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Contemporary Outcomes after the Fontan Procedure: A Pediatric Heart Network Multicenter Study

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Abstract

Background—The characteristics of contemporary Fontan survivors are not well described.

Objective—We characterized a large cohort of children who had a Fontan procedure, using measures of functional health status, ventricular size and function, exercise capacity, heart rhythm, and brain natriuretic peptide (BNP).

Methods—We enrolled 546 children (6–18 years, mean 11.9 years) and compared them within pre-specified anatomic and procedure subgroups. History and outcome measures were obtained within a three month period.

Results—Predominant ventricular morphology was left (LV) 49%, right (RV) 34%, and mixed 19%. Ejection fraction (EF) was normal for 73% of subjects; diastolic function grade was normal for 28%. Child Health Questionnaire mean summary scores were lower than for controls; however, over 80% of subjects were in the normal range. BNP concentration ranged from <4–652 pg/mL (median 13). Mean percent predicted peak oxygen consumption was 65% and decreased with age. EF and EF z-score were lowest, and semilunar and atrioventricular (AV) valve regurgitation were more prevalent in the RV subgroup. Older age at Fontan was associated with more severe AV valve regurgitation. Most outcomes were not associated with a superior cavopulmonary connection prior to Fontan.

Conclusions—Measures of ventricular systolic function and functional health status, although lower on average in the cohort compared to controls, were in the majority of subjects within two standard deviations of the mean for controls. RV morphology was associated with poorer ventricular and valvar function. Effective strategies to preserve ventricular and valvar function, particularly for patients with RV morphology, are needed.

Keywords

Fontan; cardiac magnetic resonance; exercise; brain natriuretic peptide; echocardiography; diastolic function; pediatric

INTRODUCTION

Children who have undergone a Fontan procedure for palliation of a functional single ventricle are at risk for medical complications (1). Current therapy is based on expert opinion, retrospective data collection, and single center small studies. Robust clinical trials are needed to guide care for this population. Trial design requires careful phenotyping and understanding of factors that affect outcomes. To this end, the NHLBI-funded Pediatric Heart Network (PHN) conducted the largest observational study to date in children who have undergone a Fontan procedure. The primary aim of this report is to characterize this cohort and specific subgroups, using state-of-the-science techniques to assess functional health status, ventricular size and function, exercise performance, brain natriuretic peptide (BNP) concentration, and heart rhythm.

METHODS

Study Design and Components

This cross-sectional study recruited subjects 6–18 years old who had not undergone cardiac surgical intervention in the six months prior to enrollment (2). Anatomic, clinical, and surgical data were collected at enrollment (March 2003 to April 2004) by a detailed medical record review using standardized forms. Each subject's tests were conducted within three months. The protocol was approved by each Center's Institutional Review Board. Written informed consent and assent were obtained.

Patient Sample

A total of 1,078 subjects from seven centers in the U.S. and Canada were screened, 644 were study eligible, and 546 were enrolled (86% consent rate) (2). Age, time since the Fontan procedure, and functional health status scores, collected for nearly all eligible subjects, were similar for enrolled and eligible but not enrolled subjects.

Outcome Measures

Measures of Functional Health Status—The Physical and Psychosocial Summary scores of the Child Health Questionnaire (CHQ)-Parent Form (PF)-50 were used (3). The CHQ-PF50 has been validated in healthy and chronically ill children and used as a trial endpoint in pediatrics (4).

Measures of Ventricular Function and Size

Echocardiogram: Two-dimensional echocardiograms and Doppler evaluations of standard short- and long-axis views of the ventricle(s) were centrally interpreted by one of two readers. When possible, measurements and derived indices were expressed as z-scores relative to body surface area (BSA) or age in normal children (5). Ventricular anatomic abnormalities (Table 1) were characterized as left (LV), right (RV), or mixed (e.g., unbalanced atrioventricular (AV) canal). Subjects were classified as having moderate/severe valve regurgitation if right, left, or common AV valve regurgitation was moderate or severe; both right and left AV valve regurgitation grades were mild; native aortic valve or native pulmonary valve regurgitation was moderate or severe; or both native aortic valve and native pulmonary valve regurgitation grades were mild. End-diastolic (EDV) and end-systolic volumes (ESV) and mass were obtained using the biplane-modified Simpson's method. For the mixed morphology group, the volume and mass of each ventricle were measured separately, and the combined values used for data analysis. Tei index was obtained (6). Ventricular diastolic function was assessed using measures derived from pulsed Doppler interrogation: duration of pulmonary vein flow reversal during atrial systole; tissue Doppler peak early diastolic velocity (E'); tissue Doppler peak late diastolic velocity (A'), AV valve peak early diastolic inflow velocity (E); AV valve peak late diastolic inflow velocity (A); deceleration time of the early AV valve inflow (DT); duration of AV valve late diastolic inflow (AT); and systemic ventricular flow propagation rate (FP). Two grading systems (7) were used (Table 2): I) restrictive pattern present vs. absent; II) Grades of 0 (no impairment) to 3 (greatest impairment in diastolic filling).

Cardiac Magnetic Resonance (CMR): CMR studies performed using 1.5 T scanners were centrally interpreted by a single reader. Subjects were excluded if: unable to cooperate; had a pacemaker, defibrillator, permanent pacemaker lead, implanted device considered a contraindication according to institutional guidelines, or in some instances intravascular coils; or <6 weeks from endovascular device implantation.

The standardized imaging protocol included electrocardiographically-triggered gradient echo cine MR acquisitions in the vertical and horizontal long-axis planes, followed by contiguous short-axis imaging from the atrioventricular junction through the cardiac apex. Outcomes included EDV, ESV, mass indexed to $BSA^{1.3}$, stroke volume (SV) indexed to BSA, and mass:EDV ratio (5).

Exercise Protocol: A maximal ramp exercise test was performed. Percent predicted of normal for maximum oxygen consumption (%predicted peak VO_2) and VO_2 at anaerobic threshold (%predicted VAT) were calculated (8).

Electrocardiogram: A standard 12-lead electrocardiogram (ECG) was performed and locally interpreted.

Serology: Resting BNP plasma concentration was centrally measured using the Shiniogi BNP-32 Human Assay (2).

Statistical Methods: Pre-specified subgroups were defined by ventricular morphology, Fontan procedure type, age at enrollment quartile (Table 2), age at Fontan procedure quartile (Table 4), and history of Stage II procedure (superior cavopulmonary connection or hemi-Fontan procedure). Subgroup differences in continuous outcomes were assessed using the t-test and analysis of variance, or nonparametric testing for highly skewed outcomes. Differences in categorical outcome measures were assessed using the chi-square test and, if ordinal, the Mantel-Haenszel test for linear trend. Modified Bonferroni and exact testing were applied to bootstrapped samples to obtain a p-value adjusted for multiple pairwise comparisons (9). Analysis of covariance and multivariate logistic regression were used to determine whether outcomes differed by subgroup after adjustment for age, with log transformation for BNP. Additional multivariate linear, logistic and multinomial regression modeling was used to analyze outcomes by age at Fontan and history of a Stage II procedure. All analyses were conducted using SAS version 9.1 and S-Plus version 6.2.

