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Factors Influencing Pleural Effusion after Fontan Operation: an Analysis with 95 Patients

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Key words: Fontan connection; pleural effusion; independent risk factors

Objective To investigate the association between preoperative, operative, and postoperative factors and persistent pleural effusion after the extracardiac Fontan procedure.

Methods Ninety-five consecutive patients diagnosed with univentricular heart underwent extracardiac connection using Gore-Tax conduits at the Department of Children's Heart Centre, Justus-Liebig-University Giessen in Germany from June 1996 to July 2007. The outcome measures were duration and volume of chest tube drainage after surgical intervention. The investigated factors included age and weight at the time of operation, anatomical diagnosis, preoperative oxygen saturation, mean pulmonary artery pressure, ventricular end-diastolic pressure, fenestration, cardiopulmonary bypass time, conduit size, postoperative pulmonary artery pressure, administration of angiotensin-converting enzyme inhibitors, and postoperative infection. Associations between these factors and persistent pleural effusion after the extracardiac Fontan procedure were analyzed.

Results Every patient suffered postoperative effusion. The median duration of postoperative chest tube drainage was 9 days (range, 3-69 days), and the median volume was $12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (range, $2.0\text{-}37.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$). Thirty-seven (38.9%) patients had pleural drainage for more than 15 days, and the volume in 35 (36.8%) patients exceeded $25 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. Nineteen (20%) patients required placement of additional chest tubes for re-accumulation of pleural effusion after removal of previous chest tubes. Fifteen (17.8%) patients were hospitalized again due to pleural effusion after discharge. The median length of hospital stay after the operation was 14 days (range, 4-78 days). Multivariate analysis results showed that non-fenestration, low preoperative oxygen saturation, and postoperative infections were independent risk factors for prolonged duration of pleural drainage ($P < 0.05$). Long cardiopulmonary bypass time, non-fenestration, small conduit size, and low preoperative oxygen saturation were independent risk factors for excessive volume of pleural drainage ($P < 0.05$).

Conclusions For reducing postoperative duration and volume of pleural drainage following Fontan procedure, it seems to be important to improve the preoperative oxygen saturation, use large size of conduit, shorten cardiopulmonary bypass time, and make fenestration during the operation, as well as avoid post-operative infections.

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THE Fontan procedure has been successfully used to treat univentricular heart. The procedure has undergone several modifications in an attempt to reduce the morbidity and mortality associated with this treatment. Although improvement has been achieved in the past few years, morbidity following Fontan procedure remains a challenge. Pleural effusion after the Fontan operation contributes significantly to morbidity and prolonged hospitalization. This study investigated the association between some selected preoperative, operative, and postoperative factors and persistent pleural effusion after extracardiac connection (EC) procedure.

PATIENTS AND METHODS

Patients

From June 1996 to July 2007, 95 consecutive patients diagnosed with univentricular heart underwent EC using Gore-Tax conduits at the Department of Children's Heart Centre, Justus-Liebig-University Giessen, Germany. Among them, 60 (63.2%) patients were male and 35 (36.8%) were female. The median age of these patients was 57.12 months (range, 21.96-212.4 months), and the median weight was 13.8 kg (range, 6.9-53.5 kg).

In this series, 59 (62%) patients were diagnosed with single left ventricle, and 36 (38%) with single right ventricle. In addition, 29 (31%) patients had transposition of the great arteries (TGA). The cardiac structure of all the patients fell into 8 different morphological types (Table 1).

Table 1. Anatomical diagnosis based on the morphological types of the cardiac structure of patients

Anatomical diagnosis	n (percentage)
Hypoplastic left heart syndrome	26 (27%)
Atrial-ventricular channel	7 (7%)
Double outlet right ventricle	6 (9%)
Double inlet left ventricle	9 (9%)
Pulmonary atresia with ventricular septal defect	7 (7%)
Tricuspid atresia	25 (26%)
Mitral atresia	1 (1%)
Hypoplastic right ventricle	7 (7%)
Pulmonary atresia with interventricular septum	7 (7%)

Operative technique

Most patients had previous operation (Table 2). The mean number of times of previous operations was 2.1.

