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Factors Impacting Echocardiographic Imaging after the Fontan Procedure: A Report from the Pediatric Heart Network Fontan Cross-Sectional Study

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Abstract

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Background—Echocardiographic image quality in Fontan survivors may be limited by a variety of factors. We sought to describe echocardiographic quality and factors associated with study quality in subjects participating in the Pediatric Heart Network Fontan Cross-Sectional Study.

Methods—Echocardiograms were obtained at 7 clinical sites using a standard protocol. Quality grading and analysis were performed by a core laboratory. Univariate and multivariable modeling were performed to assess factors associated with quality and ability to obtain images sufficient for pre-specified quantitative analysis.

Results—A total of 543 echocardiograms were obtained. The quality of echocardiograms improved over the duration of the study. The great arteries, systemic veins, and pulmonary veins were less likely to be adequately imaged than other cardiac structures. Quantitative analysis of ventricular volume was possible in 76% overall, but only 41% of those with mixed ventricular morphology. Factors independently associated with better quality included younger age, levocardia, acquisition of the echocardiogram at a longer time since the beginning of enrollment, absence of a pulmonary artery stent, and clinical site.

Conclusions—Patient and center-specific factors are associated with echocardiographic quality after the Fontan procedure. Increased familiarity and experience with a standard imaging protocol is likely to result in improved quality.

Keywords

Fontan procedure; echocardiographic quality

Introduction

Patients with single ventricle physiology who have undergone a Fontan procedure require long-term cardiology follow-up, including periodic noninvasive cardiac imaging. As this population ages, factors that may adversely affect echocardiographic image quality may become more prevalent, including larger body size and history of multiple cardiac surgical and catheter-based procedures. Echocardiography is the most common modality used to assess ventricular structure and function in these patients during follow-up evaluation because of its portability, ease of use, and availability. Other modalities, such as cardiac catheterization and cardiac magnetic resonance imaging, are reserved for use when there is concern regarding an important change in clinical status based on history, physical examination or echocardiography. At present, there are no studies that have systematically evaluated factors that may impact overall image quality and the ability to obtain quantitative information regarding structure and function of the single ventricle in patients who have undergone the Fontan procedure.

The Pediatric Heart Network (PHN) Fontan Cross-Sectional Study was designed primarily to assess associations between functional health status and ventricular structure and function[1]. The aims of the secondary analysis of the echocardiographic data obtained during the Fontan Cross-Sectional study reported here were to describe the quality of echocardiograms performed during the cross-sectional study, to identify specific cardiovascular structures that were difficult to image in the study participants, and to describe the percentage of patients who had echocardiographic images of sufficient quality to allow quantitative assessment of ventricular volume and function. In addition, we sought to identify patient-related and non-patient-related factors impacting subjective assessment of echocardiographic image quality and the ability to complete quantitative assessment.

Methods

Subjects

The PHN Fontan Cross-Sectional Study design and details about core laboratory measurements and interpretation of the study echocardiograms have been previously described[1,2]. Fontan survivors between 6 and 18 years of age followed at each PHN clinical site were screened for eligibility. Subjects included in the study underwent a series of evaluations, including an echocardiogram, exercise testing, completion of a functional health status questionnaire, and a blood draw for a serum B-type natriuretic peptide level. Echocardiograms were performed at PHN clinical sites using a standardized imaging protocol, and a core laboratory performed all echocardiographic measurements. Institutional review or ethics board approval was obtained at each institution. Written informed consent was obtained from a parent or guardian for each study subject. Subjects were enrolled in this cross-sectional study between March 2003 and April 2004.

Echocardiographic Assessment

The method used for obtaining and analyzing echocardiograms performed as part of the Fontan Cross-Sectional Study has been described previously[2,3]. Briefly, echocardiograms were performed without the use of sedation at the 7 PHN clinical sites using a standardized protocol. This protocol outlined a complete two-dimensional and Doppler echocardiographic evaluation of cardiac chambers, atrioventricular valves, semilunar valves, pulmonary and systemic veins, and great arteries in multiple imaging planes (parasternal, subcostal and suprasternal notch). Imaging of all cardiac structures was attempted in each study subject. The protocol also outlined standard short- and long-axis views of the single ventricle to be obtained for quantitative analysis. No subjects were sedated for their echocardiograms.