RESULTS

Overall Cohort

The 546 subjects were 11.9±3.4 years old at enrollment; 60% were male. The cohort was short (mean±SD, 34±30 percentile) and underweight (40±32 percentile). The most common diagnoses were tricuspid atresia and hypoplastic left heart syndrome (Table 1) and 59% had an intracardiac lateral tunnel Fontan procedure. A fenestration was performed in 68% and was found to be patent by echocardiography in 32%. Following the Fontan procedure, stroke and/or thrombosis occurred in 8%, seizures in 3%, and protein-losing enteropathy in 4%. The prevalences of developmental and cognitive abnormalities and surgical and catheter-based interventions have been published (10).

The distribution of ventricular morphologic subgroups was: LV, 49%; RV, 34%; and mixed, 18% (Table 2). One-third of subjects had predominant non-sinus rhythm, 10% a history of atrial tachycardia, and 13% a pacemaker. Ventricular mass and volume were obtained using echocardiography in 406 and 414 subjects, respectively, and by CMR in 161. Mean EF was 59±10% by echocardiography and 57±10% by CMR. EF was normal (echocardiographic z-score>-2) in 73%, although mean echocardiographic EDV, SV, and EF were lower and mass greater than those of normal subjects. The higher values of mass-to-volume ratio measured by echocardiography as compared with CMR reflect known echocardiography underestimating ventricular volume and overestimating mass (11). Forty nine percent of subjects had semilunar valve regurgitation, and 74% had AV valve regurgitation. Fifty-eight percent of subjects were taking an ACE inhibitor at enrollment. Diastolic function grade was normal in 28%. Median dP/dt_{ic} was 1125 mmHg/s (normal range 850–1350 mmHg/sec) (12). Tei index was 0.64±0.19 (normal range, 0.29 to 0.41). Median BNP was 13 pg/mL (range <4–652, mean 26±48 pg/mL).

The cohort had impaired exercise performance: mean %predicted peak VO_2 65±16%; %predicted VAT 78±25%. Peak VO_2 and VAT were in the normal range for 28% and 63%, respectively, independent of whether maximal effort was achieved.

Mean CHQ summary scores were lower than those of historical healthy controls (3) (45±12 vs. 53±9 for Physical and 47±10 vs. 51±9 for Psychosocial). Individual scores were in the normal range in 81% and 87%, respectively (Figure 1).

Gender

Males had lower BNP levels than females, even after adjustment for age (p=0.04). No gender differences were present for %predicted peak VO_2 and %VAT. By both echocardiography and CMR, boys had larger EDV than girls (P=0.04), lower mass:EDV ratio (median by echocardiography 1.1 vs. 1.2, p=0.002), and higher SV/BSA by CMRI (53±14 vs. 48±14, p=0.03).

Age at Enrollment

The type of Fontan procedure differed by age at enrollment (p<0.001). Older children were more likely to have undergone an atrio-pulmonary connection (36% in ≥15 year old group vs. 1%–15% in younger age groups), while younger children were more likely to have received a total cavopulmonary connection (TCPC) lateral tunnel (26% and 19% in the two younger age groups vs. <5% otherwise). Ventricular morphology differed by age (p=0.02), in particular the ≥15 year old group had a greater proportion with LV morphology than the 9 to < 11 year old group (pairwise adjusted p=0.03). BNP increased with age (medians 11 to 14 for three youngest cohorts vs. 17 pg/mL for, the ≥15 year old group, p=0.020). Most other findings on echocardiography and CMR did not differ by age. Tei index increased with age (p<.001). Exercise performance differed among age groups and decreased with age (p<0.001).

Ventricular Morphology

In general, ventricular function outcomes were worse for the RV subgroup compared with the LV, and to a lesser extent, the mixed, subgroups. EF z-score was −0.6±1.8, −1.4±2.3, and −0.5±2.1 for LV, RV, and mixed subgroups, respectively (p<0.001). Even after age adjustment, E’ was lower and E:E’ was higher in the RV subgroup (p<0.001, Figure 2). AV valve regurgitation was worst in the RV subgroup as was semilunar valve regurgitation (present in 65% for RV vs. 42% in LV and mixed subgroups, pairwise adjusted p<0.001).

Age-adjusted exercise performance was weakly associated with ventricular morphology, with the LV subgroup having higher %predicted peak VO_2 (3-group p=0.03) and %predicted VAT (3-group p=0.06) than the non-LV groups. Diastolic function grade, BNP, and CHQ summary scores did not differ by ventricular morphology (Table 3).

Type of Fontan Procedure

Few differences were found by type of Fontan procedure after adjustment for age. They included higher BNP in subjects with atriopulmonary connection (raw median 18 pg/mL) compared with BNP in subjects with extracardiac conduits and lateral tunnels (raw medians 13 and 10 pg/mL, respectively, pairwise adjusted p=0.01 and p=0.03). Age-adjusted %predicted VAT differed by type of Fontan procedure (p<0.001); those who received an intracardiac lateral tunnel (adjusted mean±SE, 73±2%) had lower %predicted VAT than those with an atriopulmonary connection (84±3%) or with an extracardiac conduit (92±4%).

Age at Fontan Procedure

Type of Fontan procedure differed by age at Fontan procedure (p<0.001). Intracardiac lateral tunnel was most commonly used for Fontan procedures performed at <2 years of age (81%), and decreased steadily with age. Conversely, extracardiac tunnel procedures were performed in 6% of subjects who underwent Fontan at <2 years and in 21% of subjects who underwent Fontan at ≥4 years. Age at Fontan was similar for those who did and did not undergo a Stage II procedure (3.5±2.0 vs. 3.2±2.3 years).

Rhythm status was associated with age at Fontan (p<0.0001). Normal sinus rhythm was present in 70%–74% of those with Fontan performed under age 3 years, and 59%–62% of those with Fontan performed ≥3 years. This association remained after adjustment for age at enrollment (p=0.01).

Age-adjusted mean Tei index (0.60, 0.62, 0.66, and 0.68 in the four Fontan age groups, p<0.001) was significantly worse for subjects who had a Fontan at later ages, even after adjustment for age at enrollment and for ventricular morphology. Moderate to severe AV valve regurgitation was more common in children with Fontan performed at ≥3 years (23%–26%) compared to children with Fontan performed at <2 or 2-<3 years (13%–16%). After adjustment for age at enrollment, greater severity of AV valve regurgitation was associated with older age at Fontan (p=0.010). Subjects with RV or mixed ventricular morphology who underwent the Fontan at older ages were more likely to have worse E', and RV subjects who underwent Fontan at older ages had worse E/E', even after adjustment for age at enrollment (morphology by age at Fontan interactions p≤0.05).

BNP, CHQ summary scores, and systolic function did not differ by age at Fontan (Table 4) and, after adjusting for age, exercise performance was also unrelated to age at Fontan.

Stage II Procedure

Subjects who underwent a Stage II procedure (66%) were younger at enrollment (10.9±2.9 vs. 14.7±3.2 years) and were less likely to have undergone an atrio-pulmonary connection (7% vs. 33%) even after age adjustment. The distribution of LV, RV, and mixed subgroup subjects who underwent a Stage II procedure (44%, 40%, 16%) was different than in those who did not (62%, 16%, 22%; p<0.001). No differences were found in predominant rhythm by Stage II status. After adjustment for age, Stage II surgery was not associated with ventricular function or exercise performance, except for higher ventricular mass in subjects who underwent Stage II surgery (age-adjusted mean±SE 1.2±0.1 vs. 0.4±0.3, p=0.008).

