SURGERY FOR CONGENITAL HEART DISEASE

FONTAN OPERATION IN FIVE HUNDRED CONSECUTIVE PATIENTS: FACTORS INFLUENCING EARLY AND LATE OUTCOME

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Objectives: The purpose of this study was to review a large, evolving, single-center experience with the Fontan operation and to determine risk factors influencing early and late outcome. **Methods:** The first 500 patients undergoing modifications of the Fontan operation at our institution were identified. Perioperative variables were recorded and a cross-sectional review of survivors was undertaken. **Results:** The incidence of early failure decreased from 27.1% in the first quartile of the experience to 7.5% in the last quartile. In a multivariate model, the following variables were associated with an increased probability of early failure: a mean preoperative pulmonary artery pressure of 19 mm Hg or more ($p < 0.001$), younger age at operation ($p = 0.001$), heterotaxy syndrome ($p = 0.03$), a right-sided tricuspid valve as the only systemic atrioventricular valve ($p = 0.001$), pulmonary artery distortion ($p = 0.04$), an atriopulmonary connection originating at the right atrial body or appendage ($p = 0.001$), the absence of a baffle fenestration ($p = 0.002$), and longer cardiopulmonary bypass time ($p = 0.001$). An increased probability of late failure was associated with the presence of a pacemaker before the Fontan operation ($p < 0.001$). A morphologically left ventricle with normally related great arteries or a single right ventricle (excluding heterotaxy syndrome and hypoplastic left heart syndrome) were associated with a decreased probability of late failure ($p = 0.003$). **Conclusions:** These analyses indicate that early failure has declined over the study period and that this decline is related in part to procedural modifications. A continuing late hazard phase is associated with few patient-related variables and does not appear related to procedural variables. (J Thorac Cardiovasc Surg 1997;114:376-91)

Since the first report of a total atriopulmonary shunt by Fontan and Baudet¹ in 1971, advances in operative technique and postoperative management²⁻⁵ have been accompanied by an improvement in early survival from 75% to 83% in the 1970s⁶⁻⁸ to over 90% in the current era.^{6,9,10} Operative mor-

tality has decreased despite application of the operation to patients with complex forms of single ventricle and to those with hemodynamic or other parameters previously considered to carry higher risk.¹¹ As more patients survive the operation and the duration of follow-up increases, physicians are

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becoming increasingly aware of a continued risk of late failure of the Fontan circulation. Two large series have provided important information about overall and late outcome,^{12,13} but these analyses have included limited numbers of patients who have had a Fontan circulation created by means of more recent technical modifications, or they have included calendar year of operation in the analysis. This variable is highly correlated with modifications in selection criteria, surgical technique, and postoperative management. Its inclusion in multivariate models may therefore mask the influence of other factors on outcome. In addition, interventional catheter techniques were not commonly used in either of these two series.

The purpose of this study was to review a large, single-center experience that has evolved over nearly two decades and to determine the patient- and procedure-related risk factors influencing early and late outcome after the Fontan procedure.

Methods

Patient population. The first consecutive 500 patients who underwent various modifications of the Fontan procedure at Children's Hospital, Boston, between April 1973 and July 1991 were identified from the databases of the Departments of Cardiac Surgery and Cardiology. Patients with an interrupted inferior vena cava and azygos extension to a superior vena cava who underwent a bidirectional cavopulmonary shunt but in whom hepatic venous blood flowed to the systemic ventricle were excluded. Also excluded were patients who had undergone only a superior vena cava-pulmonary anastomosis (bidirectional or unidirectional cavopulmonary shunt).

Perioperative data acquisition. Medical records, preoperative echocardiographic and cardiac catheterization data, and operative notes were reviewed for the perioperative data outlined in Appendix A.

Patient-related variables. Atrioventricular valve anatomy and systemic ventricular morphology were classified on the basis of findings from the preoperative cardiac catheterization and echocardiogram, as well as from operative findings. Discrepancies were settled by consensus of the authors. Previously defined diagnostic categories^{10,11} were further combined to yield six groups (Appendix A). Pulmonary artery distortion was recorded when a review of the radiologic and cardiac catheterization studies combined with the recorded operative findings demonstrated significant stenoses or distortions in the central pulmonary arteries or markedly hypoplastic central or peripheral pulmonary arteries. A quantitative measure of central pulmonary artery size was not used. Quantitative data could not be obtained in a number of patients because of the retrospective nature of the study. Many older angiograms or those performed at other institutions lacked a calibration standard or an angiogram of the descending aorta. Therefore only a qualitative

judgment about pulmonary artery size and architecture was possible.

