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Longitudinal Outcomes of Patients with Single Ventricle after the Fontan Procedure

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Abstract

Background—Multicenter longitudinal objective data for Fontan patients surviving into adulthood are lacking.

Objectives—Describe transplant-free survival and explore relationships between laboratory measures of ventricular performance and functional status over time.

Methods—Exercise testing, echocardiography, B-type natriuretic peptide (BNP), functional health assessment, and medical history abstraction were repeated 9.4 ± 0.4 years after the Fontan Cross-Sectional Study (Fontan 1) compared to previous values. Cox regression analysis explored risk factors for interim death or cardiac transplantation.

Results—From the original cohort of 546 subjects, 466 were recontacted and 373 (80%) were enrolled at 21.2 ± 3.5 years of age. Among subjects with paired testing, percent predicted maximum VO₂ decreased (69 ± 14 vs. 61 ± 16 , $p < 0.001$, $n = 95$), ejection fraction decreased (58 ± 11 vs. 55 ± 10 , $p < 0.001$, $n = 259$), and BNP increased (Median (IQR) 13 (7,25) vs. 18 (9,36) pg/mol, $p < 0.001$, $n = 340$). At latest follow-up lower Pediatric Quality of Life Inventory (PedsQL)

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physical summary score was associated with poorer exercise performance (R² adjusted = 0.20, p <0.001, n = 274). Cumulative complications since the Fontan included additional cardiac surgery (32%), catheter intervention (62%), arrhythmia treatment (32%), thrombosis (12%), and protein losing enteropathy (8%). Since Fontan 1, 54 subjects (10%) have received a heart transplant (n = 23) or died without transplantation (n = 31). The interval risk of death/transplantation was associated with poorer ventricular performance and functional health status assessed at Fontan 1, but was not associated with ventricular morphology, subject age or type of Fontan connection.

Conclusions—Interim transplant-free survival over 12 years in this Fontan cohort was 90% and was independent of ventricular morphology. Exercise performance decreased and was associated with worse functional health status. Future interventions might focus on preserving exercise capacity. (**Clinical Trials Registration #:** NCT00132782)

Keywords

Fontan procedure; single ventricle; exercise; adult congenital heart disease; functional health status

Introduction

Functional deterioration and an increasing risk of complications are thought to occur over time in patients with single ventricle physiology who have undergone a Fontan procedure, particularly into adulthood. Previous studies examining vital status over time for Fontan patients and factors associated with death or transplantation have been limited to single center reports that span large time periods and surgical eras (e.g., 25 years) (1), or have included a short length of follow up (e.g., <2 years) (2). The Pediatric Heart Network Fontan Cross-Sectional Study (Fontan 1, 2003–2004) investigated associations between measures of health status, ventricular function, and exercise performance in 546 children and adolescents, then aged 6–18 years (mean age of 11.9± 3.4 years) who had survived a Fontan procedure (3). The cross-sectional design of Fontan 1 limited the ability to assess whether observed differences between older and younger subjects were related to the length of time one lives with Fontan physiology, or to temporal changes in medical, catheter-based or surgical management strategies that had occurred. The Fontan Follow-up Study (Fontan 2) was limited to reassessment of vital status and functional health status and enrolled 85% of the Fontan 1 survivors (n = 428) between 2009–2011. There was 95% interim transplant-free survival and death or transplantation was associated with poorer performance on previously measured functional health status and measures of ventricular performance.(4)

The present study (Fontan 3) is a third assessment of the original Fontan cohort and includes reassessment of vital and health status as well as repeat measures of ventricular function and exercise performance during a time in which many of the original Fontan 1 subjects were transitioning to adulthood. The primary objectives were to: 1) determine trends in laboratory measures of ventricular performance over time (exercise, echocardiography, BNP, underlying rhythm); 2) determine relationships between current laboratory measures of ventricular performance and functional health status using the Pediatric Quality of Life Inventory (PedsQL); 3) determine factors associated with interim death or transplantation since Fontan 1 in this well characterized cohort; and 4) describe access to healthcare over time in this population of subjects who have transitioned into young adulthood.

METHODS

Study design and patient population

The methods for Fontan 1 and Fontan 2 have been previously described (4,5). Eligible patients were identified by a preliminary medical record review of all 546 children who had participated in the Fontan 1 study. Study subjects were included if they agreed to come to 1 of the 7 participating centers for repeat testing. Exclusion criteria included conversion to a biventricular circulation, heart transplantation or death. Each center's institutional review board approved the protocol. Written informed consent and assent were obtained according to local requirements. Anatomic, clinical and surgical data were collected at enrollment (October 2013 to December 2014) using standardized forms. Structured interviews with the parent/guardian and/or subject were used to assess current clinical state, socioeconomic status, emotional and social functioning, and access to healthcare.

Medical record review and assessment of vital status

For enrolled study subjects, a detailed medical record review was performed using the same standardized forms previously used to abstract data on patient demographics and outcomes for the Fontan 1 and 2 studies (3,4). Vital status was assessed annually in all subjects by direct contact or review of the social security death index for subjects who could not be located.