Table 2. Previous procedure before the Fontan operation

Procedure	n (percentage)
Shunt	94 (98.9%)
Banding	11 (11.5%)
Glenn	35 (36.8%)
PDA stent	15 (15.7%)
Giessen procedure	13 (13.6%)
Norwood procedure	24 (25.3%)

PDA: patent ductus arteriosus

Standard cardiopulmonary bypass techniques were used after median sternotomy. After bicaval cannulation, the operation was performed under mild hypothermia (33-34°C). The priming solution of the extracorporeal circulation (ECC) consisted of 450 mL Ringer solution [in children with body weight less than 8 kg, 200 mL Ringer solution was replaced by one unit (220 mL) of fresh frozen plasma], 150 mL 20% human albumin, and 35 mL 8.4% NaHCO₃. If the hemoglobin concentration of the patient was under 10 g/dL, one unit of erythrocyte concentrate (220 mL) was added to the solution. All the extracardiac conduits were connected with the heart beating and without cross-clamping the aorta. Atrial septectomy, when required, was performed during a short period of ventricular fibrillation.

For the EC procedure, polytetrafluoroethylene conduits were applied based on the weight and size of the patients. The conduit size was 20-22 mm in 82 patients, and 14-18 mm in 13 patients. The superior anastomosis between the conduit and the pulmonary artery was performed first. After allowing for the correct conduit length, the junction of inferior vena cava (IVC) and right atrium was incised to establish the IVC-conduit anastomosis, with the coronary sinus avoided.

Fenestration was performed by using a 4 or 5 mm coronary punch to the baffle, which was then connected to the right atrium side-by-side. It was done as a routine procedure if elevated pulmonary artery pressure, abnormal pulmonary artery anatomy, or severe atrioventricular valve regurgitation were present. Only when no signs of

any factors that might compromise postoperative pulmonary circulation were present before the operation did we skip the routine fenestration.

Postoperative anticoagulation treatment

The initial step in our postoperative anticoagulation treatment was systemic heparinization, prolonging the plasma thrombin time (PTT) to 60 seconds for the first five postoperative days. This is followed by antiplatelet therapy (aspirin 1 mg/kg body weight) if no risk of thrombosis or any factors reducing velocity of blood flow in pulmonary circulation were present. When those problems appeared, the patients received Phenprocumone therapy with an international normalized ration (INR) of 2-2.5. A self-checking system (Coagu-Check, Roche Ltd, Basel, Switzerland) was applied, and parents and patients were educated about its use. In the rare cases of enteropathy, low-molecular-weight heparin was administered subcutaneously.

Factors recorded before, during, and after the operation

Factors recorded before the operation included mean pulmonary artery pressure, ventricular end-diastolic pressure, preoperative oxygen saturation, and anatomical structure of the single ventricle. Operative factors included the use of fenestration, the size of the conduit used for construction of the extracardiac baffle, and the duration of cardiopulmonary bypass. After performing Fontan operation, we recorded three factors in the patients, namely postoperative pulmonary artery pressure (PAP), administration of angiotensin-converting enzyme inhibitors (ACEI), and occurrence of postoperative infection.

Evaluation of operative outcome

As a significant aspect of operative outcome, persistent pleural effusion in the present study was defined as pleural effusion lasting for more than 15 days after the operation or with an average drainage volume of more than 25 mL·kg⁻¹·d⁻¹.

Statistical analysis

The SPSS 10.0.0 version for Windows (SPSS Inc, Chicago, IL, USA) was used for data analysis. The data were presented as mean ± SD or range. All numerical data were initially analyzed for normality using the Kolmogorov-Smirnov test. Associations between persistent pleural effusion and demographic data as well as some preoperative, operative, and postoperative factors were analyzed by multivariate analysis and univariate analysis. Statistical

significance was defined as *P* values less than 0.05.

