Risk Factors for Mid-Term Liver Disease After the Fontan Procedure

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Summary

The Fontan procedure is a palliative surgery performed for patients with complex congenital heart disease who exhibit functional single ventricular physiology. Although clinical outcomes of the Fontan procedure have improved in recent years and most patients who undergo the procedure reach adulthood, Fontan-associated liver disease (FALD) is a noncardiovascular complication that has become increasingly common; its risk factors remain unknown.

A total of 95 patients who underwent the Fontan procedure and who were followed up for at least three years at Gunma Children’s Medical Center and Kitasato University Hospital between 1996 and 2015 were retrospectively enrolled in this study.

The mean age of the patients at the time of Fontan procedure was 2.3 ± 1.4 years. Overall, 21 patients (23.1%) experienced FALD. All Fontan procedures were performed with extracardiac total cavopulmonary connection using 16-mm expanded polytetrafluoroethylene grafts. The presence of systemic right ventricle, requirement of pulmonary vasodilator, application of a non-fenestrated Fontan procedure, and absence of fenestration flow at the time of follow-up catheter examination were identified as predictors of FALD using univariate analysis. All these factors, except the requirement of pulmonary vasodilator, remained significant predictors of FALD in multivariate logistic regression analysis.

Patients with a systemic right ventricle who undergo the Fontan procedure are at a high risk of FALD in the mid-term. Creating fenestration at the time of Fontan and maintaining the fenestration flow may reduce the mid-term risk of FALD.

Key words: Fenestration, Systemic right ventricle, Fontan-associated liver disease

The Fontan procedure is a palliative surgery performed in patients with complex congenital heart disease who exhibit functional single ventricular physiology due to anatomic difficulties that prevent biventricular correction. Surgical outcomes of the Fontan procedure have improved over recent years and are currently satisfactory.

Continuous and intermittent exacerbation of CVP may be the cause of FALD, increased venous pressure is merely one condition that contributes to chronic organ injury in the Fontan hemodynamic milieu; the other associated risk factors remain unknown. This study aimed to assess mid-term risk factors for the occurrence of liver disease in patients undergoing the Fontan procedure.

Methods

We retrospectively enrolled all patients who had undergone the Fontan procedure and who were followed up for at least three years at Gunma Children’s Medical Center and Kitasato University Hospital between 1996 and 2015.

Definition of liver disease: Liver disease was defined as the elevated values of two or more of the aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (t-Bil), or gamma-guanosine triphosphate...
The student's range, as appropriate for the data distribution. Categorical mean and standard deviation or medians (interquartile range). **Statistical analysis:** Continuous variables are expressed as mean and standard deviation or medians [interquartile range], as appropriate for the data distribution. Categorical variables are expressed as frequencies and percentages. The student’s *t*-test was used to compare continuous variables, and comparisons were confirmed using the Mann-Whitney *U* test for non-normally distributed data. Chi-square or Fisher’s exact tests were used to compare categorical variables. The Mann-Whitney *U* test was used to compare ordinal variables. A *P*-value of < 0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to determine independent predictors of FALD. All statistical analyses were performed using **JMP® 13** (SAS Institute Inc., Cary, NC, USA).

**Table I. Preoperative Clinical Data**

| Variable                  | Male | Female |
|---------------------------|------|--------|
| Age at Fontan (years)     | 2.3 ± 1.4 | 2.3 ± 1.4 |
| Body weight (kg)          | 10.7 ± 3.1 | 10.7 ± 3.1 |
| Ventilator morphology     |        |        |
| RV                        | 43    |        |
| LV                        | 48    |        |
| Age at BCPS (months)      | 11.0 ± 9.4 | 11.0 ± 9.4 |
| Home oxygen therapy       | 61    | 61     |
| Pulmonary vasodilator     | 30    | 30     |
| ACEI and/or β-blocker     | 38    | 38     |
| AVVR                      | 14    | 14     |

Table I. Preoperative Clinical Data

| Variable                  | Male | Female |
|---------------------------|------|--------|
| Diagnosis                 |      |        |
| HLHS                      | 10   |        |
| TA                        | 15   |        |
| PA IVS                    | 8    |        |
| DORV                      | 18   |        |
| Heterotaxy                | 24   |        |
| Others                    | 22   |        |
| PAP (mmHg)                | 11.3 ± 2.2 | 11.3 ± 2.2 |
| Rp (unit.m²)              | 1.8 ± 0.7 | 1.8 ± 0.7 |
| PA index                  | 248 ± 107 | 248 ± 107 |
| EF (%)                    | 63.1 ± 8.1 | 63.1 ± 8.1 |
| SaO₂ (%)                  | 81.6 ± 5.1 | 81.6 ± 5.1 |