Atrioventricular valve regurgitation was judged as absent, mild, moderate, or severe from preoperative angiograms or from echocardiograms when angiographic information was not available ($n = 31$). Pulmonary and systemic blood flow were calculated according to the Fick method. Pulmonary vascular resistance was calculated from the mean pulmonary artery pressure, the pulmonary venous atrial pressure, and pulmonary blood flow. A pulmonary venous wedge pressure was taken as the pulmonary artery pressure if the pulmonary artery was not entered. The pulmonary artery oxygen saturation was assumed to be equal to the aortic oxygen saturation if there was only one source of pulmonary blood flow and there was complete mixing at ventricular level. An index of ventricular work, $([Qp + Qs] \times \text{mean age-adjusted aortic pressure})$, where Qp and Qs are pulmonary and systemic blood flow indexed to body surface area, was calculated, as was an index of "total resistance to pulmonary blood flow" (adapted from that described by Mair and colleagues⁷ from the Mayo Clinic). This variable incorporates a measure of systemic ventricular compliance and of pulmonary vascular resistance; it is calculated as $(LAp/[Qp + Qs]) + ([PAp - LAp]/Qp)$, where LAp and PAp are mean left atrial and pulmonary artery pressures.

Procedure-related variables. A number of variables concerning the technique of operation were recorded (Appendix A). The various modifications of the Fontan operation were classified into three groups depending on the type of atriopulmonary connection: (1) conduit if an atriopulmonary or atrioventricular conduit had been used, (2) direct atriopulmonary anastomosis, and (3) total cavopulmonary anastomosis with an intracardiac lateral tunnel. In all cases, the operation involved separation of the systemic and pulmonary venous return by excluding the systemic venous return from the systemic ventricle; later in the series a residual atrial communication or baffle fenestration was often created with the intention of undertaking transcatheter closure after the operation.¹⁴ The myocardial preservation techniques used varied according to surgeon and calendar year. They included continuous hypothermic perfusion with ventricular fibrillation (no ischemia), hypothermic ischemia alone, and various forms of cardioplegia (glucose potassium cardioplegia, oxygenated glucose potassium cardioplegia, St. Thomas' Hospital solution, oxygenated St. Thomas' Hospital solution, and dilute blood glucose potassium cardioplegia).

Postoperative variables. Systemic venous and pulmonary venous pressures were measured on the day of the operation and on the following day through transthoracic 2.5F catheters placed during the operation. Prolonged pleural or pericardial effusions were defined as those necessitating drainage for more than 14 days. Duration of postoperative hospital stay was also recorded.

Late follow-up data acquisition. A comprehensive cross-sectional review was undertaken between September 1992 and June 1994. Contact was made with the physician of each patient who had survived the immediate postoperative period to determine the patient's likely status (alive with a Fontan circulation or otherwise). If a

patient was no longer alive with a Fontan circulation, the reason for failure was elicited from the medical record, referring physician, postmortem report, and/or death certificate. In patients with a baffle fenestration, postoperative pulse oximetry recordings, echocardiograms, and cardiac catheterization data were reviewed. Each patient was assigned to one of three groups: (1) no fenestration, (2) fenestration—open, and (3) fenestration—closed. The third group included patients who had undergone successful transcatheter closure of their baffle fenestration, those who had operative closure, and those in whom the baffle fenestration had closed spontaneously.

In six patients no follow-up data were available after hospital discharge (1.4% of the 416 who survived 30 days or to hospital discharge). The current status of a further 12 patients could not be determined during the review period. Prior follow-up in these 12 had ranged from 1.7 to 9.7 years after the operation (median 2.8 years).

Statistical analysis. The primary outcome variable in this study was survival with an intact Fontan circulation. Failure was defined as death, takedown of the Fontan circulation to an aortopulmonary or cavopulmonary shunt, or cardiac transplantation. Failure was classified as either early or late, with early failure occurring before hospital discharge or within 30 days of the Fontan operation in patients who had been discharged. Relationships between survival and perioperative variables were evaluated.

Early outcome was treated as a binary response variable. Univariate analyses for categorical predictor variables (e.g., diagnostic group) were carried out by means of χ^2 and Fisher's exact tests; when appropriate, subgroups were combined. Continuous predictor variables (e.g., pulmonary vascular resistance) were evaluated by means of logistic regression analysis. Transformations and cutpoints for continuous predictors were considered. For example, the natural logarithm of age at operation was a better predictor of early failure than age itself; similarly, a preoperative mean pulmonary artery pressure greater than or equal to 19 mm Hg was a better predictor of failure than the continuous measurement. Baffle fenestration was classified as present or absent. To assess the simultaneous effects of perioperative characteristics on early outcome, variables that were significant at the 0.1 level in a univariate analysis were included in a multivariate logistic regression model. Indicator variables were created for the levels of categorical predictors. A significance level of 0.05 was required for retention in the multivariate model. Interactions among variables included in the model were examined.

