Risk factors for persistent pleural effusions after the extracardiac Fontan procedure

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Objective: Pleural effusions after the Fontan operation contribute significantly to morbidity and prolonged hospitalization. This study investigates the association between selected preoperative, operative, and postoperative variables and persistent pleural effusions after the extracardiac Fontan procedure.

Methods: We conducted a retrospective study of extracardiac Fontan procedures. The variables analyzed as potential risk factors included age and weight at the time of the operation, anatomic diagnosis, preoperative oxygen saturation, mean pulmonary artery pressure, ventricular end-diastolic pressure, presence of an accessory source of pulmonary blood flow, presence of significant aortopulmonary collateral vessels, presence of fenestration, cardiopulmonary bypass time, conduit size, postoperative pulmonary artery pressure, use of angiotensin-converting enzyme inhibitors, and presence of postoperative infection. The outcome measures evaluated were duration and volume of chest tube drainage after surgical intervention.

Results: From June 1997 to August 2002, 100 consecutive patients underwent the extracardiac Fontan procedure. The median age at operation was 3.1 years. The median duration of chest tube drainage was 10 days, and the median volume of drainage was $14.7 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. As determined by means of multivariate analysis, significant risk factors for pleural effusions lasting more than 2 weeks were lower preoperative oxygen saturation ($P = .011$) and the presence of postoperative infections ($P = .003$). Significant risk factors for pleural effusions draining at more than $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ were lower preoperative oxygen saturation ($P = .005$), smaller conduit size ($P = .04$), and longer duration of cardiopulmonary bypass ($P = .004$).

Conclusions: Lower preoperative oxygen saturation, presence of postoperative infection, smaller conduit size, and longer duration of cardiopulmonary bypass were associated with persistent pleural effusions after the extracardiac Fontan procedure. Modifications of some of these risk factors might influence the duration and volume of pleural drainage after surgical intervention.

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The Fontan procedure for correction of single-ventricle congenital heart lesions has undergone several modifications in the recent past.^{1,2} Some of these changes have resulted in dramatically improved postoperative mortality and some sources of morbidity.³⁻⁵ The extracardiac modification of the Fontan procedure is widely recognized as the approach with the greatest potential for optimizing postoperative results.¹⁻⁵ Hemodynamically, it offers the most efficient design for preserving mechanical energy of laminar blood flow and avoiding turbulence and stasis in the Fontan circulation.^{6,7} However, persistent pleural effusions continue to be a significant source of morbidity in the postoperative period, and previous studies have demonstrated this problem to occur in 13% to 39% of patients after surgical intervention.^{3,8}

The extracardiac Fontan procedure is the standard surgical treatment for the correction of single-ventricle lesions at our institution, and persistent pleural effusions are the most troublesome complication in the early postoperative period in our experience. The risk factors that contribute to persistent pleural effusions after the extracardiac Fontan procedure have not been well established. The objective of this study was to evaluate the prevalence of persistent pleural effusions at our institution and to examine the role of select preoperative, operative, and postoperative variables that might influence the risk of this complication after the extracardiac Fontan procedure.

Methods

Study Design and Subjects

All patients undergoing an extracardiac Fontan procedure between 1997 and 2002 were identified through our institutional surgical database. Retrospective chart review was then conducted to obtain specific detailed information about the preoperative, operative, and postoperative clinical course associated with the Fontan procedure. Table 1 describes the demographic and relevant clinical information of the study subjects. The study was approved by the institutional review board at Children's Hospital Los Angeles.

Outcome Measures

The main outcomes of interest were duration and volume of pleural drainage after the Fontan procedure. The chest tube output after the operation was selected as a surrogate measure of pleural drainage. The duration of chest tube output was measured in days from the date of the operation to the final removal of the chest tube. The volume was measured as the average amount of chest tube output expressed in milliliters per kilogram per day. Persistent pleural effusions were defined as pleural effusions lasting more than 2 weeks after the operation or draining more than an average of 20 mL · kg⁻¹ · d⁻¹. The criteria for persistence of pleural effusions were selected after review of existing literature and on the basis of clinical practice. No differentiation was made between chylous and nonchylous effusions.