Measures of functional health status and quality of life

The following instruments were used in this study:

- Age-appropriate versions of the Peds-QL with a self-report and a parallel parent proxy report for those subjects < 18 years of age were used to assess quality of life (6). Peds-QL age groups versions (8–12 years old, 13–18, and 19–25) have only minor differences in language. To preserve sample size and after consultation with the developer of the instrument, we combined these versions for analytic purposes (personal communication, James Varni, MD). Items were linearly transformed to a 0–100 scale, so that higher scores indicate better functioning or quality of life.
- The Child Health Questionnaire (CHQ), which includes questionnaires for both the child and the parent, was used for subjects < 18 years (7).
- In subjects aged ≥ 19 years, functional status was measured with the Short Form Health Survey version 2 (SF-36) (8).

The Peds-QL patient report was used to determine relationships between laboratory measures of ventricular performance and functional health status, since it was the only questionnaire completed across all age groups and it has been shown to correlate highly with both the CHQ and SF-36 (9).

Echocardiographic protocol

Standardized 2-dimensional (2D) and Doppler echocardiograms were centrally interpreted. The measurements were performed by the same observer who analyzed echocardiograms

performed at Fontan 1, and all of the measurements were performed using the same method (10). When possible, measurements and derived indices were expressed as Z-scores relative to body surface area (11). Ventricular dominance was assigned as left ventricular, right ventricular, or mixed (e.g., unbalanced atrioventricular canal). End diastolic volume, end-systolic volume, and mass were obtained with 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 were used for data analysis.

Exercise protocol

Maximal exercise testing was performed with a ramp protocol on an electronically braked cycle ergometer and interpreted locally. A standard 12-lead electrocardiogram was performed prior to the exercise test to assess the underlying heart rhythm. Testing was performed with standard protocols previously used in children, adolescents, and subjects with Fontan physiology (5,12). Six exercise variables were used as outcomes: percent predicted maximum VO_2 , percent predicted maximum work rate, percent predicted maximum O_2 pulse, chronotropic index, percent predicted VO_2 at anaerobic threshold, and resting oxygen saturation. Separate analyses of the first four variables were done on those subjects able to achieve maximal effort (peak respiratory exchange ratio ≥ 1.1). Analysis of chronotropic index was further restricted to non-paced subjects.

Serology

Resting BNP plasma concentration was centrally measured with an immunochemiluminometric assay (LabCorp Clinical Trials, Cranford, New Jersey).

Statistical Methods

The demographic and anatomic characteristics of those enrolled in Fontan 3 were compared to those who were eligible but refused to participate. Subjects with the tests of interest at Fontan 3 (PedsQL patient summary scores, exercise testing, echocardiogram, and BNP) were also compared to those enrolled but without values for that particular test. The groups were compared with respect to their baseline characteristics (demographic profile, medical history, functional status and laboratory testing) from the Fontan 1 study.

The differences between values at Fontan 1 and Fontan 3 were assessed for each outcome for subjects with paired measurements at both time points. Continuous variables were tested using paired Student's t-tests for means and Wilcoxon's signed-rank test for medians. Categorical variables were tested using McNemar's test. Descriptive statistics were provided at each time point.

Regression analyses assessed univariate and multivariable associations of current functional health status (PedsQL physical summary score) with the simultaneously derived variables (exercise, echocardiography and BNP tests, as well as age, gender and type of Fontan procedure). Stepwise regression was used to inform selection of a final model. All stepwise regressions used $p=0.15$ as a criterion for entry into the model and $p=0.05$ as a criterion to stay in the model. Bootstrapping was used to estimate the reliability of each independent variable entering into a stepwise regression, equivalent to the percentage of models out of

1000 that contain the variable of interest with a p-value of 0.05 or less. The proportion of variance explained (R^2) was calculated and reported after adjusting downward (R^2_{adj}) to account for the effect of R^2 increasing with number of variables.

The relationship between transplant-free survival and baseline characteristics (assessed at Fontan 1) was examined using Cox proportional hazards regression modeling. The single subject who underwent an interval biventricular conversion was excluded yielding a cohort of 545 Fontan subjects for analysis. Follow-up time was defined as the time from Fontan 1 medical record review until either death/transplantation or the latest available assessment of vital/transplantation status (March 15, 2016). We report hazard ratios (HR) with 95% confidence intervals and p-values associated with the Wald chi-square test. The proportional hazards assumption was evaluated using a supremum test for non-proportionality based on martingale residuals, and interaction terms with time were added if appropriate. Survival and transplantation are illustrated using Kaplan-Meier survival plots. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Subject characteristics

At the time of Fontan 3 study enrollment, 466 of the 546 subjects enrolled in the Fontan 1 cohort were found to be eligible; 373 enrolled (80%) and 93 refused participation. Enrolled subjects were slightly younger than those who were eligible but declined participation (21.1 ± 3.5 vs. 22.0 ± 3.4 years, $p = 0.01$). Gender, race, ethnicity, underlying anatomic diagnosis, and type of Fontan connection performed were not different. No differences were identified in any cardiac characteristics or laboratory measures assessed at Fontan 1 between enrollees and subjects who refused (Data not shown).