In the analysis of late outcome, time to failure was the response variable of interest. The effects of early mortality were eliminated by defining survival time as the period beginning 30 days after the Fontan procedure. Patients in whom the treatment did not fail were considered to be censored at the time of last follow-up. For categorical predictor variables, survival estimates were obtained for each level of the variable by means of the Kaplan-Meier method; subgroups were compared with the use of the log-rank test. Continuous predictors

were initially broken down into quartiles and evaluated in the same way. For the variable *baffle fenestration*, patients were classified as never having had a fenestration, having an open fenestration at the time of most recent follow-up, or having a closed fenestration at the time of most recent follow-up. A Cox proportional hazards model was used to assess multivariate associations. A significance level of 0.05 was again required for retention in the model.

Results

Patient population. Age at operation in the 500 patients ranged from 0.3 to 36 years (mean 6.8 ± 5.9 years, median 4.9 years), and the mean age at operation declined from 8.6 ± 6.6 years (median 7.3 years) in the first quartile of the experience (1973 to 1984) to 5.1 ± 4.4 years (median 3.8 years) in the last quartile (1990 to 1991). Additionally, the number of operations per year increased from two in the first 12 months (April 1973 to March 1974) to 86 in the last 12 months (August 1990 to July 1991). The relative proportions of the six diagnostic groups changed over the study period, with more complex forms of single ventricle comprising a higher percentage of the experience in the later quartiles (Fig. 1). The early operative technique involved a conduit connecting the systemic venous atrium to the pulmonary artery or to a hypoplastic subpulmonic infundibular chamber ($n = 68$). The operative technique later evolved to a direct atriopulmonary anastomosis ($n = 180$) and more recently to the total cavopulmonary anastomosis ($n = 252$). A fenestration was placed in the interatrial baffle in 139 patients. A total of 130 patients with the total cavopulmonary anastomosis modification did not have a baffle fenestration. Additional procedures performed at the time of Fontan surgery are detailed in Appendix B.

Early outcome. Early failure occurred in 84 of the 500 patients (16.8%), but the prevalence decreased from 27.1% in the first quartile of the experience (1973 to 1984) to 7.5% in the last (1990 to 1991). There were 74 deaths, 54 in patients with an intact Fontan circulation and 20 after takedown to an aortopulmonary shunt ($n = 17$) or a bidirectional cavopulmonary shunt ($n = 3$). Survival after early takedown to an aortopulmonary shunt was uncommon (4/21, 19.0%); one of these patients subsequently underwent cardiac transplantation, and another died 6 months later after shunt revision. In contrast, six of the nine patients (66.7%) with early takedown to a cavopulmonary anastomosis survived, and two of these survivors subsequently underwent a

Fig. 1. Diagnostic groups by operation year. Each time period represents approximately one quarter of the 500 patients. *LV-NRGA*, Morphologically left ventricle with normally related great vessels; *LV-TGA*, morphologically left ventricle with transposition of the great arteries; *Heterotaxy*, heterotaxy syndrome; *Single RV*, morphologically right ventricle or ventricle of undetermined morphology; *HLHS*, hypoplastic left heart syndrome; *Other*, other diagnoses (see text for details).

successful Fontan operation with baffle fenestration. Causes of early failure are detailed in Appendix C.

Predictors of early failure. Univariate analyses demonstrated that early failure (<30 days or before hospital discharge) was associated with a number of perioperative variables (Table I). Significant differences were apparent among the diagnostic groups ($p = 0.004$), with the poorest outcome in patients with hypoplastic left heart syndrome (Table II). Calendar year of operation was closely associated with early outcome, and outcome improved over time within each diagnostic category (Fig. 2). Inasmuch as calendar year represents the combined effect of a number of evolutionary trends in patient selection and treatment strategies, it was not included in the multivariate analyses. Right and left atrial pressures measured on the day of the operation were also excluded. These variables were important risk factors for early outcome (right atrial pressure ≥ 17 mm Hg; odds ratio 10.7, 95% confi-

dence interval 6.2 to 18.5; left atrial pressure ≥ 11 mm Hg; odds ratio 9.6, 95% confidence interval 4.8 to 19.3), but their dominance might have obscured the impact of preoperative and intraoperative factors on outcome. In addition, pressure measurements were unobtainable in a number of patients in whom failure occurred early.

Multivariate analysis (Table I) demonstrated a significant association between early failure and the following patient-related variables: a mean preoperative pulmonary artery pressure of 19 mm Hg or more, younger age at the time of the Fontan operation (Fig. 3, A), a diagnosis of heterotaxy syndrome, a right-sided tricuspid valve as the only systemic atrioventricular valve (as in mitral atresia), and pulmonary artery distortion. Procedure-related variables also associated with early failure were (1) the right atrial body or appendage as the origin of the atriopulmonary connection and (2) longer cardiopulmonary bypass time; by contrast, a baffle

