Long-term survival after the Fontan operation: Twenty years of experience at a single center

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ABSTRACT

Objective: Existing studies of patients palliated with the Fontan operation are limited by heterogeneous patient populations and incomplete follow-up. This study aimed to describe long-term post-Fontan survival in a modern patient cohort.

Methods: All 773 patients who underwent a first Fontan operation at our institution between 1992 and 2009 were reviewed. The primary outcome was the composite endpoint of Fontan takedown, heart transplantation, or death before 2013.

Results: Follow-up rate was 99.2%. Survival with intact Fontan circulation was 94% at 1 year (95% confidence interval [95% CI], 92%-95%), 90% at 10 years (95% CI, 88%-92%), 85% at 15 years (95% CI, 82%-88%), and 74% at 20 years (95% CI, 67%-80%). Distinct risk factors were identified for early (≤ 1 year) and late composite outcomes. Independent risk factors for early outcome included prolonged pleural drainage (hazard ratio [HR], 4.4; $P < .001$), intensive care unit stay >1 week (HR, 2.4; $P < .001$), Fontan before 1997 (HR, 3.3; $P < .001$), preoperative atrioventricular valve regurgitation (HR, 2.0; $P < .001$), and longer crossclamp time (HR, 1.3 per 10 minutes; $P < .001$). Late outcome was predicted by atrioventricular valve regurgitation prior to Fontan (HR, 2.0; $P \leq .001$), and post-Fontan ICU stay >1 week (HR, 2.4; $P < .001$).

Conclusions: Long-term mortality after Fontan operation remains substantial. Risk factors for death or loss of Fontan circulation differ between the early and late postoperative periods. Long-term survival has not improved appreciably over the last decade, suggesting that alternatives to the Fontan are warranted. (J Thorac Cardiovasc Surg 2017;154:243-53)

Kaplan-Meier curves showing composite and individual post-Fontan outcomes.

Central Message

Patient-specific risk factors predict post-Fontan mortality, which remains substantial in the modern single ventricle population.

Perspective

This study examines post-Fontan outcomes in a modern single-ventricle population with a high prevalence of systemic right ventricles and exclusively total cavopulmonary connection-type operations. Patient-specific risk factors predict early and late post-Fontan mortality and need for heart transplantation. Twenty-year mortality remains substantial, and alternatives to the Fontan operation are needed.

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In the early 1970s, Fontan and Kreutzer independently described techniques to directly reroute systemic venous return to the pulmonary arterial circulation.^{1,2} Although

Scanning this QR code will take you to online appendices, figure, and table. To view the AATS 2015 Webcast, see the URL next to the video thumbnail.

Abbreviations and Acronyms

AV	= atrioventricular
AVVR	= atrioventricular valve regurgitation
CHOP	= Children's Hospital of Philadelphia
CI	= confidence interval
EC	= extracardiac conduit
HR	= hazard ratio
ICU	= intensive care unit
LT	= lateral tunnel
PA	= pulmonary artery
TCPC	= total cavopulmonary connection

initially designed to alleviate cyanosis in patients with tricuspid atresia, the “Fontan” operation has since been applied to the vast majority of single-ventricle anatomies as the final planned stage of surgical palliation.³⁻⁵ Subsequent modifications have improved early post-operative mortality,⁶⁻⁸ but significant late consequences of this inherently abnormal circulation now are being appreciated.

Long-term mortality after Fontan operation has been described in several large, single-center cohorts.⁹⁻¹⁴ Existing studies are limited, however, by a high prevalence of older atriopulmonary style operations, few patients with hypoplastic left heart syndrome or systemic right ventricle, and/or incomplete follow up, especially regarding transplant status. In this study we aimed to describe long-term survival with intact Fontan circulation in a large cohort of modern, single-ventricle patients with a high rate of follow-up.

METHODS

This was a single-center retrospective review of all patients who underwent a first Fontan operation at The Children's Hospital of Philadelphia (CHOP) between January 1, 1992, and December 31, 2009. Fontan operation was defined as any form of total cavopulmonary connection (TCPC), including the lateral tunnel (LT) and extracardiac conduit (EC) techniques, as well as extracardiac hepatic vein inclusion conduits in patients with a previous Kawashima operation. Patients undergoing Fontan revision or repeat Fontan after previous Fontan takedown were excluded. No atriopulmonary connections were performed at CHOP during this time period.

Baseline demographic, anatomic, preoperative, and perioperative characteristics were extracted from the medical record as reported previously.¹⁵ Three surgical eras were defined based on relevant changes in surgical practice at our institution: 1992 to 1996 (Era 1, *n* = 226), 1997 to 2002 (Era 2, *n* = 196), and 2003 to 2009 (Era 3, *n* = 351). Routine use of modified ultrafiltration was introduced in 1996. In Era 1, almost all Fontan operations performed were of the LT variety, whereas in Era 3, the EC type predominated. Era 2 represented a period of transition in which the numbers of LT and EC Fontan procedures were nearly equal.

For patients currently followed at CHOP, outcomes were ascertained from the medical record. About one half (51%) of patients had no recent follow-up at our institution. For these subjects, current vital status was obtained via a query of the National Death Index, maintained by the

National Center for Health Statistics (Atlanta, Ga). This contains a centralized database of death record information on file in United States vital statistics offices.¹⁶ At the time of data analysis, information was available through December 31, 2012. Transplant status and history of transplant listing were obtained through collaboration with the Scientific Registry of Transplant Recipients (Minneapolis, Minn).¹⁷ The primary endpoint was a composite of Fontan takedown, heart transplantation, or death before January 1, 2013. This study was approved by the institutional review board.