Fontan 3 cohort characteristics

The 373 enrolled subjects were studied at a mean of 9.4 ± 0.4 years following the Fontan 1 study, and 17.8 ± 3.4 years after Fontan surgery. Anatomic details of those who enrolled were not different from the original Fontan 1 cohort. The number of patients who underwent each type of test is shown in Figure 1. Of the 373 subjects enrolled, 9 were unable to complete the PedsQL patient report due to physical or mental limitations; therefore 364 subjects formed the cohort to explore associations between functional status and measures of cardiac performance. Patient characteristics are displayed in Online Table 1.

There were no differences in anatomy, demographics, or results of assessments performed at Fontan 1 between those who did not perform exercise testing and the remaining subjects. Subjects with missing mass-volume data derived from echocardiographic measurements included a higher proportion of mixed ventricular dominance (53% vs. 10%) and a lower proportion of RV (8% vs. 36%) and LV (39% vs. 54%) with an overall $p < 0.001$, but did not differ in any other anatomic or demographic variable. There were no differences between characteristics for subjects with and without BNP tests. Of the 364 subjects with PedsQL summary data, 270 (74%) had all laboratory tests performed and 223 had a maximal effort

exercise test along with complete echocardiography and BNP testing. Prevalence of interventions and complications since the Fontan procedure increased over the period between Fontan 1 and Fontan 3 (Table 1). The most prevalent type of cardiac surgical procedure performed was related to placement or revision of an electronic device. Among the 58 with electronic devices at Fontan 3, 49 were pacemakers consisting of 17 single chamber atrial and 32 dual chamber pacemakers. An implantable cardioverter defibrillator was present in 9 subjects.

Paired laboratory performance results over time

Of 336 subjects completing the exercise test in Fontan 3, 275 (82%) achieved maximum effort compared to only 40% (166/411) in Fontan 1. There were 217 subjects who performed exercise testing at both Fontan 1 and Fontan 3; 95 of them reached maximal effort for both tests. The subjects who achieved maximal effort were an average of 2.5 years older than those who had a submaximal effort, $p < 0.001$. After controlling for age, there were no anatomic or demographic differences between the 2 groups. The CHQ-P50 physical summary score at the time of Fontan 1 was lower in the group who did not achieve maximal effort during exercise in the current study, (40 ± 15 vs. 46 ± 20 , $p = 0.03$).

Table 2 presents the comparisons of paired study outcomes at Fontan 1 and Fontan 3. Subjects were included if the outcome was measured at both Fontan 1 and 3 and exercise outcomes were limited to those subjects with maximal effort at both time points ($n = 95$). Among variables assessed during exercise testing, mean values for the cohort were lower than normal and declined significantly over time for all variables measured except chronotropic index and baseline oxygen saturation. Percent predicted maximum VO_2 decreased approximately $\frac{1}{2}$ of a standard deviation from a mean of 69%-61%, $P < 0.001$. We further explored trajectories of the 95 individual subjects with paired maximal effort exercise tests by dividing them into 2 equal-sized cohorts based on age and baseline % predicted maximum VO_2 . The younger aged group (age at Fontan 1 < 13.6 years, $n = 48$) had a greater decline in % predicted maximum VO_2 than the older aged group (mean slope of change over time -1.03 vs. -0.47). The group with better exercise performance at baseline (% predicted maximum $\text{VO}_2 > 69\%$, $n = 48$) showed a greater decline in % predicted maximum VO_2 than those who had poorer exercise performance at baseline (mean slope of change over time -1.31 vs. -0.19). Percent predicted maximum work rate decreased almost one full standard deviation from a mean of 69%–56%, $P < 0.001$. Among echocardiographic outcomes, ejection fraction significantly declined (mean 58% vs. 55%, $P < 0.001$), the result of a greater degree of dilation over time in systole than diastole: end systolic volume z-score (mean change 0.8, $P < 0.001$) and end diastolic volume z-score (mean change of 0.4, $P < 0.001$). Serum BNP was significantly higher at the time of Fontan 3 (median of 18.0 pg/mL vs. 13 pg/mL), $p < 0.001$. Consistent with our earlier report describing BNP in the Fontan 1 cohort (13), mean BNP (adjusted for age and gender) among subjects with atriopulmonary connection was higher than for those with intracardiac lateral tunnel, which in turn was higher than those with an extracardiac conduit.

