Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery

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Background—To better define determinants of mortality in patients with univentricular physiology, a database registry was created of patients born in 1985 or earlier with Fontan surgery who were followed up at Children’s Hospital Boston.

Methods and Results—A total of 261 patients, 121 of whom (46.4%) were women, had a first Fontan surgery at a median age of 7.9 years: right atrium–to–pulmonary artery connection in 135 (51.7%); right atrium to right ventricle in 25 (9.6%); and total cavopulmonary connection in 101 (38.7%). Over a median of 12.2 years, 76 (29.1%) died, 5 (1.9%) had cardiac transplantation, 5 (1.9%) had Fontan revision, and 21 (8.0%) had Fontan conversion. Perioperative mortality decreased steadily over time and accounted for 68.4% of all deaths. In early survivors, actuarial freedom from death or transplantation was 93.7%, 89.9%, 87.3%, and 82.6% at 5, 10, 15, and 20 years, respectively, with no significant difference between right atrium to pulmonary artery versus total cavopulmonary connection. Late deaths were classified as sudden in 7 patients (9.2%), thromboembolic in 6 (7.9%), heart failure–related in 5 (6.7%), sepsis in 2 (2.6%), and other in 4 (5.2%). Most sudden deaths were of presumed arrhythmic origin with no identifiable predictor. Independent risk factors for thromboembolic death were lack of antiplatelet or anticoagulant therapy (hazard ratio [HR], 91.6; P = 0.0041) and clinically diagnosed intracardiac thrombus (HR, 22.7; P = 0.0002). Independent predictors of heart failure death were protein-losing enteropathy (HR, 7.1; P = 0.0043), single morphologically right ventricle (HR, 10.5; P = 0.00429), and higher right atrial pressure (HR, 1.3 per 1 mm Hg; P = 0.0016).

Conclusion—In perioperative survivors of Fontan surgery, gradual attrition occurs predominantly from thromboembolic, heart failure–related, and sudden deaths. (Circulation. 2008;117:85-92.)

Key Words: death, sudden ■ Fontan procedure ■ heart failure ■ mortality ■ survival ■ thrombosis
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Clinical Variables and Follow-Up**

The database was supplemented by a detailed retrospective review of medical records, preoperative echocardiographic and cardiac catheterization data, operative notes, and an extensive collection of postoperative clinical variables derived from diagnostic tests, interventions, functional status, long-term complications, and mortality on follow-up. Atrioventricular valve anatomy and systemic ventricular morphology were categorized in accordance with previously defined nomenclature on the basis of findings from preoperative studies and surgical observations. Type of Fontan surgery was classified into the following 4 categories: right atrium (RA)—to—PA anastomosis; RA—to–right ventricle (RV) connection; intraatrial lateral tunnel (LT); and extracardiac conduit (ECC). The latter 2 were considered subtypes of total cavopulmonary connections. In all cases, surgery involved separation of systemic and pulmonary venous return by excluding the systemic venous return from the systemic ventricle, with or without a residual atrial communication, and the baffle fenestration. Fontan fenestration, concomitant arrhythmia ablation, and attendant surgery for associated anomalies were recorded as separate variables.