Statistical Analysis

Baseline demographic and clinical variables were summarized with standard descriptive statistics. Normally distributed variables were reported as mean $\pm$ standard deviation, and non-normally distributed variables were reported as median with range. Differences across eras were assessed with analysis of variance, Kruskal-Wallis, or Pearson χ^2 tests as appropriate. Multiple imputation based on all available demographic and clinical characteristics was used to handle the small proportion of missing data (3% across all covariates). Kaplan-Meier survival curves were constructed to estimate overall survival and survival with intact Fontan circulation. Time zero was defined as date of Fontan, and failure was defined as Fontan takedown, heart transplantation, or death within the study period. Patients alive without takedown or transplant were censored at the end of the study period. The small minority for whom current information could not be obtained from the National Death Index or Scientific Registry of Transplant Recipients were censored at the date of last available follow-up.

Risk factors for the composite endpoint were ascertained with multivariable Cox regression. Nonproportional hazards behavior was observed for several clinically relevant predictors, so extended Cox models that incorporated a binary measure of time (<1 year vs $\geq$ 1 year) were used for these time-dependent predictors. For time-dependent variables, hazard ratios (HRs) were reported separately for the early (<1 year) and late ($\geq$ 1 year) post-Fontan periods. Variables considered in the analysis are presented in [Appendix E1](#). Some continuous variables were dichotomized for ease of interpretation, with cut-points chosen based on sensitivity analysis to achieve a >90% specificity for the outcome of interest. Those with a *P* value < .1 in univariable analysis and observations in at least 90% of subjects were considered for entry into the multivariable models. Variables were retained if their addition to the model generated a likelihood ratio test *P* value < .1. When more than one significant multivariable model could be constructed, the model that produced the lowest Akaike information criterion score (post-test goodness-of-fit measure) was selected.

Because fewer than 90% of patients had a pre-Fontan catheterization, subset analyses were performed to examine the effects of hemodynamic parameters. These values could not be imputed because of the potential bias to refer patients with poorer physiology for catheterization at a greater rate. All *P* values reported are 2-sided, and statistical significance was established a priori at *P* $\leq$.05. Analyses were conducted with STATA, v. 12.0 (StataCorp, College Station, Tex) and SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 773 patients underwent a first Fontan operation at CHOP between 1992 and 2009. The median number of operations performed per year was 42 (range, 26-68). Relevant demographic, preoperative, and perioperative characteristics of the study cohort are outlined in [Table 1](#). Systemic right ventricles predominated, with 50% of patients carrying a diagnosis of hypoplastic left heart syndrome. Common atrioventricular (AV) valve was present in 11%. Ninety-seven percent of patients had staged

TABLE 1. Baseline cohort characteristics

	n	Overall	1992-1996	1997-2002	2003-2009	P value
Total cases	773	773 (100%)	226 (29%)	196 (25%)	351 (46%)	
Female	773	289 (37%)	86 (38%)	66 (34%)	137 (39%)	.45
Age at Fontan, y	773	2.3 (0.9-38)	1.7 (0.9-31)	2.0 (1.0-29)	2.8 (1.3-38)	<.0001
Weight at Fontan, kg	772	12.0 (5.8-120)	10.8 (5.8-120)	11.4 (6.7-49)	12.9 (8.6-59)	<.0001
Heterotaxy	773	66 (8.5%)	17 (7.5%)	24 (12%)	25 (7.1%)	.10
Common AV valve	773	88 (11%)	20 (8.9%)	27 (14%)	41 (12%)	.28
Dominant RV	763	524 (67%)	159 (72%)	138 (73%)	227 (65%)	.11
HLHS	763	381 (50%)	128 (58%)	99 (52%)	154 (44%)	.005
Preoperative AVVR $\geq$ mild	716	323 (45%)	78 (35%)	79 (41%)	166 (56%)	<.0001
Pre-Fontan catheterization	773	671 (87%)	219 (97%)	186 (95%)	266 (76%)	<.0001
Mean PA pressure, mm Hg	627	11 (4-25)	12 (4-20)	10 (4-20)	11 (5-25)	.05
Mean PA pressure $\geq$ 15 mm Hg		75 (12%)	26 (12%)	16 (9.2%)	33 (14%)	.39
Fontan type	773					<.0001
Lateral tunnel		409 (53%)	216 (96%)	117 (60%)	76 (22%)	
Extracardiac		364 (47%)	10 (4%)	79 (40%)	275 (78%)	
Fenestration	773	693 (90%)	197 (87%)	179 (91%)	317 (90%)	.32
CPB time, min	773	64 (32-274)	59 (32-147)	62 (41-236)	66 (32-274)	<.0001
ACC time, min	773	26 (0-99)	27 (13-93)	22 (0-99)	27 (0-91)	<.0001
Ventilator time	469	8 h (0 h to 56 d)	20 h (1 h to 16 d)	5 h (0 h to 56 d)	5 h (0 h to 4 d)	<.0001
Hospital duration, d	771	8 (0-278)	13 (0-278)	6 (2-56)	8 (0-108)	<.0001
Pleural drainage time, d	745	3 (1-258)	3 (1-258)	1 (1-40)	4 (1-71)	<.0001
Pleural drainage $>$ 14 d	745	126 (17%)	58 (28%)	11 (6%)	57 (16%)	<.0001

Data reported as mean $\pm$ standard deviation, median (range), or count (% of total). AV, Atrioventricular; RV, right ventricle; HLHS, hypoplastic left heart syndrome; AVVR, atrioventricular valve regurgitation; PA, pulmonary artery; CPB, cardiopulmonary bypass; ACC, aortic crossclamp.

surgical palliation, with some form of stage 2 operation preceding the Fontan. The cohort overall was divided nearly equally between LT and EC Fontan procedures, and a fenestration was created in approximately 90%. A pre-Fontan cardiac catheterization for assessment of hemodynamics was performed in 671 of 773 (87%) of patients, with a trend toward fewer catheterizations in the most recent era. Additional baseline characteristics and complete perioperative outcomes for the cohort have been reported previously.¹⁵

Prevalence of Death, Takedown, and Heart Transplantation

Vital status as of December 31, 2012, was ascertained for 767 of 773 (99.2%) of subjects. Transplant status was

verified for 764 of 774 (98.7%). The median length of follow-up was 9 years post-Fontan procedure, accounting for 7616 total patient-years of follow-up. One quarter of the cohort had follow-up in excess of 15 years.

