Outcome of Listing for Cardiac Transplantation for Failed Fontan
A Multi-Institutional Study

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Background—The Fontan procedure is a successful palliation for children with single-ventricle physiology; however, many will eventually require heart transplantation. The purpose of this study was to determine risk factors for death awaiting transplantation and to examine results after transplantation in Fontan patients.

Methods and Results—A retrospective, multi-institutional review was performed of 97 Fontan patients <18 years of age listed at 17 Pediatric Heart Transplant Study centers from 1993 to 2001. Mean age at listing was 9.7 years (0.5 to 17.9 years); 25% were <4 years old; 53% were United Network for Organ Sharing status 1; 18% required ventilator support. Pretransplantation survival was 78% at 6 months and 74% at 12 months and was similar to 243 children with other congenital heart disease (CHD) and 747 children without congenital heart disease (No-CHD), who were also awaiting transplantation. Patients who were younger, status 1, had shorter interval since Fontan, or were on a ventilator were more likely to die while waiting. At 6 months, the probability of receiving a transplant was similar for status 1 and 2 (65% versus 68%); however, the probability of death was higher for status 1 (22% versus 5%). Seventy patients underwent transplantation. Survival was 76% at 1 year, 70% at 3 years, and 68% at 5 years, slightly less than CHD and No-CHD patients. Causes of death included infection (30%), graft failure (17%), rejection (13%), sudden death (13%), and graft coronary artery disease (9%). Protein-losing enteropathy (present in 34 patients) resolved in all who survived 30 days after transplantation.

Conclusions—Heart transplantation is an effective therapy for pediatric patients with a failed Fontan. Although early posttransplantation survival is slightly lower than other patients with CHD, long-term results are encouraging, and protein-losing enteropathy can be expected to resolve.

Key Words: heart transplantation ▪ heart failure, congestive ▪ cardiomyopathies ▪ protein-losing enteropathies ▪ heart defects, congenital

The Fontan procedure was developed in the early 1970s as the first successful palliation for children with tricuspid atresia and other forms of single-ventricle physiology1,2 and has undergone several revisions over the intervening three decades.3–6 However, despite these efforts, a significant number of patients with single-ventricle physiology, particularly those with systemic right ventricles, have late hemodynamic complications, including ventricular failure, atrioventricular valve regurgitation, atrial arrhythmias, pleural and pericardial effusions, and protein-losing enteropathy.7–12 For many of these patients, transplantation has become the next surgical “stage.” As increasing numbers of patients with complex single-ventricle physiology are palliated, the number of children and young adults requiring late secondary heart transplantation will increase. Additionally, for younger patients with early postoperative failure of their Fontan circuit, cardiac transplantation has been regarded as a rescue therapy.

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It is currently not known whether Fontan patients represent a unique risk group before or after heart transplantation. Data on the success of heart transplantation will be important in making decisions about transplantation candidacy for these patients. Previous series have been limited to small numbers of patients and have reported significantly higher risks compared with patients with cardiomyopathies.7,13–15 The
null
### Results

**Patient Characteristics**

Of the 97 Fontan patients in the study group, the mean age at listing was 9.7 ± 5.6 years (range, 0.5 to 17.9 years); 36% of patients were <6 years old, 19% between 6 and 12 years, and 43% between 12 and 18 years. The mean interval from the Fontan procedure to listing was 4.9 ± 4.4 years (range, 0 to 15 years); 22% were less than 6 months after Fontan, 31% were less than 1 year, 26% were between 1 and 6 years, and 40% were more than 6 years after Fontan. Fifty (53%) patients were classified as United Network for Organ Sharing (UNOS) status 1 at listing, and 17 (18%) patients required ventilatory support. The listing characteristics for the 743 patients without congenital heart disease (No-CHD) and for the 243 children with congenital heart disease (CHD) are also provided in Table 1. Fontan patients were slightly older than patients in the other two groups and were more likely to be male. Patients in the No-CHD group were more likely to be listed as status 1 and to be on ventilatory support at the time of listing (Table 1). Both Fontan patients and patients with CHD were more likely to have an elevated PRA (panel-reactive antibody) compared with non-CHD patients; 16.5% of Fontan patients and 12.8% of CHD patients had a pretransplantation PRA >20%, compared with only 2.3% of No-CHD patients (P < 0.0001 for Fontan or CHD versus No-CHD by χ² analysis).