**Mode of Death**

Original source material was reviewed for all fatalities. Death was considered perioperative if it occurred within 30 days of surgery or before hospital discharge and was subclassified as early (ie, within 30 days) or late (ie, after 30 days but during the same hospitalization). Death was labeled secondary to heart failure if it complicated worsening heart failure, as defined by evidence of at least one of the following: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, renal hypoperfusion (ie, worsening renal function), or radiological signs of congestive heart failure. Sudden death was defined as death occurring within 1 hour of acute symptoms. Death was considered thromboembolic in nature if deemed secondary to thrombus identified either clinically or post-humously within the systemic venous or PA circulation. The site of thromboembolism was further classified into ≥1 of the following locations: RA/Fontan, superior vena cava, inferior vena cava, systemic venous atrium, or PA. Death was attributed to sepsis if preceded by documented bacteremia in the setting of clinical symptoms such as fever, chills, malaise, hypotension, and/or mental status changes. Remaining deaths were classified as “other” and qualified as “unknown” if the cause of death could not be accurately surmised. The diagnosis of protein-losing enteropathy required the following 2 criteria: hypoalbuminemia, or radiological signs of congestive heart failure. Sudden death was classified as death occurring within 1 hour of acute symptoms. Death was considered thromboembolic in nature if deemed secondary to thrombus identified either clinically or post-humously within the systemic venous or PA circulation. The site of thromboembolism was further classified into ≥1 of the following locations: RA/Fontan, superior vena cava, inferior vena cava, systemic venous atrium, or PA. Death was attributed to sepsis if preceded by documented bacteremia in the setting of clinical symptoms such as fever, chills, malaise, hypotension, and/or mental status changes. Remaining deaths were classified as “other” and qualified as “unknown” if the cause of death could not be accurately surmised. The diagnosis of protein-losing enteropathy required the following 2 criteria: hypoalbuminemia (<3.0 mg/dL) for >3 months in the absence of liver or renal disease and accompanying ascites, pleural effusion, edema, diarrhea, or abdominal pain for >3 months.

**Statistical Analysis**

Continuous variables are summarized by mean±SD or median and interquartile range (IQR; 25th to 75th percentiles), depending on normality of distribution. Categorical variables are represented by frequencies and percentages. Baseline comparisons between patients with different types of Fontan were performed by Kruskal-Wallis or χ² tests when appropriate. Predictors of perioperative mortality were explored in univariate and multivariate logistic regression analyses from which odds ratios and 95% confidence intervals were generated. Variables that were significant at the 0.1 level in univariate analyses were included in a stepwise multivariate logistic regression model.

Survival free from transplantation according to type of Fontan was plotted using the Kaplan-Meier method and compared by log-rank statistics in all patients and in the subgroup of perioperative survivors. Time 0 was defined as time of Fontan surgery, after which patient-years were accrued until death or cardiac transplantation. Censoring occurred as separate variables.

**Results**

**Baseline Characteristics**

A total of 261 patients, 121 female (46.4%), had their first Fontan surgery at a median age of 7.9 years (IQR, 1.1 to 17.5 years), 33 (12.6%) of which were fenestrated. Type of first Fontan was as follows: RA-PA connection in 135 (51.7%), RA-RV in 25 (9.6%), LT in 98 (37.5%), and ECC in 3 (1.1%). Twelve of the 25 (48.0%) RA-RV Fontan procedures were valved. Table 1 summarizes baseline characteristics in all patients and by type of Fontan.

**Mode of Death**

Over a median follow-up of 12.2 years (IRQ, 1.1 to 17.5 years), 76 patients (29.1%) died, 5 (1.9%) had cardiac transplantation, and 21 (8.0%) had Fontan conversion to an LT or ECC in 5. Figure 1 provides an overview of the patient population. Overall, 52 deaths (68.4%) were perioperative; 7 (9.2%) were sudden, 6 (7.9%) were thromboembolic, 5 (6.6%) were due to heart failure, 2 (2.6%) were secondary to sepsis, and 4 (5.3%) were classified as “other.” The last category included aortic rupture not qualifying as sudden death in a 17-year-old male patient with an LT Fontan, periprocedural demise in the catheterization laboratory in a 24-year-old woman after fenestration closure of a converted LT Fontan, and 2 deaths of unknown cause.

