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Longitudinal Outcomes of Patients With Single Ventricle After the Fontan Procedure

Andrew M. Atz, MD,[a] Victor Zak, PhD,[b] Lynn Mahony, MD,[c] Karen Uzark, PhD,[d] Nicholas D'agincourt, MS,[b] David J. Goldberg, MD,[e] Richard V. Williams, MD,[f] Roger E. Breitbart, MD,[g] Steven D. Colan, MD,[g] Kristin M. Burns, MD,[h] Renee Margossian, MD,[g] Heather T. Henderson, MD,[i] Rosalind Korsin, RN,[j] Bradley S. Marino, MD,[k] Kaitlyn Daniels, RN,[f] Brian W. McCrindle, MD, MPH,[l] for the Pediatric Heart Network Investigators

ABSTRACT

BACKGROUND Multicenter longitudinal objective data for survival into adulthood of patients who have undergone Fontan procedures are lacking.

OBJECTIVES This study sought to 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, functional health assessment, and medical history abstraction were repeated 9.4 ± 0.4 years after the Fontan Cross-Sectional Study (Fontan 1) and compared with previous values. Cox regression analysis explored risk factors for interim death or cardiac transplantation.

RESULTS From the original cohort of 546 subjects, 466 were contacted again, and 373 (80%) were enrolled at 21.2 ± 3.5 years of age. Among subjects with paired testing, the percent predicted maximum oxygen uptake decreased ($69 \pm 14\%$ vs. $61 \pm 16\%$; $p < 0.001$; $n = 95$), ejection fraction decreased ($58 \pm 11\%$ vs. $55 \pm 10\%$; $p < 0.001$; $n = 259$), and B-type natriuretic peptide increased (median [interquartile range] 13 [7 to 25] pg/mol vs. 18 [9 to 36] pg/mol; $p < 0.001$; $n = 340$). At latest follow-up, a lower Pediatric Quality of Life Inventory physical summary score was associated with poorer exercise performance (R^2 adjusted $= 0.20$; $p < 0.001$; $n = 274$). Cumulative complications since the Fontan procedure 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 or/cardiac transplantation was associated with poorer ventricular performance and functional health status assessed at Fontan 1, but it was not associated with ventricular morphology, the subject's age, or the 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. (Relationship Between Functional Health Status and Ventricular Performance After Fontan—Pediatric Heart Network; NCT00132782) (J Am Coll Cardiol 2017;69:2735–44)

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From the [a]Medical University of South Carolina, Charleston, South Carolina; [b]New England Research Institutes, Watertown, Massachusetts; [c]University of Texas Southwestern Medical Center, Dallas, Texas; [d]University of Michigan, Ann Arbor, Michigan; [e]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [f]University of Utah, Salt Lake City, Utah; [g]Boston Children's Hospital, Boston, Massachusetts; [h]National Heart, Lung, and Blood Institute, Bethesda, Maryland; [i]Duke University Medical Center, Durham, North Carolina; [j]Columbia University Medical Center, New York, New York; [k]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and the [l]University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada.
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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CHQ = Child Health Questionnaire

CHQ-PF50 = Parent Report Child Health Questionnaire

PedsQL = The Pediatric Quality of Life Inventory

SF-36 = 36-item Short Form Health Survey version 2

$\dot{V}O_2$ = oxygen uptake

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 patients who have undergone Fontan procedures and factors associated with death or cardiac transplantation have been limited to single-center reports that span long time periods and surgical eras (e.g., 25 years) (1) or have included a short follow-up (e.g., <2 years) (2). Fontan 1 (the Pediatric Heart Network Fontan Cross-Sectional Study, 2003 to 2004) investigated associations among measures of health status, ventricular function, and exercise performance in 546 children and adolescents, then 6 to 18 years of age (mean age 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. Fontan 2 (the Fontan Follow-up Study) was limited to reassessment of vital status and functional health status and enrolled 85% of the Fontan 1 survivors (n = 428) between 2009 and 2011. There was a 95% interim transplant-free survival rate, and death or cardiac transplantation was associated with poorer performance on previously measured functional health status and measures of ventricular performance (4).