Images were sent to the data coordinating center (New England Research Institutes, Watertown, MA) and forwarded to the core laboratory (Children's Hospital Boston, Boston, MA). At the time of the Fontan Cross-sectional study very few echocardiograms were acquired in digital format (12/546, 2%). Studies that were initially recorded using video tape were digitized using proprietary software (Marcus Labs, Boston, MA) prior to core lab interpretation, allowing for electronic caliper measurements of analog recordings. The subject's weight and height were measured at the time of the echocardiogram. Other information was also collected, including age at enrollment, age at Fontan, type of Fontan, and the number of other surgical and catheter interventions. The presence or absence of respiratory problems (as reported in the Child Health Questionnaire PF-50 administered as part of the Fontan Cross-Sectional Study) was also collected since pulmonary pathology may impact echocardiographic imaging.

Prior to beginning the Fontan Cross-Sectional Study, the echocardiographic protocol was distributed to each clinical site along with an electronic presentation reviewing the specifics of image acquisition by the local PHN clinical site, including examples of images, as well as the measurements to be completed by the core laboratory. Each clinical site developed its own process for educating personnel about the protocol. Multiple sonographers were typically involved in acquiring images at each clinical site.

In order to minimize bias and interobserver error, echocardiographic images were analyzed at the core laboratory by one of two experienced pediatric echocardiographers. Echocardiograms were assigned an image quality grade of excellent, good, fair, or unacceptable (unable to perform any analysis) based on subjective composite assessment of all the images recorded, utilizing the following grading system:

- Excellent: Clear images with distinct borders to structures, Doppler signals crisp and scaled proportional to the screen size
- Good: Predominantly clear images, most Doppler signals crisp with little to no baseline artifact
- Fair: Indistinct borders for most images, prominent baseline artifact with indistinct portions of Doppler signal
- Unacceptable: Unable to define borders, Doppler signals uninterpretable

At the time of the Fontan Cross-sectional Study, the PHN echocardiographic core laboratory did not provide direct feedback to clinical sites regarding echocardiographic quality.

Core laboratory measurements included valve gradients, ventricular volume and ejection fraction using a modified biplane Simpson's algorithm, atrioventricular valve inflow Doppler analysis (peak early velocity, peak atrial velocity, early deceleration velocity, and a-wave duration), duration of pulmonary vein flow reversal, tissue Doppler parameters (peak systolic velocity, peak early and late diastolic velocities, ejection time, isovolumic contraction time and isovolumic relaxation time), and ventricular flow propagation velocity. Ventricular morphology was characterized as left ventricular dominant (e.g., tricuspid atresia), right ventricular dominant (e.g., hypoplastic left heart syndrome), or mixed (e.g., an unbalanced atrioventricular septal defect).

Color Doppler was used to evaluate atrioventricular and semilunar valve regurgitation. The degree of atrioventricular valve and semilunar valve regurgitation, if present, was qualitatively graded as mild, moderate or severe based on the appearance of the color Doppler jet(s) in relation to the surrounding chambers. Subjects were classified as having moderate/severe atrioventricular valve regurgitation if right, left, or common atrioventricular valve regurgitation was moderate or severe, or if both right and left atrioventricular valve regurgitation grades were mild. Similarly, subjects were classified as having moderate/severe semilunar valve regurgitation if either native aortic or native pulmonary valve regurgitation was moderate or severe, or if both native aortic and native pulmonary valve regurgitation grades were mild.

For quantitative assessment of systolic function, the systemic ventricle was imaged from the apical (ventricular long-axis) and parasternal short-axis views. The endocardial border of the functional single ventricle was traced at end-diastole and endsystole, and the epicardial border was traced at end-diastole in both planes. End-diastolic volume (EDV), end-systolic volume (ESV), and mass were calculated using a modified biplane Simpson's rule[4]. Ejection fraction was calculated as [end-diastolic volume – end-systolic volume]/end-diastolic volume. Ventricular mass was calculated using the following equation:

$$\text{Ventricular mass} = \text{myocardial end}-\text{diastolic volume (epicardial volume} - \text{endocardial volume)} \times \text{myocardial density (1.0}$$

For the mixed morphology group, the volume and mass of each ventricle were measured separately, and the values for each ventricle were included in their respective morphologic groups. Global ventricular systolic function was qualitatively graded as normal function and mild, moderate, or severe dysfunction. Echocardiographic data were reviewed and measurements made using custom software (Marcus Laboratories, Boston, MA).

