Liver and Cardiac Function in the Long Term After Fontan Operation

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Background. Patients who underwent Fontan operation have some degree of liver disease. We aimed to assess the long-term liver and cardiac function after Fontan operation.

Methods. Patients enrolled underwent physical examination, biochemical tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, bilirubin, international normalized ratio, coagulation factor V, protein profile, fecal alpha-1-antitrypsin), echocardiogram, and liver ultrasonography. A liver disease score was adopted to compare the degree of liver involvement with hemodynamic features.

Results. The study enrolled 34 patients, median age 14.7 years (range, 4.1 to 26.7), 26 with a residual left ventricle, 8 with a residual right ventricle, affected by tricuspid atresia (17), pulmonary atresia (4), hypoplastic left heart syndrome (5), double-outlet right ventricle (2), single left ventricle (2), and miscellaneous (4), with median follow-up of 11.5 years (range, 1.7 to 23.3). We found hepatomegaly in 18 of 34 (53%), splenomegaly in 3 of 33 (9%), abnormal transaminases in 10 of 33 (30%), elevated γGT in 19 of 31 (61%), elevated bilirubin in 10 of 31 (32%), coagulopathy in 17 of 29 (58%), and protein-losing enteropathy in 4 of 21 (19%). Median heart rate z-score was −1.72. Hepatic dysfunction was strictly correlated to low cardiac index ($r^2 = 0.34, p = 0.008$) and to a lesser extent to reduced heart rate ($r^2 = 0.18, p = 0.07$).

Conclusions. In children who underwent Fontan operation, hepatic dysfunction is correlated with low cardiac index and reduced heart rate. Maintaining or reestablishing a normal cardiac index might prevent or reduce liver disease in the long-term.


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Over the last 30 years, advances in congenital heart surgery and intensive care medicine have dramatically increased the survival of infants with critical congenital heart disease, especially those with a single-ventricle cardiac malformation [1]. Staged palliation culminating in the Fontan operation has been life-saving to infants with single-ventricle cardiac malformations. Nevertheless, in patients followed up after total cavopulmonary connection, the average central venous pressure is about three to four times higher than normal [2, 3], and this is a well-known predisposing factor for the development of chronic liver disease [4]. Quite a few studies have shown that children with cardiac disease and systemic venous congestion have some degree of liver disease [5], and that after the Fontan operation, liver function tests are commonly abnormal [6–14]. However, no correlation has been found so far between the degree of liver disease and cardiac function indicators in this setting.

We sought to identify the characteristic pattern of liver dysfunction occurring in the long term after a Fontan operation and to determine the hemodynamic factors associated with hepatic impairment in children with a functionally single ventricle.

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Table 1. Liver Disease Score

<table>
<thead>
<tr>
<th>Score of Liver Disease</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver size from costal edge</td>
<td>Normal (≤ 1 cm)</td>
<td>&gt; 1 cm and ≤ 3 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Normal</td>
<td>&gt; 20 μmol/L</td>
<td>&gt; 50 μmol/L</td>
</tr>
<tr>
<td>Clotting indicators</td>
<td>Normal</td>
<td>INR &gt; 1.2 and &lt; 2.0 or factor V &lt; 60% and &gt; 30%</td>
<td>INR &gt; 2 or factor V &lt; 30%</td>
</tr>
<tr>
<td>Doppler of the hepatic vein</td>
<td>Normal</td>
<td>Monophasic or diphasic pattern</td>
<td></td>
</tr>
<tr>
<td>Doppler of portal vein</td>
<td>Normal</td>
<td>PR &lt; 0.54</td>
<td>Reversed flow</td>
</tr>
<tr>
<td>Doppler of the hepatic artery</td>
<td>Normal RI and PI</td>
<td>RI &gt; 0.70 or PI &gt; 1.64</td>
<td>RI &gt; 0.70 and PI &gt; 1.64</td>
</tr>
</tbody>
</table>

*Normal values: total bilirubin < 20 μmol/L; INR = 0.8 to 1.2; factor V > 60%; hepatic veins, triphasic pattern; PR < 0.54; RI < 0.7; PI < 1.64. a In patients on warfarin, the activity of factor V has been considered.

