primary outcome end point of the study was defined as Fontan failure which represented a composite of all-cause mortality, listing for heart transplantation, or initiation of palliative care. Heart transplantation was defined as the patients who were listed for transplant and subsequently underwent heart transplantation within the study period. Listing for heart transplant comprised patients who were listed but did not undergo heart transplantation by the end of the study period. Palliative care was defined as being declined for heart transplant listing because of prohibitive surgical risk. Only 1 event was counted per patient.

To test the study hypothesis, we compared clinical characteristics and outcomes between patients with both elevated PVRI and low cardiac index (group 1) to remainder of the cohort (group 2). Elevated PVRI and low cardiac index were defined as PVRI >2 WU·m^2 and cardiac index <2.5 L min^{-1} m^{-2} based on partition values used in previous studies.[11,15]

Statistical Analysis

Analyses were performed with JMP software (version 10.0; SAS Institute Inc). Categorical variables were reported as percentages, and continuous variables were reported as mean±SD or median (interquartile range) for skewed data. Categorical variables were compared using the χ^2 test or Fisher exact test, and continuous variables were compared with a 2-sided, unpaired *t* test or Wilcoxon rank-sum test, as appropriate.

Freedom from Fontan failure was assessed using the Kaplan–Meier method and compared using the log-rank test. The time of the first cardiac catheterization in adulthood was considered as the time zero in this analysis. A Cox proportional hazards model was used to determine the association between the combination of high PVRI and low cardiac index and the occurrence of Fontan failure. The variables included in the univariate model were chosen a priori based on their previously demonstrated association with outcome in Fontan patients.[6,12,16,17] Variables that reached statistical significance in univariate analysis were included in the multivariate analysis. The Schoenfeld residual method was used for testing the proportional hazard assumption. The risk for each variable was expressed as hazard ratio (HR) and 95% confidence interval. For all statistical analyses, a *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Patient Characteristics

A total of 261 adult patients with prior Fontan palliation underwent cardiac catheterization during the study period (Table 1). The indications for cardiac catheterization were heart failure (n=45, 17%), arrhythmia (n=27, 11%), cyanosis (n=68, 26%), preoperative assessment (n=56, 22%), liver disease (n=33, 13%), protein-losing enteropathy (n=18, 7%), and multiple indications (n=25, 10%). The patients with >1 indication for cardiac catheterization were classified under multiple indications. The mean age at the time of cardiac catheterization was 26±3 years, 146 (56%) were men, and 144 (55%) had an atriopulmonary Fontan connection. The mean PVRI was 2.0±0.8 WU·m^2, and the median cardiac index was 2.8 L min^{-1} m^{-2} (1.9–3.6 L min^{-1} m^{-2}).

Of the 261 patients, 79 (30%) were classified into group 1, whereas 182 (70%) were classified into group 2. When compared with group 2 patients, group 1 patients were slightly older at the time of cardiac catheterization and were more likely to have atriopulmonary Fontan connection or be treated chronically with diuretics. Other comorbid conditions and clinical characteristics were similar between groups (Table 1).

