Surgical and Catheter-Based Reinterventions Are Common in Long-Term Survivors of the Fontan Operation

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Background—There are limited follow-up studies examining surgical and catheter-based reinterventions in long-term survivors of the Fontan operation.

Methods and Results—All 773 patients who underwent Fontan at our institution between 1992 and 2009 were retrospectively reviewed. Current information regarding post-Fontan intervention was available for 70%. By 20 years after Fontan, 65% of patients had experienced either surgical or transcatheter intervention. The median time to first reintervention was 9.8 years. Freedom from reoperation was 69% at 15 years and 63% at 20 years. The most common operations were pacemaker placement and Fontan revision. Risk factors for pacemaker placement included systemic left ventricle (hazard ratio [HR], 2.2; P=0.006) and lateral tunnel Fontan (HR, 4.3; P=0.001). Freedom from interventional catheterization was 53% at 15 years and 50% at 20 years. The most common procedures performed were fenestration closure and pulmonary artery intervention. Catheter intervention for anatomic indications was associated with Fontan after 2002 (HR, 2.1; P=0.007), Norwood operation (HR, 2.3; P=0.001), and longer cardiopulmonary bypass time (HR, 1.1 per 10 minutes; P=0.001). Catheter intervention for physiological indications was associated with prolonged post-Fontan pleural drainage (HR, 4.0; P<0.001) and hypoplastic left heart syndrome (HR, 2.0; P=0.01).

Conclusions—In this study of Fontan survivors, two thirds of patients required surgical or catheter-based reintervention by 20 years. Families should be counseled that the Fontan is typically not the final stage of single-ventricle palliation. **(*Circ Cardiovasc Interv*. 2017;10:e004924. DOI: 10.1161/CIRCINTERVENTIONS.116.004924.)**

Key Words: catheterization ■ cyanosis ■ Fontan procedure ■ hypoplastic left heart syndrome ■ mortality ■ tricuspid atresia

The Fontan operation was first described in the 1970s as a means to alleviate cyanosis in tricuspid atresia by directly rerouting systemic venous return to the pulmonary arterial circulation.[1,2] Today, the Fontan is used to palliate patients with a wide variety of functional single-ventricle lesions. While early postoperative mortality is low in the modern era,[3–6] the long-term consequences of this unique circulation are increasingly being appreciated. Late post-Fontan mortality has not improved significantly over the past several decades,[7–9] and Fontan-related morbidities such as protein-losing enteropathy and arrhythmia become problematic as patients age.[10]

Although the Fontan is typically described as the final stage of single-ventricle palliation, patients frequently represent for surgical or catheter-based interventions for a variety of indications. A recent single-center review suggested that more than half of Fontan patients will require reintervention by 20 years.[11] That cohort was limited, however, by small sample size and a high proportion of subjects with older style atriopulmonary Fontan operations. Additional studies are therefore needed to specifically examine the burden of reintervention after Fontan completion in the modern era. In this study, we aimed to quantify and describe surgical and catheter-based reintervention in a large single center Fontan cohort, and to identify risk factors for reintervention.

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,

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WHAT IS KNOWN

- The Fontan operation is typically described as the final stage of single ventricle palliation; however, preliminary studies suggest that at least 50% of Fontan patients require subsequent surgical or catheter-based reintervention.

WHAT THE STUDY ADDS

- In a large single-center cohort, nearly two thirds of Fontan patients require surgical or catheter-based reintervention within 20 years after Fontan.
- The most common post-Fontan surgical reintervention is pacemaker placement, and the most common nonelective catheter reintervention is pulmonary artery angioplasty.
- Risk factors for surgical and catheter-based reinterventions are identified and include both anatomic and surgical characteristics.

2009. Patients were included if they received any form of total cavopulmonary connection, including the lateral tunnel and extracardiac Fontan operations, as well as hepatic vein inclusion conduits in patients with a prior Kawashima operation. No atriopulmonary connections were performed at CHOP during this time period. Only first Fontan operations were considered—Fontan revisions or repeat Fontan operations after a previous Fontan takedown were excluded. Early perioperative outcomes from this cohort have been reported previously.[6]

Baseline demographic, anatomic, preoperative, and perioperative characteristics were extracted from the medical record as previously described.[6] The complete list of available variables is presented in Appendix A in the Data Supplement. Specifics of post-Fontan surgical and catheter-based reinterventions were ascertained from the medical record through a detailed review of clinic letters, catheterization reports, and operative notes. Records were reviewed from the time of Fontan through December 31, 2012.

Given the extended time frame of the study period, about half of subjects 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).[12] At the time of data collection, vital status records were available through December 31, 2012. Transplant status and history of transplant listing were obtained through collaboration with the Scientific Registry of Transplant Recipients (Minneapolis, MN).[13] Patients determined to be living were then contacted by telephone for permission to request their medical records from their primary institution. The families of deceased patients were not contacted.