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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 when 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, B-type natriuretic protein [BNP], underlying rhythm); 2) determine relationships between current laboratory measures of ventricular performance and functional health status by using the Pediatric Quality of Life Inventory (PedsQL); 3) determine factors associated with interim death or cardiac transplantation since Fontan 1 in this well-characterized cohort; and 4) describe access to health care 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 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) by using standardized forms. Structured interviews with the parent or guardian or the subject were used to assess current clinical state, socioeconomic status, emotional and social functioning, and access to health care.

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 PedsQL 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). PedsQL age group versions (8 to 12 old, 13 to 18, and 19 to 25 years of age) have only minor differences in language. To preserve sample size and after consultation with the developer of the instrument, we combined these versions for analytical purposes (James Varni, MD, personal communication, March 2014). Items were linearly transformed to a 0 to 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 of age (7).
- In subjects ≥19 years of age, functional status was measured with the 36-item Short Form Health Survey version 2 (SF-36) (8).

The PedsQL patient report was used to determine relationships between laboratory measures of ventricular performance and functional health status because 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 and Doppler echocardiograms were centrally interpreted. The measurements were performed by the same observer who analyzed echocardiograms performed at Fontan 1, and all 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 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.

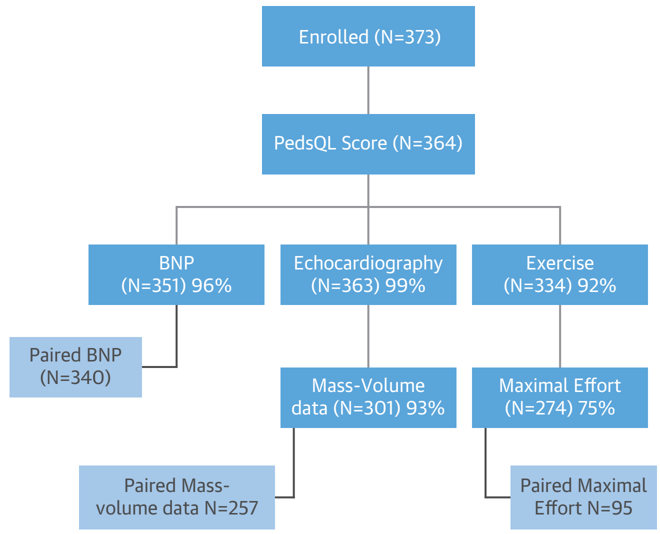
EXERCISE PROTOCOL. Maximal exercise testing was performed with a ramp protocol on an electronically braked cycle ergometer and interpreted locally. A standard 12-lead electrocardiogram was performed before the exercise test to assess the underlying heart rhythm. Testing was performed with standard protocols previously used in children, adolescents, and subjects with Fontan physiology (5,12). Six exercise variables were used as outcomes: percent predicted maximum oxygen uptake (Vo_2), percent predicted maximum work rate, percent predicted maximum oxygen pulse, chronotropic index, percent predicted Vo_2 at anaerobic threshold, and resting oxygen saturation. Separate analyses of the first 4 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 nonpaced subjects.

SEROLOGIC TESTING. 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 the subjects enrolled in Fontan 3 were compared with subjects 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 with 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 *t* tests for means and Wilcoxon signed rank test for medians. Categorical variables were tested using the McNemar test. Descriptive statistics were provided at each time point.

FIGURE 1 Laboratory Testing of Subjects Enrolled in the Fontan 3 Study



The number of tests performed by enrolled subjects at Fontan 3 is shown in **dark blue**. The number of subjects with paired tests performed at both Fontan 1 and Fontan 3 are shown in **light blue.** BNP = B-type natriuretic peptide; PedsQL = Pediatric Quality of Life Inventory.

TABLE 1 Complications and Interventions After Fontan Procedures

	Fontan 1 (N = 546)	Fontan 2 (N = 416)	Fontan 3 (N = 373)
Time since Fontan procedure, yrs	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

Values are mean ± SD or %.