TABLE 1. Demographic and clinical information of 100 patients who underwent the extracardiac Fontan procedure

Characteristic	
Demographic features	
Female sex n (%)	37 (37)
Median age, y (range)	3.1 years (1.39-17.56)
Median weight, kg (range)	13.8 kg (9.5-93)
Clinical diagnosis (n = 100)	
Hypoplastic left heart syndrome	39
Tricuspid atresia	20
Pulmonary atresia with intact ventricular septum	20
Hypoplastic left ventricle	9
Double-inlet left ventricle	8
Ebstein anomaly	3
Double-outlet right ventricle	1

Variables Analyzed

The variables selected as potential predictors of the outcome measures consisted of 3 main categories:

1. Preoperative: patient demographic characteristics, including age and weight at the time of the operation, and relevant clinical characteristics, including dominant right versus left morphology of the single ventricle, preoperative oxygen saturation, ventricular end-diastolic pressure, mean pulmonary artery pressure, presence of an accessory source of pulmonary blood flow, and presence of significant aortopulmonary collateral vessels. We were unable to access cineangiograms for several patients in the study, and therefore the presence or absence of significant aortopulmonary collateral vessels was determined by means of review of the preoperative cardiac catheterization report alone. Hence specific grading of aortopulmonary collateral vessels for this study was not possible.
2. Operative: presence of fenestration of the extracardiac baffle, size of the conduit or graft used for construction of the extracardiac baffle, and duration of cardiopulmonary bypass.
3. Postoperative: postoperative pulmonary artery pressure (central venous pressure), use of angiotensin-converting enzyme (ACE) inhibitors, and presence or absence of postoperative infection. The postoperative pulmonary artery pressure was summarized as the mean central venous pressure recorded at 6, 12, and 24 hours after the operation. Postoperative infection included bacterial or fungal infections in the blood or the respiratory tract. These infections were diagnosed in the period between the operation and before discharge and confirmed by means of positive microbiologic culture results.

The above variables were selected on the basis of a review of previous studies⁸⁻³⁰ in the literature regarding risk factors for persistent pleural effusions after the Fontan procedure.

Statistical Analysis

We tested the hypothesis of whether the duration and volume of pleural drainage after the Fontan procedure was significantly associated with the selected preoperative, operative, or postoperative

TABLE 2. Variables analyzed for persistent pleural effusions after the extracardiac Fontan procedure

Variable	
Preoperative	
Dominant left ventricular lesions	49 (49%)
Pulmonary artery pressure (mm Hg)	12 (5-20.5)
Preoperative oxygen saturation	87 (70%-97%)
Ventricular end-diastolic pressure	8.5 (2-16)
Presence of significant AP collateral vessels	17 (17%)
Accessory source of pulmonary blood flow	24 (24%)
Operative	
Presence of fenestration	15 (15%)
Graft size (mm)	
14	1
16	22
18	14
20	16
22	1
Cardiac bypass time (min)	41 (17-126)
Postoperative	
Pulmonary artery pressure (mm Hg)	13 (4-22)
Use of ACE inhibitors	87 (87%)
Presence of infection	16 (16%)

Values are given as median (range) or number (percentage). AP, Aortopulmonary; ACE, angiotensin-converting enzyme.

variables. After review of the data, we performed descriptive, univariate, and multivariate analyses. Linear and logistic regression analysis was used to identify the risk factors that were significantly predictive of the 2 main outcome measures. For linear regression, the outcomes were expressed as the total number of days and the total volume of pleural drainage. For logistic regression, the outcomes were expressed as pleural drainage lasting greater than 14 days and drainage of more than 20 mL · kg⁻¹ · d⁻¹. All statistical analyses were performed with the STATA statistical software package.

Operative Technique

A modified Fontan circulation was completed on cardiopulmonary bypass by using the extracardiac technique. An expanded polytetrafluoroethylene interposition graft was used in all cases. Unless a concomitant intracardiac procedure was required, aortic cross-clamping was not used. After the patient was weaned from bypass, Fontan hemodynamics were evaluated. If the central venous pressure was greater than 18 mm Hg, with a transpulmonary gradient of more than 12 mm Hg, placement of a fenestration was considered. This was performed by means of a direct side-to-side anastomosis of the extracardiac baffle with the right atrial free wall. Preoperative steroids and aprotinin were used in all cases. Modified ultrafiltration was not used. The postoperative regimen for anticoagulation consisted of aspirin with or without warfarin.