Statistical Analysis

For all subject-related factors, descriptive statistics are expressed as mean±standard deviation (SD) or proportions as appropriate. Subject-related factors included in the analysis

were age at Fontan, age at enrollment, weight-for-age and height-for-age z-scores, body surface area and body mass index at the time of study echocardiogram, anatomic diagnosis, ventricular looping, single ventricular morphology, type of Fontan, post-Fontan procedures and interventions (including placement of pulmonary artery stents), presence of a pacemaker, cardiac position, and a history of respiratory problems. Non-subject-related factors included center and timing of echocardiogram relative to the beginning of the Fontan Cross-Sectional Study. Time was modeled as the number of days from study launch to echocardiogram acquisition as a continuous variable, as well as in three five-month time blocks (early, middle, and late time periods). Ordinal logistic regression and a multinomial regression model for the echocardiographic quality grade were used to explore univariate associations with subject and non-subject-related factors. Echocardiographic quality grades were collapsed into excellent/good (better quality) vs. fair/unacceptable (poorer quality), and a multivariable logistic model with stepwise selection was developed to assess independent factors associated with better quality. Calculation of the proportion of echocardiograms with a non-visualized structure was based on subset of echocardiograms that indicated that the structure was present. For example, an echocardiogram on a patient with hypoplastic left heart syndrome would not be included in the subset of echocardiograms assessing visualization of the left ventricle. Univariate and multivariable logistic regression with stepwise selection were conducted to identify the factors that influence the ability to calculate ventricular volume. A p-value of less than 0.05 was considered significant. Analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Subjects

Of the 546 subjects enrolled in the Fontan Cross-Sectional Study, 543 underwent a study echocardiogram. The demographic data for the 543 subjects who had an echocardiogram are shown in Table I. The number of echocardiograms performed at each PHN clinical site ranged from 22 to 137. During the early 5-month time period 154/543 (28%) of the studies were performed. The majority of the studies were performed during the middle 5-month time period, 249/543 (46%), and 140/543 (26%) were performed during the late 5-month time period.

Echocardiographic Image Quality

Figure 1 demonstrates the proportion of echocardiograms that were of excellent, good, fair, and unacceptable quality for the 3 time periods. Only 7 studies (1.3%) were graded as having unacceptable image quality, i.e. no data were obtainable from the echocardiogram. As time progressed there was an increase in the proportion of better quality echocardiograms, and a decrease in the proportion that were poorer quality ($p<0.001$). There was significant variation in echocardiographic quality between clinical sites with the percentage of better quality ranging from 56% to 87% ($p<0.001$); however, the percentage of better quality echocardiograms increased over time at each site. After adjusting for clinical site, there was a significant association between timing of the echocardiogram relative to the beginning of the Fontan Cross-Sectional Study and quality, with a 10% increase in the odds of having a better quality echocardiogram for each month since first enrollment. Figure 2 demonstrates the proportion of echocardiograms of excellent or good quality vs. time of echocardiogram from first enrollment. Over 80% of the echocardiograms submitted at the end of the cross-sectional study were of excellent or good quality.

Assessment of core laboratory inter- and intra-observer variability of quality assessment in a subset of the echocardiograms analyzed (n=100) has been previously reported[2]. This analysis demonstrated concordance between and within observers in approximately half the

cases and two grades difference in qualitative image quality assessment in less than 5% of cases.