The primary objective was to describe freedom from surgical or catheter-based reintervention after Fontan operation. Interventions were then further divided into clinically relevant subcategories. Pacemaker implantation was evaluated separately from other operations given its frequency and less invasive nature. Major cardiac surgery in the setting of intact Fontan was defined by excluding pacemaker and hepatic vein inclusion (this procedure was limited to the early era of Fontan surgery) in patients who had not undergone transplant or Fontan takedown. Nonelective catheter interventions were defined by excluding fenestration closures, and then, further divided into anatomic versus physiological indications. Anatomic indications were defined as dilation or stenting of the pulmonary arteries, aorta, SVC, IVC, Fontan baffle, or pulmonary veins. Physiological indications were defined as creation of a fenestration or embolization of veno-venous or systemic to pulmonary arterial collaterals. Secondary objectives were to identify risk factors for surgery or interventional catheterization.

Statistical Analysis

Baseline demographic and clinical variables were summarized using standard descriptive statistics. Normally distributed variables were reported as mean±SD, and skewed variables were reported as median with range. Kaplan–Meier survival curves were constructed to estimate freedom from reintervention end points. Time zero was defined as date of Fontan. Patients were censored at the end of the study period or at the date of last available follow-up. Those who did not have complete medical records through the end of the study period were included in the analyses and censored at latest point of continuous follow-up available after the Fontan. Patients were also censored at the time of death, transplant, or Fontan takedown if they remained free of reintervention.

Risk factors for reintervention end points were ascertained primarily using multivariable Cox regression. A competing risks model accounting for competing deaths was also tested; however, no statistically significant difference was noted in any end point when compared with the Cox analyses. All covariates presented in Appendix A in the Data Supplement were tested in univariable analysis. Those with a P value <0.2 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 <0.05. The proportion of missing covariates was low (4%), and imputation was therefore not used. When >1 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. All P values reported are 2-sided, and statistical significance was established a priori at $P \leq 0.05$. Analyses were conducted with STATA, version 12.0 (StataCorp, College Station, TX). This study was approved by the Institutional Review Board.

Results

A total of 773 patients underwent a first Fontan operation at CHOP between 1992 and 2009, with a median of 42 operations performed per year. Vital status and transplant history as of January 1, 2013, were ascertained for >99% of patients through the National Death Index and Scientific Registry of Transplant Recipients databases. Approximately half (49%) of the cohort had complete medical records available at CHOP through the end of the study period. Of the 355 patients not followed at CHOP, 36 were identified through the National Death Index as deceased. Current medical records were obtained from 40% of the remaining 319 patients. In total, complete medical records describing reinterventions from the time of Fontan through the end of the study period were available for 544 out of 773 patients (70%; Figure 1). Patients without complete medical records were on average younger and smaller at the time of Fontan completion and were more likely to have hypoplastic left heart syndrome (HLHS) and a lateral tunnel Fontan. All of these characteristics were more prevalent in the earliest era of the study period,[6] so this likely reflects the tendency for patients to relocate or become lost to follow-up as they age. Despite this, there was no difference in the National Death Index and Scientific Registry of Transplant Recipients–derived 20-year transplant-free survival estimate between patients with and without complete follow-up.

All 773 patients were included in the analyses until their date of last clinical contact. This represents 5308 patient-years

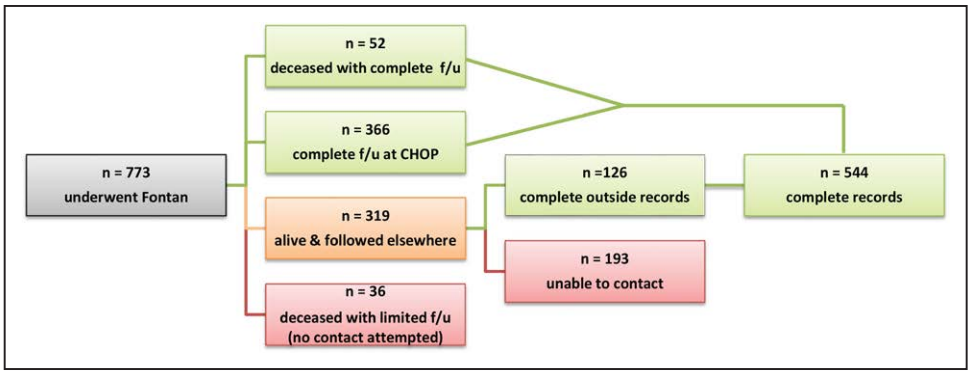

Figure 1. Flowchart describing status of patient follow-up. CHOP indicates Children's Hospital of Philadelphia; and f/u, follow-up.

of follow-up, with a median follow-up of 6.8 years after Fontan (range, 0–21 years). Thirty percent of the cohort had follow-up of at least a decade.

Relevant baseline characteristics of the patient population are outlined in Table 1. Fifty percent of the overall cohort had HLHS, and the majority had a systemic right ventricle. Nearly all patients (97%) had stage 2 palliation preceding the Fontan. The surgical strategy was divided nearly equally between lateral tunnel and extracardiac Fontan, and 90% were fenestrated.