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

Characteristic†	N	Fontan 1	Fontan 3	Change	p Value†
Age at enrollment, yrs	373	11.7 ± 3.4	21.2 ± 3.5	9.5	–
Exercise Outcomes (limited to maximal effort)					
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-to-volume ratio *z*-score	257	2.6 ± 3.2	2.4 ± 3.0	−0.2	0.45
BNP, pg/ml	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

Values are mean ± SD, median (interquartile range), or %, unless otherwise indicated. *Subjects were included if the outcome was measured at both Fontan 1 and Fontan 3. †Paired Student *t* test for means, Wilcoxon signed rank test for BNP, McNemar test for rhythm. ‡Limited to those subjects with maximal effort at both time points. §Limited to nonpaced subjects with maximal effort at both time points.

BNP = B-type natriuretic peptide; echo = echocardiographic; IQR = interquartile range; Vo_2 = oxygen uptake.

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, sex, 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 1,000 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.

TABLE 3 Association Between PedsQL Physical Summary Score and Exercise

	Univariate		Multivariable*		
Variable	Slope/PE Ratio	p Value†	Slope/PE Ratio	p Value†	Reliability, %
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	–	–	–
Percent predicted maximum work rate	0.46	<0.001	0.43	<0.001	100
Chronotropic index	18.44	0.001	–	–	–
Percent predicted peak Vo_2	0.19	0.002	–	–	–
Resting oxygen saturation	0.56	0.02	–	–	–
Percent predicted Vo_2 at anaerobic threshold	0.08	0.049	–	–	–
Percent predicted maximum oxygen pulse	0.05	0.311	–	–	–

*R^2 = 0.21 ($R^2_{adjusted}$ = 0.20); p < 0.001. †F test. ‡Student *t* test.

PE = parameter estimate, which represents the degree of change in the summary score associated with a 1-unit change in exercise variable; PedsQL = Pediatric Quality of Life Inventory; Vo_2 = oxygen uptake.

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 for analysis a cohort of 545 subjects who had undergone Fontan procedures. Follow-up time was defined as the time from Fontan 1 medical record review until either death or cardiac transplantation or the latest available assessment of vital or cardiac transplantation status (March 15, 2016). We report hazard ratios 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 nonproportionality on the basis of martingale residuals, and interaction terms with time were added if appropriate. Survival and cardiac 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 were enrolled (80%), and 93 refused participation. Enrolled subjects were slightly younger than those who were eligible but declined participation (21.1 ± 3.5 years vs. 22.0 ± 3.4 years; p = 0.01). Sex, 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 study participation (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 procedures. Anatomic details of the subjects 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 because of physical or mental limitations; therefore 364 subjects formed the cohort to explore associations between functional status and measures of cardiac performance. Patients' characteristics are displayed in Online Table 1.

There were no differences in anatomy, demographics, or results of assessments performed at Fontan 1 between those subjects 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 right ventricular (8% vs. 36%) and left ventricular (39% vs. 54%) dominance with an overall $p < 0.001$, but they 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. The 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 patients with electronic devices at Fontan 3, 49 of these devices were pacemakers consisting of 17 single-chamber atrial and 32 dual-chamber pacemakers. An implantable cardioverter-defibrillator was present in 9 subjects.

TABLE 4 **Subjects With Paired Functional Health Status Data at Fontan 1, 2, and 3**