Visualization of Specific Cardiovascular Structures

The percentage of specific cardiovascular structures that could not be adequately imaged to rule out abnormalities of structure or function in the study echocardiograms is shown in Table II. For example, in the first row in Table II, right pulmonary artery obstruction, the right pulmonary artery was not imaged well enough to rule out obstruction in 69% of study echocardiograms in which the structure was present. The pulmonary arteries were the least frequently imaged structures followed by the superior vena cava, systemic venous pathway (in adequate detail to rule out thrombus), aortic arch, and native pulmonary valve. Each of these was inadequately imaged in >45% of subjects. The atrioventricular valves and the ventricular chamber (adequate to rule out thrombus) were the most frequently imaged structures. Imaging of the single ventricular endocardial borders was adequate to allow calculation of ventricular volume in the majority of subjects (76%).

Imaging of a fenestration in this cohort has been previously reported[5]. As outlined in this previous report, 356 of the 361 subjects who had a fenestration at the time of the Fontan procedure had an available echocardiogram. Of these, the study echocardiogram demonstrated an open fenestration in 69 (10%), a closed fenestration in 227 (63%), and indeterminate fenestration status in 60 (17%).

Factors Associated with Echocardiographic Image Quality

Univariate analysis revealed that a better quality echocardiogram was associated with the following: younger age at enrollment, greater weight-for-age and body mass index z-scores, ventricular morphology other than mixed, fewer surgical interventions post-Fontan, and levocardia. In addition, subjects with hypoplastic left heart syndrome had better quality images compared to those with an unbalanced atrioventricular septal defect and heterotaxy syndrome. The type of Fontan was not associated with echocardiographic quality after adjusting for clinical site and age. The results of multivariable logistic regression analysis of factors associated with overall echocardiographic quality are shown in Table III. Clinical site, younger age at enrollment, greater time from study start to date of echocardiogram, levocardia, and the absence of a pulmonary artery stent were significant independent predictors of better echocardiographic quality. This model explained 26% of the variance in quality.

Factors Associated with Successful Quantitative Evaluation

Univariate analysis of factors associated with the ability to quantitatively assess ventricular volume revealed that clinical site, ventricular morphology other than mixed, greater time from first enrollment, levocardia, and fewer surgical and catheter interventions post-Fontan were associated with greater odds of being able to calculate ventricular volumes and ejection fraction. The percentage of echocardiograms from which quantitative analysis could be performed based on cardiac position and ventricular morphology is shown in Table IV. The results of multivariable logistic regression analysis of factors associated with the ability to calculate ventricular volume are shown in Table V. Clinical site, ventricular morphology other than mixed, greater time from first enrollment, levocardia, and fewer catheter interventions comprised the final model and explained 32% of the variance in the ability to quantify ventricular volume. Indices of body size, including weight and height for age z-score and body mass index z-score, were not independently associated with echocardiographic quality or the ability to obtain ventricular volumes in multivariable modeling.

Discussion

In this analysis of a large number of echocardiograms performed in Fontan survivors as part of the PHN Fontan Cross-Sectional Study we found that echocardiographic quality was good or excellent in most cases, and that quantitative analysis of ventricular volumes could be performed in the majority of subjects. With the exception of the great arteries and veins, most cardiovascular structures could be adequately imaged in our population, allowing assessment of single ventricular structure and function, as well as assessment of atrioventricular and semilunar valve function.

Although intra- and inter-observer variability was not specifically assessed in the current analysis, agreement has been assessed in a subset of the Fontan Cross-Sectional Study echocardiograms and reported elsewhere[2]. In this report, the intra-and inter-observer variability of subjective image quality and ventricular function were reported. Intra- and inter-observer assessments were concordant or within one grade difference in >90% for image quality, concordant in 90% and 83%, respectively, for subjective assessment of single left ventricular function, and concordant 74% and 62%, respectively, for subjective assessment of single right ventricular systolic function. Intra-class correlation coefficients for ventricular volumes within and between observers were generally high, ranging from 0.82 to 0.95.