Surgical Reintervention

Post-Fontan cardiac surgical reinterventions are described in Table 2. A total of 132 patients had 205 procedures with 236

Table 1. Baseline Cohort Characteristics

	Overall (n=773)	Patients With Recent Follow-Up (n=544)	Patients Lost to Follow-Up (n=229)	*P* Value
Female sex	289 (37)	215 (40)	81 (35)	0.25
Age at Fontan, y	2.3 (0.9–38)	2.3 (0.9–28)	2.1 (0.9–31)	0.001
Weight at Fontan, kg	12.0 (5.8–120)	12.2 (5.8–120)	11.7 (7–59)	0.004
Heterotaxy	66 (8.5)	51 (9)	15 (7)	0.19
Fontan era				<0.001
Era 1 (1992–1997)	226 (29)	127 (23)	99 (43)	
Era 2 (1997–2002)	196 (25)	135 (25)	59 (26)	
Era 3 (2003–2009)	351 (46)	280 (52)	71 (31)	
Common AV valve	88 (11)	68 (13)	20 (9)	0.13
Dominant RV	524 (67)	351 (66)	174 (76)	0.005
HLHS	381 (50)	241 (45)	140 (61)	<0.001
Preoperative AVVR ≥ mild	323 (45)	228 (46)	95 (43)	0.40
Pre-Fontan PA pressure, mm Hg (n=619)	11 (4–25)	11 (4–25)	11 (5–10)	0.90
Pre-Fontan EDP, mm Hg (n=619)	7 (1–18)	7 (1–18)	7 (1–18)	0.83
Fontan type				<0.001
Lateral tunnel	409 (53)	257 (47)	152 (66)	
Extracardiac	364 (47)	286 (53)	78 (34)	
Fenestration	693 (90)	490 (90)	203 (88)	0.41
CPB time, min	64 (32–274)	64 (32–274)	62 (32–149)	0.03
ACC time, min	26 (0–99)	26 (0–96)	26 (0–99)	0.73
Ventilator time (n=469)	8 h (0 h to 56 d)	14 h (0 h to 56 d)	7 h (0 h to 16 d)	0.02
ICU stay >7 d (n=752)	87 (12)	36 (16)	51 (9)	0.005
Pleural drainage >14 d (n=745)	126 (17)	87 (17)	39 (18)	0.62

Data presented as count (%) or median (range). ACC indicates aortic cross clamp; AV, atrioventricular; AVVR, AV valve regurgitation; CPB, cardiopulmonary bypass; EDP, end-diastolic pressure; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; PA, pulmonary artery; and RV, right ventricle.

Table 2. Post-Fontan Surgical Reinterventions

Surgery	Total	Early*	Surgery	Total	Early*
Pacemaker	100	11	Fontan takedown	10	10
Hepatic vein inclusion	21	6	Aortic valve repair/replace	7	0
Fontan revision	19	4	Atrial septectomy	7	2
Heart transplant	19	4	Pulmonary arterioplasty	5	4
Miscellaneous†	17	7	Maze procedure	3	0
AV valve repair/replace	14	1	Arch revision	1	0
Create fenestration	13	7	…	…	…

AV indicates atrioventricular; and VSD, ventricular septal defect.

*Within 1 year post-Fontan.

†Miscellaneous: aortic root replacement (3), fenestration closure (3); pericardial window (2), aortic aneurysm repair, repair intraoperative injury, resect subaortic stenosis, VSD enlargement, thoracic duct ligation, ligate left superior vena cava, thrombectomy, and sutureless pulmonary vein repair.

distinct surgical interventions. The most frequent operation was pacemaker implantation, accounting for 42% of surgical procedures performed. Also, prevalent were revision of the Fontan circuit and reinclusion of previously excluded hepatic veins (hepatic vein exclusion Fontan operations were performed in the early 1990s as an early method of fenestration). Valve interventions and surgical corrections of aortic arch or pulmonary artery obstruction were uncommon, occurring less frequently than heart transplantation in this cohort.

Freedom from first surgical reintervention is shown in Figure 2. A steady rate of reoperation was noted, beginning essentially at the time of Fontan. Overall freedom from any surgical procedure was 69% at 15 years (95% confidence interval [CI], 63%–75%) and 63% at 20 years (95% CI, 55%–70%; Figure 2A). Freedom from pacemaker was 84% at 15 years (95% CI, 79%–89%) and 79% at 20 years (95% CI, 71%–85%). Freedom from major surgery in patients who retained their Fontan physiology was 87% at 15 years (95% CI, 82%–90%) and 86% at 20 years (95% CI, 81%–90%; Figure 2B).