INR = international normalized ratio; PI = pulsatility index; PR = pulsatility ratio; RI = resistance index.

Evaluation of Liver Disease

LIVER ULTRASOUND AND DOPPLER. Measurements were made with an Esaote Technos MP (Esaote Group, Genova, Italy) using a broadband convex transducer. Pulsed-wave Doppler recordings of the hepatic vein, inferior vena cava, portal vein, and hepatic artery were performed with each patient breathing quietly in the supine position and after fasting. The transducer was placed in a subxyphoid and right intercostal position. Each result was the mean of three measurements.

The study was carried out according to previously published methods, and the values obtained were compared with normal age-matched subjects, as previously described [15–17]. Doppler data included direction, velocity, and flow pattern in the hepatic vein, inferior vena cava, portal vein, and hepatic artery. Pulsatility ratio (PR = minimal flow velocity/maximal flow velocity [normal value greater than 0.54]) of the portal vein as a marker of hepatic vein congestion [18–21], resistance index (RI = peak systolic velocity – end diastolic velocity/peak systolic velocity [normal value lower than 0.7]), and pulsatility index (PI = peak systolic velocity – end diastolic velocity/mean velocity [normal value lower than 1.64]) of the hepatic artery were also calculated [22].

LABORATORY TESTS. We tested full blood count, alanine aminotransferase (normal values, 10 to 40 IU/L), aspartate aminotransferase (normal value, 10 to 40 IU/L), gamma glutamyl transpeptidase (normal value, 10 to 40 IU/L), lactic dehydrogenase (normal value, 0 to 580 IU/L), total bilirubin (normal value, less than 20 μmol/L), total protein, albumin, prothrombin time, international normalized ratio, and partial activated thromboplastin time. In patients taking oral anticoagulants (warfarin) factor V activity was determined for evaluation of coagulopathy (normal activity, greater than 60%) [23]. A stool sample was obtained for alpha-1-antitrypsin measurement (normal value, less than 5 mg/g dry stool).

SCORE OF LIVER DAMAGE. For the global evaluation of liver disease, a score of liver injury was introduced, including clinical, laboratory, and echographic data. The liver score has been formulated upon expert consensus with the aim to assess liver function in patients with potential hemodynamic imbalance. We included synthetic function (international normalized ratio and factor V activity), biliary function (serum bilirubin), and liver blood flow and congestion (liver size and Doppler ultrasonography). The score was then compared with cardiac anatomy, type of intervention, and cardiac function of each patient (Table 1).

EVALUATION OF CARDIAC FUNCTION. Medical records, operative notes, electrocardiograms, echocardiography reports, and recent (within the last 2 years) cardiac catheterization reports when available were reviewed. Blood pressure was measured during echocardiography evaluation. All these patients were studied with a 12-lead and a 24-hour Holter electrocardiogram. None of them had a pacemaker.

After positioning of the subject in a partial left decubitus position, a two-dimensional and M-mode echocardiogram was performed with a Hewlett-Packard Sonos 2500 echocardiographer (Hewlett-Packard Company, Palo Alto, CA) during morning hours. This evaluation was considered reliable only if the left ventricle normal geometry was maintained. Measurements of interventricu-

Table 2. Characteristics of Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid atresia</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>5</td>
<td>14.8</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>Holmes heart</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attriopulmonary connection</td>
<td>8</td>
<td>23.5</td>
</tr>
<tr>
<td>Total cavopulmonary connection</td>
<td>26</td>
<td>76.5</td>
</tr>
</tbody>
</table>
lar septal thickness, posterior wall thickness, and left ventricle dimensions were taken at or just below the mitral valve tips by the leading edge-to-leading edge method at the onset of the electrocardiographic Q wave, according to the American Society of Echocardiography [24].

Left ventricular end-diastolic and end-systolic volumes were calculated with the Teichholz correction of the cube formula [25]. Left ventricle chamber volumes and stroke volume determined by this approach have been shown to correlate well with invasive and with two-dimensional and Doppler-echocardiographic volume measurements in a variety of populations with symmetrical left ventricle wall motion [26–28].