Stage II surgery was associated with lower age-adjusted mean log BNP for LV subgroup but not RV and mixed subgroups (Stage II by ventricular morphology interaction p=0.008). The Psychosocial summary score was lower in Stage II subjects (age-adjusted mean±SE 46.4±0.6 vs. 49.7±1.0, p=0.008) and was not explained by ventricular morphology or other factors. No other age-adjusted study outcomes differed significantly by Stage II surgery status within morphologic subgroup.

DISCUSSION

This study is the largest to date of children who have undergone the Fontan operation. Systematic data on medical history, demographic variables and quantitative measures of ventricular systolic and diastolic function, exercise performance, neurohormonal response, heart rhythm, and functional health status were obtained. Strengths of the study design are contemporaneous data collection, central interpretation of key measures, and large cohort size from multiple geographically dispersed centers. The novelty of the study follows, in part, from sophisticated measurement of ventricular diastolic function, using tissue Doppler echocardiography, BNP plasma concentration measurement, and large size of the study that permitted for the first time a statistically robust assessment of how outcomes differ by ventricular morphology, age at Fontan, and history of Stage II procedure.

OVERALL COHORT

Ventricular Function

EF was normal in the majority (73%) of subjects. Our finding of smaller-than-normal EDV contrasts with a study where EDV was 1.6 times larger than normal (13). Such differences are most likely related to changes in management over time such as earlier volume-unloading surgery. Smaller EDV, as compared with normal subjects, may be a reflection of aerobic deconditioning and may contribute to the blunted ability to increase stroke volume with exercise (14).

Our finding of abnormal diastolic function in 72% of children who had undergone a Fontan has not been previously reported and is concerning. These indices are dependent on cardiac loading conditions and are unable to distinguish between enhanced chamber compliance and impaired relaxation (7). However, given our findings, future studies, using invasive approaches, are needed to ascertain whether these children are at risk for diastolic heart failure.

Functional Health Status

Over 80% of subjects scored in the normal range on the CHQ. However, on average the parents perceived their children as having lower physical and psychosocial functional status than that of historic healthy controls. The lower Physical summary scores are similar to those for children who have undergone thoracic organ transplantation or cardioverter defibrillator implantation (15,16).

Exercise Performance

Maximal exercise performance was lower than normal and worse in older subjects, consistent with previous studies (14). The same mechanisms proposed previously to impair exercise performance in single ventricle subjects, including absence of a subpulmonary pumping chamber, abnormal endothelial cell function, increased systemic vascular resistance, decreased muscle mass, and deconditioning, are likely present in our subjects (1,14). The finding that exercise performance (%predicted VAT) was lowest in the intracardiac lateral tunnel group, among Fontan types, was an unexpected and unexplained finding.

Brain-Type Natriuretic Peptide (BNP)

The subjects demonstrated a wide range of BNP plasma concentrations. The mean concentration was similar to subjects without congenital heart disease and those with congenital heart disease without ventricular dysfunction, and lower than that of single ventricle patients with systemic ventricular failure (17). Our finding of lower age-adjusted BNP concentrations in male versus female subjects is consistent with adult data, but not with a report of a gender difference only in healthy post-pubertal children (18).

VENTICULAR MORPHOLOGIC SUBGROUPS

Systolic and Diastolic Function

Our finding of apparently impaired systolic function in the RV subgroup relative to the LV and mixed subgroups is consistent with the general opinion that the structure of the right ventricle is suboptimal for a systemic ventricle (1). The greater prevalence of diastolic dysfunction in the RV subgroup, measured by E' and E:E', is not likely a consequence of difference in loading conditions compared to the LV and mixed subgroups (19). Of note, the majority of subjects in each morphologic subgroup had Tei Index, E', and E:E' values outside a two-standard deviation range for normal children (20).

Valve regurgitation

Similar to concerns about the relative inadequacy of the RV as a systemic ventricle, the tricuspid valve is thought to be more likely to fail as a systemic AV valve. Consistent with that notion, subjects with RV morphology were most likely and those with LV morphology least likely to have AV valve regurgitation. The higher prevalence of semilunar valve regurgitation in subjects with RV morphology may be related to the aortic reconstruction and intrinsic characteristics of the pulmonary (neo-aortic) valve in patients with hypoplastic left heart syndrome.

Functional Health Status and BNP

Although measures of ventricular performance and exercise capacity varied according to ventricular morphology, CHQ scores and BNP levels did not.

AGE AT FONTAN

Subjects who were older at time of Fontan had worse AV valve function and decreased likelihood of being in sinus rhythm. Poorer valve function and a decrease in sinus rhythm may be related to a longer period of volume overloading (21). These negative associations with older age at Fontan might be used as a rationale to complete the Fontan at an earlier age.

HISTORY OF STAGE II PROCEDURE

The performance of a Stage II procedure in single ventricle patients follows from the general assumption that this procedure decreases volume loading and its negative effects. Although we postulated that Stage II surgery might be beneficial in some patients, we found that a Stage II procedure was not associated with laboratory measures except for BNP and ventricular mass and a negative association with Psychosocial Summary score. Our findings suggest that further study is needed to assess the impact of performing a Stage II procedure.

STUDY LIMITATIONS

This study was limited in several respects. Because only survivors of the Fontan procedure were studied, our findings may not reflect the characteristics of subjects who died in the years following the Fontan. Although the generalizability of our findings is supported by the enrolled subjects being of similar age and functional health status as the eligible but non-consenting subjects (2) and being from geographically dispersed regions, our subjects were recruited exclusively from major medical centers. Functional health status was measured using parental report instruments which may not match child perception (22).