Table 1. Baseline Clinical Characteristics*

	All (n=261)	Group 1 (n=79)	Group 2 (n=182)	*P* Value
Age at time catheterization, y	26±3	29±4	23±3	0.01
Age at Fontan operation, y	8±4	9±4	7±4	0.06
Male	146 (56%)	45 (57%)	101(56%)	0.3
Body surface area, m^2	1.8±0.4	1.9±0.4	1.8±0.2	0.2
Estimated plasma volume, mL	3125±642	3206±287	3041±683	0.07
Left ventricle	157 (60%)	49 (62%)	108 (59%)	0.13
Atriopulmonary Fontan	144 (56%)	52 (66%)	92 (51%)	0.02
Fontan-associated diseases				
Protein-losing enteropathy	22 (8%)	9 (11%)	13 (7%)	0.3
Thromboembolism	45 (17%)	15 (19%)	30 (17%)	0.3
Cirrhosis	56 (21%)	11 (14%)	45 (25%)	0.052
Atrial arrhythmia	101 (39%)	33 (39%)	68 (37%)	0.4
Heart failure hospitalization	29 (11%)	11(14%)	18 (10%)	0.5
Creatinine clearance <60 mL/min	66 (25%)	25 (32%)	41 (23%)	0.11
Laboratory tests				
Hemoglobin, g/dL	13.2±1.4	13.6±1.1	13.0±0.9	0.14
Platelet, ×10^3/L	134±46	108±31	167±27	0.01
Creatinine, mg/dL	1.2±0.4	1.3±0.3	1.1±0.4	0.3
Albumin, g/dL	4.2±0.6	4.0±0.5	4.2±0.3	0.2
Aspartate aminotransferase, U/L	33±6	36±4	32±5	0.15
Alanine aminotransferase, U/L	46±9	49±7	43±6	0.09
NT-proBNP, pg/mL	365±106	398±68	343±59	0.06
FEV1 (% predicted) (n=63)	79±16	78±12	79±15	0.12
FVC (% predicted) (n=63)	75±10	76±11	75±9	0.36
Therapies				
Paced rhythm	52 (20%)	18 (23%)	34 (19%)	0.2
BB or CCB therapy	58 (22%)	19 (24%)	39 (21%)	0.4
RAAS antagonist	61 (23%)	18 (23%)	43 (24%)	0.3
Warfarin	69 (24%)	23 (30%)	45 (25%)	0.12
Diuretics	75 (29%)	31 (39%)	44 (24%)	0.01

BB indicates β-blocker; CCB, calcium channel blocker; FEV1, volume of air exhaled in first second of forced expiration; FVC, forced vital capacity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and RAAS, renin–angiotensin–aldosterone system.

*Baseline clinical characteristics at the time of cardiac catheterization.

Invasive and Noninvasive Hemodynamics

All patients underwent transthoracic echocardiography contemporaneously with cardiac catheterization. The interval between echocardiogram and cardiac catheterization was 5±2 days. Cardiac magnetic resonance imaging and cardiopulmonary exercise tests were performed in 82

(31%) and 148 (57%) patients, respectively. The magnetic resonance imaging scans and the cardiopulmonary exercise tests were performed a mean of 8±5 months and 13±7 months of the cardiac catheterization, respectively.

By design, PVRI was higher and cardiac index lower in groups 1 when compared with group 2. However, all other invasive hemodynamic variables were similar (Table 2). Group 1 patients had lower stroke volume index by magnetic resonance imaging, 36±3 versus 45±6 mL/m^2, *P*=0.031, and lower peak oxygen consumption during cardiopulmonary exercise testing, 17.1±2.9 versus 21.3±1.4 mL kg^{-1} min^{-1}, *P*=0.042. Other noninvasive hemodynamic and cardiopulmonary exercise data were similar in the groups (Table 2).

Table 2. Hemodynamic and Cardiopulmonary Exercise Data

	All (n=261)	Group 1 (n=79)	Group 2 (n=182)	*P* Value
Invasive				
Heart rate, beats per minute	65±8	62±5	69±7	0.18
Mean systemic pressure, mm Hg	75±6	63±2	81±5	<0.001
Fontan pressure, mm Hg	15±4	14±3	15±4	0.6
Ventricular EDP, mm Hg (n=106)	11±2	11±2	11±3	0.6
Wedge pressure, mm Hg	11±3	11±3	10±2	0.4
Systemic O_2 saturation, %	85±7	83±5	86±8	0.7
Cardiac index, L min^{-1} m^{-2}	2.8 (1.9–3.6)	1.9 (1.6–2.2)	3.2 (2.3–3.9)	<0.001
SV index, mL/m^2	43±7	31±4	46±6	<0.001
PVRI, WU·m^2	2.2±0.8	2.7±0.9	1.6±0.5	<0.001
SVRI, WU·m^2	23±7	25±6	23±7	0.16
Noninvasive				
Estimated ejection fraction by echo, %	42±5	40±5	43±4	0.2
Ejection fraction by CMRI, % (n=82)	47±8	48±9	47±6	0.4
SV index by CMRI, mL/m^2 (n=82)	41±8	36±3	45±6	0.03
≥Moderate AVV regurgitation	51 (20%)	18 (23%)	33 (18%)	0.4
AVV E velocity, m/s	6±2	7±1	6±2	0.6
Average e′ velocity, cm/s (n=98)*	6±3	5±2	7±3	0.5
Average E/e′ (n=98)	10±3	13±3	9±4	0.3
Peak Vo_2, mL kg^{-1} min^{-1} (n=148)	19.3±3.4	17.1±2.9	21.3±1.4	0.04
Peak Vo_2, % predicted (n=148)	56±9	47±8	61±7	0.04

AVV indicates atrioventricular valve; CMRI, cardiac magnetic resonance imaging; EDP, end-diastolic pressure; PVRI, pulmonary vascular resistance index; SV, stroke volume; SVRI, systemic vascular resistance index; and Vo_2, oxygen consumption.