We found that the quality of echocardiograms improved throughout the course of the Fontan Cross-Sectional Study, with more than 80% of the echocardiograms graded as good or excellent quality by the end of study enrollment compared to approximately 60% during the first third of the study. This study was one of the first conducted by the PHN, and all echocardiograms were performed and submitted to the data coordinating center prior to the implementation of standardized procedures for providing feedback from the echocardiographic core laboratory to clinical sites. Therefore, the improvement in echocardiographic quality was not a result of feedback and critique from the core laboratory, but likely due to increasing familiarity and experience with the study protocol. Although feedback from core laboratories is important and has been shown to improve the quality and reliability of quantitative echocardiographic data obtained in clinical trials[6–8], our results demonstrate that quality may improve during participation in a clinical study without specific core laboratory feedback or quality control. These findings suggest that implementation of a standardized imaging protocol for Fontan patients within a clinical pediatric laboratory may result in improved image quality as has been shown with other quality improvement initiatives[9].

While many cardiovascular structures were adequately imaged in the majority of subjects in the Fontan Cross-Sectional Study, others proved challenging, as might be expected. The structures that were most difficult to image and, therefore, to allow comment on abnormalities of structure or function, were the great arteries and venous pathways (not adequately visualized in over 45% of studies). The fact that Fontan patients have typically undergone multiple surgical procedures involving these structures likely contributes to the difficulty in imaging these structures. However, imaging of the pulmonary arteries has also proven challenging even in younger patients with single ventricle physiology prior to the superior cavopulmonary anastomosis, or stage II procedure[10]. Other investigators have shown that these structures are difficult to image using echocardiography in the post-Fontan population, and that cardiac magnetic resonance imaging is superior to echocardiography in the noninvasive evaluation of these specific structures[11–13]. It is important to note that no imaging modality is ideal for imaging all cardiac structures in all Fontan patients. For instance in our cohort, cardiac magnetic resonance imaging would not have been feasible in the 13% with a pacemaker, and suboptimal due to significant artifact in the 4% with

pulmonary artery stents. This study provides information relevant to study design for future investigations in the Fontan population and represents a benchmark for echocardiographic image acquisition in this challenging population to which future noninvasive modalities can be compared.

Most factors affecting echocardiographic quality and the ability to obtain ventricular volumes were not modifiable, including ventricular morphology, cardiac position, age at enrollment, and number of post-Fontan procedures. Although non-cardiac patient factors, including obesity, gender and race, are associated with echocardiographic quality and missing data in adult trials[14], studies in pediatric and young adult populations have not reported significant associations between the quality of echocardiograms and patient characteristics, particularly body size[6,15]. However, in our cohort of Fontan survivors obesity was quite uncommon[16]. We found that both clinical site and later timing of the echocardiogram relative to the beginning of the cross-sectional study were significantly associated with overall echocardiographic quality and the ability to calculate ventricular volumes. Although there are likely difficult to modify factors at individual sites, such as the quality of the echocardiographic imaging equipment and methods of image storage, with training and familiarity with a standardized protocol good quality echocardiographic information can be obtained in this challenging population.

Limitations

Although there was no formal feedback from the core laboratory during the time images were obtained, the sonographers and physicians at the clinical sites were aware the images were to be submitted to a core laboratory for analysis and quality evaluation, and this may have provided additional incentive for optimizing image quality. Data regarding the specifics of image acquisition at the clinical sites (e.g., sonographer education, specific number of sonographers participating, years of sonographer experience) were not obtained. Finally, the Fontan Cross-Sectional Study was conducted at 7 medium to large volume academic pediatric cardiology centers with experienced pediatric sonographers; therefore, our findings may not be generalizable to all pediatric cardiology programs.

Conclusions

In this study we demonstrate that echocardiography can be used to adequately visualize most cardiovascular structures with generally good quality in subjects who have undergone a Fontan procedure. Non-modifiable factors associated with poor echocardiographic quality included cardiac position other than levocardia and mixed ventricular morphology. The potentially modifiable factors associated with echocardiographic quality, including clinical site and timing of the echocardiogram relative to the beginning of the Fontan Cross-Sectional Study; suggest that familiarity and experience with a standard imaging protocol, which could be implemented as part of a quality improvement initiative, will result in an improvement in quality.