Ninety-nine (12.9%) patients experienced at least one component of the composite outcome (Table 2). Seventy-nine patients died, 25 required heart transplantation, and 10 had Fontan takedown. Twenty-seven deaths occurred during the initial post-Fontan hospitalization and 37 during the first postoperative year. The causes of death were unable to be assessed in detail for the entire cohort because of the limitations of the data available in the National Death Index. For the patients whose cause of death was known, the vast majority were cardiac in etiology.

TABLE 2. Early and late post-Fontan outcomes by era

	Overall (n = 773)	1992-1996 (n = 226)	1997-2002 (n = 196)	2003-2009 (n = 351)
Early outcomes (<1 y post-Fontan)				
Death*	37	25	5	7
Fontan takedown	10	3	2	5
Transplant	5	1	2	2
Late outcomes (>1 y post-Fontan)				
Death*	42	27	12	3
Transplant	20	14	4	2
All outcomes				
Death*	79	52	17	10
Fontan takedown	10	3	2	5
Transplant	25	15	6	4

*Includes patients with previous transplant or takedown.

All Fontan takedowns occurred within the first postoperative year, at a median of 6 days after Fontan, and all except 2 occurred during the initial post-Fontan hospitalization. One half of takedowns were performed for physiologic Fontan failure, 1 for acute thrombosis of the Fontan circuit, 1 for endocarditis, and the indication for the remaining 3 could not be ascertained from available records.

Listing for heart transplantation occurred in 34 patients at a median age of 11 years, or 6 years after Fontan (range, 0 days to 19 years). Outcomes of transplant listing are shown in [Figure E1, A](#). Transplantation occurred in 25 of 34 candidates (74%). Four patients died awaiting transplantation, and 4 were removed from consideration, 2 because of clinical improvement and 2 because of clinical deterioration. One patient remains actively listed. For those successfully transplanted, the median wait time after listing was 54 days (range, 3-452). The primary indication for transplantation was ventricular dysfunction in 5 of 25 patients, Fontan failure in 8, combined Fontan and ventricular failure in 5, and was unable to be accurately ascertained from the available records in 7. Survival after transplant is depicted in [Figure E1, B](#). Significant early mortality occurred, with an estimated survival of 50% at 5 years posttransplant.

Mortality and Survival With Intact Fontan Circulation

Survival with intact Fontan circulation was 94% at 1 year (95% confidence interval [95% CI], 92%-95%), 90% at 10 years (95% CI, 88%-92%), 85% at 15 years (95% CI, 82%-88%), and 74% at 20 years (95% CI, 67%-80%). Risk of transplant was 8% at 20 years, and risk of Fontan takedown was <1% ([Figure 1](#)). In patients surviving to 1 year with intact Fontan circulation, conditional late freedom from composite outcome was 96% at 10 years (95% CI, 94%-98%), 91% at 15 years (95% CI, 87%-93%), and 79% at 20 years (95% CI, 71%-85%).

Examining mortality alone as the endpoint, survival was 95% at 1 year (95% CI, 93%-96%), 92% at 10 years (95% CI, 90%-94%), 88% at 15 years (95% CI, 85%-91%), and 79% at 20 years (95% CI, 72%-85%). For those patients who survived the first postoperative year, conditional late survival was 97% at 10 years (95% CI, 95%-98%), 93% at 15 years (95% CI, 90%-95%), and 83% at 20 years (95% CI, 76%-89%).

Risk Factors for Death, Transplantation, or Fontan Takedown

Risk factors for death, transplantation, or takedown are presented in [Table 3](#). Several covariates demonstrated statistically significant interactions with time, indicating differing effects on early and late post-Fontan outcomes. In the multivariable extended Cox model ([Table 4](#)), postoperative pleural drainage >2 weeks (HR, 4.4; $P < .001$),

FIGURE 1. Survival and cumulative incidence of outcomes after Fontan. Kaplan-Meier survival estimate for composite outcome overlaid with cumulative hazard rates for death, transplant, and Fontan takedown. Please see [Appendix E2](#) for 95% confidence intervals of the survival functions.

Fontan before 1997 (HR, 3.3; $P < .001$), intensive care unit (ICU) stay >1 week (HR, 2.4; $P < .001$), mild or greater preoperative AV valve regurgitation (HR, 2.0; $P < .001$), and longer aortic crossclamp time (HR, 1.3 per 10 minutes; $P < .001$) all were associated with death, transplant, or Fontan takedown in the first postoperative year, after we adjusted for the effect of the other covariates.