### Actuarial Survival Before Transplantation

In the Fontan group, 15 patients died before transplantation, 10 were still awaiting transplantation, and 2 were removed from the list as too well. Actuarial survival was 90% at 1 month, 78% at 6 months, 74% at 12 months, and 71% at 24 months (Figure 1A). The major causes of death before transplantation are shown in Table 2. The majority of deaths before transplantation occurred during the first 6 months after listing, as demonstrated by the early phase characteristic of the hazard function (Figure 1A). Actuarial survival while awaiting transplantation was not different from the 747 children without congenital heart disease (No-CHD, Figure 1B) or from the 243 children >1 year of age with previous open heart surgery (CHD, Figure 1B).

### Risk Factors for Death Before Transplantation

By univariate analysis, patients who at listing were <4 years of age (P = 0.01), status 1 (P = 0.002), had shorter interval since Fontan (P = 0.0007), or were on a ventilator (P < 0.001) were more likely to die while waiting. These risk factors tended to correlate (for example, patients who were younger also tended to be those with a shorter interval since Fontan as well as status 1), so that the multivariable analysis was only able to identify one risk factor and statistically could not identify an additional risk factor. The small sample size also prevented the identification of multiple risk factors.

Of the 17 patients on a ventilator at listing, 41% died, compared with only 10% who were not ventilator dependent (P < 0.0001, Figure 2A). Age at listing was also a risk, greatest for patients younger than 4 years at listing (P < 0.009, Figure 2B). Of those patients who were UNOS status 1, 22% died while waiting, compared with 7% of those who were status 2 (Figure 2C). Of the 15 Fontan patients who died on the waiting list before transplantation, 11 were initially listed as status 1. Of these, 6 remained status 1 at the time of death, 1 patient was “on hold,” and data were unavailable in 4. Of the patients who were initially listed as status 2, none were upgraded to status 1 at the time of death. In comparison, for CHD patients, 50% of those initially listed as status 2 were upgraded to status 1, and for No-CHD patients, 53% were upgraded to status 1 at the time of death.

The time interval from Fontan procedure to listing also correlated with survival on the waiting list. Of those patients who were <6 months from their Fontan procedure, 33% died while waiting, compared with 11% of those >6 months after Fontan (P = 0.0007, Figure 2D).

By competing outcomes analysis, the probability at 12 months of a Fontan patient receiving a transplant was 69%, whereas that of dying while waiting was 16%. Another 16% of patients were still waiting at study closure, and 2% had been removed from the list because they had improved clinically. Comparing status 1 (Figure 3A) and status 2 (Figure 3B) patients, the probability at 6 months of receiving

<table>
<thead>
<tr>
<th>TABLE 2. Causes of Death Before Transplantation</th>
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<tbody>
<tr>
<td>Fontan Patients (n=15)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Sudden death</td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Infection</td>
</tr>
<tr>
<td>Multiorgan failure</td>
</tr>
<tr>
<td>Neurological</td>
</tr>
<tr>
<td>Pulmonary embolus/hypertension</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

Values are given as number (percentage).
a transplant was 68% for status 2 versus 65% for status 1, whereas the probability of death while waiting at 6 months was 5% for status 2 versus 22% for status 1.

**Results of Transplantation**

Seventy Fontan patients underwent transplantation during the study period. The mean age at transplantation was 10.7 ± 5.4 years. Nineteen (27%) of these patients were ≤6 years old at transplantation. The mean interval from Fontan to transplantation was 5.7 ± 4.4 years (range, 0.02 to 15.6 years).