Risk factors for first surgical reintervention are outlined in Table 3. In multivariable analysis, morphological systemic left ventricle (hazard ratio [HR], 2.2; P=0.006) and lateral tunnel Fontan (HR, 4.3; P=0.001) were independently associated with the need for pacemaker. The most common arrhythmia diagnoses in patients receiving a pacemaker were sinus node dysfunction alone (23/66, 35%), sinus node dysfunction plus a tachyarrhythmia (13/66, 20%), and complete heart block (13/66, 20%). The remaining patients receiving pacemakers had multiple arrhythmia diagnoses, and in 3, the reason for pacemaker placement was not known. In this cohort as whole, freedom from sinus node dysfunction was not statistically different between patients with extracardiac and lateral tunnel Fontans (HR, 1.4; P=0.09).

A separate set of risk factors was associated with first major cardiac surgery in patients who retained Fontan physiology. These were lack of a Fontan fenestration (HR, 2.5; P=0.01), prolonged postoperative pleural drainage >14 days (HR, 2.3; P=0.01), and mild or greater atrioventricular valve regurgitation before Fontan (HR, 2.0; P=0.02). Anatomic risk factors such as morphology of the systemic ventricle, presence of HLHS, or heterotaxy were not associated with major surgical reintervention. Pre-Fontan hemodynamic parameters were likewise not associated with reoperation.

Catheter Reintervention

Catheter-based interventions after Fontan are outlined in Table 4. In total, 694 catheterizations (including diagnostic-only procedures) were performed in 375 patients. Two-hundred sixteen (216) patients had at least

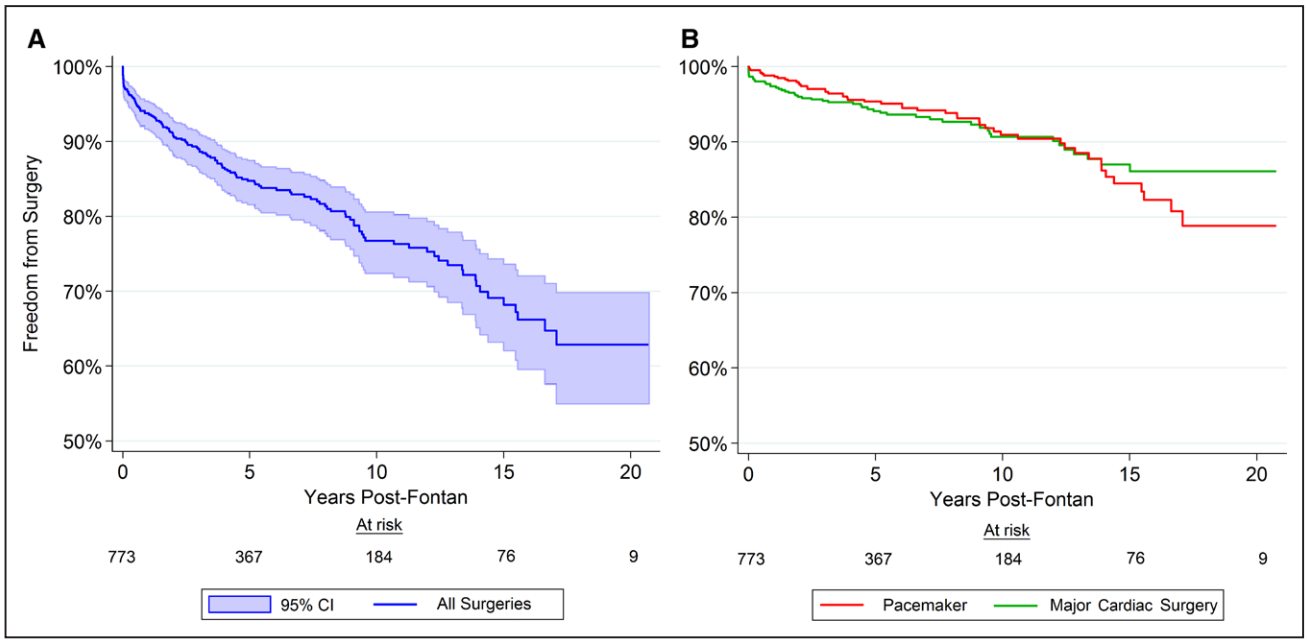

Figure 2. Freedom from surgical reintervention. **A**, Kaplan–Meier freedom from first surgical reintervention. Shaded area represents 95% confidence intervals (CIs) of the survival function. **B**, Kaplan–Meier freedom from first pacemaker and first major cardiac surgery in patients with intact Fontan. Y axis in both panels begins at 50%.