*Average e′ velocity: mean of medial and lateral e′ velocities in patients with both velocities recorded.

Outcomes

During a mean follow-up of 8.6±2.4 years, the following Fontan failure events occurred: death (n=39, 15%), heart transplant listing with transplantation (n=6, 2%), heart transplant listing without transplantation (n=12, 5%), and initiation of palliative care after assessment of ineligibility for transplant (n=11, 4%). Thus, the overall incidence of Fontan failure was 26% in this cohort. Out of the 6 patients that underwent heart transplantation, 1 patient had combined heart–liver transplantation. Among the 39 patients who died, the cause of death was perioperative death after cardiac surgery in 13, perioperative death after noncardiac surgery in 1, sudden death in 8, heart failure/thromboembolism in 3, sepsis in 2, and unknown/multifactorial in 12.

Freedom from Fontan failure was significantly lower in group 1 when compared with group 2 patients, 66% versus 89% at 5 years, and 42% versus 69% at 10 years (*P*=0.003; (Figure 1). A further analysis performed in the cohort was divided into 4 groups: high PVRI/low cardiac index, high PVRI/high cardiac index, low PVRI/high cardiac index, and low PVRI/low cardiac index. The freedom from Fontan failure at 5 years was 66% (high PVRI/low cardiac index) versus 84% (high PVRI/high cardiac index) versus 91% (low PVRI/high cardiac index) versus 90% (low PVRI/low cardiac index; Figure 2).

The combination of high PVRI and low cardiac index (group 1) was an independent risk factor for Fontan failure (HR, 1.84; 95% confidence interval, 1.09–2.85; *P*=0.042) after accounting for the other known predictors identified on univariate analysis (Table 3). Patients with elevated PVRI alone, irrespective of cardiac index, also tended to display increased risk of Fontan failure. The freedom from Fontan failure for the patients

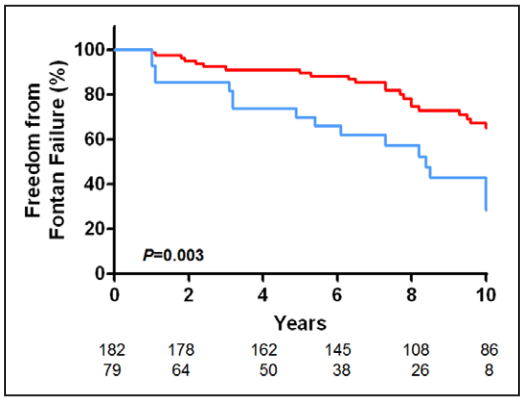

Figure 1. Kaplan–Meier curves comparing freedom from Fontan failure between group 1 (blue) and group 2 patients (red).

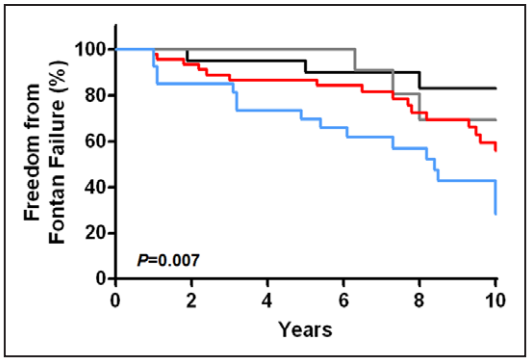

Figure 2. Kaplan–Meier curves comparing freedom from Fontan failure between high pulmonary vascular resistance index (PVRI)/low cardiac index (n=79; blue), high PVRI/high cardiac index (n=54; red), low PVRI/high cardiac index (n=61; grey), and low PVRI/low cardiac index (n=67; black).

with elevated PVRI alone compared with the rest of the cohort was 78% versus 87% at 5 years and 49% versus 61% at 10 years (*P*=0.05; Figure II in the Data Supplement), but the risk was not as great as observed in patients with PVRI elevation coupled with low cardiac index. Low cardiac index was alone was also evaluated as a risk factor, and there was no significant difference in survival between low cardiac index versus normal cardiac index (*P*=0.41; data not shown).