Association between PedsQL and lab tests and patient characteristics measured at Fontan 3

To assess associations between PedsQL physical summary score at follow-up and each of the laboratory tests at follow-up, multivariable regression models were fit. The proportion of variation in PedsQL physical functioning summary scores explained by laboratory testing was highest for exercise performance ($R^2_{adj} = 0.20$, model $p < 0.001$, $n = 274$), and lowest for echocardiographic variables ($R^2_{adj} = 0.04$, $p < 0.001$, $n = 301$) and BNP ($R^2_{adj} = 0.06$, $p < 0.001$, $n = 351$). There was a strong association between worse PedsQL scores and lower exercise testing variables (Table 3). Five of 6 univariate relationships were significant, but the multivariable model included only % predicted maximum work rate and gender. For a subset of subjects achieving max effort at both time points ($n = 95$) the multivariable model included a single variable, % predicted maximum work rate. There was an inverse relationship between PedsQL physical summary score and logBNP. A one-point increase in logBNP was associated with a 2.8 decrease in physical summary score. There were no associations between the PedsQL summary score and echocardiographic variables. (Data not shown) Combining variables from all tests (exercise, echocardiography, BNP) into one model resulted in the same model as for exercise only. ($R^2_{adj} = 0.20$, $p < 0.001$, $n = 274$).

Functional health status over time

For subjects who were 18 years at Fontan 3, the CHQ-P50 parent-report was administered at 3 time points, Fontan 1, 2, and 3 ($n = 106$). No change was seen in the physical summary score over 9.3 years between Fontan 1 and Fontan 3, and a statistical (but not clinically meaningful) improvement was seen in the psychosocial summary score as perceived by parents (Table 4). The other instruments (PedsQL and SF-36) were not administered at Fontan 1, so comparisons were made over a mean of 2.8-year period since Fontan 2. No significant changes were seen in any of the summary or component scores of either instrument over this relatively short interval (Table 4).

Associations between interim death or transplantation and patient characteristics assessed at Fontan 1

As of March 15, 2016, 54 subjects (10%) had received a heart transplant ($n = 23$) or died ($n = 31$) since Fontan 1 (Central Illustration). We found no differences in the composite risk of death/transplantation based on subject age, gender, race, ethnicity, ventricular morphology, or type of Fontan.

The risk of death/transplantation after Fontan 1 was significantly associated in univariate analysis with the following conditions measured at Fontan 1 (Table 5): a poorer CHQ physical summary score, a higher BNP value, not completing an exercise test, decreased resting oxygen saturation, lower percent predicted VO₂ at anaerobic threshold, poorer ventricular performance (abnormally low ventricular function and increased (abnormal) ventricular volume). The hazard of death/transplantation for the subjects with the highest tertile BNP (>21 pg/mL) and the lowest tertile CHQ P50 Physical Summary Score (<44) assessed at Fontan 1 was 3.65 times higher than for the rest of the cohort. Analyzed as a whole, family income was not associated with death or transplantation. However, when

compared to families with the lowest income, those reporting an income >\$100,000 annually had improved outcomes.

To determine whether there were differences between subjects who received a heart transplant and those who died without receiving a transplant we compared the Kaplan-Meier survival plots for death and transplantation separately. No differences were noted over time ($p = 0.4$ log-rank test, $p = 0.7$ Wilcoxon test). There were no differences in the risk of death when compared to the risk of transplantation based on gender, race, ethnicity, ventricular morphology, or age. There was a trend toward a difference between Fontan surgical types with 5 deaths and no transplantations in the atriopulmonary connection category. ($p = 0.059$) There were no differences between death and transplantation regarding laboratory testing variables assessed at Fontan 1. The frequencies of deaths since Fontan 1 differed by center, from 3% (3/105 subjects) to 14% (3/22 subjects). The frequencies of transplantations since Fontan 1 varied among centers from 0% (0 of 22 subjects) to 21% (8 of 38 subjects) (Table 6).

Healthcare utilization

Few differences were observed in the frequencies for relevant healthcare access variables between Fontan 2 and the present data collection. (Online Table 2) The vast majority of subjects (96%) continued to have health insurance with a nearly equal distribution between private and public support. Subjects at the time of Fontan 3 were slightly more likely to have visited an adult cardiologist in the past 2 years (35% vs. 30%) and to have seen an adult congenital heart specialist (33% vs. 24%). Visits to an obstetrician/gynecologist increased among female subjects (41% vs. 32%) while those receiving educational support decreased from 36%–26%.

Discussion

Currently, >1,000 single ventricle patients undergo a Fontan procedure in the U.S annually. This represents 4.1% of all pediatric cardiac surgical procedures performed annually. (Society of Thoracic Surgeons Congenital Heart Disease Database, Spring 2016 Harvest, not shown) A number of reports describe declining survival over time with an increasing and substantial burden of complications (2,14–17). Projections suggest that the number of patients living with a Fontan circulation will double over the next 20 years thereby increasing the demand for care and services (18). Few studies report serial follow-up of individual subjects (19) and most are limited either by the small number of patients followed or by a short period of follow-up. This study comprises the largest to date multicenter study of children and young adults who have undergone a Fontan procedure followed longitudinally over a decade. The novel aspect of the present study was the ability to report the change over time in laboratory measures assessed in an identical manner in individual patients. Virtually all measures of ventricular performance declined over time. The most frequently used metric of aerobic capacity, % predicted maximum VO_2 decreased from 69%–61% in those with paired maximal effort tests.