Results

Between 1997 and 2002, 100 extracardiac Fontan procedures were performed at our institution. Ninety-seven

TABLE 3. Risk factors that were statistically significantly ($P < .05$) associated with persistent pleural effusions after the extracardiac Fontan procedure

Variable	P value
Prolonged duration of pleural drainage (>2 wk)	
Multivariate analysis	
Lower preoperative oxygen saturation	.011
Presence of postoperative infection	.003
Univariate analysis	
Dominant right ventricular lesions	.040
Use of ACE inhibitors postoperatively	.030
Excessive volume of pleural drainage (>20 mL · kg ⁻¹ · d ⁻¹)	
Multivariate analysis	
Longer cardiopulmonary bypass time	.005
Smaller graft size	.040
Lower preoperative oxygen saturation	.004
Univariate analysis	
Younger age	.050
Higher preoperative pulmonary artery pressure	.040

ACE, Angiotensin-converting enzyme.

(97%) patients underwent the extracardiac Fontan procedure as the first Fontan operation. Three (3%) patients had previously undergone other modifications of the Fontan procedure and subsequently received revision to the extracardiac Fontan procedure. The survival to hospital discharge after the Fontan operation was 100%. No patient required takedown of the Fontan procedure for poor postoperative hemodynamics. Ninety-seven (97%) patients had undergone a bidirectional Glenn shunt before the Fontan operation. Twenty-four (24%) patients had the presence of an accessory source of pulmonary blood flow in addition to the Glenn shunt. Fourteen of these were in the form of modified Blalock-Taussig shunts, and the remaining 10 had antegrade main pulmonary arterial flow.

The median duration of chest tube output after the operation was 10 days (range, 3-71 days), and the median volume was 14.7 mL · kg⁻¹ · d⁻¹ (range, 2-37.5 mL · kg⁻¹ · d⁻¹). Thirty-seven (37%) patients had pleural drainage lasting greater than 2 weeks, and 30 (30%) patients had pleural drainage exceeding 20 mL · kg⁻¹ · d⁻¹. Eighteen (18%) patients required placement of additional chest tubes for reaccumulation of pleural effusions after removal of previous chest tubes. Eleven (11%) patients required readmission for pleural effusions after hospital discharge. The median hospital length of stay after the operation was 12 days (range, 4-78 days).

Tables 1 and 2 demonstrate demographic and descriptive information of the variables that were evaluated for persistent pleural effusions after the extracardiac Fontan procedure. Table 3 lists the risk factors that were found to be significantly ($P < .05$) associated with prolonged duration (>2 weeks) or increased volume (>20 mL · kg⁻¹ · d⁻¹) of

pleural drainage, as determined by means of statistical analysis. In the multivariate analysis lower preoperative oxygen saturation ($P = .011$) and the presence of postoperative infections ($P = .003$) were significantly associated with prolonged duration of chest tube output. Smaller graft size ($P = .005$), longer cardiopulmonary bypass time ($P = .04$), and lower preoperative oxygen saturation ($P = .004$) were significantly associated with increased volume of chest tube output.

In addition to the risk factors listed, the univariate analysis showed that dominant right ventricular lesions and the use of postoperative ACE inhibitors were significantly associated with prolonged duration, and younger age and higher preoperative mean pulmonary artery pressure were significantly associated with increased volume of pleural drainage after the operation. We did not find weight at the time of the operation, ventricular end-diastolic pressure, presence of an accessory source of pulmonary blood flow, postoperative mean pulmonary artery pressure, or presence of a fenestration to be significantly associated with either prolonged duration or excessive amount of pleural drainage.

Several different therapies were used for the treatment of pleural effusions in patients with pleural drainage lasting more than 2 weeks or draining at more than $20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. Diuretics were given to all patients. A low-fat diet was used in 36 (95%) patients, and total parenteral nutrition was used in 4 (10%) patients. Somatostatin therapy was used in 2 (5%) patients. Eight (22%) patients with persistent pleural effusions underwent cardiac catheterization for occlusion of aortopulmonary collateral vessels.