CONCLUSIONS

This largest-to-date multi-center study of children who have undergone a Fontan procedure provides an overview of functional health status, ventricular performance and exercise performance in current survivors of the Fontan procedure. Ventricular systolic function and functional health status were within normal range in the majority of subjects. Ventricular function and valvar function were negatively associated with RV morphology. AV valve function was negatively associated with older age at Fontan completion. Continued follow-up of these subjects will determine if functional health status is eventually related to measures of ventricular diastolic function. Effective strategies to preserve ventricular and valvar function, particularly for patients with RV morphology, are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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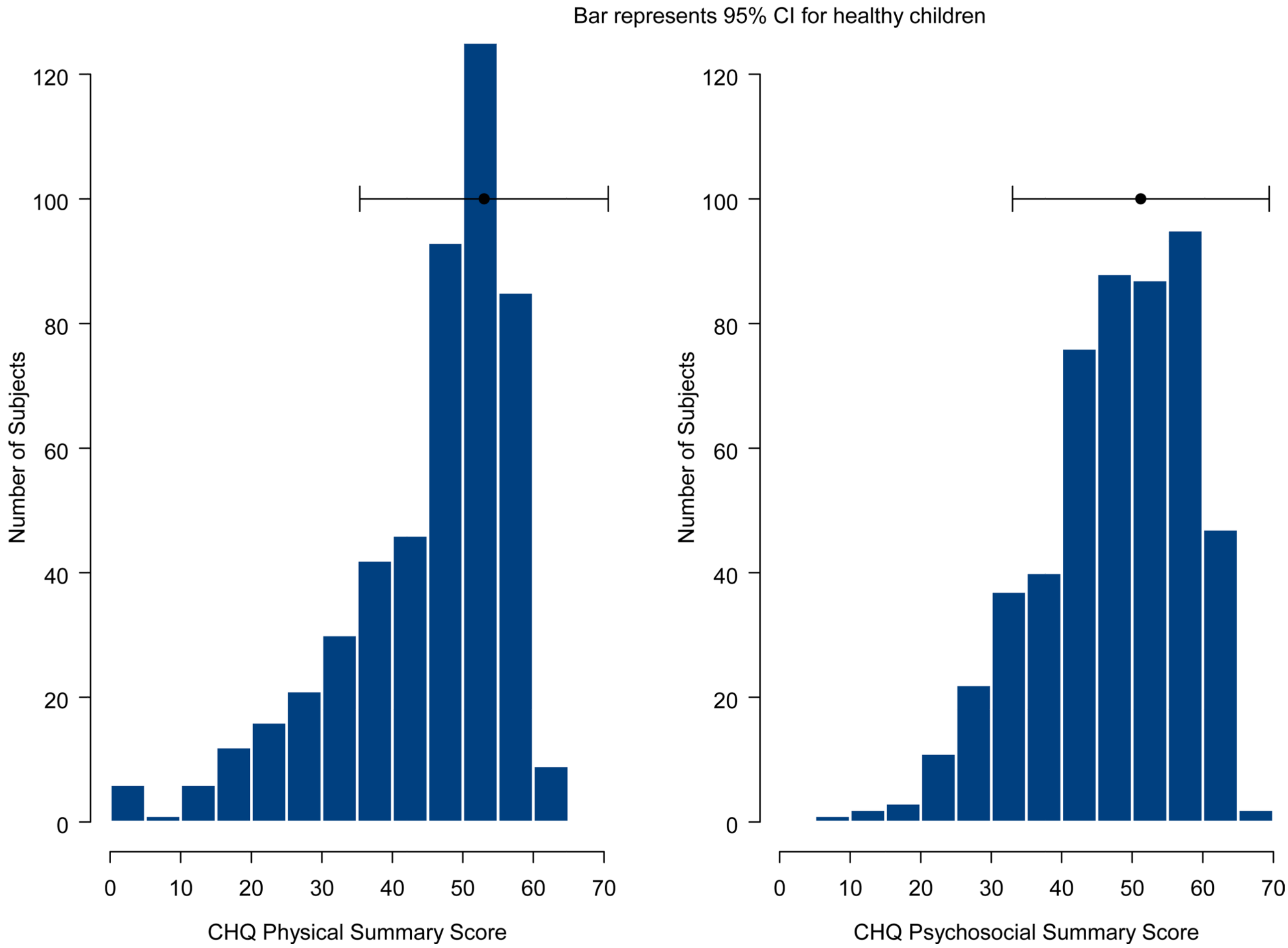

Figure 1. CHQ-PF Summary Scores

The distribution of CHQ-PF Physical and Psychosocial Summary Scores from 543 children enrolled in the Pediatric Heart Network Fontan Cross-Sectional Study. The bar represents the 95% confidence interval around the historical mean score for healthy children.

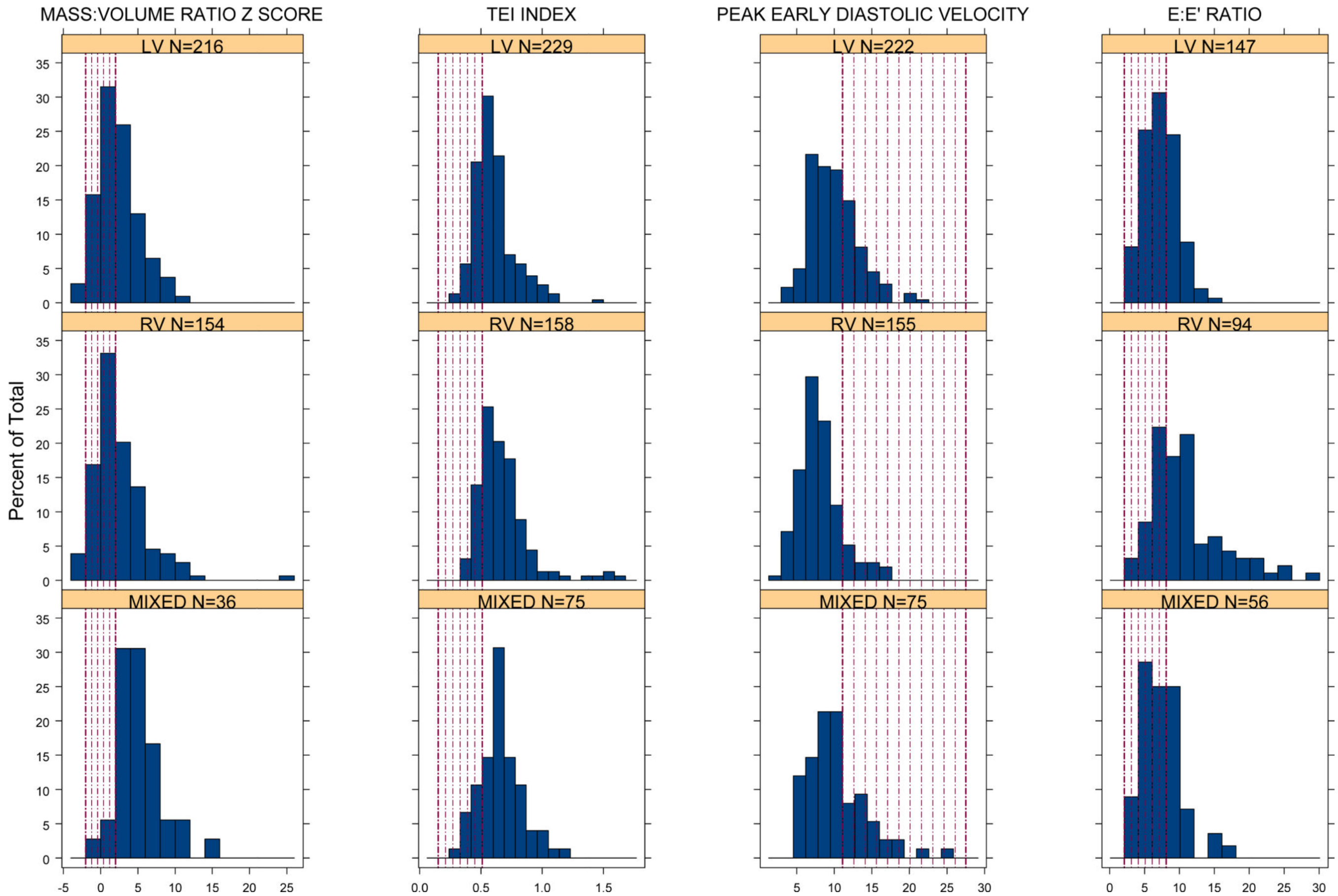

Figure 2. Mass/EDV Ratio and Diastolic Function

Histograms of echocardiographic mass to EDV ratio z score and measures of diastolic function assessed from tissue Doppler techniques, by ventricular morphology. Shaded regions indicate the 95% confidence interval for normal children aged 6 to 18 years old (19).