Table I. Predictors of early outcome

Risk factor for failure	Univariate	Multivariate		
	<i>p</i> Value	OR	95% CI	<i>p</i> Value
Patient-related				
Younger age at operation	<0.001	1.9†	1.3-2.7	0.001
Earlier year of operation	<0.001			
Diagnostic category				
HLHS	<0.001			
Single RV	0.05			
Heterotaxy	0.1	2.8	1.1-6.9	0.03
Systemic ventricle-right ventricle	0.02			
Left AVV stenosis or atresia	<0.001			
Systemic AVV-right-sided tricuspid valve*	<0.001	3.5	1.7-7.3	0.001
Pulmonary artery distortion	<0.001	1.9	1.0-3.7	0.04
Prior pulmonary artery band	0.04			
Prior PA-Ao anastomosis or VSD enlargement	0.01			
Prior coarctation repair	0.002			
Prior atrial septectomy	<0.001			
Lower preop. aortic saturation	0.04			
Preop mean pulmonary artery pressure ≥ 19 mm Hg	<0.001	5.5	2.3-13.2	<0.001
Lower mean aortic pressure	0.02			
Higher preoperative PVR	0.001			
Procedure-related				
Conduit-type Fontan procedure	0.009			
Atriopulmonary connection from RA appendage or body	0.001	3.3	1.6-6.8	0.001
Right AVV and RA baffle	<0.001			
No baffle fenestration	0.001	3.9	1.6-9.1	0.002
Longer cardiopulmonary bypass time	<0.001	1.1‡	1.1-1.2	0.001
Postoperative				
RA pressure ≥ 17 mm Hg on day of operation	<0.001			
LA pressure ≥ 11 mm Hg on day of operation	<0.001			

All variables from Appendix A were entered into univariate analysis; those with $p < 0.1$ were entered into the multivariate model excepting year of operation and postoperative left and right atrial pressures (see text for details). *OR*, Odds ratio; *CI*, confidence interval; *HLHS*, hypoplastic left heart syndrome; *single RV*, single right ventricle or ventricle with unknown morphology; *AVV*, atrioventricular valve; *PA-Ao*, pulmonary artery-ascending aorta; *VSD*, ventricular septal defect; *PVR*, pulmonary vascular resistance; *RA*, right atrial; *LA*, left atrial.

*Both left- and right-sided tricuspid valve were significantly associated with failure in the univariate analysis, but only a right-sided tricuspid valve was associated with failure in the multivariate model.

†The relative odds of experiencing early failure for each one-unit decrease in log(age).

‡The relative odds of experiencing early failure for each 10-minute increase in cardiopulmonary bypass time.

fenestration was associated with a reduced probability of failure (Fig. 3, B). The analysis was repeated with diagnosis excluded from the model, and the aforementioned associations were unchanged, except for the addition of a common atrioventricular valve as a predictor of poor outcome ($p = 0.01$).

Late outcome. Later follow-up information was obtained in 410 (98.6%) of the 416 early survivors. A total of 36 late failures occurred in 2464 patient-years of follow-up (late failure rate 1.5 per 100 patient-years). Putative causes of late failure are listed in Appendix C. Of note, pacemakers had been placed before the operation in 10 patients; failure occurred in one of these patients in the early postoperative period, and five had late failure (four deaths, one transplantation). Two of these five patients had

severe ventricular dysfunction late after the Fontan operation (one successful transplantation, one death while awaiting transplantation), and two died suddenly and unexpectedly. The other patient died after reoperation for pacemaker generator change.

Fenestration status. Of the 139 patients with baffle fenestration, 129 survived the early postoperative period with a Fontan circulation (93.5%). Device (clamshell) closure was undertaken in 74 patients (range 0.2 to 150 months, median 3.5 months after the Fontan operation). The fenestration was closed surgically in one patient, and in a further 29 patients it closed spontaneously. Hence 25 patients had a fenestration that remained open 7.2 to 50.4 months after the operation (median 31.2 months).

Probability of survival with a Fontan circulation.

Considering both early and late events (with time zero as the time of the Fontan operation), a sharp decline in survival probability over the first postoperative month was followed by a slow but continuing hazard phase (Fig. 4, *A*). The probability of survival in the Fontan state was 84.9% at 1 month, 80.5% at 1 year, 78.5% at 5 years, and 71.4% at 10 years. The probability of survival has increased in the more recent operative years, largely as a result of the declining early failure rate (Fig. 4, *B*).

Predictors of late failure. Further analyses were restricted to patients surviving the operative period with an intact Fontan circulation. Variables associated with failure in univariate analyses are detailed in Table III. In a multivariate model only two patient-related variables were associated with late outcome status: the diagnostic groups having a left ventricle with normally related great arteries and a right ventricle or unknown ventricular morphology were associated with a better outcome than were the other four diagnostic categories (Tables III and IV and Fig. 5), whereas a prior pacemaker was associated with late failure ($p < 0.001$) (Fig. 6). Operative year, the operative variable baffle fenestration (yes/no), the fenestration status at late follow-up (never/open/closed), prolonged pleural effusions, and the length of hospital stay were not associated with late outcome.

