

# Liver and Cardiac Function in the Long Term After Fontan Operation

Sonia Camposilvan, MD, Ornella Milanese, MD, Giovanni Stelling, MD, Andrea Pettenazzo, MD, Lucia Zancan, MD, and Lorenzo D'Antiga, MD

Departments of Pediatric Hepatology, Pediatric Cardiology, and Pediatric Cardiac Surgery, University of Padova, Padova, Italy

**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  $\gamma$ GT 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.

(Ann Thorac Surg 2008;86:177–82)

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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.

Accepted for publication March 31, 2008.

Address correspondence to Dr D'Antiga, Paediatric Department, University of Padova, Via Giustiniani 3, Padova, 35128, Italy; e-mail: [lorenzo.dantiga@pediatria.unipd.it](mailto:lorenzo.dantiga@pediatria.unipd.it).

## Patients and Methods

### Study Design

Between December 2003 and September 2004, patients who had previously undergone a Fontan operation at our institution and were attending the follow-up program were contacted on the phone to propose to enter a noninvasive study of cardiac and liver function. Thirty-four of 40 patients accepted to be enrolled in the study. Informed consent was obtained from the patients or their parents, and the Ethics Committee of our institution approved this study. Patients having comorbidities involving the liver such as chronic viral hepatitis were excluded from the study.

### Patient Evaluation

The work-up comprised history and physical examination including weight, height, heart rate and blood pressure at rest and in supine position, liver and spleen clinical measurement expressed as distance of the lower border from the costal margin, and presence of ascites. A venous blood sample and a stool sample were obtained for laboratory tests. Liver ultrasonography and Doppler sonography were performed with the patient at rest and in the supine position. Echocardiography to evaluate cardiac function by two-dimensional M-mode measurements was also carried out.

Table 1. Liver Disease Score

| Score of Liver Disease           | Score According to Considered Variables <sup>a</sup> |   |                                |
|----------------------------------|--|---|--------------------------------|
|                                  | 0  | 1   | 2                              |
| Liver size from costal edge      | Normal ( $\leq 1$ cm)                                | $> 1$ cm and $\leq 3$ cm                                  | $> 3$ cm                       |
| Total bilirubin                  | Normal   | $> 20$ $\mu\text{mol/L}$                                  | $> 50$ $\mu\text{mol/L}$       |
| Clotting indicators <sup>b</sup> | Normal   | INR $> 1.2$ and $< 2.0$ or factor V $< 60\%$ and $> 30\%$ | INR $> 2$ or factor V $< 30\%$ |
| Doppler of the hepatic vein      | Normal   | Monophasic or diphasic pattern                            |                                |
| Doppler of portal vein           | Normal   | PR $< 0.54$   | Reversed flow                  |
| Doppler of the hepatic artery    | Normal RI and PI                                     | RI $> 0.70$ or PI $> 1.64$                                | RI $> 0.70$ and PI $> 1.64$    |

<sup>a</sup> Normal values: total bilirubin  $< 20$   $\mu\text{mol/L}$ ; INR = 0.8 to 1.2; factor V  $> 60\%$ ; hepatic veins, triphasic pattern; PR  $> 0.54$ ; RI  $< 0.7$ ; PI  $< 1.64$ . <sup>b</sup> 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  $\mu\text{mol/L}$ ), 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 hemo-

dynamic 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

|                                 | Number          | %    |
|---------------------------------|-----------------|------|
| Male                            | 20              | 59   |
| Female                          | 14              | 41   |
| Median age, years (range)       | 14.7 (4.1-26.7) |      |
| Age at operation, years (range) | 3.3 (0.9-14.4)  |      |
| Follow-up, years (range)        | 11.5 (1.7-23.2) |      |
| Diagnosis                       |                 |      |
| Tricuspid atresia               | 17              | 50   |
| Pulmonary atresia               | 4               | 11.8 |
| Hypoplastic left heart syndrome | 5               | 14.8 |
| Double-outlet right ventricle   | 2               | 5.8  |
| Holmes heart                    | 2               | 5.8  |
| Miscellaneous                   | 4               | 11.8 |
| Type of intervention            |                 |      |
| Atriopulmonary connection       | 8               | 23.5 |
| Total cavopulmonary connection  | 26              | 76.5 |

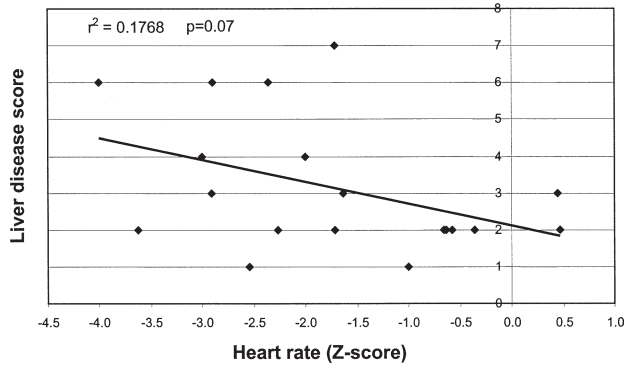


Fig 1. Correlation between increased liver disease score and low heart rate. The equation of the straight line relating liver disease score and heart rate is estimated as: liver disease score = (2.1250) + (−0.5949) heart rate.