TABLE 1

Cardiac Anatomic Diagnosis of 546 Fontan Cross-Sectional Study Subjects*

Diagnosis	Number	Percent
Tricuspid Atresia	119	22%
Hypoplastic Left Heart Syndrome	112	21%
Double Inlet Left Ventricle	80	15%
Heterotaxia	42	8%
Double Outlet Right Ventricle	41	8%
Pulmonary Atresia Intact Ventricular Septum	33	6.0%
Mitral Atresia	31	6%
Abnormal Tricuspid Valve	22	4%
Atrio-Ventricular Canal Defect	22	4%
Other	38	7%

*The percentages have been rounded up here and in the other tables.

TABLE 2

Fontan Cross-Sectional Study Patient Characteristics by Age at Enrollment

Characteristic	N	Overall Mean ± SD Median or %	<9 years Mean ± SD Median or %	9 to <11 years Mean ± SD Median or %	11 to <15 years Mean ± SD Median or %	≥15 years Mean ± SD Median or %	P-value
N		546	138(25%)	120(22%)	169(31%)	119(22%)	
Age at enrollment, yr		11.9±3.4	7.9±0.7	10.0±0.6	12.8±1.2	17.0±1.1	
Age at Fontan, yr		3.4±2.1	3.0±1.3	3.0±1.5	3.2±1.9	4.6±3.0	<.001
Age at volume unloading surgery, yr		1.6±1.6	0.9±0.9	1.1±1.0	1.4±1.0	3.4±2.1	<.001
Male	546	60%	58%	62%	65%	55%	.305
Race	544						.014
White		80%	70%	80%	82%	87%	
Black		10%	14%	7%	11%	8%	
Asian		3%	4%	3%	2%	<1%	
Other		8%	13%	10%	4%	3%	
Hispanic	517	7%	8%	10%	4%	6%	.318
Growth							
Percentile for stature-for-age	544	26	22	31	22	31	0.242*
Z-score for stature-for-age	544	−0.7±1.3	−0.7±1.4	−0.6±1.3	−0.8±1.3	−0.6±1.0	0.316
Percentile for weight-for-age	545	37	36	27	29	48	0.021*
Z-score for weight-for-age	545	−0.4±1.4	−0.4±1.2	−0.5±1.4	−0.6±1.5	−0.2±1.2	0.085
Body mass index z-score	544	−0.05±1.13	0.07±0.97	−0.23±1.25	−0.15±1.24	0.13±0.99	0.030
Fontan Type	513						<.001
Atriopulmonary connection		13%	<1%	3%	15%	36%	
TCPC intracardiac lateral tunnel		59%	52%	62%	70%	50%	
TCPC extracardiac lateral tunnel		13%	26%	19%	4%	3%	
TCPC extracardiac conduit		13%	21%	15%	9%	6%	
Other		2%	0%	<1%	2%	5%	
Ventricular type	546						0.023
Left Ventricular		49%	46%	38%	53%	57%	

Characteristic	N	Overall Mean ± SD Median or %	<9 years Mean ± SD Median or %	9 to <11 years Mean ± SD Median or %	11 to <15 years Mean ± SD Median or %	≥15 years Mean ± SD Median or %	P-value
Right Ventricular		34%	36%	41%	34%	24%	
Mixed		18%	19%	22%	13%	19%	
Stage II surgery performed	546	75%	93%	88%	78%	35%	<.001
Predominant rhythm	518						0.255
Normal sinus rhythm		67%	63%	69%	71%	63%	
Atrial escape		9%	11%	10%	7%	9%	
Junctional escape		6%	9%	6%	5%	3%	
Paced		8%	10%	4%	9%	11%	
Other		11%	8%	12%	9%	15%	
Currently on pacemaker	546	13%	12%	12%	11%	20%	0.087
Serology							
Brain natriuretic peptide, pg/mL	510	13 (7, 26)	11	11	14	17	0.020*
Echocardiographic Measures							
Heart rate z-score	437	−0.20±0.98	−0.27±0.95	−0.05±0.93	−0.20±0.98	−0.27±1.04	0.318
End-diastolic volume z-score	414	−0.7±1.9	−0.5±1.8	−0.6±1.9	−1.0±1.5	−0.4±2.5	0.134
End-systolic volume z-score	414	0.2±2.4	0.4±2.1	0.2±2.4	−0.1±2.1	0.6±3.3	0.206
Ejection fraction z-score	414	−0.9±2.0	−0.8±2.0	−0.6±1.9	−0.9±2.1	−1.2±2.1	0.265
Stroke volume z-score	414	−1.1±1.8	−0.9±1.9	−1.0±1.7	−1.3±1.5	−1.0±2.2	0.246
Mass z-score	406	1.0±2.3	0.7±2.0	0.9±2.3	0.8±2.1	1.7±2.7	0.011
Ejection fraction, %	414	59±10	59±10	60±10	59±11	57±11	0.252
Mass:volume ratio g/mL	406	1.21±0.39	1.16±0.41	1.20±0.38	1.23±0.38	1.26±0.38	0.321
Mass:volume ratio z-score	406	2.65±3.22	1.97±3.06	2.41±2.97	2.86±3.15	3.49±3.63	0.011
dP/dt_{ic}, mm Hg/s	449	1125 (802,1700)	1257 (N=115)	1134 (N=106)	1114 (N=134)	997 (N=94)	0.027*
Tei index (by Tissue Doppler)	462	0.64±0.19	0.60±0.17 (N=117)	0.62±0.14 (N=99)	0.63±0.17 (N=144)	0.70±0.24 (N=102)	<.001
E’, cm/sec	452	9.3±3.3	9.5±3.3 (N=113)	9.6±2.9 (N=97)	9.0±3.3 (N=141)	9.5±3.8 (N=101)	0.517

		Overall	<9 years	9 to <11 years	11 to <15 years	≥15 years	
Characteristic	**N**	**Mean ± SD Median or %**	**Mean ± SD Median or %**	**Mean ± SD Median or %**	**Mean ± SD Median or %**	**Mean ± SD Median or %**	**P-value**
E:A ratio	344	1.48 (1.21,1.92)	1.45 (N=88)	1.46 (N=80)	1.55 (N=105)	1.48 (N=71)	0.883*
E:E’ ratio	297	7.79 (5.94,9.89)	8.03 (N=74)	7.15 (N=66)	8.12 (N=94)	7.63 (N=63)	0.216*
Systemic ventricular FP rate, cm/sec	143	64±20	63±16 (N=39)	64±19 (N=40)	69±24 (N=41)	57±15 (N=23)	0.107
Restrictive pattern present	344	52%	52%	54%	56%	44%	0.421
Diastolic dysfunction grade	327						0.438†
Normal		28%	23%	27%	25%	38%	
Impaired relaxation		9%	12%	8%	9%	8%	
Pseudonormalization		41%	45%	47%	42%	29%	
Restrictive		22%	20%	18%	24%	26%	
Overall AV valve regurgitation	528						0.541†
None		26%	27%	17%	33%	22%	
Mild		55%	53%	59%	50%	60%	
Moderate		19%	19%	23%	17%	17%	
Severe		<1%	0%	<1%	0%	0%	
Semilunar valve regurgitation	314						0.148†
None		51%	57%	52%	54%	37%	
Mild		40%	37%	42%	36%	50%	
Moderate		9%	7%	6%	10%	13%	
Cardiac MRI							
N	161	161	33	37	50	41	
End-diastolic volume /BSA , mL/m		85±25	96±26	89±29	81±20	79±23	0.011
End-systolic volume /BSA[13], mL/m^2		37±16	41±17	38±19	36±16	35±14	0.395
Ejection fraction, %		57±10	58±8	59±9	56±12	56±9	0.476
Stroke volume /BSA, mL/ m^2		51±14	52±12	52±14	48±14	51±15	0.500
Mass/BSA[13], g/m^2		72±21	75±17	70±18	68±19	76±26	0.182
Mass:volume ratio g/mL		0.89±0.31	0.83±0.24	0.83±0.29	0.87±0.25	1.01±0.40	0.036