**Table II. Operative and Postoperative Clinical Data**

| Variable                  | Operation time (minutes) | CPB time (minutes) | Fenestration | Intubation (days) | Hospital stay (days) | Chest tube (days) | Home oxygen therapy | Pulmonary vasodilator | ACEI and/or β-blocker | AVVR | PAP (mmHg) | Rp (unit.m²) | PA index | EF (%) | SaO₂ (%) | Patent fenestration |
|---------------------------|--------------------------|-------------------|-------------|------------------|--------------------|-------------------|--------------------|---------------------|----------------------|------|------------|-------------|----------|--------|----------|---------------------|
|                           | 349 ± 198                | 159 ± 69          | 57          | 1.7 ± 4.0        | 25.8 ± 19.2        | 13.0 ± 10.7       | 46                 | 32                  | 40                  | 14   | 11.7 ± 2.7 | 1.4 ± 0.7   | 206 ± 63  | 63.2 ± 9.8 | 93.3 ± 2.5 | 11                  |

**Table II. Operative and Postoperative Clinical Data**

(γGTP) in two consecutive blood tests.

**Fontan procedure:** All Fontan procedures were performed with extracardiac total cavo pulmonary connection (eTCPC) using 16-mm expanded polytetrafluoroethylene (ePTFE) grafts. Patients with the pulmonary resistance greater than 1.5 unit.m² were indicated for fenestration. The adhesion surrounding the heart was dissected through median sternotomy, and the inferior vena cava (IVC) was resected from the right atrium under cardiopulmonary bypass support. A 16-mm ePTFE graft was sutured to the IVC and the pulmonary artery. Thereafter, a side hole was created in the ePTFE graft, and the graft was sutured to the atrium by side-to-side anastomosis. Most operations in this series were performed without cardiac arrest, except for cases of intra-atrium eTCPC.

**Statistical analysis:** Continuous variables are expressed as mean and standard deviation or medians [interquartile range], as appropriate for the data distribution. Categorical variables are expressed as frequencies and percentages. The student’s *t*-test was used to compare continuous variables, and comparisons were confirmed using the Mann-Whitney *U* test for non-normally distributed data. Chi-square or Fisher’s exact tests were used to compare categorical variables. The Mann-Whitney *U* test was used to compare ordinal variables. A *P*-value of < 0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to determine independent predictors of FALD. All statistical analyses were performed using **JMP® 13** (SAS Institute Inc., Cary, NC, USA).

**Results**

There were 95 patients recruited for this study; four patients were excluded because they died during the study period. Finally, 91 patients were enrolled (36 female and 55 male). The mean follow-up period was 8.7 ± 4.7 years. The predominant diagnosis was heterotaxy. Patient characteristics and preoperative data at the time of Fontan procedure are summarized in Table I. Operative data, postoperative clinical data, and catheter examination results are summarized in Table II. The creation of a fenestration was achieved with side-to-side anastomosis between the eTCPC graft and the atrium. Out of 57 fenestrations created, 46 closed spontaneously by the time of follow-up catheter examination (performed at a mean of 1.0 ± 0.3 years after the Fontan procedure). Sixty-five patients were weaned from mechanical ventilation and extubated in the operating theater or pediatric intensive care unit within a few hours of surgery. Overall, 21 patients (23.1%) experienced FALD, and the analysis of clinical factors indicated that the presence of systemic right ventricle, requirement of pulmonary vasodilator, application of a non-fenestrated Fontan procedure, and absence of fenestration flow at the time of follow-up catheter examination were predictors of FALD by univariate analysis (Table III). However, the presence of systemic right ventricle, ap-
Complication of a non-fenestrated Fontan procedure, and absence of fenestration flow at the time of follow-up catheter examination remained significant predictors of FALD in multivariate logistic regression analysis (Table IV).

### Discussion

The current literature indicates high survival rates after the Fontan procedure. However, patients continue to be at risk for various morbidities associated with Fontan circulation. After Fontan circulation is established, there is a sudden increase in venous pressures, causing cardiac output to diminish. Exercise induces a rise in CVP to reach levels of up to 30 mmHg. This rise is accompanied by a reduction in cardiac output relative to the demands of the exercising muscle, which contributes to the development of tissue hypoxia and ischemia. Fontan circulation creates an environment conducive to chronic hepatic injury, and it is speculated that the continuous increase in CVP associated with Fontan physiology may be a more significant cause of liver injury than intermittent or pulsatile increases in systemic venous pressure, which may occur in patients with right ventricle dysfunction. Elevated CVP causes the hepatic veins and sinusoids to be subjected to high afterload, resulting in poor portal vein inflow due to increased portal vein pressure. Although the hepatic arterial buffer response results in greater arteriolarization, this cannot sufficiently compensate for venous pressures exceeding 25 mmHg. These pressures can lead to reduced liver perfusion and concomitant liver injury, especially when cardiac output is impaired. Furthermore, impaired lymphatic drainage due to high CVP and elevated hepatic venous pressure causes sinusoidal dilatation around the central veins in the liver, which leads to pericentral and perisinusoidal fibrosis and, ultimately, liver cirrhosis.