**Perioperative Mortality**

Of 52 perioperative deaths, 41 (78.9%) were early and 11 (21.1%) were late. All perioperative deaths complicated cardiac surgery: 49 (94.2%) after Fontan palliation and 3 (5.8%) other surgeries. Perioperative Fontan deaths were early in 39 patients (35 initial Fontan, 3 conversion, 1 revision) and late in 10 (9 initial Fontan, 1 revision). The crude perioperative mortality rate for initial Fontan surgery was 16.9% (44 of 261), subcategorized as follows: RA-PA, 27.4% (37 of 135); RA-RV, 0% (0 of 25); LT, 7.1% (7 of 98); and ECC, 0% (0/3). Two of 7 and 3 of 21 patients with Fontan revision and conversion, respectively, died perioperatively. Importantly, perioperative mortality rates decreased steadily over time, from 36.7% (18 of 49) for a first Fontan surgery performed before 1982 to 15.7% (25 of 159) from 1982 to
1989 and 1.9% (1 of 53) in 1990 or later. Independent predictors of perioperative mortality were early surgical era (odds ratio, 3.5 for surgery before 1982; 95% confidence interval, 1.7 to 7.5; \( P \leq 0.0011 \)), hypoplastic left heart syndrome (odds ratio, 15.2; 95% confidence interval, 4.0 to 57.5; \( P \leq 0.0001 \)), and RA-PA connection (odds ratio, 3.9; 95% confidence interval, 1.8 to 8.4; \( P \leq 0.0005 \)).

### Long-Term Survival

Freedom from death or cardiac transplantation according to type of Fontan is depicted in Figure 2. In Fontan survivors, the mean age at last follow-up was 25.1 ± 9.8 years. Considering all patients, actuarial event-free survival rates at 1, 5, 10, 15, and 25 years were 80.1%, 77.7%, 74.4%, 71.8%, 65.0%, and 57.4%, respectively. Univariate and independent predictors of all-cause mortality or cardiac transplantation are summarized in Table 2.

In an intention-to-treat approach that did not censor at the time of Fontan conversion or change the Fontan category, actuarial event-free survival rates at 1, 5, 10, 15, 20, and 25 years were 80.5%, 77.7%, 74.4%, 71.8%, 65.0%, and 57.4%, respectively. Overall freedom from death or cardiac transplantation in early survivors was 97.5%, 95.0%, 91.7%, 88.8%, 82.3%, and 70.7% at 1, 5, 10, 15, 20, and 25 years, respectively. Actuarial freedom from death or transplantation according to type of initial Fontan is depicted in Figure 2C and 2D.

### Predictors of Mortality by Mode of Death

Cumulative hazards according to mode of death are plotted in Figure 3. For sudden death, a steep rise in cumulative hazard

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**Table 1. Baseline Characteristics by Type of First Fontan Surgery**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA-PA (n=135)</th>
<th>RA-RV (n=25)</th>
<th>TCPC (n=101)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Fontan, y</td>
<td>6.6 (3.2–12.2)</td>
<td>11.9 (8.8–16.7)</td>
<td>8.1 (4.8–15.8)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>58 (43.0)</td>
<td>12 (48.0)</td>
<td>51 (50.5)</td>
<td>0.2936</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>39 (28.9)</td>
<td>23 (92.0)</td>
<td>20 (19.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Double-inlet left ventricle</td>
<td>32 (23.7)</td>
<td>0 (0)</td>
<td>25 (24.8)</td>
<td>0.0462</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>8 (5.9)</td>
<td>0 (0)</td>
<td>4 (4.0)</td>
<td>0.1575</td>
</tr>
<tr>
<td>Other</td>
<td>56 (41.5)</td>
<td>2 (8.0)</td>
<td>52 (51.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Morphological left ventricle</td>
<td>89 (65.9)</td>
<td>24 (96.0)</td>
<td>58 (57.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Morphological right ventricle</td>
<td>42 (31.1)</td>
<td>1 (4.0)</td>
<td>36 (35.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right and left ventricle</td>
<td>4 (3.0)</td>
<td>0 (0)</td>
<td>7 (6.9)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

PVR indicates pulmonary vascular resistance; TCPC, total cavopulmonary connection.