Late outcome excluding patients with an open fenestration. The aforementioned analysis of late outcome was repeated after excluding the 25 patients with an open fenestration in case they were not representative of patients with a complete Fontan circulation; the results were unchanged.

Discussion

In this report we have analyzed early and late outcome separately to specifically address the important questions facing the clinician: which factors increase the risk of operative failure and which factors predispose to failure of the Fontan circulation in the longer term. Inasmuch as risk factors for early and late failure were different, an analysis of overall outcome was less meaningful. Multiple patient and procedural variables influenced early outcome, but late outcome appeared to be less influenced by patient selection and was independent of procedural variables. In particular, there was no suggestion that the improvement in operative outcome evident during the review period had resulted in increased late risk.

Table II. Early outcome by diagnostic groupings

Diagnostic groups	Failures	Total	Failure %
Single left ventricle with NRGA	20	151	13.2
Single left ventricle with TGA*	28	196	14.3
Heterotaxy syndrome	9	41	22.0
Single right ventricle or unknown ventricular morphology†	14	60	23.3
Hypoplastic left heart syndrome	11	27	40.7
Other‡	2	25	8.0

NRGA, Normally related great arteries; TGA, transposition of the great arteries.

*Includes D-loop and L-loop ventricles.

†Excludes hypoplastic left heart syndrome.

‡Includes patients with two ventricles and uncommitted ventricular septal defect, usually with double-outlet right ventricle or transposition.

Patient-related risk factors. Younger age at operation was an independent risk factor for early failure. This finding has been reported previously by us¹⁰ and by others,¹⁵⁻¹⁷ but the mechanism remains speculative. Possible contributing factors include smaller patient anatomy and a more reactive pulmonary vascular bed after cardiopulmonary bypass. In addition, patient selection may be important, particularly in our earlier experience when a Fontan operation was occasionally attempted in young patients with unremitting congestive heart failure or severe cyanosis. Nevertheless, the multivariate analysis suggests that age is a risk factor for early failure independent of other patient- or procedure-related variables. Furthermore, although the impact of age on operative outcome has diminished over the study period and appears to be attenuated by use of a fenestration (Fig. 3, *B*), age less than 4 years was associated with increased risk of early failure even in the most recent patient quartile (Fig. 7).

The higher risk in younger patients must be balanced against the potential consequences of delaying the Fontan operation, including prolonged congestive heart failure and cyanosis, pulmonary artery distortion from additional shunt procedures,¹⁸ ventricular hypertrophy and dysfunction,^{16, 19} atrioventricular valve regurgitation, and pulmonary hypertension, all of which may increase the risk of a Fontan operation at a later age. Many centers now use an intermediate bidirectional cavopulmonary shunt in very young patients who are at higher risk for a complete Fontan operation; this has been our practice since 1988.²⁰ We did not find a prior bidirectional cavopulmonary shunt to be associated with improved operative survival for the Fontan procedure, but only a small number of

Fig. 2. Early failure by year of operation and diagnostic grouping. Abbreviations as for Fig. 1.

patients had undergone this intermediate operation so that its impact on operative outcome could not be adequately assessed.

We have found that certain anatomic diagnoses were related to both early and late failure. When the right-sided tricuspid valve was the predominant atrioventricular valve, early risk was increased more than threefold. Hypoplastic left heart syndrome, which we have previously noted as a risk factor,¹¹ was the most common diagnosis with this atrioventricular valve morphology, but D-loop ventricles with mitral atresia or stenosis were also included in this diagnostic group. Heterotaxy syndrome was also an independent risk factor for early outcome, as has been previously reported.¹² Anomalies of pulmonary and systemic venous return are prevalent in these patients with heterotaxy syndrome, and almost all had a common atrioventricular valve. We cannot identify precisely which of these factors is the most important, but the presence of a common atrioventricular valve was a significant predictor of poor early outcome when diagnosis was excluded from the multivariate model. In a previous study from our institution, we found that use of the lateral tunnel

technique of separating the systemic and pulmonary venous returns was associated with reduced risk in these subgroup, and we believe that use of this technique reduces the opportunity for pulmonary venous obstruction to occur.¹⁰ The degree of atrioventricular valve regurgitation was not associated with failure by univariate or multivariate analysis, but numbers with significant regurgitation and a common atrioventricular valve were too small to assess this combination of factors in a meaningful way. Also, we did not consider patients who were not offered Fontan operations because of severe atrioventricular valve or ventricular dysfunction. We do consider severe atrioventricular valve regurgitation and ventricular dysfunction to be important concerns, but it may be difficult to predict postoperative valve and ventricular function when ventricular volume load is reduced by the Fontan procedure.