The cardiac index (heart rate × systolic output/body surface [mL · min⁻¹ · m⁻²]) and the stroke volume were calculated for each patient, or retrieved from a recent cardiac catheterization in those with a residual right ventricle [29–30]. Heart rate was derived by a 24-hour Holter electrocardiographic recording on each patient.

Statistics
We performed the Student t test for paired and unpaired couples of data. Linear regression analysis was used for correlations between hepatic and cardiac values (NCSS 2000 package and Excel for Windows).

Results
Overall, 34 patients accepted to enter the study. Twenty were male, and 14 female; the median age at assessment was 14.7 years (range, 4.1 to 26.7). Patients’ diagnoses and type of Fontan procedure are summarized in Table 2. Eight patients (23.5%) had a morphologic right ventricle, and 26 (76.5%) had a morphologic left ventricle.

Twenty-three patients underwent a total cavopulmonary connection, 11 underwent an atroipulmonary connection. Three patients of the latter group underwent a new operation to convert their original atroipulmonary anastomosis to a total cavopulmonary connection; therefore, in our study, they are included in the former group of patients. None of the patients was taking drugs known to be associated with liver dysfunction.

The median age at intervention was 3.3 years (range, 0.9 to 14.4), with a median follow-up after Fontan operation of 11.5 years (range, 1.7 to 23.2). Patients with an atroipulmonary connection have a follow-up significantly longer (mean duration, 18.7 ± 5.8 years) than those with a total cavopulmonary connection (mean duration, 9.6 ± 11.3 years; p = 0.00014, Student t test).

Clinical Observations
All patients lead a nearly normal life. Median heart rate was 65 beats per minute (range, 42 to 110). Median heart rate z-score was –1.72 (range, 0.9 to –4); 22 of 34 (65%) had a heart rate less than 1 SD of normal, and 12 of 34 (35%) less than 2 SD of normal. Hepatomegaly was clinically observed in 18 patients (54.5%); liver size from costal edge was equal to or greater than 4 cm in 6 cases (17.6%). Splenomegaly was found in 3 of 33 patients (9%). One patient had asplenia. There was a clear tendency to significance for the correlation between low heart rate and increased liver disease score (r² = 0.18, p = 0.07; Fig 1). In fact, only 3 patients (9%) had a heart rate z-score above zero with respect to normal values for age. A linear regression analysis was used for correlations between hepatic and cardiac values (NCSS 2000 package and Excel for Windows).

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Table 3. Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Value</th>
<th>Number of Patients Tested</th>
<th>Median (range)</th>
<th>Number Abnormal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase</td>
<td>15–40 U/L</td>
<td>33</td>
<td>35 (20–69)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>5–40 U/L</td>
<td>33</td>
<td>31 (13–62)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Gamma glutamyl transpeptidase</td>
<td>3–40 U/L</td>
<td>31</td>
<td>44 (3–184)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.7–20 μmol/L</td>
<td>31</td>
<td>17 (1–32)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0–7 μmol/L</td>
<td>29</td>
<td>4.7 (0.1–10)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Total protein</td>
<td>60–80 g/L</td>
<td>30</td>
<td>74.4 (35–92)</td>
<td>&gt; 2 SD: 4 (13)</td>
</tr>
<tr>
<td>Albumin</td>
<td>35–46 g/L</td>
<td>28</td>
<td>45 (16.6–64)</td>
<td>&gt; 2 SD: 10 (36)</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt; 1.20</td>
<td>23</td>
<td>1.2 (1.09–2.9)</td>
<td>15/23 (65)</td>
</tr>
<tr>
<td>Factor V&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60%–150%</td>
<td>6</td>
<td>71 (42–104)</td>
<td>2 (30)</td>
</tr>
<tr>
<td>Fecal alpha-1-antitrypsin</td>
<td>0–5 mg/g</td>
<td>21</td>
<td>2 (1–72)</td>
<td>4 (19)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excluded patients on warfarin.  <sup>b</sup> Only patients on warfarin.
junctival rhythm was found in 8 of 34 patients (23%). Considering only the presence of coagulopathy or increased bilirubin, the patients with no coagulopathy had a mean heart rate z-score of −1.5 versus −1.8 in patients who had coagulopathy—lower but not statistically different; patients with increased bilirubin had a mean heart rate z-score of −2.1 versus −1.6 in patients with normal bilirubin—still lower but not statistically different.