Characteristic	N	Overall Mean ± SD Median or %	<9 years Mean ± SD Median or %	9 to <11 years Mean ± SD Median or %	11 to <15 years Mean ± SD Median or %	≥15 years Mean ± SD Median or %	P-value
Exercise Performance Measures							
N		412	68	95	152	97	
Peak VO_2, mL/kg/min	403	26±7	27±8 (N=65)	28±7 (N=94)	26±6 (N=148)	25±7 (N=96)	0.028
Percent predicted peak VO_2	403	65±16	67±19	68±17	65±15	59±14	<.001
Peak VO_2 consumption at AT, mL/kg/min	317	19±6	24±8 (N=35)	20±7 (N=65)	19±6 (N=131)	16±5 (N=86)	<.001
Percent predicted VAT	317	78±25	95±30	82±26	77±22	69±20	<.001
Maximum heart rate, bpm	405	154±23	152±22 (N=64)	156±24 (N=95)	157±21 (N=150)	150±26 (N=96)	0.122
Measures of Functional Status							
CHQ-PF Physical Summary Score	511	45.3±11.9	45.7±12.1	45.8±10.7	45.4±12.6	44.1±11.7	0.689
CHQ-PF Psychosocial Summary Score	511	47.2±10.8	47.9±10.6	47.2±11.1	45.5±10.9	49.1±10.5	0.052

Percentages may not add to 100 due to rounding

P-value is from analysis of variance for continuous outcomes and chi-square test for categorical outcomes unless otherwise specified

*Kruskal-Wallis test p-value

†Mantel-Haenszel test for linear trend p-value

N = number of subjects for whom data are available
BMI = Body Mass Index
TCPC = Total Cavopulmonary Connection
CHQ-PF = Child Health Questionnaire-Parent Form
dP/dt_{IC} = Estimated maximum first derivative of ventricular pressure
E’ = Tissue Doppler peak early diastolic velocity
E:A ratio = Ratio of early to late atrioventricular valve diastolic velocities
E:E’ ratio = Ratio of atrioventricular valve to Tissue Doppler peak early diastolic velocity
FP = Flow propagation
BSA=Body surface area
AV = Atrioventricular
VO_2 = Rate of oxygen consumption
AT = Anaerobic threshold
VAT = Peak VO_2 consumption at anaerobic threshold
Stage II = Superior cavopulmonary anastomosis

MRI = Magnetic resonance imaging

Restrictive pattern $E/A>2$, or $1<E/A<2$ and $DT<140$ ms

Diastolic dysfunction grades: 0, Normal = [($1<E/A\leq2$) and ($DT\geq140$ ms) and ($E/E'\leq10$)]; 1, Impaired relaxation = [$E/A=1$]; 2, Pseudonormalization = [($1<E/A\leq2$) and [($DT<140$ ms) or ($E/E'>10$) or ($FP<55$ cm/s)]]; 3. Restrictive = [$E/A>2$]

Table 3

Fontan Cross-Sectional Study Patient Characteristics by Ventricular Morphology

Characteristic	LV	RV	MIXED		
	Mean ± SD, Median or %	Mean ± SD, Median or %	Mean ± SD, Median or %	P-value	Age-adj. P-value
N	265(49%)	184(34%)	97(18%)		
Age at enrollment, yr	12.0	10.8	10.7	0.011*	
Age at Fontan, yr	3.5±2.0	3.2±2.1	3.7±2.4	0.240	
Age at volume unloading surgery, yr	1.2	0.7	1.2	<.001*	
Fontan Type				0.017	.102
Atriopulmonary Connection	19%	7%	10%		
TCPC intracardiac lateral tunnel	54%	67%	60%		
TCPC extracardiac lateral tunnel	11%	14%	13%		
TCPC extracardiac conduit	14%	11%	11%		
Other	2%	1%	3%		
Stage II surgery performed	68%	88%	69%	<.001	<.001
Serology					
Brain natriuretic peptide, pg/mL	12	15	13	0.553*	0.417
Echocardiographic Measures					
Heart rate z-score	−0.27±0.99	−0.10±0.97	−0.21 ±0.93	0.238	0.243
End-diastolic volume z-score	−0.8±1.9 (N=219)	−0.4±2.0 (N=156)	−1.1±1.5 (N=39)	0.044	0.045
End-systolic volume z-score	−0.1±2.2	0.8±2.7	−0.4±2.1	<.001	<.001
Ejection fraction z-score	−0.6±1.8	−1.4±2.3	−0.5±2.1	<.001	<.001
Stroke volume z-score	−1.0±1.8	−1.1±1.9	−1.4±1.4	0.460	0.384
Mass z-score	0.8±2.2 (N=216)	1.1±2.3 (N=154)	1.9±1.8 (N=36)	0.018	0.006
Ejection fraction, %	60±9 (N=219)	56±12 (N=156)	61±11 (N=39)	<.001	<.001
Mass:volume ratio, g/mL	1.17±0.33 (N=216)	1.19±0.43 (N=154)	1.52±0.42 (N=36)	<.001	<.001
Mass:volume ratio z score	2.37±2.74	2.50±3.63	4.99±3.18	<.001	<.001

Characteristic	LV	RV	MIXED		
	Mean ± SD, Median or %	Mean ± SD, Median or %	Mean ± SD, Median or %	P-value	Age-adj. P-value
dP/dt_{ic}, mm Hg/s	1209 (N=220)	1077 (N=150)	1073 (N=79)	0.071*	0.062
Tei index (by Tissue Doppler)	0.58 (N=216)	0.63 (N=158)	0.64 (N=75)	<.001*	<.001
E', cm/sec	10.0±3.2 (N=222)	8.0±2.8 (N=155)	10.4±3.9 (N=75)	<.001	<.001
E:A ratio	1.48 (N=169)	1.45 (N=109)	1.54 (N=66)	0.730*	0.593
E:E' ratio	7.21 (N=147)	10.00 (N=94)	6.96 (N=56)	<.001*	<.001
Systemic ventricular FP rate, cm/sec	64±18 (N=71)	64±22 (N=51)	**62±19** (N=21)	0.907	0.899
Restrictive pattern present	53%	51%	52%	0.974	0.879
Diastolic dysfunction grade				0.035	0.100
Normal	32%	19%	32%		
Impaired relaxation	9%	10%	8%		
Pseudonormalization	33%	53%	42%		
Restrictive	26%	18%	18%		
Overall AV valve regurgitation				<.001	<.001
None	38%	12%	20%		
Mild	48%	69%	49%		
Moderate	15%	18%	31%		
Severe	0%	<1%	0%		
Semilunar valve regurgitation **				.004	0.001
None	58%	35%	58%		
Mild	34%	55%	32%		
Moderate	8%	10%	10%		
Cardiac MRI					
N	100	55	38		
End-diastolic volume /$BSA^{1.3}$, mL/m^2	79±22 (N=86)	93±29 (N=44)	92±24 (N=31)	0.003	0.012
End-systolic volume /$BSA^{1.3}$, mL/m^2	34±14	43±21	38±11	0.011	0.019