In 1990, Bridges et al. described the efficacy of fenestration in the Fontan procedure for patients with increased risk of acute mortality. They suggested that fenestration may reduce the rate of acute postoperative mortality among high-risk patients. While fenestration has contributed to expansion of the indications for Fontan procedure and have led to improvements in acute postoperative mortality by allowing venous return partially bypassing the pulmonary circulation, the chronic benefits remain unknown. Fenestration may represent a potential bypass in the context of elevated Fontan pressures due to abnormal pulmonary artery anatomy or elevated pulmonary vascular resistance. Thus, fenestration may reduce CVP and improve loading of the single ventricle, through the use of a right-to-left shunt and cyanosis. Fenestration in the context of the Fontan procedure remains controversial. While several studies have reported that its use may improve perioperative outcomes including duration of the chest tube stays, others have indicated that avoiding fenestration in these patients reduces the risk of desaturation, thrombotic events, and arrhythmia. Harada et al. reported that fenestration in the Fontan circuit is not necessary for eTCPC and concluded that the Fontan procedure can be satisfactorily completed without fenestration with the aid of pulmonary vasodilation therapy. In their report on fenestration in Fontan circulation for chronic cardioprotection, Saiki et al. concluded that patients with patent fenestration have high survival rates after the Fontan procedure.
tration had more robust hemodynamics with secured preload reserve, reduced afterload, suppressed beta-adrenergic response, and a lower heart rate at baseline than patients with naturally closed fenestration.\textsuperscript{19} However, these benefits are reduced by an increased heart rate, and the authors also reported that patent fenestration was associated with lower baseline CVP and a rise in rapid pacing. In our series, most of the patients who received fenestration exhibited spontaneous closure within one year. We consider that routine fenestration creation during the Fontan procedure can increase the safety of the operation. In terms of ventricular morphology, several reports have indicated that the outcomes of Fontan procedure are inferior in the case of systemic right ventricle.\textsuperscript{20,21} In contrast, a recent meta-analysis by Schwartz et al. reported that ventricular morphology does not affect mortality.\textsuperscript{22} The tricuspid valve and right ventricle are designed to sustain competency and function of low-resistance pulmonary circulation and are believed to be more susceptible to pressure or volume overload.

It is often difficult to detect FALD because liver dysfunction rarely causes subjective complaints. However, with the current awareness of FALD, many pediatric cardiologists routinely assess liver function using various modalities, such as magnetic resonance imaging (MRI) and ultrasound. Bulut et al. reported the efficacy of MRI for the assessment of FALD,\textsuperscript{23} demonstrating that all patients who underwent the Fontan procedure exhibited morphologic liver changes and varying degrees of reticular contrast enhancement compatible with fibrosis and congestion. However, in terms of laboratory data, only AST levels were found to be elevated in patients with hepatomegaly.\textsuperscript{24} According to the conference report of the American College of Cardiology, the typical evaluation of FALD involves identification of abnormalities during routine testing and subsequent referral to hepatology. Thus, routine laboratory testing, such as liver and spleen ultrasound, should be performed every 1-2 years.\textsuperscript{25} In our institute, liver MRI and ultrasound are routinely performed for patients who undergo the Fontan procedure. Liver enzyme and bilirubin levels often remain within the normal ranges after the Fontan procedure, despite morphologic liver changes. A previous report has demonstrated that the degree of liver enzyme elevation does not correlate with the degree of histological fibrosis.\textsuperscript{26} Silva-Sepulveda et al. concluded that Fontan pressures and time since the Fontan correlated with liver fibrosis scores and fenestration do not reduce the risk of fibrosis in the long term.\textsuperscript{27} In our study, multivariate logistic regression analysis revealed that the presence of systemic right ventricle, application of a non-fenestrated Fontan procedure, and absence of fenestration flow at the time of follow-up catheter examination are significant predictors of FALD in the mid-term. Therefore, while it may be difficult to prevent liver fibrosis and cirrhosis in the long term by Fontan procedure with fenestration combined with attempts to sustain its flow because time since the Fontan procedure is a strong risk factor, it is expected to reduce the risk of FALD, at least in the mid-term, through improved cardioprotection and reduced CVP at rest and during exercise.

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Disclosure

Conflicts of interest: All authors have nothing to disclose.

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