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 [ $\text{mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ]) 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 atriopulmonary connection. Three patients of the latter group underwent a new operation to convert their original atriopulmonary 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 atriopulmonary connection have a follow-up significantly longer (mean duration,  $18.7 \pm 5.8$  years) than those with a total cavopulmonary connection (mean duration,  $9.6 \pm 11.3$  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 ( $r^2 = 0.18$ ,  $p = 0.07$ ; Fig 1). In fact, only 3 patients (9%) had a heart rate z-score above zero with respect to normal values for age. A

Table 3. Laboratory Tests

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

<sup>a</sup> Excluded patients on warfarin. <sup>b</sup> Only patients on warfarin.

junctional 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 atriopulmonary connection repair had a significantly greater gamma glutamyl transaminase 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 ( $p > 0.1$ , Student  $t$  test). 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

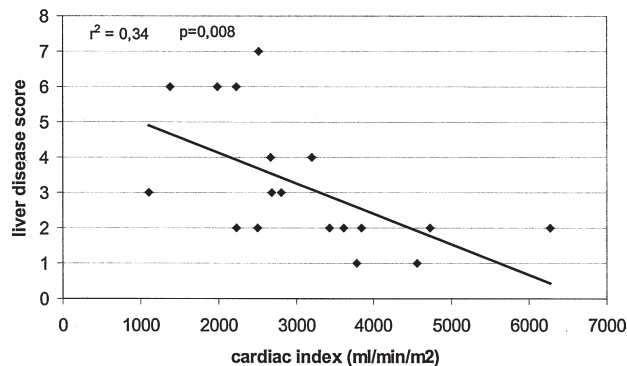


Fig 2. Correlation between increased liver disease score and low cardiac index. The equation of the straight line relating liver disease score and cardiac index is estimated as: liver disease score =  $(5.8568) + (-0.0009)$  cardiac index.

(20%). Median cardiac index was  $2,934 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  (range, 1,111 to  $6,269 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ), reduced in 50%; median stroke volume was  $48 \text{ mL/m}^2$  (range, 17 to  $81 \text{ mL/m}^2$ ), reduced in 2 patients (8%). There was an apparent trend to correlation between reduced cardiac index and increased liver disease score ( $r^2 = 0.34$ ;  $p = 0.008$ ; 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  $2,485 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $p = 0.03$ ). 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  $3,494 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $p = 0.02$ , 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 physiolog-

ogy 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-unaffected 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

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;26:240–8.
2. Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorf G. Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. *Heart* 1997;78:154–9.
3. Stamm C, Friehs I, Mayer JE Jr, et al. Long-term results of the lateral tunnel Fontan operation. *J Thorac Cardiovasc Surg* 2001;121:28–41.
4. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. *Am Heart J* 2000;140:111–20.
5. Mace S, Borkat G, Liebman J. Hepatic dysfunction and cardiovascular abnormalities: occurrence in infants, children, and young adults. *Am J Dis Child* 1985;139:60–5.
6. Cromme-Dijkhuis AH, Hess J, Hahlen K, et al. Specific sequelae after Fontan operation at mid- and long-term follow-up. *J Thorac Cardiovasc Surg* 1993;106:1126–32.
7. Cromme-Dijkhuis AH, Henkens CM, Bijleveld CM, Hillege HL, Bom VJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. *Lancet* 1990;336:1087–90.
8. van Nieuwenhuizen RC, Peters M, Lubbers LJ, Trip MD, Tijssen JG, Mulder BJ. Abnormalities in liver function and coagulation profile following the Fontan procedure. *Heart* 1999;82:40–6.
9. Tomita H, Yamada O, Ohuchi H, et al. Coagulation profile, hepatic function, and hemodynamics following Fontan-type operations. *Cardiol Young* 2001;11:62–6.
10. Rauch R, Ries M, Hofbeck M, Buheitel G, Singer H, Klinge J. Hemostatic changes following the modified Fontan operation (total cavopulmonary connection). *Thromb Haemost* 2000;83:678–82.
11. Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E. Coagulation factor abnormalities after the Fontan procedure and its modifications. *J Thorac Cardiovasc Surg* 1997;113:989–92.
12. Jahangiri M, Kreutzer J, Zurakowski D, Bacha E, Jonas RA. Evaluation of hemostatic and coagulation factor abnormalities in patients undergoing the Fontan operation. *J Thorac Cardiovasc Surg* 2000;120:778–82.