**Laboratory Tests**

Results of laboratory tests are reported in Table 3. Ten patients of 31 (32%) showed elevated total bilirubin; 17 of 29 (58%) had an abnormal clotting profile. Total protein was low in 2 of 30 patients (7%), and both showed high levels of alpha-1-antitrypsin in stools (65 and 72 mg/dL [normal value, less than 5 mg/g dry stool]). Elevation of alpha-1-antitrypsin in stool was found in 4 of 21 patients (19%), 2 of whom had clinically overt protein-losing enteropathy.

Severity of liver disease according to the score did not correlate with patient age, age at operation, length of follow-up, residual left or right ventricle, type of surgical repair (atriopulmonary connection versus total cavopulmonary connection), or protein-losing enteropathy. However, patients with an atrio pulmonary connection repair had a significantly greater gamma glutamyl transpeptidase level (92 versus 44 U/L, \( p = 0.01 \)). The presence of a fenestration, as assessed by echocardiography performed at the time of the study, did not correlate with any indicator of liver function.

**Liver Ultrasonography and Doppler**

An abnormal flow pattern in the hepatic vein was found in 6 of 33 patients (18%). The diameter of the portal vein was greater than normal in 2 of 34 patients (6%); the median flow velocity was 21 cm/s (range, 9 to 34), abnormally reduced in 9 patients (26%). The flow was hepatopetal in 30 cases (88%), whereas a diastolic reversed flow was recorded in 4 patients (12%). An abnormally fluctuating portal flow with a reduced pulsatility ratio was found in 17 of 34 (50%). However, there was no strict correlation between portal pulsatility ratio and liver disease score \( (r^2 = 0.10, p > 0.1) \), nor between pulsatility ratio and coagulopathy \( (p > 0.1) \). The resistance index in the hepatic artery showed a mean value of 0.74 (range, 0.48 to 0.95), above the normal range in 63% and below in 12%. The mean pulsatility index was 1.38 (range, 0.67 to 3.4), above the normal range in 22% and below the normal range in 13%.

**Cardiac Function**

Nine patients (26%), including all of those with a morphologic right ventricle, had their cardiac index obtained from a recent cardiac catheterization, whereas the others were studied by echocardiography. Six of 34 patients had an open fenestration when assessed for this study. The presence of an open fenestration did not correlate with the degree of liver dysfunction.

Median ejection fraction was 62%, median shortening fraction was 34%; both were reduced in 5 of 25 patients (20%). Median cardiac index was 2,934 mL · min \(^{-1} \) · m\(^{-2} \) (range, 1,111 to 6,269 mL · min \(^{-1} \) · m\(^{-2} \)), reduced in 50%; median stroke volume was 48 mL/m\(^2 \) (range, 17 to 81 mL/m\(^2 \)), reduced in 2 patients (8%). There was an apparent trend to correlation between reduced cardiac index and increased liver disease score \( (r^2 = 0.34; p = 0.008; \text{Fig } 2) \). Considering only the presence of coagulopathy, the patients with no coagulopathy had a cardiac index significantly greater than patients who had coagulopathy (mean, 3,591 versus 2,485 mL · min \(^{-1} \) · m\(^{-2} \); \( p = 0.03 \)). Considering the level of total bilirubin, patients with an abnormally high value had a lower cardiac index than patients with normal bilirubin (2,087 versus 3,494 mL · min \(^{-1} \) · m\(^{-2} \); \( p = 0.02 \), Student \( t \) test).

**Comment**

Total cavopulmonary connection is considered the best palliation of complex congenital heart defects with functionally single ventricle. In this condition, several adverse events have been described but strict correlations between long-term complications and type of surgical repair or hemodynamics are lacking, especially as far as liver disease is concerned [31, 32].