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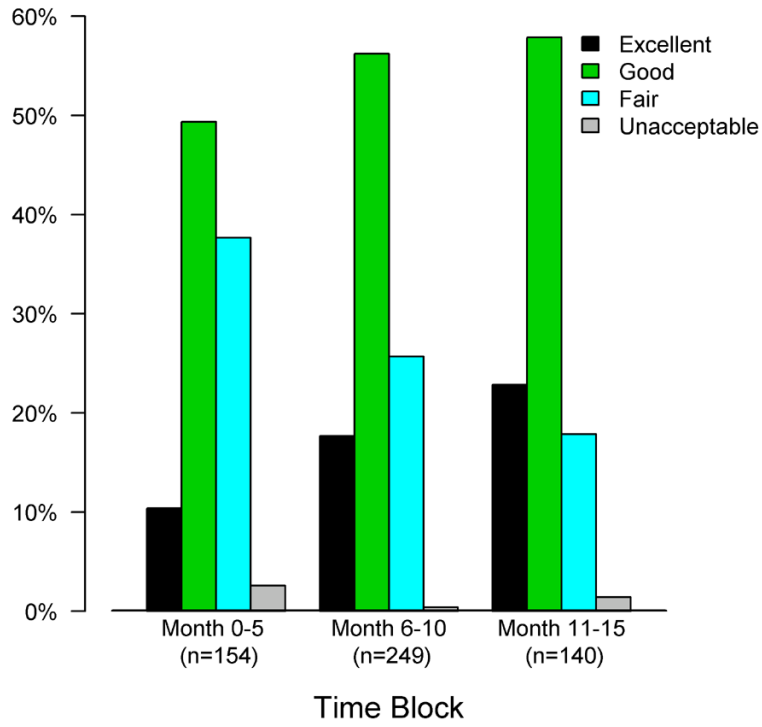

Figure 1.
Distribution of echocardiographic quality grade by study time period.

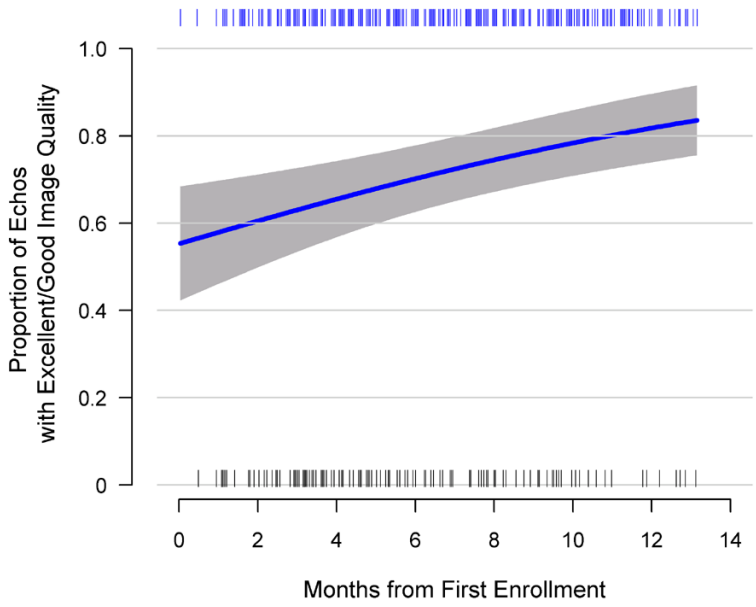

Figure 2.

Relationship between excellent/good quality echocardiograms and study time period using a logistic regression (smoothed). Pointwise 95% confidence bands are shown. Fringe marks on top and bottom of plot denote the time of echocardiogram for excellent/good and fair/poor images, respectively.

Table I

Patient Characteristics at Enrollment for 543 Subjects Undergoing an Echocardiogram.