Discussion

Postoperative pleural effusions are a major source of morbidity after the Fontan procedure. Our study was undertaken to identify select preoperative, operative, and postoperative variables that increase the risk of persistent pleural effusions after surgical intervention. Our data showed that 37% of patients had prolonged duration, and 30% of patients had increased volume of pleural drainage after the extracardiac Fontan procedure. As determined by means of multivariate analysis, lower preoperative oxygen saturation and the presence of postoperative infections were independent risk factors for prolonged duration of pleural drainage. Longer cardiopulmonary bypass time, smaller graft size, and lower preoperative oxygen saturation were independent risk factors for excessive volume of pleural drainage.

Some findings of our study are different from those of the existing literature.^{3-5,8-30} There also does not seem to be much consensus between other reported large series. The objective of our study was to assess the risk factors for persistent pleural effusions after the extracardiac Fontan procedure. By focusing selectively on the patients who underwent the extracardiac Fontan procedure, we had a

relatively homogenous patient population. We were also able to exclude the effect of other Fontan modifications on the outcomes selected. In addition, the patients included in the study underwent surgical intervention over a relatively short period of calendar time (5 years). This provided more uniformity in the management of preoperative and postoperative care. We believe we were able to adequately assess significant risk factors while conserving the power of our data by reducing the effect of other confounding variables in our study.

Three main mechanisms contribute to the development of persistent pleural effusions after the Fontan procedure: inflammatory, hydrostatic, and hormonal. The inflammatory response results mainly from exposure to cardiopulmonary bypass,¹⁷ causing increased capillary leakage and subsequent fluid retention. Increased hydrostatic pressure in the Fontan circulation results from factors increasing the pulmonary vascular resistance. Lack of atrioventricular synchrony also contributes to this mechanism. The hormonal mechanism involves activation of the renin-angiotensin system,³¹ and more recent evidence suggests involvement of the atrial natriuretic peptide and vasopressin.³²

Lower preoperative oxygen saturation was an independent risk factor for both prolonged duration and increased volume of pleural drainage after surgical intervention. The mechanism by which lower preoperative oxygen saturations increase the risk of persistent pleural effusions after the Fontan procedure remains speculative. Preoperative oxygen saturation is a marker of total pulmonary blood flow, which is dependent on pulmonary vascular resistance. On the basis of the physiology of pulmonary blood flow, patients with higher pulmonary vascular resistance are likely to have lower preoperative saturations, and this might consequently explain the occurrence of persistent pleural effusions.

Significant aortopulmonary collateral vessels and the presence of an accessory source of pulmonary blood flow might also influence the total pulmonary blood supply and, consequently, the preoperative oxygen saturation. The role of significant aortopulmonary collateral vessels in causing persistent pleural effusions is controversial.⁹⁻¹³ Although statistically insignificant, our data suggest that patients with aortopulmonary collateral vessels are less likely to have persistent pleural effusions. One previous study¹¹ has correlated lower pulmonary vascular pressure with the development of significant aortopulmonary collateral vessels. This is the likely mechanism by which the presence of aortopulmonary collateral vessels is correlated with reduced duration of pleural effusions. The presence or absence of an accessory source of pulmonary blood flow was not found to be associated with persistent pleural effusions in our study.

Postoperative bacterial or fungal infections were also shown to contribute to prolonged pleural effusions after surgical intervention. However, because of the retrospective

design of the study, we could not conclusively demonstrate which factor of the 2 came first. Prolonged pleural effusions after the Fontan procedure have been demonstrated to result in loss of immunologic factors,¹⁴ including lymphocytes and plasma proteins that might predispose to bacterial or fungal infections after the procedure. Prolonged hospital stay caused by persistent pleural effusions might also result in exposure to iatrogenic infections. One previous study¹⁵ has demonstrated an increased risk of prolonged pleural effusions after the Fontan procedure performed in the respiratory viral season.