The risk conferred by prolonged pleural drainage, aortic crossclamp time, and surgical era did not persist beyond 1 year post-Fontan procedure. [Figure 2](#) demonstrates this effect with regard to surgical era, showing no impact of Fontan era on the long-term outcomes of patients who survived the first postoperative year. The only identified independent predictors of late post-Fontan mortality were mild or greater preoperative AV valve regurgitation and prolonged post-Fontan ICU stay ([Figure 3](#)). Morphology of the systemic ventricle and type of Fontan did not predict early or late failure ([Figure 4](#)). Age or weight at the time of stage 2 palliation, timing of Fontan, presence of common AV valve, and heterotaxy syndrome also did not predict adverse outcome.

In a subset analysis of the 602 patients with available catheterization-based hemodynamic data, pre-Fontan pulmonary artery (PA) pressure >15 mm Hg (HR, 4.1; $P < .001$) was the strongest predictor of early composite outcome. The risk did not persist after 1 year post-Fontan, however ([Table 5](#)).

TABLE 3. Risk factors for post-Fontan death, transplant, or takedown: Univariable analysis

	Time < 1 y		Time ≥ 1 y		P value for time interaction*
	HR (95% CI)	P value	HR (95% CI)	P value	
Pleural drainage > 14 d	7.1 (3.9-12)	<.001	0.9 (0.4-1.8)	.68	<.001
ICU stay > 1 wk	3.7 (2.4-5.7)	<.001	3.7 (2.4-5.7)	<.001	.15
Fontan before 1997	3.3 (1.9-6.0)	<.001	1.2 (0.6-2.3)	.66	.02
Lateral tunnel Fontan	2.5 (0.9-6.5)	.42	1.9 (1.0-3.5)	.04	.05
Lack of fenestration	1.5 (0.8-2.6)	.18	1.5 (0.8-2.6)	.18	.40
Common AV valve	2.1 (1.3-3.6)	.004	2.1 (1.3-3.6)	.004	.65
Systemic RV	1.9 (1.1-3.1)	.01	1.9 (1.1-3.1)	.01	.65
HLHS	1.4 (0.9-2.1)	.10	1.4 (0.9-2.1)	.10	.49
Preoperative AVVR ≥ mild	2.0 (1.3-3.0)	<.001	2.0 (1.3-3.0)	<.001	.19
Aortic crossclamp time, per 10 min	1.1 (0.9-1.3)	.21	1.4 (1.2-1.6)	<.001	.08
Weight at Fontan, kg	1.04 (1.01- 1.06)	<.001	1.0 (0.9-1.03)	.53	.06

Not significant: age at Fontan, sex, heterotaxy syndrome, Norwood operation as initial palliation. HR, Hazard ratio; CI, confidence interval; ICU, intensive care unit; AV, atrioventricular; RV, right ventricle; HLHS, hypoplastic left heart syndrome; AVVR, atrioventricular valve regurgitation. *Extended Cox modeling with time interaction variable. Significant P value indicates covariates with differing effects in early versus late post-Fontan time periods.

DISCUSSION

In this study, we present long-term follow up of 773 consecutive patients who underwent a first Fontan operation at our institution during an 18-year period. With a 99% follow-up rate, the 20-year estimate for survival with intact Fontan circulation was 74%. When we examined mortality alone, 20-year survival was 79%. Independent risk factors for death or loss of Fontan circulation were identified, but several of these characteristics conferred risk only in the early post-Fontan period. Prolonged pleural drainage and elevated PA pressure pre-Fontan were the strongest risk factors for early composite outcome, and late outcome was predicted only by presence of AV valve regurgitation pre-Fontan and length of post-Fontan ICU stay. Ventricular morphology and type of Fontan operation were not associated with early or late outcome.

The 15- and 20-year survival estimates for this cohort are within the range reported in the literature, although direct comparisons to other series are challenging because of differences in patient population and methodology. Table E1 summarizes key characteristics of selected Fontan follow-up studies from the last decade.⁹⁻¹⁴ Not surprisingly, cohorts with large numbers of atriopulmonary Fontan procedures tended to show worse long-term survival.^{11,12} Those with exclusively TCPC-

type operations had similar survival rates to ours despite variability in surgical technique and patient selection.^{10,13}

It does not appear that long-term survival for Fontan patients has improved substantially since the advent of the TCPC. Two studies examining Fontan operations performed in the 1980s to 1990s reported 15- and 20-year survival rates for the TCPC subgroups that were nearly identical to those seen in this study.^{11,18} What clearly has improved with time is early postoperative survival. Era of Fontan was identified as a risk factor for early death or loss of Fontan circulation in this cohort, a finding that has been observed in several previous studies^{10,12,13} and that presumably reflects advances in perioperative and ICU care. The era in which the Fontan operation was performed, however, did not have an impact on long-term survival in those patients who survived the first postoperative year.

Independent of surgical era, longer aortic crossclamp time was found to predict early failure. Duration of intraoperative support has been implicated as a risk factor previously,¹² and may result in myocardial injury or serve as a marker of operative complexity (including performance of concomitant procedures). Duration of ICU stay is likewise a potential surrogate for underlying complexity and postoperative morbidity. Although it is not possible to identify the exact reasons that an individual patient in this cohort

TABLE 4. Risk factors for post-Fontan death, transplant, or takedown: Multivariable analysis

	Time < 1 y		Time ≥ 1 y	
	HR (95% CI)	P value	HR (95% CI)	P value
Pleural drainage > 14 d	4.4 (2.4-8.2)	<.001	0.7 (0.3-1.4)	.31
Fontan before 1997	3.3 (2.6-4.3)	<.001	1.1 (0.6-2.3)	.71
ICU stay > 1 wk	2.4 (1.5-3.8)	<.001	2.4 (1.5-3.8)	<.001
Preoperative AVVR ≥ mild	2.0 (1.4-3.1)	<.001	2.0 (1.4-3.1)	<.001
Aortic crossclamp time (per 10 min)	1.3 (1.1-1.6)	<.001	1.1 (0.9-1.3)	.48

HR, Hazard ratio; CI, confidence interval; ICU, intensive care unit; AVVR, atrioventricular valve regurgitation.