Table 3. Risk Factors for First Surgical Reintervention

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	*P* Value*	Hazard Ratio (95% CI)	*P* Value*
Pacemaker placement				
Fontan era 1	7.8 (2.7–22.9)	<0.001	…	…
Fontan era 2	3.7 (1.2–11.7)	0.02	…	…
Heterotaxy	0.2 (0.03–1.3)	0.09	…	…
Systemic LV	1.9 (1.1–3.4)	0.02	2.2 (1.3–3.9)	0.006
CAVV	0.3 (0.1–1.4)	0.13	…	…
LT Fontan	3.3 (1.5–7.2)	0.002	4.3 (1.9–9.7)	0.001
No MUF	2.9 (1.6–5.2)	0.001	…	…
Hospital time (per day)	1.007 (1.0009–1.01)	0.03	…	…
Major cardiac surgery				
Norwood	1.7 (0.9–3.1)	0.09	…	…
AVVR pre-Fontan	2.3 (1.3–4.0)	0.004	2.0 (1.1–3.6)	0.02
PAP >15 mm Hg	2.1 (1.0–4.6)	0.05	…	…
No fenestration	2.5 (1.2–4.9)	0.01	2.5 (1.2–5.2)	0.01
Hospital time (per day)	1.01 (1.01–1.02)	<0.001	…	…
ICU stay >1 wk	2.0 (0.9–4.2)	0.08	…	…
Pleural drainage > 14 d	2.6 (1.4–4.9)	0.003	2.3 (1.2–4.4)	0.01

AVVR indicates atrioventricular valve regurgitation; CI, confidence interval; ICU, intensive care unit; LT, lateral tunnel; LV, left ventricle; MUF, modified ultrafiltration; and PAP, pulmonary artery pressure.

*Cox regression.

1 interventional catheterization, undergoing a total of 371 distinct interventions. The most common indication for intervention was closure of the Fontan fenestration, although many of these occurring in the early era were elective. Other common interventions were balloon dilation and stent placement to relieve pulmonary artery stenosis and embolization of either veno-venous or systemic to pulmonary arterial collaterals.

Table 4. Post-Fontan Catheter Reinterventions

Procedure	Total	Early*	Procedure	Total	Early*
Fenestration closure	99	14	Dilate/stent aorta	13	1
Dilate/stent PAs	79	22	Dilate/stent Fontan/SVC/IVC	12	0
Embolize SPCs	55	25	Thrombolysis	8	6
Embolize VVCs/LSVC	54	6	Dilate/stent pulm veins	6	2
Dilate/stent fenestration	37	15	Miscellanous†	15	2

AVM indicates arteriovenous malformation; IVC, inferior vena cava; LSVC, left superior vena cava; PA, pulmonary artery; SPC, systemic to pulmonary collateral; SVC, superior vena cava; and VVC, veno-venous collateral.

*Within 1 year post-Fontan.

†Miscellanous: dilate atrial septum (3), transcatheter hepatic vein exclusion (3), coil coronary fistula (2), coil/device to pulmonary AVMs (2), dilate systemic vein (2), hepatic vein re-routing, dilate systemic artery, coronary stent.

Freedom from first interventional catheterization is shown in Figure 3A. Freedom from any intervention was 53% at 15 years (95% CI, 47%–58%) and 50% (95% CI, 44%–56%) at 20 years. Excluding fenestration closures that were often elective, freedom from first nonelective intervention was 64% at 15 years (95% CI, 58%–69%) and 59% at 20 years (95% CI, 52%–66%). Figure 3B shows nonelective interventions further categorized into interventions for anatomic and physiological indications. Freedom from first physiological intervention was 84% at 15 years (95% CI, 88%–88%) and 81% at 20 years (95% CI, 73%–87%). Freedom from first anatomic intervention was 81% at 15 years (95% CI, 76%–85%) and 69% at 20 years (96% CI, 54%–80%).

Factors associated with first anatomic and physiological intervention are presented in Table 5. Catheter intervention for anatomic indications was associated with history of Norwood operation (HR, 2.3; *P*=0.001), Fontan Era 3 (HR, 2.1; *P*=0.007), and longer cardiopulmonary bypass time during Fontan operation (HR, 1.1 per 10 minutes; *P*=0.001). Intervention for physiological indications was associated with prolonged post-Fontan pleural drainage (HR, 4.0; *P*<0.001) and HLHS (HR, 2.0; *P*=0.01).

Freedom from any intervention, surgical or catheter-based, is shown in Figure 4. By 20 years after Fontan, 65% of patients in this cohort had experienced some form of reintervention. The median time to reintervention was 9.8 years. In patients with at least 15-year follow-up (n=107), the median number of post-Fontan interventions was 1, with a range of 0 to 7.

The association of post-Fontan intervention with survival with intact Fontan circulation is described in Table 6. Intervention itself, even in patients with ≥3 distinct interventions, was not associated with the combined end point of death, transplant, or Fontan takedown. There was a trend toward increased risk with major intracardiac surgery, but the intervention most strongly associated with death or loss of Fontan circulation in this cohort was pacemaker placement (HR, 2.6; *P*=0.005). Interventional catheterization for physiological reasons was also associated with the composite outcome (HR, 2.1; *P*=0.01), whereas anatomic intervention was not.

Discussion

The Fontan operation is traditionally considered to be the final stage of surgical palliation for patients with single-ventricle congenital heart disease. In practice, however, reintervention seems to occur frequently. This study confirmed the overall high rate of surgical and percutaneous reinterventions in post-Fontan patients and identified risk factors for pacemaker, major intracardiac surgery, and interventional catheterization.