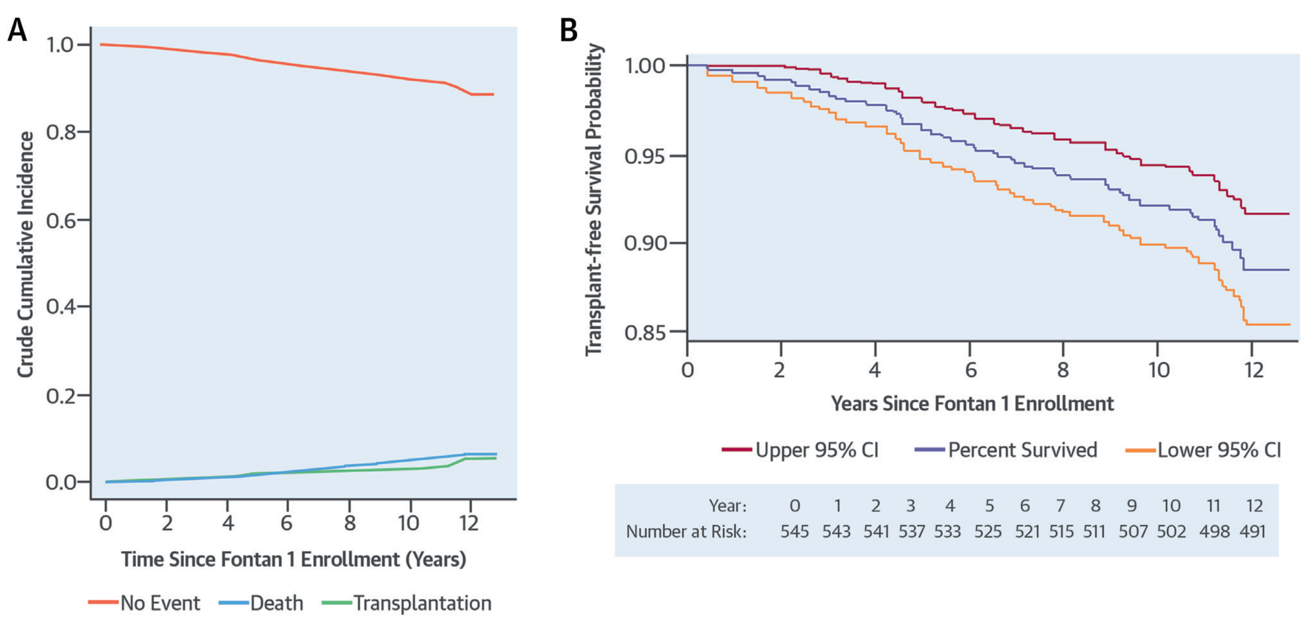
	N	Fontan 1	Fontan 2	Fontan 3	p Value
Age, yrs	–	11.9 ± 3.4	18.4 ± 3.4	21.2 ± 3.5	–
CHQ-PF50 physical summary score	106	50 (40–55)	48 (41–53)	49 (41–53)	0.6*
CHQ-PF50 psychosocial summary score	106	51 (42–57)	51 (42–57)	52 (43–59)	0.04*
PedsQL physical functioning score	322	NA	78 (63–88)	75 (63–91)	0.6†
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), unless otherwise indicated. *Wilcoxon signed rank test for medians, comparing Fontan 1 with Fontan 3. †Wilcoxon signed rank test for medians, comparing Fontan 2 with Fontan 3.

CHQ-PF50 = Parent Report Child Health Questionnaire; NA = not applicable; PedsQL = Pediatric Quality of Life Inventory; SF-36 = 36-item Short Form Health Survey version 2.

PAIRED LABORATORY PERFORMANCE RESULTS OVER TIME. Of 336 subjects completing the exercise

CENTRAL ILLUSTRATION **Survival of Single-Ventricle Patients After the Fontan Procedure**



Atz, A.M. et al. J Am Coll Cardiol. 2017;69(22):2735–44.

(A) Cardiac transplant-free survival. Proportion of subjects in each of 3 competing mutually exclusive states: death, cardiac 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 to 1.0.

TABLE 5 Cox Model for Predictors of Death or Cardiac Transplantation (Total N = 545; 54 Events)

	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 yrs		Reference	
10–13 yrs		1.25 (0.65–2.41)	0.50
>13 yrs		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 at latest Fontan procedure as of enrollment in Fontan 1, yrs	54/545	1.10 (1.00–1.21)	0.05
Age ≥3 at latest Fontan procedure as of enrollment in Fontan 1, yrs	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