Early operative survivors with heterotaxy syndrome, hypoplastic left heart syndrome, a morphologically left ventricle, and transposed great arteries (including tricuspid atresia type II), and patients with "other complex" anatomy had a significantly

Fig. 3. Estimated probability of early failure by age at Fontan operation for the total group (A) and for those with and without baffle fenestration (B). Point estimates and exact 95% confidence intervals for outcome probabilities are plotted for the means of the age groups categorized as less than 4 years, 4 to 15 years, and 16 years or greater.

Fig. 4. The probability of survival with a Fontan circulation with time zero as the time of the Fontan operation. Patients who did not experience a failure of the Fontan circulation (death, takedown, or cardiac transplantation) were censored at the time of last follow-up. **A**, Kaplan-Meier estimates with Greenwood confidence bands for the entire group of 500 patients. Numbers are sample size at 4-year intervals. **B**, Kaplan-Meier estimates of the probability of survival with a Fontan circulation by year of operation for the first 5 years of follow-up.

higher likelihood of late failure. The relatively poor late outcome seen in patients with hypoplastic left heart syndrome may be a consequence of coronary and myocardial abnormalities, myocardial damage

related to the first stage of palliation, or residual arch obstruction rather than ventricular morphology. Pulmonary venous obstruction and common atrioventricular valve regurgitation may be impor-

Table III. Predictors of late outcome

Variable	Univariate		Multivariate		
	Association with failure	p Value	Hazard ratio	95% CI	p Value
Diagnosis—left ventricle with NRG4 or single RV	—	0.02	0.3	0.1-0.6	0.003
Anomalous pulmonary venous drainage	+	0.06			
Prior aortopulmonary shunt	—	0.05			
Prior atrial septectomy	+	0.10			
Prior pacemaker	+	<0.001	7.7	2.9-20.6	<0.001
Type of Fontan procedure—direct*	+	0.05			1

All variables from Appendix A were entered into univariate analysis; those with $p < 0.01$ were entered into the multivariate model (see text for details). CI, Confidence interval; NRG4, normally related great arteries; single RV, single right ventricle or ventricle with unknown morphology; —, inverse association; +, direct association.

*Direct atriopulmonary anastomosis.

tant factors in late failure in patients with heterotaxy syndrome. Others have found ventricular hypertrophy to be an important risk factor for both early and late outcome, and to account for much of the risk associated with anatomic diagnoses other than tricuspid atresia.¹⁶ The retrospective nature of perioperative data acquisition prevented us from accounting specifically for ventricular hypertrophy or subaortic stenosis in the current analysis. Certainly patients with a single left ventricle and transposed great arteries are predisposed to the development of subaortic stenosis with secondary ventricular hypertrophy, as well as systolic and diastolic dysfunction.²¹ It is likely that these factors account for much of the increased risk associated with this anatomic subgroup.

Pacemaker insertion before the Fontan operation was associated with poor late outcome but was not associated with early failure. Although the mechanism for this association is not clear, a detailed analysis of the long-term outcome in the subgroup of patients with pacemakers implanted both before and after the Fontan operation suggests that survival is adversely affected when atrioventricular synchrony is not attained.²²

Pulmonary artery distortion^{10, 11, 15} and elevated pulmonary artery pressure^{10, 12, 15} are both widely recognized risk factors for early failure. In this series pulmonary arteriolar resistance was not an independent predictor of early failure, but this variable had a large number of missing values that limited power in the analyses. We would certainly consider elevated pulmonary resistance important; we¹¹ and others^{7, 23} have previously found pulmonary arteriolar resistance to be associated with an increased risk of early failure. Neither pulmonary artery distortion, preoperative pulmonary artery pressure, total resis-

Table IV. Late failure and diagnostic groupings

Diagnostic category	Late failure		Follow-up time (yr) (mean $\pm$ SD)
	No.	%	
Single left ventricle with normally related great arteries	6/131	4.6	7.6 $\pm$ 4.7
Single left ventricle with transposition of the great arteries	20/168	11.9	5.4 $\pm$ 3.0
Heterotaxy syndrome	4/32	12.5	4.3 $\pm$ 2.6
Single right ventricle or unknown ventricular morphology	1/46	2.2	5.7 $\pm$ 2.8
Hypoplastic left heart syndrome	2/16	12.5	4.5 $\pm$ 2.6
Other	3/23	13.0	4.0 $\pm$ 2.3

SD, Standard deviation.

tance to pulmonary blood flow, nor pulmonary vascular resistance was a risk factor for late outcome.

Procedure-related risk factors. The absence of a baffle fenestration, the origin of the atriopulmonary connection from the right atrial body or appendage (i.e., all technical modifications excepting the total cavopulmonary anastomosis), and prolonged cardiopulmonary bypass time were associated with a higher likelihood of early failure. Late outcome appeared independent of any procedure-related variables. In particular, late outcome did not appear to be influenced by placement of a baffle fenestration or the status (open or closed) of the baffle fenestration at follow-up. These results suggest that the major advantage of baffle fenestration is in the improvement in early outcome (an almost fourfold reduction in operative risk) that does not adversely

Fig. 5. Kaplan-Meier estimates of the probability of late survival with a Fontan circulation as a function of diagnosis. Time zero is 30 days after the Fontan operation. *LV-NRGA*, Left ventricle with normally related great vessels; *Single RV/?V*, single right ventricle or ventricle with unknown morphology.