Table 3. Hemodynamic and Clinical Risk Factors for Fontan Failure

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
High PVRI and low cardiac index	2.87 (1.76–3.95)	0.001	1.84 (1.09–2.85)	0.042
Older age at catheterization, per y	2.21 (1.32–3.42)	0.02	1.75 (0.68–3.05)	0.2
Older age at Fontan operation, per y	1.73 (0.66–1.92)	0.16	…	…
Left ventricle	1.83 (0.61–3.93)	0.3	…	…
Atriopulmonary Fontan	2.61 (1.18–4.11)	0.018	1.66 (0.90–3.12	0.061
Heterotaxy	1.41 (0.22–2.75)	0.4	…	…
Protein-losing enteropathy	2.11 (0.84–6.43)	0.14	…	…
Cirrhosis	2.01 (1.22–3.62)	0.03	1.13 (0.81–2.91)	0.3
Atrial arrhythmia	1.59 (0.64–2.53)	0.09	…	…
Heart failure hospitalization	2.18 (0.92–2.97)	0.13	…	…
Creatinine clearance <60 mL/min	1.13 (0.49–3.26)	0.3	…	…
Paced rhythm	1.62 (0.42–5.77)	0.4	…	…
Warfarin	1.53 (0.68–2.52)	0.2	…	…
Diuretics	2.03 (1.26–5.06)	0.008	0.89 (0.28–5.22)	0.3

High PVRI and low cardiac index: PVRI >2.0 WU·m^2 and cardiac index <2.5 L min^{-1} m^{-2}. CI indicates confidence interval; HR, hazard ratio; and PVRI, pulmonary vascular resistance index.

DISCUSSION

Congenital heart disease is an important cause of heart failure among young adults, and within this group, patients with the Fontan circulation can be the most challenging to care for. Survival after the Fontan palliation remains suboptimal even in the current era, and there is a need for a better understanding of the hemodynamic mechanisms underlying Fontan failure. We hypothesized that because there is no effective subpulmonary ventricle in the Fontan circulation, these patients would be more susceptible to even mild elevations in PVRI, and that when coupled with low cardiac output, this would identify patients at greater risk for events. We show that among consecutively examined adults with the Fontan palliation undergoing cardiac catheterization over a 25-year period, the combination of high PVRI and low cardiac index identifies patients at the highest risk for Fontan failure. This suggests that even low-grade pulmonary vascular disease plays an important role in the pathophysiology of Fontan failure and justifies further efforts to understand the mechanisms for pulmonary vascular disease and treat it using novel therapies in patients with the Fontan circulation.

Prior Invasive Studies

In the current study, the mean PVRI was 2.0±0.8 WU·m^2, median cardiac index was 2.8 (1.9–3.6) L min^{-1} m^{-2}, and a composite end point of Fontan failure occurred in 68 (26%) patients. Thirty percent of the cohort had a combination high PVRI and low cardiac index (group 1), and these patients were older, more likely to have atriopulmonary Fontan, and more likely to be on chronic diuretic therapy. The freedom from Fontan failure was significantly lower in group 1 patients. The invasive hemodynamic indices observed in our cohort were comparable to other previously published hemodynamic studies.[18,19]

Mori et al[18] retrospectively reviewed outcomes after cardiac catheterization in a smaller series of 60 adult Fontan patients with similar age, Fontan connection types, and ventricular morphology, reporting adverse events (death or transplant) in 18 patients (30%). In that study, higher cardiac output (rather than lower) was observed in patients with events when compared with nonevents. Hemodynamics were not predictive of outcome in multivariate analysis, but the low number of events precluded adequate power for multivariable adjustment. The reasons for the differential results with the current study are not clear, but may relate in part to the characteristics of the patients studied. Mori et al[13] included a patient pop-

ulation with high burden of liver disease, which causes intense systemic vasodilation and secondary increases in cardiac output that may lead to high output failure.[20] Thus, the higher output observed in patients with events in that trial may be related more to their greater burden of liver disease rather than being a direct contributor to Fontan failure. The differential results may also relate in part to the much larger sample size and longer duration of follow-up in the current study.