RESULTS

Preoperative, operative, and postoperative factors

Some preoperative, operative, and postoperative factors recorded for the analysis of the association with operative outcome are summarized in Table 3.

Table 3. Factors measured before, during, and after the Fontan procedure^s

Factor	Value
Preoperative, means±SD (range)	
Mean PAP (mm Hg)	10.3±2.4 (5-21)
Right ventricular end-diastolic pressure (mm Hg)	8.2±4.1 (0-19)
Left ventricular end-diastolic pressure (mm Hg)	9.9±3.9 (0-18)
Oxygen saturation (%)	82.9±5.5 (70-96)
Operative	
Fenestration, <i>n</i> (%)	58 (61%)
Cardiopulmonary bypass time (min), median (range)	31 (17-126)
Graft size, <i>n</i> (%)	
14 mm	1 (1.1%)
16 mm	2 (2.1%)
18 mm	10 (10.5%)
20 mm	81 (85.3%)
22 mm	1 (1.1%)
Postoperative	
PAP (mm Hg), means±SD (range)	12.5±2.1 (4-22)
Infection, <i>n</i> (%)	17 (17.9%)
Use of ACEI, <i>n</i> (%)	90 (94.7%)

PAP: pulmonary arterial pressure; ACEI: angiotensin-converting enzyme inhibitors.

Operative outcome evaluated by pleural effusion

For all the 95 patients operated with Fontan procedure, the overall mortality was 3.2% (3 cases of death). Every patient developed postoperative pleural effusion. The median duration of chest tube output after the operation was 9 days (range, 3-69 days), and the median volume was 12 mL·kg⁻¹·d⁻¹ (range, 2.0-37.5 mL·kg⁻¹·d⁻¹). Thirty-seven (38.9%) patients had pleural drainage lasting more than 15 days, and the volume in 35 (36.8%) patients exceeded 25 mL·kg⁻¹·d⁻¹. Nineteen (20%) patients required placement of additional chest tubes for re-accumulation of pleural effusion after removal of previous chest tubes. Fifteen (17.8%) patients required re-hospitalization because of pleural effusion after discharge. The median length of hospital stay after the operation was 14 days (range, 4-78 days).

Factors associated with persistent pleural effusion

Demographic data and some preoperative, operative, and postoperative factors were evaluated for the association with persistent pleural effusion after the extracardiac Fontan procedure. Results showed that weight was not significantly related to the persistent pleural effusion. However, some risk factors were found to be significantly associated with prolonged duration (>15 days) or large volume (>25 mL·kg⁻¹·d⁻¹) of pleural drainage. The multivariate analysis showed that low preoperative oxygen saturation, non-fenestration, and postoperative infections were significantly associated with prolonged duration of chest tube output (*P*<0.05). Small conduit size, long cardiopulmonary bypass time, non-fenestration, and low preoperative oxygen saturation were significantly associated with excessive volume of chest tube output (*P*<0.05). In addition, the univariate analysis showed that dominant right ventricular lesions and the use of ACEI after the operation were significantly associated with prolonged duration; younger age and high preoperative PAP were significantly associated with excessive volume of pleural drainage (*P*<0.05) (Table 4). The analysis results of other factors did not reach the significance level.

Table 4. Risk factors significantly associated with persistent pleural effusion after the extracardiac Fontan procedure

Risk factor	<i>P</i> value
Prolonged duration of pleural drainage (>15 days)	
Multivariate analysis	
Low preoperative oxygen saturation	0.015
Non-fenestration	0.004
Postoperative infection	0.003
Univariate analysis	
Dominant right ventricular lesions	0.040
Postoperative use of ACEI	0.030
Excessive volume of pleural drainage (>25 mL·kg ⁻¹ ·d ⁻¹)	
Multivariate analysis	
Long cardiopulmonary bypass time	0.005
Small conduit size	0.040
Low preoperative oxygen saturation	0.004
Non-fenestration	0.003
Univariate analysis	
Younger age	0.050
Higher preoperative pulmonary artery pressure	0.040