FIGURE 2. Impact of surgical era on transplant free survival. Kaplan-Meier survival estimate stratified by era of Fontan: (A) all patients, and (B) conditional on survival to 1 year with intact Fontan circulation. Please see supplementary [Appendix E3](#) for 95% confidence intervals of the survival functions.

remained in the ICU, duration of mechanical ventilation was the factor most closely correlated with duration of ICU stay in our patient cohort.

The strongest risk factor identified for early Fontan failure in the overall cohort was prolonged postoperative pleural drainage. This traditionally has been implicated as a marker of suboptimal hemodynamics, although the underlying mechanism is poorly understood and attempts to identify risk factors have produced conflicting results.^{6,19-22} A high burden of systemic to pulmonary arterial collaterals pre-Fontan recently has emerged as a fairly consistent predictor of prolonged effusions.²³⁻²⁵ Data on pre-Fontan

collateral burden were not available for this cohort, but this is an area that warrants further study. Two previous Fontan follow-up studies identified prolonged pleural drainage as a risk factor for late post-Fontan death,^{9,10} although our study did not replicate that finding. In this cohort, duration of pleural drainage did not predict outcome in patients who survived to 1 year with intact Fontan.

In patients with available hemodynamic data, the most important predictor of early post-Fontan failure was elevated preoperative PA pressure. The number of patients referred for pre-Fontan catheterization has decreased in recent years, with a concurrent increase in noninvasive

FIGURE 3. Conditional late survival stratified by duration of post-Fontan ICU stay (A) and preoperative AV valve regurgitation (B). *Dashed lines* represent 95% confidence intervals of the survival functions. *ICU*, Intensive care unit; *AVVR*, atrioventricular valve regurgitation.

FIGURE 4. Conditional late survival stratified by (A) ventricular morphology and (B) Fontan type. *Dashed lines* represent 95% confidence intervals of the survival functions.

imaging methods such as cardiac magnetic resonance imaging. Although magnetic resonance imaging alone may be an appropriate strategy in low-risk patients, these findings do reinforce the potential importance of understanding not just the patient’s pre-Fontan anatomy but also the physiology.

Independent risk factors for late outcome in our patients were limited to the presence of atrioventricular valve regurgitation (AVVR) before Fontan, and post-Fontan ICU stay > 1 week. In contrast to many other studies, we defined AVVR as any degree of regurgitation more than trivial, and it persisted as a risk factor despite the fact that 50% of patients with AVVR were categorized as mild. This finding suggests that even degrees of AVVR that would not warrant surgical intervention by current indications may influence late outcomes and deserve close follow-up. The association of duration of ICU stay, an early postoperative event, with late post-Fontan outcome is interesting. This may relate at least in part to noncardiac comorbidities, which were not explicitly captured as covariates in this study.

Importantly, we demonstrated no association between long-term transplant-free survival and type of Fontan operation, presence of hypoplastic left heart syndrome, or morphology of the systemic ventricle. This cohort should be well-powered to detect those risk factors, given the equal numbers of LT and EC Fontans, and the high percentage of

systemic right ventricle and hypoplastic left heart syndrome. However, although the difference in long-term transplant free survival between morphologic right and left ventricles was not statistically significant at this duration of follow-up, close examination of the Kaplan-Meier curve (Figure 4) suggests some divergence in the later post-Fontan period. It may be that a survival advantage for a systemic left ventricle is not clinically apparent until the third or fourth decade of life. The potential difference in long-term outcome between systemic left and right ventricles warrants repeat assessment in 5 to 10 years.

In the 25 patients who underwent heart transplantation, survival was 50% at just over 5 years. This finding is consistent with previous reports,²⁶⁻²⁸ although there are limited studies dedicated to transplant in the single-ventricle population. Given the relative infrequency of transplantation, multicenter studies will be required to investigate long-term outcomes in these patients.

There are several limitations to this study that should be noted. First, this was a retrospective study design, and as such there was a small percentage of missing covariate information. This did not exceed the preestablished tolerance level of 10% for any of the analyzed risk factors. Second, there is always the potential for unmeasured covariates. Our analysis suggests that the identified predictors explain only a modest portion of the observed variability in

TABLE 5. Risk factors for post-Fontan death or transplant: Multivariable analysis of subset with hemodynamic data

	Time < 1 y		Time ≥ 1 y	
	HR (95% CI)	P value	HR (95% CI)	P value
PA pressure > 15 mm Hg	4.1 (2.1-7.9)	<.001	1.0 (0.9-4.4)	.11
Pleural drainage > 14 d	3.6 (1.2-3.4)	<.001	0.7 (0.3-1.5)	.33
Fontan before 1997	2.5 (1.3-4.8)	.005	1.3 (0.6-2.7)	.49
ICU stay > 1 wk	2.0 (2.0-3.4)	.007	2.0 (1.2-3.4)	.007
Preoperative AVVR ≥ mild	2.1 (1.4-3.3)	.007	2.1 (1.4-3.3)	<.001
Aortic cross-clamp time, per 10 min	1.3 (1.03-1.5)	<.001	1.1 (0.9-1.3)	.35

HR, Hazard ratio; CI, confidence interval; PA, pulmonary artery; ICU, intensive care unit; AVVR, atrioventricular valve regurgitation.

outcomes. Finally, as with any single-center study, institutional practices influence the cohort characteristics. This study was not powered to assess the impact of Fontan fenestration, for example, because only 10% of the cohort was nonfenestrated. In addition, the current status of the fenestration is not known for many of the subjects.