For Fontan patients, actuarial survival after transplantation was 80% at 6 months, 77% at 1 year, 73% at 3 years, and 67% at 5 years (Figure 4). Survival at 1 year after transplantation was 8% less than in CHD patients, although this difference was not statistically significant. However, the numbers of fatalities was small in both groups, so that this study was not powered to directly make this comparison. Survival at 1 year was 14% lower than in No-CHD patients, and overall survival was significantly lower compared with that group (P=0.0004). However, after the first year after transplantation, survival curves of the Fontan and No-CHD patients are similar, suggesting that the highest risk for these patients is in the early posttransplantation period. There was no difference in survival after transplantation between patients listed as status 1 versus status 2 (Figure 5). There were 23 deaths in Fontan patients, representing 33% of patients given transplantation. Leading causes of death were infection (30%), early graft failure (17%), rejection (13%), sudden death (13%), acute hemorrhage/technical/operative (9%), and graft coronary artery disease (9%). There were no significant differences between Fontan patients and the two other groups in cause of death after transplantation (Table 3), although there were trends in the Fontan group toward a higher rate of early graft failure (17% in Fontan, 11% in CHD, 8% in No-CHD), infections (30% in Fontan, 21% in CHD, 13% in No-CHD), and acute hemorrhage/operative complications (9% in Fontan, 2% in CHD, 1% in No-CHD), although none of these reached statistical significance.

**Protein-Losing Enteropathy**

Protein-losing enteropathy (PLE) was present in 34 (37%) patients at the time of listing. Other pretransplantation complications included intracardiac thrombi (19%), pe-
ripheral edema (60%), and arrhythmia (57%). Five patients (6%) had all four complications. The presence of PLE did not influence outcome after listing for transplantation: Of patients with PLE, 73% were given transplantation and 21% died while waiting, compared with 73% and 12%, respectively, in patients without PLE. The presence of PLE also did not influence survival after transplantation (Figure 6). Of the 25 patients with PLE before transplantation who underwent transplantation, 19 survived >30 days after transplantation, and, for these patients, PLE resolved in 100%. The remaining 6 patients died <30 days after transplantation, too early to determine whether their PLE would have eventually resolved. An additional 4 patients died late after transplantation. In patients with PLE, the causes of death before transplantation included 3 cases of cardiac failure (43%) and single cases (14%) of sudden death, infection, respiratory failure, and other/unknown. Causes of death after transplantation included 3 cases of acute rejection (30%), 2 cases each (20%) of infection, early graft failure, and hemorrhage, and 1 case of sudden death (10%). The incidence of these complications was not different from that of Fontan patients as a whole, although there was a nonsignificant trend toward an increased incidence of acute rejection in the PLE group.

Discussion

The purpose of this study was to determine whether patients with a failed Fontan operation represent acceptable candidates for heart transplantation. The issue of transplantation after the Fontan procedure is one of growing importance, with an increasing number of patients with single-ventricle physiology surviving into adolescence and young adulthood. Data obtained from the 17 centers participating in the PHTS were used to provide an in-depth analysis that no single center could have provided. Our data demonstrate that Fontan patients represent acceptable candidates for listing for transplantation. Their actuarial survival while awaiting transplantation is not different from pediatric patients without CHD or those with other forms of CHD who have had at least one previous surgical procedure.

Although our results are encouraging for Fontan patients being considered for transplantation, there are certain patients who are at increased risk of dying while awaiting transplantation. Younger patients were found to be at higher risk, similar to previous findings in patients with
complex CHD who had not had the Fontan operation. This higher-risk group also consisted of patients who were <6 months from their Fontan procedure, ventilator dependent, or listed as UNOS status 1. Hazard function and competing outcomes analysis suggests that most Fontan patients who die while waiting will do so within the first 6 months after listing. Fontan patients who deteriorate to the point of requiring status 1 listing are more than twice as likely to die in the first 6 months as those listed as status 2 (22% versus 5%). This emphasizes the importance of early referral for transplantation before the onset of marked clinical deterioration. Although approximately 50% of patients with CHD or No-CHD were upgraded from status 2 to status 1 at the time of death before transplantation, this was not the case for Fontan patients. This difference may be a reflection of the criteria for listing as status 1 (driven predominantly by inotropic drug requirements). We speculate that patients with failing Fontan may have preterminal complications (worsening effusions, protein loss, or infections) that may be less amenable to treatment with high-dose inotropes, therefore making these patients ineligible for status 1 listing.