Continuous variables are expressed as median (IQR).

*Intergroup comparisons between the 3 types of Fontan.

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**Figure 1.** Overview of the study population.
was noted over the first 5 to 10 years after Fontan surgery. In contrast, the hazard for heart failure–related death was minimal initially and increased progressively after 5 to 10 years. The cumulative hazard for thromboembolic death increased steadily 15 years after Fontan surgery.

Death resulting from thromboembolism occurred at a median age of 24.9 years (IQR, 15.8 to 33.9 years), 8.7 years (IQR, 0.1 to 18.5 years) after Fontan surgery. Actuarial freedom from thromboembolic death was 98.7% at 10 years and 90.8% at 25 years. All patients had RA-PA Fontan surgeries except for 1 patient with an LT. In 2 cases, thromboembolism was limited to PA; clot was identified within the RA/Fontan in the remainder. In 1 patient, thrombolysis with recombinant tissue plasminogen activator was unsuccessful, and a second patient died despite attempted thrombectomy. At the last follow-up visit preceding thromboembolic death or a diagnosis of clinical thromboembolism, 28.5% and 22.1% of perioperative survivors received anticoagulation and antiplatelet therapy, respectively. Predictors of thromboembolic death are listed in Table 3.

Heart failure–related deaths occurred at a mean age of 22.9 ± 7.6 years, 11.9 ± 4.3 years after Fontan surgery. Actuarial freedom from death caused by heart failure was 99.5% at 10 years and 95.8% at 25 years. Univariate and independent predictors are summarized in Table 4.

Sudden death occurred at a median age of 20.2 years (IQR, 11.3 to 25.4 years) in 7 patients—3 with RA-PA, 3 with LT, and 1 with RA-RV Fontan—2.9 years (IQR, 1.8 to 7.0 years) after Fontan surgery. Actuarial freedom from sudden cardiac death was 97.0% at 10 years and 96.3% at 25 years. No
independent predictor was identified. Three had permanent pacemakers, and no patient had a history of ventricular arrhythmia or identified thrombus. However, pulmonary embolism was suspected in a 6-year-old boy with an LT Fontan who consulted his primary caregiver for cough, was prescribed a nebulizer, was discharged, and experienced dyspnea shortly before cardiac arrest. Autopsy was not performed. Two patients with sudden death had previously documented intraatrial reentrant tachycardia. A 13-year-old boy with an RA-PA Fontan and intraatrial reentrant tachycardia on quinidine had DC cardioversion days before sudden death at school, heralded by palpitations, chest discomfort, dizziness, and headache. A second patient with an LT Fontan died suddenly at 32 years, 2 weeks after atrioventricular node ablation for recalcitrant atrial tachyarrhythmia. Additionally, a 36-year-old woman with an RA-RV Fontan survived cardiac arrest caused by documented intraatrial reentrant tachycardia with rapid 1:1 conduction but suffered neurological impairment.

Discussion

Benefits and long-term sequelae associated with Fontan palliation are increasingly appreciated as the first recipients with univentricular physiology enter their fourth decade of follow-up. Fontan physiology has been called paradoxical because systemic venous hypertension is imposed with concomitant PA hypotension.24 This hemodynamic compromise underlies many potential previously described late complications, including arrhythmias, heart failure, thromboemboli, hepatic dysfunction, protein-losing enteropathy, and worsening cyanosis.1 Despite these recognized sources of morbidity, mortality outcomes remain incompletely defined. It was our objective, therefore, to conduct a detailed analysis of actuarial long-term survival, modes of death, and predictors of mortality in patients with diverse forms of Fontan palliation.