Characteristic	LV	RV	MIXED		
	Mean ± SD, Median or %	Mean ± SD, Median or %	Mean ± SD, Median or %	P-value	Age-adj. P-value
Ejection fraction, %	57±9	55±11	59±7	0.176	0.122
Stroke volume /BSA, mL/ m^2	49±13	51±13	57±16	0.015	0.019
Mass / $BSA^{1.3}$, mL/m^2	70±20	75±21	73±20	0.328	0.290
Mass:volume ratio, mL/mL	0.92±0.32	0.87±0.33	0.82±0.22	0.274	0.402
Exercise Performance Measures					
N	219	128	65		
Peak VO_2, mL/kg/min	27±7 (N=216)	26±7 (N=124)	26±7 (N=50)	0.445	0.226
Percent predicted peak VO_2	66±17	63±16	63±16	0.141	0.031
Peak VO_2 consumption at AT, mL/kg/min	19±6 (N=173)	19±7 (N=94)	18±6 (N=50)	0.795	0.352
Percent predicted VAT	80±24	76±25	75±24	0.269	0.061
Maximum heart rate, bpm	155±23 (N=215)	153±23 (N=126)	153±25 (N=64)	0.837	0.795
Measures of Functional Status					
CHQ-PF Physical Summary Score	44.7±12.4	45.5±11.4	46.4±11.0	0.487	0.531
CHQ-PF Psychosocial Summary Score	48.0±10.0	46.4±11.8	46.7±11.1	0.261	0.288

Percentages may not add to 100 due to rounding

P-value is from analysis of variance for continuous outcomes and chi-square test for categorical outcomes unless otherwise specified

* Kruskal-Wallis test p-value

See Table 1 footnote for abbreviations legend

N = number of subjects for whom data are available

Table 4

Fontan Cross-Sectional Study Patient Characteristics by Age at Fontan Procedure

Characteristic	<2 yr Mean ± SD Median or %	2 to <3 yr Mean ± SD Median or %	3 to <4 yr Mean ± SD Median or %	≥4 yr Mean ± SD, Median or %	P-value	Age-adj. P-value
N	113	191	104	138		
Age at enrollment, yr	11.1	10.8	10.8	13.3	<.001*	
Age at volume unloading surgery, yr	0.9±0.5	1.2±0.8	1.7±1.2	2.8±2.4	<.001	
Fontan type					<.001	<.001
Atriopulmonary connection	6%	15%	15%	15%		
TCPC intracardiac lateral tunnel	81%	62%	54%	42%		
TCPC extracardiac lateral tunnel	6%	9%	15%	21%		
TCPC extracardiac conduit	4%	13%	12%	20%		
Other	2%	1%	4%	2%		
Ventricular type					0.200	0.150
Left ventricular	40%	49%	57%	49%		
Right ventricular	42%	35%	28%	30%		
Mixed	19%	16%	15%	21%		
Stage II surgery performed	69%	77%	73%	78%	0.365	<.001
Serology						
Brain natriuretic peptide, pg/mL	15	12	15	13	0.661*	0.418
Echocardiographic Measures						
Heart rate z score	−0.14±0.82	−0.36±1.04	−0.32±1.00	0.07±0.95	0.003	0.002
End-diastolic volume z-score	−0.9±1.8	−0.6±1.7	−0.5±2.3	−0.6±1.9	0.471	0.470
End-systolic volume z-score	0.0±2.3	0.2±2.6	0.4±2.8	0.2±2.2	0.739	0.730
Ejection fraction z-score	−0.9±2.0	−0.8±2.1	−1.0±1.8	−1.0±2.2	0.839	0.924
Stroke volume z-score	−1.4±1.6	−1.0±1.6	−1.0±2.0	−1.0±2.0	0.407	0.378
Mass z-score	1.1±2.5	0.8±2.1	1.1±2.3	1.1±2.2	0.806	0.895
Ejection fraction, %	58±10	59±11	58±9	58±11	0.837	0.924
Mass:volume ratio, g/mL	1.29±0.41	1.18±0.37	1.19±0.37	1.20±0.41	0.166	0.154

Characteristic	<2 yr Mean ± SD Median or %	2 to <3 yr Mean ± SD Median or %	3 to <4 yr Mean ± SD Median or %	≥4 yr Mean ± SD, Median or %	P-value	Age-adj. P-value
Mass:volume ratio z-score	3.27±3.32	2.34±2.97	2.51±3.00	2.68±3.62	0.205	0.205
dP/dt_{ic}, mm Hg/s	1209	1164	1039	1081	0.257*	0.595
Tei index (by Tissue Doppler)	0.57	0.60	0.62	0.65	<.001*	0.012
E’, cm/sec	8.7±3.2	9.2±3.2	9.8±2.9	9.8±3.9	0.054	0.035
E:A ratio	1.50	1.50	1.49	1.37	0.047*	0.052
E:E’ ratio	8.37	7.46	7.78	7.75	0.363*	0.034
Systemic ventricular FP rate, cm/sec	62±17	64±20	68±20	62±20	0.555	0.583
Restrictive pattern present	47%	58%	54%	45%	0.228	0.324
Diastolic dysfunction grade					0.218†	0.515
Normal	30%	22%	33%	31%		
Impaired relaxation	8%	7%	7%	14%		
Pseudonormalization	41%	45%	38%	39%		
Restrictive	21%	26%	22%	17%		
Overall AV valve regurgitation					0.002†	0.010
None	32%	27.1%	26.7%	18.8%		
Mild	55%	57.5%	50.5%	55.6%		
Moderate	13%	14.9%	22.8%	25.6%		
Severe	0%	<1%	0%	0%		
Semilunar valve regurgitation					0.314†	0.620
None	53%	56%	46%	46%		
Mild	39%	38%	48%	40%		
Moderate	8%	6%	7%	15%		
Cardiac MRI						
N	39	65	35	54		
End-diastolic volume /$BSA^{1.3}$, mL/m^2	82±24	88±27	86±27	84±22	0.739	0.785
End-systolic volume /$BSA^{1.3}$, mL/m^2	35±15	38±16	37±17	39±16	0.635	0.477
Ejection fraction, %	58±9	58±8	58±10	54±11	0.112	0.206