There is little existing literature specifically examining the issue of reintervention after Fontan. In 2015, Van Dorn et al[11] presented a series of 91 patients followed for a median of 18 years. The rate of reintervention was high at >70% at 20 years after Fontan. Surgical procedures were particularly common, with a 5-year freedom from surgery of only 57%. No specific patient-level risk factors for surgery were identified. Catheter-based interventions were more frequent in patients with total

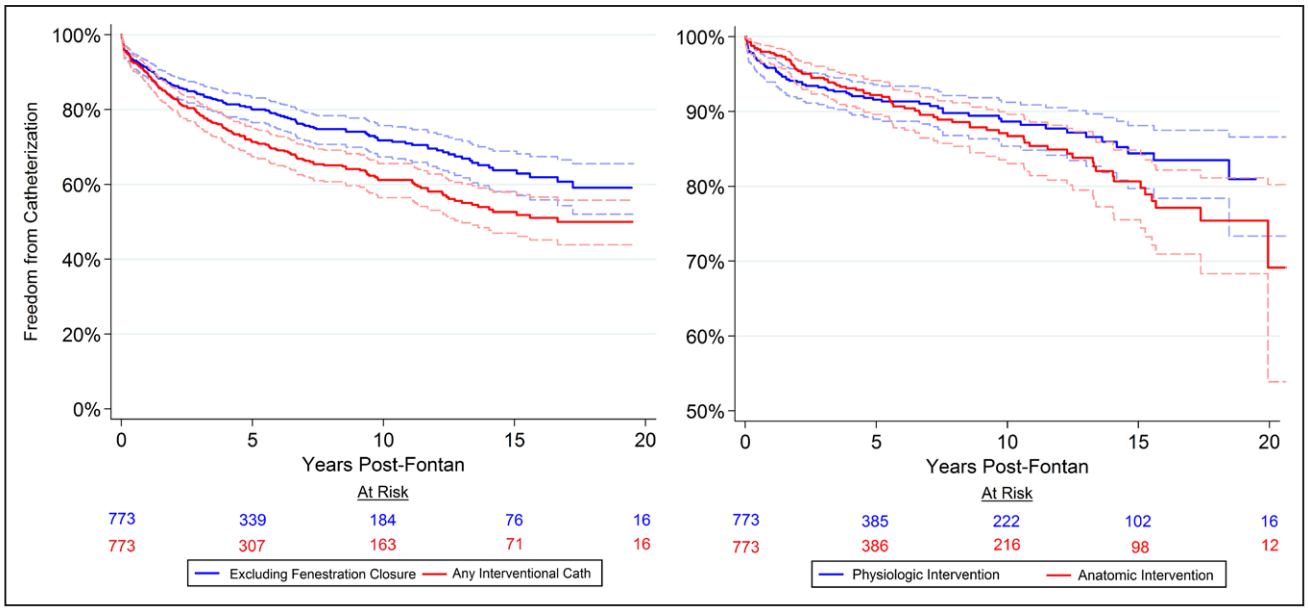

Figure 3. Freedom from catheterization. **A**, Kaplan–Meier curves showing freedom from first interventional catheterization and first nonelective catheterization (excluding fenestration closure). **B**, Kaplan–Meier curves showing freedom from first interventional catheterization for anatomic and physiological indications. Dashed lines represent 95% confidence intervals (CIs) of the survival function. Y axis begins at 50%.

cavopulmonary connections than in those with atriopulmonary Fontans. The percentage of atriopulmonary Fontan patients in that cohort was high, though, potentially limiting applicability to today's Fontan population.

In this larger population of exclusively total cavopulmonary connection–type Fontan patients, we found a similarly high rate of overall reintervention, estimated at 65% at 20 years after Fontan. For residual anatomic lesions, transcatheter intervention was far more common than reoperation, suggesting that in the modern era the first attempt at treatment typically occurs in the catheterization laboratory. The need for at least one cardiac catheterization, diagnostic or interventional, seems to be the rule rather than the exception as Fontan patients age.

By far, the most frequent surgical procedure in this population was placement or revision of a pacing system. Several previous Fontan outcomes studies have examined frequency of pacemaker placement, but interpretation is limited by heterogeneous patient populations and variable duration and completeness of follow-up. In cohorts with follow-up <10 years, pacemaker prevalence has been reported at 7% to 11%.[14–16] In those with longer follow-up, need for pacemaker varies by Fontan type but has been estimated anywhere from 5% to 41% at 15 to 20 years.[9,17–20] Our estimate of 79% freedom from pacing at 20 years in patients is consistent with these reports, although it could be an overestimate if patients lost to follow-up have a lower rate of intervention.