CONCLUSIONS

In a large single-center cohort with a 99% follow-up rate, the 20-year estimate for survival with intact Fontan circulation is 74%. Distinct risk factors were identified for early versus late mortality. Choice of EC or LT Fontan did not affect survival. Morphology of the systemic ventricle likewise did not predict outcome at this duration of follow-up, although longer-term observation is warranted.

Although early perioperative mortality has improved over time, late survival after Fontan surgery has not changed appreciably during the past 2 decades. Mortality or loss of Fontan circulation in nearly a quarter of patients by 20 years suggests that alternative management strategies or significant improvements to the Fontan operation are needed.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Monday/04-27-15_6A_1440_Downing.mp4.

Conflict of Interest Statement

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Key Words: congenital heart disease, cardiovascular surgery, mortality/survival, transplantation

Discussion

Dr J. Kirklin (*Birmingham, Ala*). I'd first like to congratulate you on a very nice presentation and really the entire Children's Hospital of Philadelphia (CHOP) team on really spectacular long-term outcomes after the Fontan operation. You know, your results particularly are impressive, realizing that nearly one half of the patient cohort had hypoplastic left heart syndrome, making this really a unique long-term experience.

So I have 3 questions for you:

You've identified important atrioventricular (AV) valve regurgitation as a risk factor for late mortality, which was replaced by pre-Fontan pulmonary artery pressures in the multivariable analysis in the subset with pre-Fontan catheterizations. Assuming a relationship exists between AV valve regurgitation and these greater pre-Fontan pressures, what's your current policy regarding surgical management of AV valve regurgitation either prior to or at the time of the Fontan operation?

Dr Downing. Thank you very much, Dr Kirklin, for your comments. I think the question regarding AV valve regurgitation is a very important one and certainly one that we confront clinically on a weekly basis at our interdisciplinary surgical conference.

To clarify a little bit the relationship between pulmonary artery pressure and AV valve regurgitation in our data, you're correct in that the final multivariate model for the patients who did have a catheterization, elevated pulmonary artery pressure replaced AV valve regurgitation. The relationship is not quite so simple, however; although there was a trend toward elevated pulmonary artery pressure in patients with greater degrees of AV valve regurgitation, the one did not clearly predict the other—in the sense that those were not truly collinear covariates. It was simply that elevated pulmonary artery pressure is a just a better predictor, and so that entered the model whereas AV valve regurgitation, which was weaker, fell out of the model. And that being said, it's clearly important.

And to address the second part of your question as to what's our surgical strategy, we tend to try to avoid operating on the AV valve at the same time as doing the Fontan operation, and we really reserve that for the patients with significant degrees of AV valve regurgitation. In this cohort, there were only a total of 8 patients who had AV valve regurgitation that was classified as severe at the time of the Fontan, and approximately 50% of those had an AV valve intervention done at the same time. There were, I think, approximately 7% to 8% who had moderate AV valve regurgitation, and we actually tend to

leave most of those patients alone in the hope that they will improve.

Dr Kirklin. Question 2: Your outstanding experience with the Fontan operation after hypoplastic left heart syndrome is particularly instructive, but perhaps you could enlighten us on your current policy for those patients with hypoplastic left heart syndrome who do not proceed to the Fontan pathway.

Dr Downing. In terms of which patients would not be candidates for the Fontan; is that your question?

Dr Kirklin. Correct.

Dr Downing. I think for us the predisposing characteristics that would indicate that somebody is not a Fontan candidate probably are things that are not surprising to anybody here. The 2 that spring to mind are significant ventricular dysfunction or significantly elevated pulmonary artery pressure or pulmonary vascular resistance.

To address the issue of hypoplastic left heart syndrome, I think what our data have shown us is that the outcomes for those patients are not necessarily different than patients with other diagnoses that lead to the Fontan operation. And so I don't believe we have a separate set of exclusion criteria reserved specifically for patients with HLHS versus other single-ventricle diagnoses.

Dr Kirklin. And finally, I can't resist the temptation to ask you, with these really superior long-term outcomes, has this affected your calculus for decision-making in the determination of Fontan pathway versus 2-stage reconstructions for certain of the high-risk groups that perhaps have marginal indications for 2-ventricle repair?

Dr Downing. That's a difficult question to answer, and I don't think that we'll ever see a randomized trial of single-ventricle palliation versus attempt at left ventricular rehabilitation in the marginal left ventricle. And I would say that, while our survival is good, it's certainly not necessarily what somebody would hope for if you were counseling the parent of a future single-ventricle patient. If you said, "we have a great survival, there is a 25% chance that your child won't be alive in 20 years," that might not be perceived as excellent. But, I don't know that we have the data to say what that outcome would be with a biventricular approach instead. The Boston group has spoken at several national meetings this year about their experience in trying to rehabilitate the small left ventricle. What I do know is it seems like those patients have a lot of reinterventions even if you are successful, and so do the Fontan patients. I haven't presented all of the morbidity data here because we're still analyzing that, but we have a lot of reinterventions. So, I think that's a question that's still open and I don't know the definitive answer.

Dr E. Bacha (*New York, NY*). Very nice study and the follow-up in particular. It's hard to get all these patients to get an update on them, so very nice job.

My question is about the fenestration. You said that 90% of your patients were fenestrated at the initial

Fontan. Can you enlighten us a little bit about the effect of that? Maybe I missed it. What data do you have?