We found an overall 90% transplant-free survival over 12 years since enrollment in the Fontan 1 study. This compares favorably to a previous report, which estimated a 5-year

transplant-free survival of 86% (2). Consistent with some single center reports (17), we did not detect a significant difference in the slope of the survival curve over time among these Fontan survivors. Moreover, we did not find a survival benefit in those subjects with dominant left ventricles. When considering functional single ventricles from birth, right ventricular dominance is the most important risk factor for death overall, but this does not appear to be a risk factor beyond the neonatal period (16,17). As we have discovered in other investigations of the PHN Fontan cohort (20), substantial center differences exist. We found a difference in rate of transplantation across centers, ranging from 0%–21%. Significant regional differences in rates of heart transplantation among Fontan patients have recently been reported in Australia and New Zealand (21). Although many factors are likely responsible for this variability, our findings suggest that there remains an unmet need for standardization in criteria used for consideration of heart transplantation in the Fontan population.

We found that 80% of the eligible original Fontan 1 cohort was willing to participate in the present study. Similar to the Fontan 2 study, older patients were less likely to agree to return, which may be due to the known challenges facing subjects as they transition to assuming care for themselves (4,22). For Fontan survivors, significant morbidity is reflected by rates of additional interventions and complications over time. In this cohort, additional catheter interventions occurred in 62%. Many of these may have been planned for Fontan fenestration closure (23). However, catheter interventions continued to increase even 15 years after the Fontan surgery. Complications increased over time, including arrhythmia requiring treatment, which increased from 20%–32% of subjects, and placement of an implanted electronic device, which increased from 13%–16% of subjects. In our previous assessments of the Fontan cross sectional cohort we identified low incidences of some complications associated with the Fontan circulation including rates of stroke, thrombosis, cirrhosis, protein losing enteropathy, and plastic bronchitis. Although not surprising, it is concerning that the rates of each of these complications increased over this decade of follow-up.

Poor exercise capacity has been associated with a greater risk of morbidity (2) and mortality (24) in patients with a Fontan circulation. We previously reported a weak association between functional health status (CHQ-P50 Physical Functioning Summary Score) and exercise at Fontan 1 (25). In the present study we found an even stronger association between functional health status (PedsQL) and exercise performance. Lower exercise capacity at initial testing was the best predictor of the decrease seen in exercise at subsequent testing. We did not find associations between exercise performance over time with either ventricular morphology or age at which the Fontan was performed (26,27). A few studies have documented acute improvements in exercise function in children with heart disease (28), including Fontan patients (29,30) after participation in a formal exercise training program. A recent pilot study has shown improvement in quality of life with a home based physical activity program in this population (31). Our study did not collect detailed descriptions of activity level or utilize activity trackers. Future studies should investigate whether exercise programs can lead to sustained improvements in exercise capacity that are linked with decreases in morbidity and mortality.

The results of this study must be viewed in light of certain limitations. The original Fontan 1 cohort was by necessity a subset of subjects with single ventricle physiology who survived multi-stage surgical palliation culminating in the modified Fontan procedure and who were well enough to complete most of study testing. The timeframe between Fontan 1 and 3 may have been a period of relative clinical stability and too short to observe meaningful changes in functional health status, medical conditions, or laboratory measures of ventricular performance beyond those reported here. We have previously reported some inherent limitations of the echocardiographic evaluation of Fontan subjects, especially as they age (32). However, even though 2D echocardiographic measurements systematically underestimate ventricular volume measurements acquired by magnetic resonance imaging, the reproducibility of measurements are comparable by both modalities (10). Our assessment was also restricted to the 80% of eligible Fontan 1 survivors who agreed to participate in this follow-up study. In this longitudinal analysis, we report mean differences in this cohort over time that may not be applicable to each individual subject. Characterizing individual subjects with better or worse functional outcomes remains poorly defined (19).

Conclusions

In this follow-up study of a large, well characterized cohort of Fontan survivors there was a significant decline in exercise performance, which was associated with poorer functional health status at follow-up. In addition, there was an increase in the proportion of subjects undergoing interventions and suffering complications over nearly a decade. Transplant-free survival from the time of initial enrollment was 90% at 12 years and was independent of underlying ventricular morphology or age. Further study might focus on interventions aimed at preserving or enhancing exercise capacity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BNP	brain natriuretic peptide
CHQ	Childhood Health Questionnaire
CHQ-PF50	Parent Report Child Health Questionnaire
Peds-QL	The Pediatric Quality of Life Inventory
SF-36	Short Form Health Survey Version 2
VO₂	oxygen uptake

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PERSPECTIVES

Competency in Patient Care

Among survivors of the Fontan procedure, complications and the need for additional interventions increase over time, but transplant-free survival is independent of ventricular morphology or age.

Translational Outlook

Further research is needed to develop more effective strategies to improve transplant-free survival in patients with single ventricle.