Table 2. Predictors of All-Cause Mortality or Transplantation in Perioperative Survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-losing enteropathy</td>
<td>2.2</td>
<td>1.2–4.1</td>
<td>0.0157</td>
</tr>
<tr>
<td>Digoxin therapy</td>
<td>3.7</td>
<td>1.1–12.7</td>
<td>0.0349</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>9.9</td>
<td>3.3–29.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Absence of aspirin or warfarin therapy</td>
<td>3.7</td>
<td>1.8–7.7</td>
<td>0.0005</td>
</tr>
<tr>
<td>PVR on follow-up, wood units</td>
<td>1.5</td>
<td>1.2–1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA pressure on follow-up, mm Hg</td>
<td>1.12</td>
<td>1.05–1.20</td>
<td>0.0007</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7.8</td>
<td>3.0–20.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombus within Fontan</td>
<td>1.7</td>
<td>1.0–2.7</td>
<td>0.0371</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
<td>2.5</td>
<td>1.1–5.3</td>
<td>0.0217</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>10.1</td>
<td>1.0–98.3</td>
<td>0.0472</td>
</tr>
<tr>
<td>RA pressure on follow-up, mm Hg</td>
<td>1.20</td>
<td>1.07–1.36</td>
<td>0.0023</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>8.7</td>
<td>1.9–40.7</td>
<td>0.0058</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PVR, pulmonary vascular resistance.

Table 3. Predictors of Thromboembolic Death in Perioperative Survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>5.4</td>
<td>1.0–29.4</td>
<td>0.0529</td>
</tr>
<tr>
<td>Lack of aspirin or warfarin therapy</td>
<td>5.7</td>
<td>1.0–32.3</td>
<td>0.0515</td>
</tr>
<tr>
<td>RA pressure on follow-up, mm Hg</td>
<td>1.26</td>
<td>1.03–1.53</td>
<td>0.0247</td>
</tr>
<tr>
<td>Thrombus within Fontan</td>
<td>4.9</td>
<td>2.1–11.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Thrombus within Fontan</td>
<td>22.7</td>
<td>4.3–120.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lack of aspirin or warfarin therapy</td>
<td>91.6</td>
<td>4.2–2004.8</td>
<td>0.0041</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

Table 4. Predictors of Heart Failure Death in Perioperative Survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-losing enteropathy</td>
<td>10.1</td>
<td>2.7–38.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>Systemic right ventricle</td>
<td>13.9</td>
<td>1.5–124.8</td>
<td>0.0188</td>
</tr>
<tr>
<td>RA pressure on follow-up, mm Hg</td>
<td>1.18</td>
<td>1.03–1.36</td>
<td>0.0173</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>9.1</td>
<td>1.0–81.4</td>
<td>0.0493</td>
</tr>
<tr>
<td>Thrombus within Fontan</td>
<td>2.8</td>
<td>1.1–7.5</td>
<td>0.0379</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>8.4</td>
<td>0.9–76.0</td>
<td>0.0575</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
<td>7.1</td>
<td>1.9–27.2</td>
<td>0.0043</td>
</tr>
<tr>
<td>Single right ventricle</td>
<td>10.5</td>
<td>1.1–100.4</td>
<td>0.0429</td>
</tr>
<tr>
<td>RA pressure on follow-up, mm Hg</td>
<td>1.30</td>
<td>1.05–1.62</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
To provide data relevant to the adult with Fontan palliation, inclusion criteria were limited to birth before 1985. Considering that many such patients had surgery in an earlier era, it is perhaps not surprising that perioperative mortality was the leading cause of death. Encouragingly, surgical mortality rates decreased steadily over time, with deaths in 1990 or later limited to 1 of 53 initial Fontan procedures. These results are consistent with our broader experience with the first 500 Fontan surgeries at Children’s Hospital Boston and perioperative mortality rates reported by other high-volume centers.\textsuperscript{5,6,25} In addition to early surgical era, we and others noted higher perioperative mortality rates in hypoplastic left heart syndrome.\textsuperscript{8,26,27} In a crude analysis, Ono et al\textsuperscript{13} similarly found significantly higher mortality with RA-PA versus total cavopulmonary connection. Although our multivariate analyses controlled for date of surgery and Fontan fenestration, relevant surgical variables not considered include cardiopulmonary bypass time, aortic cross-clamping, and modified ultrafiltration.\textsuperscript{5,8,28,29}