In a different study, Hebson et al[19] reported that symptomatic Fontan patients had lower systemic vascular resistance in comparison to asymptomatic patients.[19] In the current study, we did not observe any significant difference in the systemic vascular resistance between groups 1 and 2. A possible explanation for the observed difference between our data and that of the Hebson et al[19] study again may relate to a higher prevalence of liver disease in their cohort as well, which decreases systemic vascular resistance independent of cardiac status for the reasons outlined above.[20–22] Neither of these previous studies related pulmonary vascular properties to clinical outcomes in patients with the Fontan circulation.

Pulmonary Vascular Disease as a Mediator of Fontan Failure

Several studies have the described clinical risk factors for Fontan failure both in pediatric and adult Fontan patients.[2–4,17,23] These risk factors include heterotaxy, hypoplastic left heart syndrome, systemic right ventricle, protein-losing enteropathy, high central venous pressure, and portal hypertension. In the studies based exclusively on the adult Fontan population, the reported risk factors for Fontan failure include high central venous pressure, portal hypertension, and protein-losing enteropathy.[17,19,23]

Most of these established risk factors for Fontan failure are actually Fontan-associated comorbidities, rather than the hemodynamic perturbations that are initially responsible for these complications. We sought to identify the hemodynamic mechanisms that precede and contribute to Fontan failures, with a goal of identifying potential treatment targets, and hypothesized that even low-grade pulmonary vascular disease may play a pivotal role. Studies in humans and animal models suggest that nonpulsatile pulmonary blood flow causes endothelial dysfunction and dysregulation of the nitric oxide pathway in the pulmonary vascular bed.[9,10] In contrast to patients with a biventricular circulation, the diagnosis of pulmonary vascular disease is not readily apparent in patients with Fontan physiology because of the low cardiac output state, which can mask significant pulmonary vascular disease.[5,8,24–26]

In the absence of a subpulmonary ventricle, pulmonary vascular resistance plays a dominant role in the regulation of pulmonary blood flow.[5,8] As pulmonary vascular disease progresses in patients with single ventricle physiology, cardiac output can only be maintained at the expense of high central venous pressure and increased transpulmonary gradient.[5,8] In the current study, we described a unique group of patients with a combination of high PVRI and low cardiac index. We speculate that the compensatory mechanism required for maintaining cardiac index may be inadequate in these patients because of either advanced pulmonary vascular disease and abnormalities of systemic venous compliance, ultimately resulting in low cardiac index in the context of high PVRI. This may explain, at least to some extent, the similar central venous pressures in groups 1 and 2 patients.

Our observation that even low-grade elevations in PVRI are associated with increased risk is consistent with a retrospective study of 14 patients who underwent heart transplantation for failing Fontan physiology.[11,27] Four of these patients required heart transplantations within 1 year after Fontan operation (early Fontan failure), whereas 10 patients required heart transplantation a mean of 8 years after Fontan operation (late Fontan failure). All patients had normal PVRI before heart transplantation, but after transplant, mean PVRI increased from 1.8 to 2.7 WU·m^2 in the patients with early Fontan failure and from 1.5 to 3.5 WU·m^2 in the patients with late Fontan failure. The improved cardiac index after heart transplantation (with the addition of a subpulmonary ventricle) unmasked the presence of occult pulmonary vascular disease that was not apparent in the setting of Fontan failure and low cardiac index. This study demonstrates that occult pulmonary vascular disease can be unmasked with improvement in cardiac index. These data are consistent with our observation that the combination of elevated PVRI and low cardiac index are indicators of increased risk for Fontan failure.