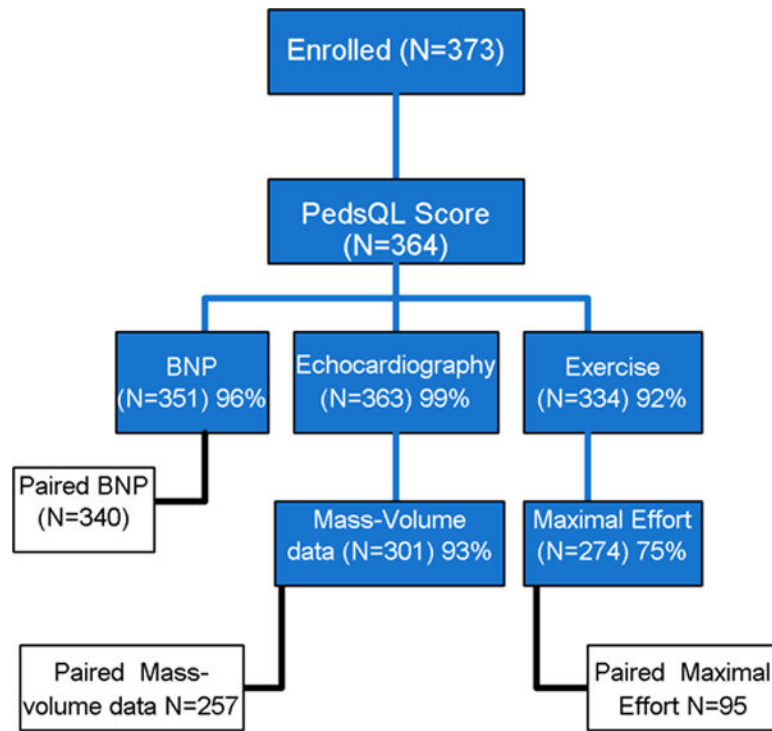
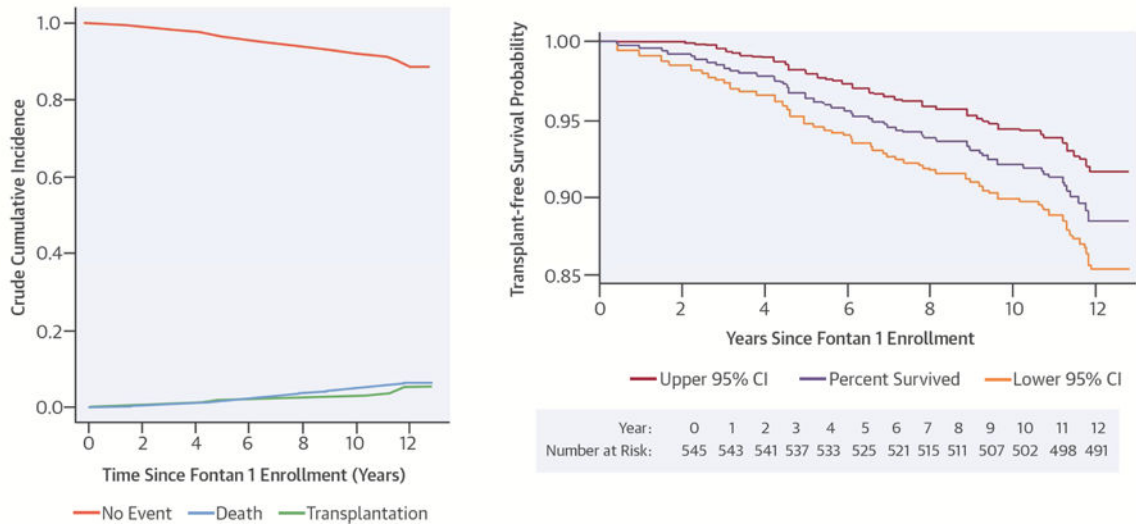


Figure 1. Laboratory testing of subjects enrolled in the Fontan 3 Study

Number of tests performed by enrolled subjects at Fontan 3 is shown in blue. Number of subjects with paired tests performed at both Fontan 1 and Fontan 3 are shown in white.



Central Illustration. Survival of Single Ventricle Patients after the Fontan Procedure

- A) Transplant-free survival. Proportion of subjects in each of 3 competing mutually exclusive states: death, transplantation, and alive without transplantation for all 545 subjects.
- B) Transplant-free survival since Fontan 1 (with 95% confidence intervals) in all subjects with complete follow-up data. For improved resolution, the scale on the y-axis is limited to 0.85–1.0.

Table 1
Complications and Interventions After Fontan Surgery

	Fontan 1 N = 546	Fontan 2 N = 416	Fontan 3 N = 373
Time since Fontan (Years)	8.7 ± 3.4	15.2 ± 3.4	17.8 ± 3.4
Cardiac surgery	23%	28%	32%
Catheter intervention	48%	57%	62%
Electronic device	13%	13%	16%
Stroke	2%	2%	4%
Seizures	3%	5%	7%
Thrombosis	8%	9%	12%
Arrhythmia treatment	20%	28%	32%
Protein losing enteropathy	4%	7%	8%
Cirrhosis	0.4%	4%	8%
Plastic bronchitis	0.1%	0.5%	1%

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Table 2
Main Study Outcomes at Fontan 1 and Fontan 3*