The increased risk for pacemaker after lateral tunnel (versus extracardiac) Fontan has also been demonstrated in prior studies.[19,20] The reason for this is not entirely clear, however, and there is conflicting literature as to whether the type of total cavopulmonary connection affects the incidence of late arrhythmias.[19–23] In our cohort, sinus node dysfunction was the most common indication for pacemaker placement, but there was no statistically significant difference in the incidence of sinus node dysfunction between the lateral tunnel and extracardiac groups. This supports the notion that the reasons for pacemaker placement in this patient population are multifactorial. Underlying anatomy seems to contribute, as we found that patients with systemic left ventricle had a greater requirement for pacing. This might be because of an increase in conduction abnormalities in patients with ventricular L-looping; however, that degree of anatomic detail was not available for all patients in this cohort, so a formal analysis was not possible.

Importantly, although pacemaker placement is common and the morbidity of the procedure itself is low, in this cohort, the need for pacemaker was significantly associated with decreased transplant-free survival. This highlights the impact of post-Fontan arrhythmias on late outcomes in single ventricle patients and the notion that arrhythmias may be a manifestation of an unwell Fontan patient.

Patients who retained their Fontan physiology were much less likely to have additional major cardiac surgery than they were to have a pacemaker, but the rate was still not insignificant at 14% at 20 years. The identified risk factors of prolonged pleural drainage, atrioventricular valve regurgitation, and lack of a fenestration are all potentially associated with suboptimal Fontan physiology characterized by higher Fontan pressure and lower cardiac output. Major intracardiac surgery was not found to be definitively associated with mortality or loss of Fontan circulation in this group, although the study may have been underpowered to detect this outcome.

Common indications for interventional catheterization included pulmonary artery stenosis, arch obstruction, and significant collaterals. These issues were addressed in the catheterization laboratory far more often than with surgery. The high number of percutaneous fenestration closures in this cohort

Table 5. Risk Factors for First Nonelective Catheter Reintervention

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	*P* Value*	Hazard Ratio (95% CI)	*P* Value*
Anatomic intervention				
Fontan era 3	2.4 (1.4–4.1)	0.002	2.1 (1.2–3.7)	0.007
Norwood	2.2 (1.3–3.6)	0.003	2.3 (1.4–3.8)	0.001
ICU stay† >1 wk	1.8 (0.9–3.4)	0.09	…	…
AVVR pre-Fontan ≥mild	1.7 (1.1–2.7)	0.02	…	…
HLHS	1.6 (1.0–2.5)	0.04	…	…
No fenestration	1.6 (0.8–3.2)	0.15	…	…
CPB time (per 10 min)	1.1 (1.03–1.2)	0.003	1.1 (1.04–1.2)	0.001
Hospital stay† (per day)	1.01 (1.004–1.02)	0.001	…	…
Heterotaxy	0.4 (0.1–1.2)	0.10	…	…
Physiological intervention				
Prolonged pleural drainage	4.5 (2.8–7.5)	< 0.001	4.0 (2.4–6.7)	<0.001
ICU stay† >1 wk	2.4 (1.3–4.5)	0.006	…	…
HLHS	2.2 (1.4–3.7)	0.002	2.0 (1.2–3.3)	0.01
Systemic RV	2.2 (1.2–4.1)	0.009	…	…
Norwood	1.9 (1.1–3.3)	0.02	…	…
AVVR pre-Fontan ≥mild	1.8 (1.1–2.9)	0.03	…	…
Fontan era 3	1.7 (1.0–3.0)	0.047	…	…
CPB time (per 10 min)	1.1 (0.99–1.2)	0.08	…	…
Hospital stay† (per day)	1.01 (1.01–1.02)	0.006	…	…
Heterotaxy	0.6 (0.1–1.5)	0.19	…	…

AVVR indicates atrioventricular valve regurgitation; CI, confidence interval; CPB, cardiopulmonary bypass; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; and RV, right ventricle.

*Cox regression.

†After Fontan operation.

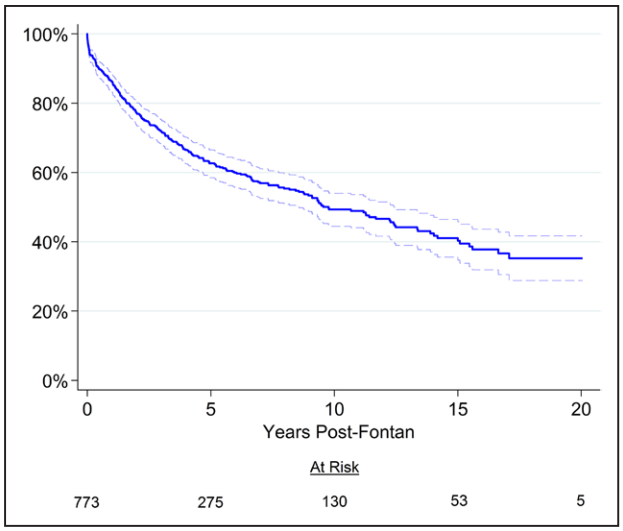

Figure 4. Freedom from any reintervention. Kaplan–Meier freedom from first surgical or catheter-based intervention. Dashed lines represent 95% confidence limits of the survival function.