Pulmonary Vascular Disease as a Target in the Fontan Circulation

The existence of pulmonary vascular disease has been circumstantially demonstrated in small studies documenting positive responses to pulmonary vasodilators, even in the setting of marginally elevated baseline PVRI in patients with the Fontan palliation.[24–26,28,29] A prospective study evaluated the effect of endothelin receptor antagonists in 24 Fontan patients with pulmonary vascular disease defined as PVRI >2 WU·m^2.[25] There was a significant drop in PVRI in all patients after 6 months therapy with bosentan or macitentan, and 70% of the patient had PVRI <2 WU·m^2 post-therapy. Most of the patients had concomitant increase in cardiac index and improvement in functional class and exercise capacity.[25]

In a different study, 24 Fontan patients with baseline PVRI >2.5 WU·m^2 received sildenafil for 3 months. This resulted in a drop in PVRI from 3.9 to 1.7 WU·m^2

that was coupled with improvements in cardiac index, functional class, and 6-minute walk distance.[26] Other small studies have demonstrated the beneficial effect of pulmonary vasodilators in Fontan patients both in terms of reduction in PVRI, cardiac output augmentation, and improvement in exercise capacity.[24,28,29] The current data complement and importantly extend on these small studies, identifying for the first time an important role for pulmonary vascular disease as an independent risk factor for Fontan failure, and emphasizing the importance of maintaining very low PVRI to treat and prevent Fontan failure, a concept that merits further prospective evaluation in trials.

Limitations

This is a single-center retrospective study reporting outcomes in an older Fontan cohort, the majority of whom have atriopulmonary Fontan connections. Although known predictors of outcome were adjusted for, there is still the possibility of residual or unmeasured confounding that might contribute to excess risk of Fontan failure. There were some differences in the baseline characteristics of the 2 groups, but most of these differences did not reach statistical significance perhaps because of small sample size.

Conclusions

Among the large population of adults with congenital heart disease, Fontan failure remains a major problem, and there is need to identify and treat high-risk patients to prevent or at least delay adverse outcomes. We show that the combination of high PVRI and low cardiac index is a hemodynamic predictor of patients at high risk for Fontan failure. This suggests that pulmonary vascular disease is an important underlying mechanism that requires future study from a mechanistic perspective and as a treatment target in future prospective clinical trials.

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DISCLOSURES

None.

AFFILIATIONS

From the Department of Cardiovascular Medicine (A.C.E., H.M.C., W.R.M., N.M.A., B.A.B.) and Division of Pediatric Cardiology (D.J.H.), Mayo Clinic, Rochester, MN; and Department of Pediatrics, Cincinnati Children's Hospital, OH (B.A.B.).

FOOTNOTES

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Hemodynamics of Fontan Failure: The Role of Pulmonary Vascular Disease

Alexander C. Egbe, Heidi M. Connolly, William R. Miranda, Naser M. Ammash, Donald J. Hagler, Gruschen R. Veldtman and Barry A. Borlaug