Characteristic ^{††}	N	Fontan 1	Fontan 3	Change	P Value ^{††}
Age at enrollment, years	373	11.7 ± 3.4	21.2 ± 3.5	9.5	-----
Exercise Outcomes					
Percent predicted VO ₂ at anaerobic threshold	196	80 ± 25	72 ± 25	-7.9	<0.001
Percent predicted maximum VO ₂ [‡]	95	69 ± 14	61 ± 16	-7.1	<0.001
Percent predicted maximum work rate [‡]	95	69 ± 15	56 ± 16	-13.1	<0.001
Percent predicted maximum oxygen pulse [‡]	95	91 ± 23	80 ± 21	-11.3	<0.001
Chronotropic index [‡]	79	0.7 ± 0.1	0.7 ± 0.2	-0.1	0.64
Oxygen saturation (%)	267	92 ± 5	93 ± 5	1.1	0.23
Echo outcomes					
Total echo end diastolic volume z score	259	-0.7 ± 1.7	-0.3 ± 2.2	0.4	<0.001
Total echo end systolic volume z score	259	0.2 ± 2.2	1.0 ± 3.7	0.8	<0.001
Total echo ventricular mass z score	257	0.9 ± 2.0	1.0 ± 2.6	0.1	0.42
Total echo stroke volume z score	259	-1.1 ± 1.7	-1.0 ± 1.6	0.1	0.31
Total echo ejection fraction z score	259	-1.0 ± 2.0	-1.5 ± 1.9	-0.5	0.001
Total ejection fraction	259	58 ± 11	55 ± 10	-2.5	<0.001
Echo mass:volume ratio z score	257	2.6 ± 3.2	2.4 ± 3.0	-0.2	0.45
BNP, pg/mL median (IQR)	340	13(7,25)	18(9,36)	3.9	<0.001
Log BNP	340	2.6 ± 0.9	2.9 ± 1.1	0.3	<0.001
Sinus rhythm (%)	355	67	70	3	0.30
Paced rhythm (%)	355	7	14	7	<0.001

* Subjects were included if the outcome was measured at both Fontan 1 and 3. Values are mean±SD, %, or median (interquartile range). BNP= B-type natriuretic peptide; VO₂=oxygen uptake.

[†]Limited to those subjects with maximal effort at both time points.

[‡]Limited to non-paced subjects with maximal effort at both time points.

^{††}Paired T-test for means. Wilcoxon signed rank test for BNP. McNemar's test for rhythm.

Table 3
Association Between PedsQL Physical Summary Score and Exercise

Variable	Univariate			Multivariable*		
	Slope/PE	P-value [†]	Slope/PE	P-value [†]	Reliability	
Gender (Female)	-8.92	<0.001	-7.35	<0.001	84%	
Fontan Type categories	-	0.077				
Intracardiac lateral tunnel		Reference				
Extracardiac conduit	-5.33	0.026 [‡]				
Atriopulmonary connection	-3.66	0.279 [‡]				
Other	5.81	0.352 [‡]				
Age at Fontan 3	0.03	0.920				
%Predicted Max Work Rate	0.46	<0.001	0.43	<0.001	100%	
Chronotropic index	18.44	0.001				
%Predicted Peak VO ₂	0.19	0.002				
Resting oxygen saturation	0.56	0.02				
%Predicted VO ₂ at anaerobic	0.08	0.049				
%Predicted maximum oxygen pulse	0.05	0.311				

PE= parameter estimate-represents the degree of change in the Summary Score associated with one unit change in exercise variable; VO₂=oxygen uptake

* R-sq=0.21 (R2 adjusted=0.20), p<0.001

[†]F test

[‡]T test

Table 4
Subjects with Paired Functional Health Status Data at Fontan 1, 2 and 3

	N	Fontan 1	Fontan 2	Fontan 3	P Value
Age (Years)		11.9 ± 3.4	18.4 ± 3.4	21.2 ± 3.5	
CHQ-P50 Physical summary score	106	50 (40,55)	48 (41,53)	49 (41,53)	0.6*
CHQ-P50 Psychosocial summary score	106	51 (42,57)	51 (42,57)	52 (43,59)	0.04*
PedsQL Physical functioning score	322	NA	78 (63,88)	75 (63,91)	0.6 [†]
PedsQL Psychosocial health score	324	NA	73 (62,87)	77 (64,88)	0.08 [†]
SF-36 Aggregated Mental health score	121	NA	75 (65,90)	80 (65,90)	0.9 [†]
SF-36 Aggregated Physical health score	120	NA	94 (69,100)	94 (75,100)	0.4 [†]

Values are Mean±SD or Median (interquartile range)

* Wilcoxon signed-rank test for medians, comparing Fontan 1 to Fontan 3

[†] Wilcoxon signed-rank test for medians, comparing Fontan 2 to Fontan 3

CHQ-P50 = Parent Report Child Health Questionnaire; PedsQL= Pediatric Quality of Life Inventory; SF-36 = Short Form Health Survey Version 2

Table 5
Cox model for predictors of death/transplant (total N=545, 54 events)