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test in Fontan 3, 275 (82%) achieved maximum effort compared with only 40% (166 of 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-PF50 (Parent Report CHQ) physical summary score at the time of Fontan 1 was lower in the group of patients 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 V_{O_2} decreased approximately one-half of an SD from a mean of 69% to 61% ($p < 0.001$). We further explored trajectories of the 95 individual subjects with paired maximal effort exercise tests by dividing them into 2 cohorts of equal size on the basis of age and baseline percent predicted maximum V_{O_2}. The younger group (age at Fontan 1 <13.6 years; $n = 48$) had a greater decline in percent predicted maximum V_{O_2} than the older group (mean slope of change over time −1.03 vs. −0.47). The group with better exercise performance at baseline (percent predicted maximum V_{O_2} >69%; $n = 48$) showed a greater decline in percent predicted maximum V_{O_2} than did the subjects 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 1 full SD from a mean of 69% to 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 18.0 pg/ml vs. 13.0 pg/ml; $p < 0.001$). Consistent with our earlier report describing BNP in the Fontan 1 cohort (13), mean BNP (adjusted for age and sex) among subjects with an atriopulmonary connection was higher than for subjects with an intracardiac lateral tunnel, which in turn was higher than for subjects with an extracardiac conduit.

ASSOCIATION BETWEEN PedsQL AND LABORATORY TESTS AND PATIENTS' 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 percent predicted maximum work rate and sex. For a subset of subjects achieving maximal effort at both time points (n = 95), the multivariable model included a single variable, percent predicted maximum work rate. There was an inverse relationship between PedsQL physical summary score and logBNP. A 1-point increase in logBNP was associated with a 2.8-point 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 a single 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 of age at Fontan 3, the CHQ-PF50 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 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 CARDIAC TRANSPLANTATION AND PATIENTS' CHARACTERISTICS ASSESSED AT FONTAN 1. As of March 15, 2016, 54 subjects (10%) had received a heart transplant (n = 23) or had died (n = 31) since Fontan 1 (Central Illustration). We found no differences in the composite risk of death or cardiac transplantation on the basis of subjects' age, sex, race, ethnicity, ventricular morphology, or type of Fontan procedure.

The risk of death or cardiac 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 V_{O_2} at anaerobic threshold; and poorer ventricular performance (abnormally low ventricular function and increased (abnormal) ventricular volume). The hazard of death or cardiac transplantation for the subjects with the highest tertile BNP (>21 pg/ml) and the lowest tertile CHQ-PF50 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 cardiac transplantation. However, when compared with families with the lowest income, those families 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 cardiac 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 with the risk of cardiac transplantation on the basis of sex, race, ethnicity, ventricular morphology, or age. There was a trend toward a difference between Fontan surgical types, with 5 deaths and no cardiac transplantations in the atriopulmonary connection category (p = 0.059). There were no differences between death and cardiac transplantation regarding laboratory testing variables assessed at Fontan 1. The frequency of death since Fontan 1 differed by center,

TABLE 5 Continued

	Events/Total	Hazard Ratio (95% CI)	p Value*
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 V_{O_2} at anaerobic threshold, %	22/316	0.98 (0.96–1)	0.038
With maximum effort	32/400	0.82 (0.4–1.68)	0.59
Percent predicted maximum V_{O_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-U 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-to-volume ratio	33/406	0.70 (0.27–1.82)	0.47
Total mass-to-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-PF50 physical summary score <44	48/482	3.65 (2.00–6.65)	<0.001

*Wald chi-square test.
CI = confidence interval; other abbreviations as in Tables 2 and 4.

TABLE 6 Rate of Death and Cardiac Transplantation Since Fontan 1 by Center

Center	Death	Cardiac Transplantation	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)

Values are n (%).

from 3% (3 of 105) to 14% (3 of 22) of subjects. The frequency of cardiac transplantation since Fontan 1 varied among centers from 0% (0 of 22) to 21% (8 of 38) of subjects (**Table 6**).

HEALTH CARE USE. Few differences were observed in the frequencies for relevant health care access variables between Fontan 2 and the present data collection (Online Table 2). Most 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 or gynecologist increased among female subjects (41% vs. 32%), whereas subjects receiving educational support decreased from 36% to 26%.

DISCUSSION

Currently, >1,000 single-ventricle patients undergo a Fontan procedure in the United States annually. This number represents 4.1% of all pediatric cardiac surgical procedures performed annually (The Society of Thoracic Surgeons Congenital Heart Disease Database, Spring 2016 Harvest, not shown). Several reports describe declining survival rates over time with an increasing and substantial burden of complications (2,14–17). Projections suggest that the number of patients living with 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 studies are limited either by the small number of patients followed up or by a short period of follow-up. This large, multicenter study of children and young adults who underwent a Fontan procedure and were followed up longitudinally over a decade was able 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, percent predicted maximum V_{O_2}, decreased from 69% to 61% in those subjects with paired maximal effort tests.