Dr Downing. We specifically didn't really analyze the presence of fenestration as a variable in the model simply because 90% were fenestrated and so we really didn't have enough nonfenestrated patients to adequately answer that question. And also, there is a significant era effect. Almost all the nonfenestrated patients were from the early era of Fontan.

Dr Bacha. I understand. But 90% fenestration initially doesn't mean they're all patent. Most of them would not be patent. I'm talking about long-term fenestration patency.

Dr Downing. Oh, I see what you're asking. We do not have data on the current status of the fenestration on the patients.

Dr Backer (*Chicago, Ill*). And do you actively close them or not close them?

Dr Downing. It is our institutional preference generally not to close them unless there is a clear provocation or reason to do so—the patient has had a stroke, we close them—but we do not have a policy of going back at X so many years and just routinely closing the fenestration.

Dr C. Fraser (*Houston, Tex*). I first want to say this was a very elegantly presented talk. The slides were clear, readable, and you're to be congratulated. It's a real model for oral presentation, so I thank you very much.

I wanted to make sure I understood the methodology. You linked your

CHOP Fontan database with the National Death Index; is that correct?

Dr Downing. That's correct.

Dr Fraser. So you had 99% vital statistics on all these patients?

Dr Downing. That's correct. The only patients for whom we were unable to obtain current vital status were those who are currently living outside of the United States and would not be covered by the National Death Index (NDI).

Dr Fraser. I have to claim ignorance about how to use the NDI. How does one obtain informed consent from a family when you're going to link an existing database and a national index, how do you do that?

Dr Downing. The retrospective chart review portion of the study was granted a waiver of informed consent by the CHOP institutional review board.

Dr Fraser. Initially?

Dr Downing. Yes. And included in that was the query of the NDI. But the National Death Index, you have to understand, is public record. So the deaths and death dates and death certificates are a matter of public record and the NDI is simply a centralized database, a way to access it.

Dr Fraser. But it's organized by social security number, right?

Dr Downing. It was previously housed under the Social Security Administration and now it is with the National Center for Health Statistics, yes.

Dr Fraser. Well, it's an incredible tool. I think we could all learn how to use it better, because so many of our studies that we claim long-term follow-up, we have huge percentages of our patients that are lost. So this is a real opportunity as I see it.

So the question, so 20% mortality at 20 years roughly; is that right?

Dr Downing. Yes.

Dr Fraser. Your mean age at Fontan completion is 2.3 years. I've always pondered why you need to go forward with a Fontan operation at age 2 years. So, another speculation: based on this information, might you push out the age of Fontan completion as another potential conclusion from this, speculating that human beings can't live with hepatic venous pressure of 12 or 15 mm Hg for a normal lifespan?

Dr Downing. It could. I mean it's certainly a reasonable speculation to say if we can get 75% survival 20 years out why not do the Fontan operation at 7 and then they'll be a little older. But I guess one of my biases, one of the things that I spend some of my time doing is taking care of adults with congenital heart disease, and while it might be very nice to move the target from 20 years to 27 years, what about 60 and 70? And so while you might say that that could buy you an extra 5 years, I might think a little bigger and say what's going to buy us an extra 50 years. And I don't have the answer to that. I don't think it's the Fontan.

Dr G. Sarris (*Athens, Greece*). I'd like to congratulate you for a very nice paper and fantastic results. This is really a landmark paper.

Would you be able to tell us a little bit about your anticoagulation strategy and whether this has impacted on the results in any way and, also, if you have studied the modes of Fontan failure and the causes of death in this particular paper.

Dr Downing. We're getting a lot of excellent questions on the non-mortality and morbidity aspects of the data, and I'll qualify my answers by saying we are collecting that and I can give some interim analysis. We're about 75% through the nonmortality data.

So in regards to your question about anticoagulation, the vast majority of patients that we follow at CHOP in childhood are anticoagulated with aspirin alone. In older adulthood, we tend to transition a lot of our patients to warfarin, but those would be at an age range of sort of outside of this study. So the vast majority of the patients in this study were on aspirin alone.

And we are collecting data on thromboembolic events. That's not completely analyzed yet and so we will have that but I can't give you an eloquent answer on that at this point.

Dr Sarris. Well, we look forward to listening to the update in the future.

Dr C. Pizarro (*Wilmington, Del*). Beautiful job. Just a quick question. A few years ago, we looked at our own data in a few hundred patients and it seems that the patients who had prolonged effusions were patients who had issues related to recoarctation.

Did you have an opportunity to look at the influence of recoarctation on the incidence of prolonged effusions and the effectiveness of balloon intervention to address this issue?

Dr Downing. Are you asking about recoarctation prior to the Fontan?

Dr Pizarro. Correct.

Dr Downing. That is not data that's directly linked to this data set, so I can't specifically correlate the patients who might have had that with the prolonged drainage, but that's an excellent question.

Dr d'Udekem (*Victoria, Australia*). It appears that ventricular dominance was not related to death in your study. Did you analyze heterotaxia? Was heterotaxia related to deaths, or did you look at it?

Dr Downing. So the question is: is heterotaxy syndrome related to death? And yes, we did analyze that. Approximately 8% of our patients had heterotaxy, and it was actually not found to be a significant predictor for early or late death, which was actually somewhat of a surprise to me. In fact, none of the patients who died early had heterotaxy syndrome, so we were unable to even include it in the model. It was a divide-by-zero phenomenon.

Dr C. Backer. I'm intrigued by the fact that you slowly appear to have transitioned from lateral tunnel to extracardiac Fontan. I want to ask this august audience for a quick show of hands: In the current era how many people are doing lateral tunnel Fontans as their primary Fontan strategy?

(Show of hands.)