Including patients who died perioperatively, 75% actuarial freedom from death or transplantation was noted at 10 years, comparable to prior reports of 69% at 9 years,\textsuperscript{11} 71% at 10 years,\textsuperscript{17} 70% at 10 years in patients with tricuspid atresia,\textsuperscript{9} and 75% at 10 years in those with RA-PA connections.\textsuperscript{13} Our observed 68% transplantation-free survival at 20 years is consistent with the 60% reported in 137 patients with tricuspid atresia.\textsuperscript{9} We further extended results to 25 years, with 54% actuarial transplantation-free survival.

In perioperative survivors, 90% freedom from all-cause death or transplantation was observed at 10 years, 83% at 20 years, and 70% at 25 years. Of the independent risk factors for mortality or transplantation, diuretic therapy is likely a surrogate marker for heart failure, as evidenced by strong correlations with digoxin ($p=0.57$, $P<0.0001$) and angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist ($p=0.56$, $P<0.0001$) therapy. Protein-losing enteropathy is a recognized marker of poor outcome.\textsuperscript{23,30} Precedingly identified risk factors for protein-losing enteropathy include longer cardiopulmonary bypass time and morphological RV anatomy.\textsuperscript{23} With generalized edema, the 5-year survival rate approximates 50%.\textsuperscript{30} In support of our finding of higher risk associated with hypoplastic left heart syndrome, some\textsuperscript{7,27,31,32} but not all\textsuperscript{8} studies have noted increased late mortality with single RV morphology. Cetta et al\textsuperscript{48} similarly reported higher mortality in patients with elevated postoperative RA pressure and those on daily diuretics.

We further scrutinized the distribution of mode of death, analyzed time-dependent patterns, and assessed risk factors for each subtype. In perioperative survivors, the 3 most common modes of death were thromboembolic, heart failure–related, and sudden. Thromboembolic complications are a well-recognized source of morbidity,\textsuperscript{25–27} and asymptomatic pulmonary emboli frequently are found.\textsuperscript{36} Multiple clotting factor abnormalities have been reported, including decreased levels of protein C, protein S, and antithrombin III.\textsuperscript{37} Increased platelet reactivity also has been recognized.\textsuperscript{38} Nevertheless, thromboemboli have not previously been linked to mortality in patients with Fontan surgery. We found a sharp increase in risk for thromboembolic death 15 years after Fontan surgery, with 90.8% actuarial event-free survival at 25 years. The presence of recognized clot independently predicted this outcome.

Clinically, the literature is fraught with controversy around prophylactic antiplatelet and/or anticoagulation therapy,\textsuperscript{1} with some retrospective reviews supporting antiplatelet therapy,\textsuperscript{39} others suggesting that anticoagulants are more effective,\textsuperscript{34,40} and still others discouraging routine anticoagulation.\textsuperscript{41} We found the absence of aspirin or warfarin therapy to be a powerful independent predictor of mortality from thromboembolism. Our own institutional practice, initiated in 1990, was to administer antiplatelet therapy before discharge after Fontan surgery, with the duration at the treating physician’s discretion. No formal departmental policy was implemented for anticoagulation therapy, although standard indications were generally respected.

Interestingly, independent risk factors for death caused by heart failure were similar to predictors of all-cause mortality or transplantation: protein-losing enteropathy, increased RA pressure on follow-up, and single RV morphology. Although no comparable studies on long-term mortality are available, a prior report noted lower peak oxygen uptake consumption on exercise testing in patients with RV morphology.\textsuperscript{42} We found risk of death from heart failure to be minimal the first 10 years, with 99.5% actuarial event-free survival. The incidence increased thereafter, with 95.8% freedom from heart failure mortality at 25 years.