DISCUSSION

Three main mechanisms that may contribute to the development of persistent pleural effusion after the Fontan

procedure were inflammatory, hydrostatic, and hormonal. The inflammatory response results mainly from exposure to cardiopulmonary bypass,¹ causing increased capillary leakage and subsequent fluid retention. Increased hydrostatic pressure in the Fontan circulation is caused by increased pulmonary vascular resistance, which is exacerbated by the absence of atrioventricular synchrony. The hormonal mechanism involves activation of the renin-angiotensin system,² and more recent evidence suggests involvement of atrial natriuretic peptide and vasopressin.³

Fenestration of the atrial baffle was recommended on the basis that it allows a protective right-to-left shunt at the atrial level to overcome the low cardiac output in early postoperative period.⁴⁻⁷ Lemler et al⁸ demonstrated that fenestration significantly reduced both duration and volume of chest tube drainage, which is consistent with the findings of the present study. Benefits of baffle fenestration include improved ventricular preload, increased cardiac output, improved oxygen delivery, reduced systemic venous pressure, and decreased severity of pleural effusion. Fenestration has been reported to significantly reduce the duration of pleural effusion in several previous reports.⁹⁻¹² We routinely perform fenestration of the extracardiac baffle on patients with high risk in hemodynamics. In general, fenestration is recommended for patients with any of the following indicators: elevated pulmonary artery pressure, abnormal pulmonary artery, abnormal right ventricular anatomy, or significant atrioventricular valve regurgitation. Risk factors influencing pleural effusion include pulmonary artery pressure of or above 18 mm Hg, end-diastolic pressure of or above 12 mm Hg, valve regurgitation, pulmonary artery distortion, pulmonary vascular resistance of or above 2 Wood units, ventricular outflow obstruction, and complex anatomy.

The present study found low preoperative oxygen saturation is an independent risk factor for both prolonged duration and increased volume of pleural drainage after surgical intervention. Yet the underlying mechanism remains unclear. 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 saturation, and this might explain the occurrence of persistent pleural effusion.

Cardiopulmonary bypass time influences postoperative pleural drainage through development of inflammatory sequelae. The use of modified ultrafiltration has been reported to significantly reduce the incidence of postoperative pleural and pericardial effusion, demand for blood

products, and hospital stay after the Fontan procedure.¹³ The size of conduit used for construction of the extracardiac baffle was also found associated with excessive volume of pleural drainage after the operation. Although conduit size was partly determined by age and weight at the time of the operation, multivariate analysis showed that the effect of conduit size was independent of those two factors. In patients with conduit size smaller than 18 mm, 83% developed persistent pleural effusion, compared with 13% in patients with larger conduits. We found small conduit size was positively correlated with high postoperative PAP, though statistically insignificant.

The use of ACEI after the operation was found positively associated with prolonged duration of pleural effusion by univariate analysis in the present study. There are conflicting reports about the influence of ACEI on the duration of pleural effusion after the Fontan procedure.^{14,15} ACEI 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 effusion after the Fontan procedure.¹⁶

Most previous studies have demonstrated that age is a risk factor for Fontan failure, but not a risk factor for persistent pleural effusion.¹⁷⁻¹⁹ Because our study only involved extracardiac Fontan procedure, our patient population might differ slightly from those of other studies, which could be the reason for our contradictory results. High preoperative pulmonary artery pressure has also been reported as a risk factor for Fontan failure after the operation,^{20,21} but not for persistent pleural effusion.^{18,21} However, it was found to be significantly associated with increased volume of pleural drainage after the operation in our study.

In conclusion, for reducing postoperative duration and volume of pleural drainage following Fontan procedure, it seems to be important to improve the preoperative oxygen saturation, use large size of conduit, shorten cardiopulmonary bypass time, and make fenestration during the operation, as well as avoid postoperative infections.

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