Characteristic	<2 yr Mean ± SD Median or %	2 to <3 yr Mean ± SD Median or %	3 to <4 yr Mean ± SD Median or %	≥4 yr Mean ± SD, Median or %	P-value	Age-adj. P-value
Stroke volume /BSA, mL/m^2	50±13	53±13	51±14	49±16	0.622	0.748
Mass / BSA$^{1.3}$, mL/m^2	70±20	70±18	69±17	77±26	0.236	0.252
Mass:volume ratio, g/mL	0.90±0.32	0.86±0.36	0.85±0.23	0.94±0.27	0.538	0.859
Exercise Performance Measurements						
N	80	140	81	111		
Peak VO_2, mL/kg/min	26±7	27±7	27±8	25±7	0.132	0.425
Percent predicted peak VO_2	64±16	66±17	65±18	63±15	0.441	0.893
Peak VO_2 consumption at AT, mL/kg/min	18±6	20±7	20±7	17±6	0.006	0.102
Percent predicted VAT	74±23	83±27	80±26	74.4±20.8	0.049	0.151
Maximum heart rate, bpm	156±21	155±22	153±26	153±25	0.695	0.736
Measures of Functional status						
CHQ-PF Physical Summary Score	45.4±12.2	45.0±12.8	44.8±12.4	46.0±9.6	0.862	0.736
CHQ-PF Psychosocial Summary Score	45.4±11.8	47.2±11.1	48.4±9.5	47.9±10.3	0.210	0.227

Percentages may not add to 100 due to rounding

P-value is from analysis of variance for continuous outcomes and chi-square test for categorical outcomes unless otherwise specified

*Kruskal-Wallis test p-value

†Mantel-Haenszel test for linear trend p-value

See Table 1 footnote for abbreviations legend

N = number of subjects for whom data are available

Table 5

Fontan Cross-Sectional Study Patient Characteristics by Superior Cavopulmonary Connection (Stage II Surgery) Performed

Characteristic	With Stage II Mean ± SD Median Or %	Without Stage II Mean ± SD Median Or %	P-value	Age-adjusted pvalue
N	N=408	N=138		
Age at enrollment, yr	10.3	15.7	<.001*	–
Age at Fontan, yr	3.5±2.0	3.2±2.3	0.318	<.001
Age at volume unloading surgery, yr	0.8	2.8	<.001*	<.001
Male	60%	60%	1.00	.497
Race			0.024	.491
White	78%	86%		
Black	11%	9%		
Asian	2%	3%		
Other	9%	2%		
Hispanic	7%	5%	0.550	.588
Growth				
Percentile for stature-for-age	24	31	0.085*	.195
Z-score for stature-for-age	−0.7±1.3	−0.5±1.1	0.056	.054
Percentile for weight-for-age	32	48	<.001*	.005
Z-score for weight-for-age	−0.5±1.4	−0.1±1.1	0.001	<.001
Body mass index z-score	−0.13±1.17	0.18±1.00	0.004	.003
Fontan type			<.001	.022
Atriopulmonary connection	7%	33%		
TCPC Intracardiac lateral tunnel	61%	56%		
TCPC extracardiac lateral tunnel	16%	3%		
TCPC extracardiac conduit	16%	2%		
Other	<1%	7%		
Ventricular type			<.001	.108
Left Ventricular	44%	62%		
Right Ventricular	40%	16%		
Mixed	16%	22%		
Currently on pacemaker	14.2%	13.8%	1.000	.059
Serology				
BNP, pg/ml†	11.8	17.6	0.001*	.066
Predominant rhythm			0.772	.292
Normal sinus rhythm	66%	70%		
Atrial escape	9%	9%		
Junctional escape	6%	4%		
Paced	9%	6%		

Characteristic	With Stage II Mean ± SD Median Or %	Without Stage II Mean ± SD Median Or %	P-value	Age-adjusted pvalue
Other	10%	11%		
Echo				
Heart rate z-score	−0.17±0.99	−0.29±0.92	0.267	.247
End-diastolic volume z-score	−0.6±1.8	−0.9± 2.3	0.167	.111
End-systolic volume z-score	0.3± 2.2	−0.0±3.0	0.400	.190
Ejection fraction z-score	−0.9±2.1	−0.9±2.0	0.983	.340
Stroke volume z-score	−1.0±1.8	−1.3±1.8	0.086	.168
Mass z-score	1.0±2.1	0.8±2.6	0.323	.008
Ejection fraction, %	59±11	58±10	0.966	.343
Mass:volume ratio, g/ml	1.21±0.39	1.21±0.39	0.957	.316
Mass:volume ratio z-score	2.57±3.10	2.92±3.63	0.356	.380
dp/dt_{ic}, mmHg/s	1182 (N=341)	1030 (N=108)	0.044*	.368
Tei index (by Tissue Doppler)	0.6 (N=346)	0.6 (N=116)	0.303*	.175
E’, cm/sec	9.5±3.4 (N=338)	9.0±3.2 (N=114)	0.226	.293
E: A ratio	1.48 (N=247)	1.48 (N=97)	0.985*	.530
E: E’ ratio	7.79 (N=215)	7.80 (N=82)	0.400*	.177
Systemic ventricular FP rate, cm/sec	65±21	60±15	0.111	.219
Restrictive pattern present	53%	49%	0.472	.932
Diastolic dysfunction grade			0.280	.830
Normal	25%	33%		
Impaired relaxation	9%	9%		
Pseudonormalization	44%	33%		
Restrictive	21%	24%		
Overall AV valve regurgitation grade			0.725	.406
None	25%	29%		
Mild	56%	54%		
Moderate	19%	17%		
Severe	<1%	0%		
Semilunar valve regurgitation grade			0.830	.482
None	52%	48%		
Mild	39%	44%		
Moderate	9%	8%		
Cardiac MRI				
N	108	53		
End-diastolic volume / BSA[1.3], ml/m^2	87±27	81±21	0.109	.658
End-systolic volume / BSA[1.3], ml/m^2	38±17	36±14	0.391	.739

Characteristic	With Stage II Mean ± SD Median Or %	Without Stage II Mean ± SD Median Or %	P-value	Age-adjusted pvalue
Ejection Fraction, %	57±10	56±9	0.555	.986
Stroke volume/ BSA, mL/m^2	51±14	50±13	0.596	.884
Mass / BSA$^{1.3,}$ g/m^2	73±21	69±19	0.205	.130
Mass:volume ratio g/mL	0.88±0.28	0.90±0.36	0.751	.455
Exercise Performance Measurements				
Peak VO_2, ml/kg/min	27±7.0	25±7	0.015	.207
Percent predicted peak VO_2	66±17	60±15	<.001	.067
Peak VO_2 consumption at AT, ml/kg/min	20±7	17±6	0.001	.658
Percent predicted VAT	81±26	72±21	0.001	.346
Max heart rate, bpm	155±24	153 ± 22	0.390	.490
Measures of Functional Status				
CHQ-PF Physical Summary Score	45.3±12.1	45.3±11.3	0.974	.555
CHQ-PF Psychosocial Summary Score	46.5±11.1	49.3±9.8	0.010	.008

Percentages may not add to 100 due to rounding

P-value is from analysis of variance for continuous outcomes and chi-square test for categorical outcomes unless otherwise specified

*Wilcoxon rank sum test p-value

†There was significant age-adjusted interaction of Stage II status and ventricular morphologic subtype (p=0.008), with lower BNP for subjects who underwent Stage II surgery compared with those who did not in the LV subgroup (log BNP 2.51±0.07 vs. 2.98±0.11, p<.001), but no difference in BNP by Stage II surgery status for subjects with RV or mixed type morphology.

N = number of subjects for whom data are available

See Table 1 footnote for abbreviations legend