The high risk of death for younger patients, particularly those <6 months after Fontan surgery, suggests that these patients may be less than ideal candidates for heart transplantation. Our database does not provide insight into whether these patients had factors that made them “high risk” candidates for the Fontan operation in the first place. However, the presence of younger patients (especially those <1 year old) in this high-risk group suggests that many were higher-risk Fontan candidates. Some have suggested that transplantation can be used as rescue therapy for patients who fail the Fontan procedure. Our data suggest that this is not a viable strategy for younger patients who are early Fontan failures. Our study did not include patients with failed Fontan who had their Fontan circuits taken down before transplantation. It remains to be determined whether this strategy is preferable for this high-risk group of patients. Other patients with single-ventricle physiology may be better candidates for transplantation instead of Fontan surgery. In contrast to the younger patient group, heart transplantation remains an acceptable option for older children and adolescents who are late Fontan failures.

Our study also demonstrates that Fontan patients, once given transplantation, have a very good chance of short- and medium-term survival. Their actuarial survival at 1 year is 75%, which is 8% lower than that of patients with other CHD and 14% lower than patients without CHD. Although the difference between Fontan patients and those

### Table 3. Causes of Death After Transplantation

<table>
<thead>
<tr>
<th></th>
<th>Fontan Patients (n=23)</th>
<th>Congenital Heart Disease (n=47)</th>
<th>Non-Congenital Heart Disease (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>3 (13)</td>
<td>6 (13)</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Early graft failure</td>
<td>4 (17)</td>
<td>5 (11)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (30)</td>
<td>10 (21)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Graft CAD</td>
<td>2 (9)</td>
<td>0</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3 (13)</td>
<td>10 (21)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Hemorrhage/technical/operative</td>
<td>2 (9)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tumor</td>
<td>0</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Neurological</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Multisystem failure</td>
<td>0</td>
<td>4 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Nonspecific graft dysfunction</td>
<td>0</td>
<td>4 (9)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>1 (2)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (4)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

Values are given as number (percentage). None are significant. Early graft failure, P=0.23; infection, P=0.09; rejection, P=0.7.
with other CHD did not reach statistical significance, the numbers of fatalities was small in both groups, so that our study was not sufficiently powered to directly make this comparison. The increased risk early after transplantation in patients with CHD versus cardiomyopathy has been previously described.\textsuperscript{18} This increased risk in Fontan patients is predominantly in the early period after transplantation; longer-term survival appears to be similar to cardiomyopathy and CHD patients, although the numbers of patients followed >5 years is smaller, and thus a longer-term study will be required to assess late complications more accurately.

The causes of death in Fontan patients are not significantly different from those in other transplant recipients, although there are several trends that are worth discussion. The first is a trend toward increased risk of death from infection (30% versus 21% in CHD patients and 13% in No-CHD patients). We speculate that Fontan patients may be more susceptible to infection secondary to malnutrition and PLE. Further study of these patients will be required to elucidate the mechanisms of this altered risk profile and could lead to altered immunosuppressive regimens in the early period after transplantation. There was also a trend toward increased early graft failure in the Fontan patients; however, this was not attributable to an increased incidence of preformed antibodies, because both Fontan and CHD patients were equally likely to have an elevated PRA before transplantation. Finally, there was also a trend toward increased hemorrhage/technical-operative deaths in the Fontan group. It must be emphasized, however, that none of these risks reached statistical significance in our large series of patients.