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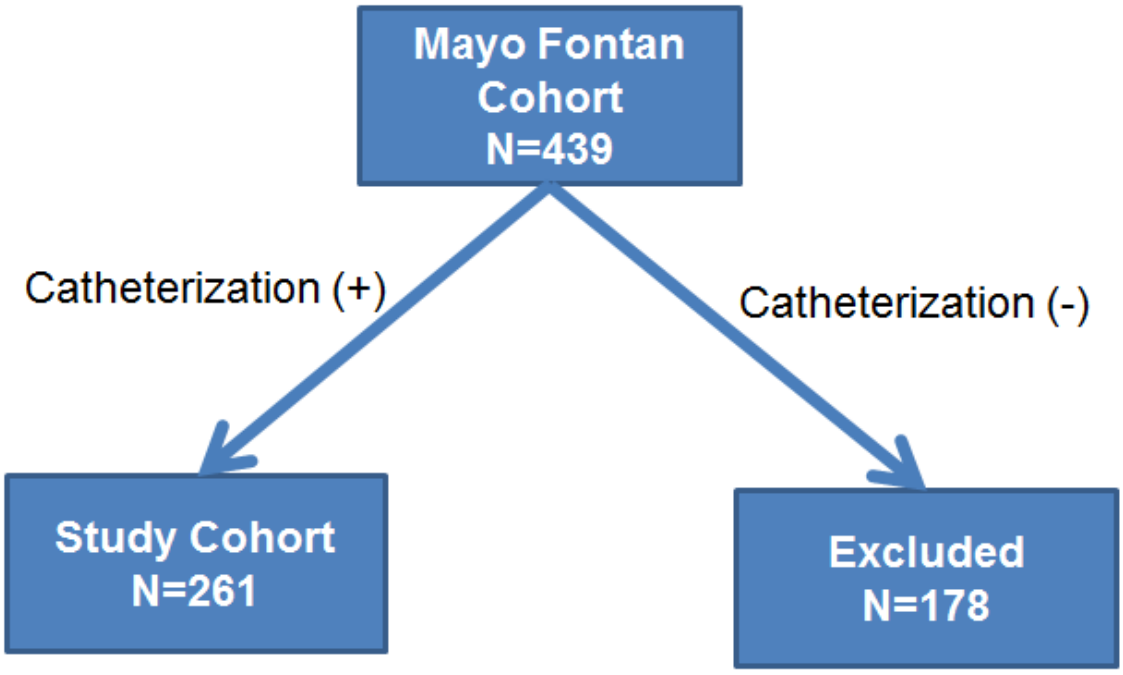
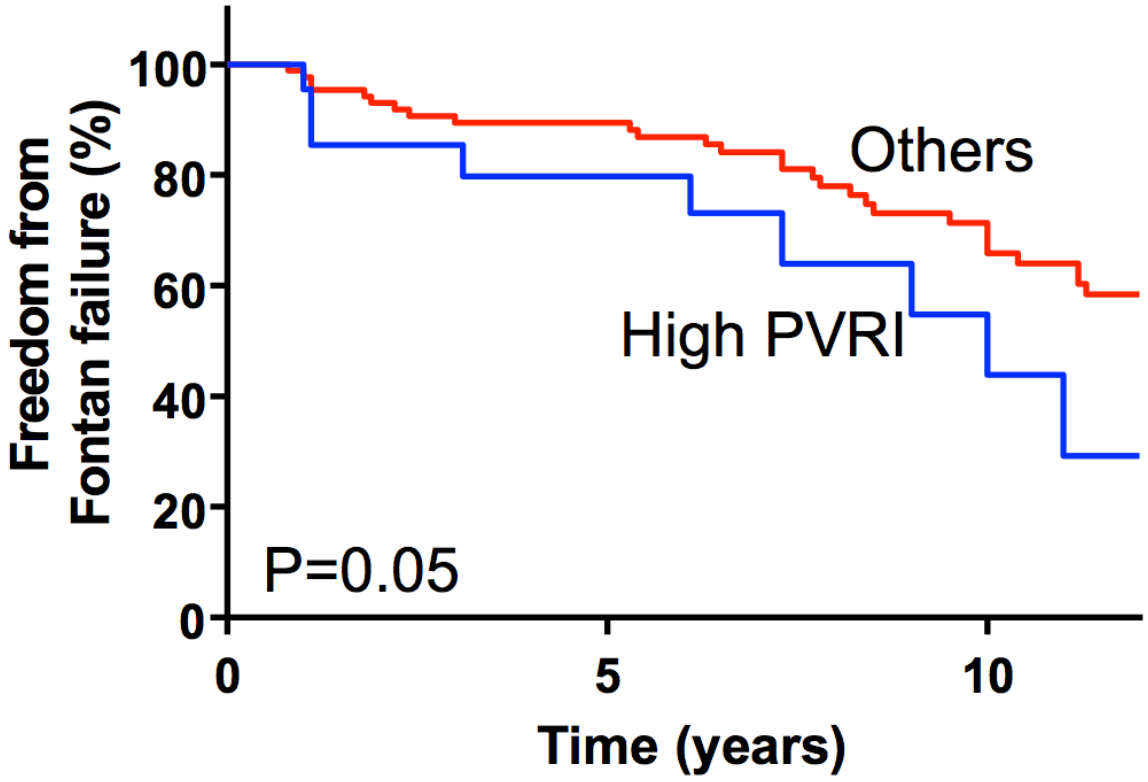
SUPPLEMENTAL MATERIAL

Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 1: Flow chart showing cohort selection

Supplementary Figure 2: Kaplan Meier curves comparing freedom from Fontan failure between patients with high PVRI (blue) and others (red).

PVRI: pulmonary vascular resistance index