Looks like about maybe 10 hands.

And how many people have used the extracardiac Fontan?

(Show of hands.)

So it looks like it's about 90% extracardiac and 10% lateral tunnel.

You were using the fenestration in all your patients with excellent results. How many people in the audience are using fenestrations routinely?

(Show of hands.)

And how many are not?

(Show of hands.)

That looks to me like about a 50/50 split.

So should we be using fenestrations in everybody, yes or no?

Dr Downing. I can't answer that question. We do it on all of them.

Dr Backer. This was an excellent presentation, I congratulate you on outstanding results, and that was a very nice discussion.

APPENDIX E1. Variables considered in risk factor analysis

- Demographic factors: sex, era of Fontan operation.
- Pre-Fontan surgical factors: type of stage 1 palliation (Norwood vs non-Norwood), type of stage 2 palliation, age at stage 2 palliation, weight at stage 2 palliation.
- Anatomic and physiologic factors: heterotaxy syndrome, presence of common atrioventricular valve, morphology of systemic ventricle, hypoplastic left heart syndrome, pre-Fontan pulmonary artery pressure,* pre-Fontan ventricular end-diastolic pressure.*
- Fontan surgical factors: type of Fontan operation, age at Fontan, weight at Fontan, presence of fenestration, use of modified ultrafiltration, cardiopulmonary bypass time, crossclamp time.
- Perioperative factors: duration of intensive care unit stay, duration of mechanical ventilation, duration of pleural drainage, duration of hospital stay.

*Catheterization parameters were incorporated into subset analyses only, as described in the text.

APPENDIX E2. Supplementary data for survival analysis (supplementary data for Figure 1)

Time from Fontan, y	Estimated survival*	95% confidence interval (%)
Overall survival		
0.083 (1 mo)	97%	95-98
1	94%	92-95
5	92%	90-94
10	90%	88-92
15	85%	82-88
20	74%	67-80
Cumulative hazard†		
Death		
0.083 (1 m)	3%	2-4
1	5%	4-7
5	7%	5-9
10	8%	6-10
15	12%	9-16
20	23%	16-32
Transplant		
0.083 (1 m)	0%	0-1
1	1%	0-2
5	2%	1-3
10	3%	1-4
15	5%	3-7
20	8%	5-14
Fontan takedown		
0.083 (1 m)	0%	0-2
1	1%	1-2
5	1%	1-2
10	1%	1-2
15	1%	1-2
20	1%	1-2

*Kaplan-Meier survival function. †Nelson-Aalen cumulative hazard function.

APPENDIX E3. Supplementary data for Figure 2

Time from Fontan, y	Estimated survival*	95% confidence interval (%)
All patients (Figure 2, A)		
Era 1 (1992-1996)		
0.083 (1 mo)	93%	89-96
1	88%	83-92
5	86%	80-90
10	85%	79-89
15	80%	74-84
20	69%	61-76
Era 2 (1997-2002)		
0.083 (1 mo)	98%	95-99
1	96%	92-98
5	94%	90-97
10	92%	88-95
15	87%	80-92
Era 3 (2003-2009)		
0.083 (1 mo)	99%	97-99
1	97%	94-98
5	95%	92-97
9	94%	89-96
Conditional on survival to 1 y (Figure 3, B)		
Era 1 (1992-1996)		
5	97%	93-99
10	96%	92-98
15	90%	85-94
20	78%	70-85
Era 2 (1997-2002)		
5	98%	95-99
10	96%	92-98
15	91%	84-95
Era 3 (2003-2009)		
5	98%	96-99
9	97%	92-99

*Kaplan-Meier survival function.

FIGURE E1. Transplantation after Fontan operation. A, Outcome of transplant listing. B, Kaplan-Meier estimate for survival after heart transplantation. Dashed lines represent 95% confidence intervals of the survival function.

TABLE E1. Comparison of population characteristics and survival outcomes in recent Fontan follow-up studies

Study	Cohort years	n	Median follow-up, y	Follow-up rate	Fontan type	Systemic RV	HLHS	Survival
CHOP cohort	1992-2009	773	9	99%	0% AP 53% LT 47% EC	67%	50%	● 83% overall survival at 20 y ● 79% transplant/takedown-free survival at 20 y
Pundi et al, ¹² 2015	1973-2012	1052	15	68%	59% AP 25% LT 11% EC	<45%	2%	● 61% overall survival at 20 y ● 59% transplant-free survival at 20 y
Nakano et al, ¹⁴ 2015	1994-2014	500	7	NR	0% AP 0% LT 100% EC	NR	15%	● 93% overall survival at 15 y ● No transplants performed
d'Udekem et al, ⁹ 2014	1975-2010	1006	NR	96%	20% AP 27% LT 53% EC	31%	9%	● 90% overall survival at 20 y for perioperative survivors ● 2% of patients underwent heart transplantation
Dabal et al, ¹³ 2014	1988-2011	207	5	89%	0% AP 29% LT 71% EC	NR	9%	● 77% overall survival at 20 y ● Only 1 patient underwent heart transplantation
Khairy et al, ¹¹ 2008	1973-2008	261	12	< 50%	62% AP 37% LT 1% EC	30%	5%	● 68% transplant-free survival at 20 y
Hirsch et al, ¹⁰ 2008	1992-2007	636	4	NR	0% AP 92% LT 8% EC	64%	52%	● 91% overall survival at 14 y for perioperative survivors

RV, Right ventricle; HLHS, hypoplastic left heart syndrome; CHOP, Children's Hospital of Philadelphia; AP, atriapulmonary; LT, lateral tunnel; EC, extracardiac conduit; NR, not reported.