The incidence of sudden death in patients with Fontan surgery had not previously been defined.\textsuperscript{43} Here, we report a small but steady decline in freedom from sudden death, with actuarial event-free survival of 96.3% at 25 years. This corresponds to an average annualized incidence of 0.15%, which is similar to reported rates in tetralogy of Fallot and aortic coarctation but lower than complete transposition of the great arteries with an atrial level repair and aortic stenosis.\textsuperscript{43} Although the cause of sudden death is likely multifactorial, arrhythmias clearly are responsible for a subset of events as evidenced by documented intra-atrial reentrant tachycardia with rapid 1:1 conduction, leading to cardiac arrest. Atrial tachyarrhythmias are highly prevalent, dependent on type of surgery, and are associated with substantial morbidity.\textsuperscript{44}

**Study Limitations**

To maximize the accuracy of outcome ascertainment and comprehensiveness of the data set, the study population was deliberately limited to patients operated on and followed up at Children’s Hospital Boston. This resulted in the inclusion of <50% of patients having undergone Fontan surgery at our institution. The observed actuarial 10-year survival of 74.8%, however, is comparable to 71.4% in the first 500 consecutive patients,\textsuperscript{17} suggesting that the study population is reasonably representative of the target population with respect to overall mortality. Definitions for each mode of death were elaborated and applied to the entire cohort for uniformity of classification. Nevertheless, mode of death could not be reliably classified for 2 of 76 events (2.6%). Finally, few patients had ECCs, limiting the interpretation of mortality rates for this specific Fontan subtype.
Conclusions
In this large single-center cohort of patients with various forms of Fontan surgery, the leading cause of death was perioperative, particularly in an earlier era. Gradual attrition was noted thereafter, predominantly from thromboembolic, heart failure–related, and sudden deaths, with 70% actuarial freedom from all-cause death or cardiac transplantation at 25 years. Risk of death from thromboembolism increased 15 years after Fontan surgery and was predicted by clinically identified thrombus and lack of aspirin or warfarin therapy. Heart failure–related mortality was minimal the first 10 years. Independent risk factors were single RV morphology, higher postoperative RA pressure, and protein-losing enteropathy. The incidence of sudden death was 0.15% per year, with most events of presumed arrhythmic origin.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

The univentricular heart encompasses a spectrum of rare congenital cardiac defects often ultimately managed by a Fontan procedure, which diverts systemic venous return to the pulmonary artery. As patients survive into adulthood, it is increasingly pertinent to define modes and predictors of death. In a database registry of patients born in 1985 or earlier with Fontan surgery and follow-up at Children’s Hospital Boston, 261 patients were followed up for 12.2 years; of them, 76 (29.1%) died, 5 (1.9%) received transplants, 5 (1.9%) had Fontan revision, and 21 (8.0%) had Fontan conversion. Not unexpectedly, perioperative mortality decreased steadily over time and accounted for 68.4% of all deaths. Gradual attrition was noted thereafter, predominantly from thromboembolic, heart failure–related, and sudden deaths. In perioperative survivors, 90% freedom from all-cause death or transplantation was observed at 10 years, 83% at 20 years, and 70% at 25 years. Risk of death from thromboembolism increased 15 years after Fontan surgery and was predicted by clinically identified thrombus and lack of aspirin or warfarin therapy. Heart failure mortality was minimal the first 10 years. Independent risk factors were single right ventricular morphology, higher postoperative right atrial pressure, and protein-losing enteropathy. The incidence of sudden death was 0.15% per year, with most events of presumed arrhythmic origin. Therefore, this analysis extends our knowledge of long-term outcomes in the first adult cohort of patients with Fontan surgery by elucidating modes of death, time-dependent patterns, and risk factors for each subtype.
Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery
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