Fig. 6. Kaplan-Meier estimates of the probability of late survival with a Fontan circulation in patients with and without a pacemaker before the Fontan operation. Time zero is 30 days after the Fontan operation.

Fig. 7. Estimated probability of early failure as a function of age at the Fontan operation by year of operation.

affect late outcome, at least at this point in follow-up.

The rationale for the use of the fenestration or an adjustable atrial septal defect has been previously described.^{14, 24, 25} In the immediate postoperative period, cardiac output can be maintained with lower systemic venous pressures that may modulate other risk factors such as residual pulmonary artery distortion or hypoplasia, bypass-related increases in pulmonary vascular resistance, and ventricular dysfunction. In our initial experience, baffle fenestration was used only in patients thought to be at high risk for failure. Subsequently, we have found that the prevalence of prolonged pleural effusions and the length of hospital stay were also reduced when this technique was used.²⁵ These findings have led us to place a baffle fenestration in an increasing number of patients at the time of the Fontan operation. A baffle fenestration was placed in 21% of patients in the 1988 to 1989 quartile and in 87% in the 1990 to 1991 quartile. This technical modification was associated with a marked decline in the prevalence of prolonged pleural effusions, from 51% in the

1985 to 1987 quartile to 31% in the most recent cohort (1990 to 1991). This decline does not appear to be related to other technical modifications, such as the total cavopulmonary anastomosis; prolonged effusion was seen in 37 of 121 (30.6%) patients with a total cavopulmonary anastomosis and a baffle fenestration and in 53 of 119 (44.5%) patients with a total cavopulmonary anastomosis and no baffle fenestration ($p = 0.03$).

The Mayo Clinic group has reported improved survival and a reduction in the prevalence of prolonged pleural effusions in recent years without the use of baffle fenestration.⁹ Unfortunately, a comparison of outcome measures between institutions is not possible without fully accounting for patient selection and technical modifications. Our current analysis indicates that baffle fenestration has a positive influence on early outcome independent of other patient- or procedure-related variables including technical modifications such as the total cavopulmonary anastomosis.

Limitations. Our study population included only those patients with single ventricle who underwent

the Fontan operation and hence cannot be generalized to all patients with single ventricle. Thus we cannot quantify the relative risks and benefits of an early Fontan operation versus alternative palliative procedures. A longitudinal study that enrolls all patients with a single ventricle at the time of diagnosis would be of great value in addressing this question. The retrospective cohort study design and the high degree of association of some variables prevented us from determining the causality of some risk factors. Although it is possible that these associations have confounded the multivariate analysis, variables such as calendar year of operation and postoperative atrial pressures were excluded to minimize this effect. It is also important to emphasize that duration of follow-up is limited, particularly in patients with more recent technical modifications.

Current management strategies. These analyses support recent trends in management of patients with single ventricle anatomy and physiology. Management of these patients must begin in the newborn period and should be directed toward minimizing the likelihood of development of risk factors for a Fontan procedure. This involves early identification and correction of systemic ventricular outflow tract obstruction, the use of smaller (3.5 mm) systemic-pulmonary shunts to provide limited pulmonary blood flow, and an early bidirectional cavopulmonary shunt in many patients.²⁰ These strategies attempt to minimize the likelihood of elevated pulmonary artery pressure and resistance and ventricular dysfunction resulting from volume overload or outflow obstruction. We then proceed to a Fontan procedure with baffle fenestration on the basis of decreasing arterial saturation or symptoms. This occurs not infrequently at 2 to 3 years of life in patients with a previous shunt or in those without previous surgical treatment. It remains unclear to us whether a staged approach of a bidirectional cavopulmonary shunt followed by a later Fontan operation will provide a better result in patients younger than 4 years who are otherwise at low risk for a Fontan procedure. In young patients with additional risk factors we currently prefer an intermediate bidirectional cavopulmonary shunt. It is also unclear when to proceed to a Fontan procedure in patients with a bidirectional cavopulmonary shunt, although most patients with this form of palliation become increasingly cyanotic with growth.²⁶ Throughout all these operative stages we have a low threshold for investigative procedures, and we will attempt to correct even minor anatomic abnormalities such as

mild pulmonary artery stenoses or aortopulmonary collaterals in the catheterization laboratory,^{27, 28} both before and after the Fontan procedure.