Patient Characteristic	Mean±SD/%
Age at enrollment (years)	11.9±3.4
Age at Fontan (years)	3.4±2.1
Weight for age z-score	−0.4±1.4
Height for age z-score	−0.7±1.3
Body mass index z-score	−0.04±1.1
Anatomic diagnosis	
Tricuspid atresia	22%
Hypoplastic left heart syndrome	21%
Double inlet left ventricle	15%
Single ventricle, heterotaxy syndrome	7%
Single ventricle, mitral atresia	6%
Unbalanced atrioventricular septal defect	4%
Double inlet right ventricle	2%
Other	24%
Cardiac position	
Levocardia	90%
Dextrocardia	8%
Mesocardia	2%
L-loop	18%
Ventricular morphology	
Left	49%
Right	34%
Mixed	17%
Type of Fontan	
Atriopulmonary connection	13%
TCPC intracardiac lateral tunnel	60%
TCPC extracardiac conduit	24%
Other	3%
Post Fontan pulmonary artery stent	4%
*__Total number of surgical procedures__	5.2±2.4
*__Total number of catheter interventions__	1.6±1.7
Current Pacemaker	13%
History of respiratory problems	22%

TCPC – Total cavopulmonary connection.

*Including pre-Fontan, concurrent with Fontan and post-Fontan procedures.

Table II

Ability of Echocardiographic Core Laboratory to Adequately Evaluate Function of Various Cardiac Structures in the 543 Fontan Study Echocardiograms.

	Number (%) Not Visualized	# Excluded Because Structure Not Present
Right pulmonary artery obstruction	376 (69%)	1
Left pulmonary artery obstruction	344 (64%)	2
Aortic arch obstruction	262 (48%)	0
Systemic venous pathway thrombus	261 (48%)	0
Superior vena cava pathway obstruction	244 (45%)	5
Native pulmonary valve regurgitation *	154 (45%)	203
Inferior vena cava pathway obstruction	204 (38%)	7
Systemic venous pathway baffle leak	196 (36%)	5
Right-sided ventricular dysfunction	105 (33%)	225
Left-sided ventricular dysfunction	97 (26%)	164
Quantitative ventricular volume	129 (24%)	0
Native aortic valve regurgitation	88 (19%)	74
Systemic venous pathway fenestration patent	73 (18%)	143
Pulmonary atrial thrombus	86 (16%)	0
Common atrioventricular valve regurgitation	8 (16%)	492
Right atrioventricular valve regurgitation	50 (14%)	176
Pulmonary venous obstruction	69 (13%)	0
Ventricular thrombus	69 (13%)	0
Left atrioventricular valve regurgitation	41 (10%)	145

* Includes neo-aortic regurgitation in those subjects undergoing a Stansel-type procedure.

Table III

Multivariable Model for Better Echocardiographic Quality (N=543, max-rescaled $R^2 = 0.26$).

Patient Factor	Odds Ratio for Better Quality (95%CI)	p
Clinical site		**<.001**
Age at enrollment	0.90 (0.84, 0.95)	**<.001**
Time from study start to echo acquisition	1.14* (1.07, 1.23)	**<.001**
Cardiac position:		**<.001**
Dextrocardia vs. levocardia	0.11 (0.05, 0.23)	
Mesocardia vs. levocardia	0.10 (0.02, 0.51)	
Post-Fontan PA stent	0.21 (0.08, 0.58)	**0.003**

* hazard ratio per 1 month increment after study start, PA – pulmonary artery.

Table IV

Percentage of Echocardiograms with Quantification of Ventricular Volume.

	N	% with Volume Calculated	P-value
Cardiac position			**<0.001**
Levocardia	489	80.8%	
Dextrocardia	45	33.3%	
Mesocardia	9	35.6%	
Ventricular morphology			**<0.001**
Left	265	82.6%	
Right	183	85.3%	
Mixed	95	41.1%	

Table V

Multivariable Model for the Ability to Calculate Ventricular Volume (N=543, max-rescaled R^2 =0.32).

	Odds Ratio for Success in Calculating Ventricular Volume (95%CI)	p
Clinical site		**0.010**
Ventricular morphology		**<.001**
Left	4.70 (2.64, 8.34)	
Right	6.89 (3.66, 13.00)	
Mixed	--	
Time from study start to echo acquisition	1.09 * (1.01, 1.17)	**0.035**
Cardiac position		**<.001**
Levocardia	--	
Mesocardia	0.12 (0.02, 0.73)	
Dextrocardia	0.14 (0.07, 0.31)	
Number of catheter interventions post-Fontan	0.74 (0.60, 0.91)	**0.004**

* hazard ratio per 1 month increment after study start