Prolonged cardiopulmonary bypass time was significantly associated with increased volume of pleural drainage after the operation. This finding is supported by several previous studies.^{4,16,17} Longer cardiopulmonary bypass influences postoperative pleural drainage through exposure to inflammatory sequelae. Reducing the exposure to cardiopulmonary bypass has been shown to facilitate more rapid recovery and shorter hospital stay after the Fontan operation.¹⁷ The use of modified ultrafiltration¹⁸ has also been reported to significantly reduce the incidence of postoperative pleural and pericardial effusions, requirement for blood products, and hospital stay after the Fontan procedure.

The smaller graft size used for construction of the extracardiac baffle was also associated with an increased volume of pleural drainage after the operation. We did not find other reports in the literature relating the influence of graft size on pleural effusions. Although smaller graft size was highly correlated with lower age and weight at the time of the operation, the multivariate analysis showed that the effect of graft size was independent of the other 2 variables. Forty-eight percent of patients with graft sizes of smaller than 18 mm had persistent pleural effusions compared with 25% of patients with graft sizes of larger than 18 mm. We found a statistically nonsignificant positive correlation between smaller graft size and higher postoperative pulmonary artery pressure after the operation. We speculate that this might be the contributing mechanism for the effect of smaller graft size on excessive pleural drainage.

The use of ACE inhibitors postoperatively was positively associated with prolonged duration of pleural effusions in the univariate analysis. There are conflicting reports in the literature about the influence of ACE inhibitors on the duration of pleural effusions after the Fontan procedure.^{19,20} ACE inhibitors influence pleural drainage after surgical intervention through their action on the renin-angiotensin axis, which has been shown to contribute to the occurrence of prolonged pleural effusions after the Fontan procedure.²¹ The contradictory results we obtained could have been related to patient selection factors in a retrospective study, even though there was no statistically significant difference between the patients treated with and without ACE inhibitors in our data.

Dominant right ventricular lesions were also a risk factor for prolonged duration of pleural drainage in the univariate analysis. This finding has been previously reported.^{16,22} Although mortality after the Fontan procedure for hypoplastic left heart syndrome has dramatically improved,¹⁶ it still remains a risk factor for persistent pleural effusions. Younger age at the time of the operation was significantly associated with increased volume of pleural drainage after the operation in the univariate analysis. Most previous studies have demonstrated that although age is a risk factor for Fontan failure, it is not a risk factor for persistent pleural effusions.^{12,15,23} Because our study only includes extracardiac Fontan procedures, our patient population might differ slightly from those of other series, and this could be the reason for our contradictory results.

Higher preoperative pulmonary artery pressure was also significantly associated with increased volume of pleural drainage after the operation in the univariate analysis. This variable also has previously been reported as a risk factor for Fontan failure^{24,25} after the operation but not for persistent pleural effusions.^{15,26} It appears logical that higher mean pulmonary artery pressure contributes to poor postoperative hemodynamics with failure of the Fontan physiology and persistent pleural effusions by means of a similar mechanism.

Fenestration of the Fontan baffle has been reported to significantly reduce the duration of pleural effusions in several previous reports.²⁷⁻³⁰ Although the presence of fenestration was not found to significantly affect persistent pleural effusions in our study, we do not routinely perform fenestration of the extracardiac baffle at our institution. This procedure is reserved for patients with higher-risk hemodynamics. Hence our contradictory results might have been biased by patient selection.

The most significant limitation to our study is that there was no uniform protocol for management of persistent pleural effusions after the Fontan operation. The criteria for removal of chest tubes and evaluation of potential risk factors were not standardized and were based mostly on physician preference. These limitations might have confounded the evaluation of our main outcome measures and potential risk factors. Additionally, the causal association of these risk factors could not be adequately established because of the retrospective design of the study. Also, because the study was focused on early postoperative outcome alone, the correlation of these risk factors to intermediate and long-term outcomes remains to be established. Finally, we were unable to assess certain other variables that might contribute to persistent pleural effusions, such as anatomy of the pulmonary arteries, hormonal disturbances, and diaphragmatic paralysis, in the present study.

In summary, persistent pleural effusions are a major source of morbidity after the extracardiac Fontan procedure,

especially in view of the dramatically improved early survival. Certain patient- and procedure-related risk factors influence the occurrence of this complication. These risk factors can be used to predict which patients would have persistent pleural effusions after the operation. We also speculate that modification of some of these risk factors might improve early postoperative outcomes.

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