Conclusions

The incidence of early failure after a modified Fontan operation has declined dramatically over the study period, despite the application of the Fontan operation in increasingly high-risk candidates. This decline in risk appears related in part to technical modifications of the procedure, particularly the use of the lateral tunnel with baffle fenestration. Preoperative physiologic and anatomic factors remain important risk factors for early outcome. There is a continuing late risk to the patient with a Fontan circulation. This late risk is associated with few patient-related variables and appears independent of procedural variables. It remains unknown whether the late risk is due to the "Fontan state" or whether improved management strategies, including the intermediate bidirectional cavopulmonary shunt and the total cavopulmonary anastomosis modification of the Fontan procedure, will alter this risk.

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For appendixes see page 390.

Appendix A. Perioperative variables

Patient-related	
Demographics	Age at operation Year of operation Sex
Diagnosis	Left ventricle with normally related great arteries Left ventricle with transposed great arteries Right ventricle and ventricle with unknown morphology Hypoplastic left heart syndrome Heterotaxy syndrome Other
Atrioventricular valve anatomy	
Systemic ventricular morphology	
Anomalous pulmonary venous drainage	Yes, no
Anomalous systemic venous drainage	Yes, no
Atrioventricular valve regurgitation	None, mild, moderate, severe
Pulmonary artery distortion	Yes, no
Previous procedures	Aortopulmonary shunt Atrial septectomy Pulmonary artery band PA-Ao anastomosis or VSD enlargement Coarctation repair Unidirectional cavopulmonary shunt (Glenn) Bidirectional cavopulmonary shunt (bidirectional Glenn) Pulmonary artery reconstruction Pacemaker
Preoperative hemodynamics	Ao saturation, hemoglobin LAp, RAp, Aop, PAp Qp, Qs, Qp/Qs, Qp + Qs, PVR Ventricular work $([Qp + Qs] \times Aop)$ Total resistance to pulmonary blood flow $([LAp/(Qp + Qs)] + PVR)$
Procedure-related	
Type of atriopulmonary connection	Conduit Direct Total cavopulmonary anastomosis with lateral tunnel
Baffle fenestration	Yes, no
Coronary sinus position	Left, right
Origin of the atriopulmonary connection	Left, right
Distal connection points	
Valve in atriopulmonary connection	Yes, no
Valve anywhere on right side	Yes, no
Additional major procedures	
Myocardial preservation technique	
Cardiopulmonary bypass time	
Aortic crossclamp time	
Postoperative—immediate	
Systemic atrioventricular valve	
Systemic ventricle	Left, right, both, indeterminant
Systemic atrioventricular valve/baffle relationship	
Postoperative pressures on day of surgery	Systemic venous atrium and pulmonary venous atrium
Postoperative—other (for late outcome analysis only)	
Prolonged effusions (drainage ≥ 14 days)	Yes, no
Duration of hospital stay	
Reoperations	None, minor, major Never, open, closed
Baffle fenestration	

PA-AO, Pulmonary artery–ascending aorta; VSD, ventricular septal defect; LAp, mean left atrial pressure; RAp, mean right atrial pressure; Aop, mean aortic pressure; PAp, mean pulmonary artery pressure; Qp, indexed pulmonary blood flow; Qs, indexed systemic blood flow; PVR, indexed pulmonary vascular resistance (see text for details).

Appendix B. Major procedures in addition to the Fontan operation (26 procedures in 22 patients)

Main pulmonary artery–ascending aorta anastomosis	10
Repair of anomalous pulmonary venous connection	5
Atrioventricular valve repair or replacement	4
Suture or patch closure of atrioventricular valve	3
Glenn shunt	2
Myocardectomy	2

Appendix C. Causes of early and late failure

	<i>Alive with takedown</i>	<i>Died with takedown</i>	<i>Died with Fontan</i>	<i>Total</i>	
				<i>No.</i>	<i>%</i>
Early failure (<i>n</i> = 84)					
High pulmonary vascular resistance	3	9	9	21	25.0
Low cardiac output—cause unclear	3	5	12	20	23.8
Ventricular failure	1	4	13	18	21.4
Pulmonary venous obstruction	1	1	4	6	7.1
Systemic venous obstruction		1	2	3	3.6
Sepsis			3	3	3.6
Cerebral damage			3	3	3.6
Arrhythmia	1		1	2	2.4
Intractable effusions	1		1	2	2.4
Other			6	6	7.1
Total	10*	20	54	84	
Late failure (<i>n</i> = 36)					
Systemic ventricular failure		4	7†	11	30.6
Intractable effusions	2		6	8	22.2
Probable or definite arrhythmia			6	6	16.7
Reoperation			3‡	3	8.3
Pulmonary venous obstruction			2	2	5.6
High pulmonary vascular resistance		1		1	2.8
Other			2	2	5.6
Unknown			3	3	8.3
Total	2	5	29	36	

*Includes one patient who died 6 months after the operation during revision of an aortopulmonary shunt and another patient who subsequently underwent cardiac transplantation.

†Includes three patients with poor ventricular function who died suddenly.

‡Includes one patient who died after pacemaker generator change.