Variable	Events / Total	Hazard Ratio (95% CI)	P value*
Age at Fontan 1 enrollment	54 / 545	1.01 (0.94–1.09)	0.79
Age at Fontan 1 enrollment	54 / 545		0.75
<10		Reference	
10–13		1.25 (0.65–2.41)	0.50
>13		1.01 (0.53–1.95)	0.97
Male	54 / 545	0.65 (0.38–1.12)	0.12
Race	54 / 543		0.98
White		Reference	
Black		0.85 (0.34–2.15)	0.74
Asian		0.72 (0.10–5.25)	0.75
Indian or Alaskan		1.00 (0.36–2.78)	0.99
Hispanic	52 / 516	0.58 (0.14–2.40)	0.45
Income	41 / 467		0.26
< \$20,000		Reference	
\$20,000–39,999		0.47 (0.17–1.31)	0.15
\$40,000–59,999		0.51 (0.18–1.42)	0.19
\$60,000–79,999		0.84 (0.33–2.12)	0.71
\$80,000–99,999		0.60 (0.21–1.69)	0.33
> \$100,000		0.29 (0.10–0.87)	0.03
Ventricular type	54 / 545		0.11
Left		0.63 (0.30–1.32)	0.22
Right		1.19 (0.59–2.44)	0.63
Mixed		Reference	
Fontan type	54 / 545		0.60
Atriopulmonary Connection		Reference	
Intracardiac Lateral Tunnel		1.29 (0.50–3.32)	0.60
Extracardiac Conduit		1.75 (0.65–4.75)	0.27
Other		2.00 (0.39–10.31)	0.41
Age (years) at latest Fontan surgery as of enrollment in Fontan 1	54 / 545	1.10 (1.00–1.21)	0.05
Age (years) ≥3 at latest Fontan surgery as of enrollment in Fontan 1	54 / 545	1.49 (0.87–2.54)	0.14
Fontan 1 CHQ PF50 Physical summary score	49 / 510	0.97 (0.95–0.98)	<0.001
Fontan 1 CHQ PF50 Physical summary score	49 / 510		0.001
<44		4.78 (1.98–11.59)	<0.001
44–52		2.59 (1.01–6.63)	0.047
>52		Reference	
Fontan 1 CHQ PF50 Psychosocial summary score	49 / 510	1.00 (0.98–1.03)	0.91
Fontan 1 exercise test completed	54 / 545	0.51 (0.29–0.88)	0.015
Resting oxygen saturation (%)	33 / 404	0.86 (0.81–0.91)	<0.001
Percent predicted VO ₂ at anaerobic threshold (%)	22 / 316	0.98 (0.96–1)	0.038

Variable	Events / Total	Hazard Ratio (95% CI)	P value*
With maximum effort	32 / 400	0.82 (0.4–1.68)	0.59
Percent predicted maximum VO ₂ (%)	12 / 165	0.99 (0.95–1.02)	0.46
Percent predicted maximum work rate (%)	12 / 165	0.98 (0.94–1.01)	0.22
Chronotropic index (0.1 unit increase)	9 / 140	1.85 (1.01–3.38)	0.045
Fontan 1 echo Mass-volume data	54 / 545	0.54 (0.31–0.93)	0.028
Total echo end diastolic volume z-score	34 / 414	1.35 (1.18–1.55)	<0.001
Total echo end systolic volume z-score	34 / 414	1.27 (1.18–1.37)	<0.001
Total echo ventricular mass z-score	33 / 406	1.25 (1.11–1.41)	<0.001
Total echo stroke volume z-score	34 / 414	1.11 (0.92–1.32)	0.27
Total echo ejection fraction z-score	34 / 414	0.76 (0.65–0.88)	<0.001
Total echo ejection fraction	34 / 414	0.95 (0.92–0.97)	<0.001
Total mass-volume ratio	33 / 406	0.70 (0.27–1.82)	0.47
Total mass-volume ratio z-score	33 / 406	0.95 (0.85–1.07)	0.41
BNP, pg/mL, adjusted for age and sex	53 / 509	1.01 (1.01–1.01)	<0.001
BNP (pg/mL)	53 / 509		0.039
<8		Reference	
8–21		1.25 (0.59–2.67)	0.56
>21		2.24 (1.13–4.44)	0.02
BNP>21 and CHQ P50 physical summary score<44	48 / 482	3.65 (2.00–6.65)	<0.001

BNP= B-type natriuretic peptide; CHQ P50= Parent Report Child Health

Questionnaire; VO₂=oxygen uptake

*Wald Chi-square test

Table 6
Rate of Death and Transplant since Fontan 1 by Center

Center	Death (%)	Transplant (%)	Total (%)
A	5 (3.6%)	2 (1.4%)	7 (5.0%)
B	3 (2.9%)	7 (6.7%)	10 (9.5%)
C	3 (3.8%)	2 (2.5%)	5 (6.3%)
D	9 (8.7%)	3 (2.9%)	12 (11.7%)
E	3 (13.6%)	0 (0%)	3 (13.6%)
F	4 (6.7%)	1 (1.7%)	5 (8.3%)
G	4 (10.5%)	8 (21.1%)	12 (31.6%)
Total	31 (5.7%)	23 (4.2%)	54 (9.9%)

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