Previous studies have shown significantly higher risks for Fontan patients undergoing transplantation. Michielon et al\textsuperscript{13} found a high risk of postoperative hemorrhage in a series of 6 patients and a long-term survival of only 33%. Petko et al\textsuperscript{7} reported results in 9 patients, ranging from 6 months to 20 years after Fontan, with a perioperative mortality rate of 44%. Carey et al\textsuperscript{14} described 9 patients (4 adults and 5 children), 6 months to 12 years after Fontan and reported a risk of perioperative hemorrhage and a perioperative survival of only 66%. However, not all previous studies have been discouraging. Gamba et al\textsuperscript{15} reported on 14 patients with an 86% perioperative and 71% 5-year survival. However, none of these previous studies were large enough to adequately assess the risks before and after transplantation in this population, supporting the importance of large, multicenter studies for evaluation of risk factors in pediatric transplantation populations.

Finally, refractory PLE represents one of the indications for transplantation in Fontan patients.\textsuperscript{19,20} Although PLE usually occurs in the setting of additional hemodynamic abnormalities, it can occur without ventricular dysfunction. There have been previous case reports suggesting that PLE resolves after transplantation.\textsuperscript{15,19} Our data show that 100% of patients with PLE who survive sufficiently long (30 days) after transplantation will improve. Furthermore, our data do not indicate an increased risk of death, either before or after transplantation, in patients with PLE.

An important caveat is that our results may not be applicable to older adults with failed Fontan physiology. Adults with long-standing single-ventricle physiology may have additional comorbidities such as hepatic cirrhosis and chronic malnutrition, which could substantially increase the risk of transplantation. Although a separate study of adult patients is clearly warranted, our data suggest that early referral of patients with a failed Fontan, before the development of irreversible end-organ damage or the necessity for ventilator support or listing at status 1, is the best strategy for successful bridging to transplantation.

In conclusion, heart transplantation is an effective therapy for children and adolescents with a failed Fontan. Survival while waiting for transplantation and medium-term results after transplantation compare favorably with pediatric transplantation patients with other forms of CHD. In this large, multicenter series, there was a slight increase in early mortality rate after transplantation compared with other CHD patients, but the 1-year survival of 76% is far from the extremely high mortality rate reported previously in small single-center series. Protein-losing enteropathy, one of the major reasons for referral of Fontan patients for transplantation, can be expected to resolve in those patients surviving beyond the first month after transplantation. The high risk of death while waiting in younger patients, those ventilated or listed as status 1, and those <6 months after Fontan suggests that better strategies need to be developed to determine which patients may be at risk for early Fontan failure, as these patients are not easily rescued by transplantation.

Disclosures
None.

References
CLINICAL PERSPECTIVE

The Fontan procedure is a successful palliation for children with single-ventricle physiology; however, a significant number of these patients have late complications, including ventricular failure and protein-losing enteropathy. As increasing numbers of patients with complex single-ventricle physiology are palliated, the number of children and young adults requiring late secondary heart transplantation will increase. This study represents the first large, multi-institutional evaluation of the results of listing for transplantation in children and adolescents after a Fontan procedure. Ninety-seven patients under 18 years of age were evaluated retrospectively. Pretransplantation survival rate was 78% at 6 months and 74% at 12 months and was similar to children with other congenital heart disease and to those without congenital heart disease also awaiting transplantation. Patients who were younger, United Network for Organ Sharing status 1, had shorter interval since Fontan, or were on a ventilator were more likely to die while waiting. Seventy patients underwent transplantation, with survival of 76% at 1 year and 68% at 5 years. Protein-losing enteropathy (present in 34 patients) resolved in all who survived >30 days after transplantation. Thus, heart transplantation is an effective therapy for children and adolescents with a failed Fontan. The 1-year survival is slightly lower than for patients without congenital heart disease but is considerably better than the high mortality rate reported previously in small, single-center series. Protein-losing enteropathy, one of the major reasons for referral of Fontan patients for transplantation, can be expected to resolve in those patients surviving beyond the first month after transplantation.
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