results in part from an institutional practice change, which occurred during the follow-up period. In the early years of this study, the fenestration was often closed electively 1 to 2 years after Fontan completion, but currently this is undertaken only when indicated because of cyanosis or thromboembolism. Ultimately, the long-term importance of a Fontan fenestration remains unclear. Other recent studies have failed to demonstrate a late effect from fenestration, either positive or negative, although most are limited by an institutional preference toward one strategy.[9,16,17,24] It is interesting that despite the smaller numbers of nonfenestrated patients in this cohort, an increased risk for major surgery was detected. This may lend support to our current strategy, although further study is needed.

Factors associated with first interventional catheterization for anatomic indication included later era of Fontan, history of Norwood operation, and longer cardiopulmonary bypass times. It is logical that patients with longer bypass times are those with more complex anatomy that might predispose to repeat intervention. Likewise, history of Norwood operation identifies a cohort at risk for multiple types of residual lesions, including pulmonary artery stenosis and recurrent arch obstruction. The association of Fontan Era 3 with anatomic catheterization likely reflects a transition in practice over time, such that residual anatomic lesions that were previously addressed surgically can be treated in the catheterization laboratory in the modern era.

Catheter-based intervention for physiological indication was associated with prolonged pleural drainage after Fontan

Table 6. Effect of Reinterventions on Survival With Intact Fontan Circulation

Type of Intervention	Hazard Ratio* (95% CI)	*P* Value
Any Intervention	1.1 (0.7–1.8)	0.67
≥3 interventions	1.5 (0.8–3.0)	0.25
Major intracardiac surgery	1.9 (1.0–3.7)	0.06
Pacemaker	2.6 (1.3–5.2)	0.005
Any nonelective catheter intervention	1.2 (0.7–2.1)	0.40
Anatomic intervention	1.0 (0.5–2.1)	0.92
Physiological intervention	2.1 (1.2–4.0)	0.01

CI indicates confidence interval.

*Univariable Cox regression, hazard ratio for combined end point of death, transplant, or Fontan takedown.

and HLHS. Prolonged pleural drainage has previously been shown to correlate with other markers of suboptimal Fontan physiology such as an increased burden of systemic to pulmonary collaterals,[25] as well as early post-Fontan mortality.[26] It is important to note that the increased need for intervention was specific to patients with HLHS, not simply those with systemic right ventricle. This implies additional risk for the unique anatomy of HLHS—one of the most common diagnoses we encounter in the single ventricle population.

Patients who required a catheterization for suboptimal Fontan physiology had increased likelihood of death or loss of Fontan circulation. It may be that physiological interventions such as collateral embolization are simply markers of overall sicker patients, and it may also be that the success rate is greater when treating discrete anatomic lesions such as PA stenosis versus attempting to correct an entire complex of hemodynamic derangement.

Limitations of this analysis should be recognized and are common to single-center retrospective studies. Although the baseline cohort was relatively large, complete follow-up regarding reinterventions was not available for all patients. It is possible that patients who could not be contacted may be disengaged from medical follow-up and may, thus, have had fewer interventions. We think that the contacted and noncontacted groups are of overall similar acuity, because the rates of death and transplant as ascertained from national databases were the same. This does not completely eliminate the potential for sampling bias, however. The patients lost to follow-up were also more likely to be from the earliest surgical era. These patients were younger at the time of Fontan and more commonly had a lateral tunnel, which might introduce bias. Specific institutional practices such as the tendency to fenestrate the Fontan also affect the studied population. Finally, the unique characteristics of this cohort, including the high prevalence of HLHS and dominant right ventricular morphology, must be considered. These results may not generalize to centers with a different patient population.

Conclusions

The majority of modern Fontan survivors will require some form of surgical or percutaneous reintervention by 20 years after Fontan. The median time to reintervention in this cohort was just <10 years. Pacemaker placement is common, as are catheterization procedures to address residual anatomic and physiological lesions. Need for pacemaker and catheterization for physiological indications were associated with decreased survival with intact Fontan circulation. Patients and their families should be counseled about the likelihood of reintervention, and description of the Fontan operation as the Final procedure should be avoided.

Disclosures

None.

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Surgical and Catheter-Based Reinterventions Are Common in Long-Term Survivors of the Fontan Operation

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SUPPLEMENTAL MATERIAL

Appendix A: 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 & Physiologic Factors
Heterotaxy syndrome
Common AV valve
Degree of Pre-operative AV valve regurgitation
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 (lateral tunnel vs. extracardiac)
Age at Fontan
Weight at Fontan
Presence of fenestration
Use of modified ultrafiltration
Cardiopulmonary bypass time
Cross-clamp time

Peri-operative Factors
Duration of ICU stay
Duration of mechanical ventilation
Duration of pleural drainage
Duration of hospital stay