We found an overall 90% transplant-free survival rate over the 12 years since enrollment in the Fontan 1 study. This finding compares favorably with that of a previous report, which estimated a 5-year transplant-free survival rate 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 survivors of Fontan procedures. 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 Pediatric Heart Network Fontan cohort (20), substantial intercenter differences exist. We found a difference in the rate of cardiac transplantation across centers, ranging from 0% to 21%. Significant regional differences in rates of heart transplantation among patients who have undergone Fontan procedures 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 population of patients who have undergone Fontan procedures.

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, a finding that may reflect the known challenges facing subjects as they transition to assuming care for themselves (4,22). For survivors of Fontan procedures, 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 interventions may have been planned for Fontan fenestration closure (23). However, catheter interventions continued to increase even 15 years after the Fontan procedure. Complications increased over time, including arrhythmia requiring treatment, which increased from 20% to 32% of subjects, and placement of an implanted electronic device, which increased from 13% to 16% of subjects. In our previous assessments of the Fontan cross-sectional cohort, we identified low incidences of some complications associated with 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 Fontan circulation. We previously reported a weak association between functional health status (CHQ-PF50 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 procedure was performed (26,27). A few studies documented short-term improvements in exercise function in children with heart disease (28), including patients who have undergone Fontan procedures (29,30), after participation in a formal exercise training program. A recent pilot study showed 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 use 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.

STUDY LIMITATIONS. The original Fontan 1 cohort was by necessity a subset of subjects with single-ventricle physiology who survived multistage surgical palliation culminating in the modified Fontan procedure and who were well enough to complete most of the 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 previously reported some inherent limitations of the echocardiographic evaluation of subjects who have undergone Fontan procedures, especially as they age (32). However, even though 2-dimensional echocardiographic measurements systematically underestimate ventricular volume measurements acquired by magnetic resonance imaging, the reproducibility of measurements is 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 survivors of Fontan procedures, there was a significant decline in exercise performance that was associated with poorer functional health status at follow-up. In addition, there was an increase in the proportion of subjects undergoing interventions and having complications over nearly a decade. The rate of cardiac 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 could focus on interventions aimed at preserving or enhancing exercise capacity.

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Protocol Chair: Lynn Mahony, University of Texas Southwestern Medical Center

Clinical Site Investigators: Children's Hospital Boston: Jane Newburger (Principal Investigator), Roger Breitbart, Carolyn Dunbar-Masterson, Jill Handisides, Lisa-Jean Buckley, Bethany Trainor; Children's Hospital of New York: Wyman W. Lai* (Principal Investigator), Rosalind Korsin; Children's Hospital of Philadelphia: Robert Shaddy, J. William Gaynor, Stephen M Paridon, (Principal Investigators), David Goldberg, Kaitlyn Daniels, Tonia Morrison, Nicole Mirarchi*; Duke University: Jennifer S. Li (Principal Investigator), Piers Barker, Mingfen Xu; Medical University of South Carolina: Andrew M. Atz (Principal Investigator), Patricia Infinger, Ann Harvey Frampton; Primary Children's Hospital, Salt Lake City, Utah: LuAnn Minich (Principal Investigator), Richard Williams, Linda Lambert; The Hospital for Sick Children, Toronto: Brian McCrindle (Principal Investigator), Elizabeth Radojewski*, Svetlana Khaikin, Patricia Walter; Cincinnati Children's Medical Center, Bradley Marino*, Karen Uzark*

*No longer at the institution listed.

ADDRESS FOR CORRESPONDENCE: Dr. Andrew M. Atz, Department of Pediatrics, Division of Cardiology, Medical University of South Carolina, MSC 915, Room 601, Children's Hospital, 165 Ashley Avenue, Charleston, South Carolina 29425. E-mail: atzam@musc.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among survivors of the Fontan procedure, complications and the need for additional interventions increase over time, but cardiac 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 a single ventricle.

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APPENDIX For supplemental tables, please see the online version of this paper.