The Fontan operation carries features possibly leading to chronic hepatopathy, such as an average central venous pressure about three to four times higher than normal. Venous congestion is a known predisposing factor for chronic liver disease in adults, and has proved to be a feature, confirmed histologically, in keeping with liver dysfunction after Fontan [3, 33-35]. Although venous congestion is the most logical cause of liver dysfunction in a circulation lacking a pulmonary pump, previous findings have suggested that other mechanisms might be implicated and that longstanding increased systemic venous pressure is probably just one of the factors influencing liver function in this setting. Indeed, abnormal coagulation factors levels have been observed in patients after bidirectional cavopulmonary anastomosis, with presumably low splanchnic venous pressure [36], as well as in patients with single-ventricle physiol-
therapy before the bidirectional cavopulmonary anastomosis [37]. It is well known that during a staged Fontan approach, thromboembolic complications may occur, but the cause of perioperative coagulation abnormalities is rather unclear. Procelewska and colleagues [38] recently reported that the hemodynamic status is important as far as coagulation abnormalities and liver dysfunction after hemi-Fontan and Fontan procedures are concerned. The study suggests that elevated concentration of factor VIII and significant influence of hemodynamics on coagulation profile could contribute to postoperative thromboembolic complications [38].

These findings support the hypothesis that, beside venous congestion, other factors may contribute to liver dysfunction in these patients. We have investigated liver venous congestion using the portal pulsatility ratio, a reliable noninvasive test [18–21], and found that 50% of our patients have features of hepatic vein congestion. Nevertheless, there was no correlation between this index and liver disease score or presence of coagulopathy. We therefore hypothesized that other factors might be implicated in the development of liver damage in these patients.

One of the main laboratory features suggesting liver function derangement is the occurrence of coagulopathy, and has previously been described in this setting by several studies [8, 11–14]. Chaloupecky and coworkers [39] observed reduced mean concentrations of factor VII, factor V, protein C, and fibrinogen in patients after total cavopulmonary connection. The same study suggested that the abnormalities in the coagulation profile observed in patients after Fontan operation are related to protein production in the liver [39]. We decided to test coagulopathy using also the measurement of factor V, a vitamin K–independent and therefore also a warfarin-affected marker of deranged hepatic synthetic function. This marker is very trustworthy and used commonly in the setting of liver failure [40]. Interestingly, we have found that coagulopathy and liver disease score are correlated with reduced cardiac index and, to a lesser extent, with heart rate, suggesting a probably reduced liver blood flow after Fontan operation.

The same hemodynamic mechanism has been implicated in liver disease of different etiology. Children with portal hypertension due to portal vein thrombosis have a selective impairment of clotting factors and otherwise normal liver function tests [41], similar to Fontan patients [8, 11]; restoring a normal liver blood flow in children with portal vein thrombosis leads to complete normalization of clotting profile [42]. Narkewicz and colleagues [43] found an abnormal galactose elimination in a group of children after the Fontan procedure. This test represents the functional hepatic mass receiving arterial or venous blood flow, being an indirect marker of liver blood flow. Tomita and associates [9] found that Fontan patients’ coagulopathy and overall liver function tests were more deranged as compared with a group of patients with increased atrial pressure due to other cardiac diseases, and that prothrombin time correlated to some extent to hemodynamic features, including cardiac index [9]. All these findings support the hypothesis that reduced liver blood flow plays a role in liver disease of Fontan patients.

It is rather well known that most of the children who undergo Fontan operation are bradycardic and have a reduced variability of heart rate [44]. In our study, we have shown that bradycardia is a feature of Fontan’s patients with reduced cardiac index. Indeed, there was an apparent trend to correlation between liver disease and low heart rate.

In conclusion, in our study, we have suggested that, in the long-term after Fontan operation, liver dysfunction correlates with reduced cardiac index. The effect of hepatic venous congestion has been demonstrated to be a feature of these patients but could not explain entirely liver disease in this setting. These preliminary findings, if confirmed by a larger prospective study, suggest that the reduction of liver blood flow could affect the hepatic function after the Fontan procedure and that strategies aimed at maintaining or reestablishing a normal cardiac index might prevent or improve liver disease in the long term after a Fontan operation.

References