13. Ravn HB, Hjortdal VE, Stenbog EV, et al. Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection. *Heart* 2001;85:61-5.
14. Odegard KC, McGowan FX Jr, Zurakowski D, et al. Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis. *J Thorac Cardiovasc Surg* 2003;125:1260-7.
15. Ayabakan C, Özkutlu S. Normal patterns of flow in the superior cava, hepatic and pulmonary veins as measured using Doppler echocardiography during childhood. *Cardiol Young* 2003;13:143-51.
16. Meyer RJ, Goldberg SJ, Donnerstein RL. Superior vena cava and hepatic velocity patterns in normal children. *Am J Cardiol* 1993;72:238-40.
17. Vocke AK, Kardorff R, Ehrlich JHH. Sonographic measurements of the portal vein and its intrahepatic branches in children. Clinical report. *Eur J Ultrasound* 1998;7:121-7.
18. Duerinckx AJ, Grant EG, Perrella RR, Szeto A, Tessler FN. The pulsatile portal vein in cases of congestive heart failure: correlation of Duplex Doppler findings with right atrial pressures. *Radiology* 1990;176:655-8.
19. Hosoki T, Arisawa J, Marukawa T, et al. Portal blood flow in congestive heart failure: pulsed duplex sonographic findings. *Radiology* 1990;174:733-6.
20. Catalano D, Caruso G, Di Fazzio S, Carpinteri G, Scalisi N, Trovato GM. Portal vein pulsatility ratio and heart failure. *J Clin Ultrasound* 1998;26:27-31.
21. Rengo C, Brevetti G, Sorrentino G, et al. Portal vein pulsatility ratio provides a measure of right heart function in chronic heart failure. *Ultrasound Med Biol* 1998;24:327-32.
22. Sacerdoti D, Merkel C, Bolognesi M, Amodio P, Angeli P, Gatta A. Hepatic arterial resistance in cirrhosis with and without portal vein thrombosis: relationships with portal hemodynamics. *Gastroenterology* 1995;108:1152-8.
23. Flanders MM, Phansalkar AR, Crist RA, Roberts WL, Rodgers GM. Pediatric reference intervals for uncommon bleeding and thrombotic disorders. *J Pediatr* 2006;149:275-7.
24. Sahn DJ, DeMaria A, Kisslo J, Weyman A, for the Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
25. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determination: echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 1976;37:7-12.
26. Kronik G, Slany J, Mossbacher H. Comparative value of eight M-mode echocardiographic formulas for determining left ventricular stroke volume: a correlative study with thermodilution and left ventricular single plane cineangiography. *Circulation* 1979;60:1308-16.
27. Wallerson DC, Ganau A, Roman MJ, Devereux RB. Measurement of cardiac output by M-mode and two-dimensional echocardiography: application to patients with hypertension. *Eur Heart J* 1990;11(Suppl 1):67-78.
28. Wallerson DC, Devereux RB. Reproducibility of echocardiographic left ventricular measurements. *Hypertension* 1987;9(Suppl 2):6-18.
29. Tibby SM, Hatherill M, Marsh MJ, Morrison G, Anderson D, Murdoch IA. Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. *Intens Care Med* 1997;23:987-91.
30. de Simone G, Devereux RB, Daniels SR, et al. Stroke volume and cardiac output in normotensive children and adults: assessment of relations with body size and impact of obesity. *Circulation* 1997;95:1837-43.
31. Driscoll DJ, Offord KI, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. *Circulation* 1992;85:469-96.
32. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25 year experience with 216 patients. *J Am Coll Cardiol* 2001;37:933-9.
33. Marino BS. Outcomes after the Fontan procedure. *Curr Op Ped* 2002;14:620-6.
34. Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. *J Thorac Cardiovasc Surg* 2005;129:1348-52.
35. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. *Heart* 2007;93:579-84.
36. Odegard KC, McGowan FX Jr, Zurakowski D, et al. Coagulation factor abnormalities in patients with single-ventricle physiology immediately prior to the Fontan procedure. *Ann Thorac Surg* 2002;73:1770-7.
37. Odegard KC, McGowan FX Jr, DiNardo JA, et al. Coagulation abnormalities in patients with single-ventricle physiology precede the Fontan procedure. *J Thorac Cardiovasc Surg* 2002;123:459-65.
38. Procelewska M, Kolcz J, Januszewska K, Mroczek T, Malec E. Coagulation abnormalities and liver function after hemi-Fontan and Fontan procedures—the importance of hemodynamics in the early postoperative period. *Eur J Cardiothorac Surg* 2007;31:866-72.
39. Chaloupecky V, Svobodova I, Hadacova I, et al. Coagulation profile and liver function in 102 patients after total cavopulmonary connection at mid term follow up. *Heart* 2005;91:73-9.
40. Devictor D, Tahiri C, Rousset A, Massenavette B, Russo M, Huault G. Management of fulminant hepatic failure in children—an analysis of 56 cases. *Crit Care Med* 1993;21(Suppl):348-9.
41. Mack CL, Superina RA, Whittington PF. Surgical restoration of portal flow corrects procoagulant and anticoagulant deficiencies associated with extrahepatic portal vein thrombosis. *J Pediatr* 2003;142:197-9.
42. Superina R, Bambini DA, Lokar J, Rigsby C, Whittington PF. Correction of extrahepatic portal vein thrombosis by the mesenteric to left portal vein bypass. *Ann Surg* 2006;243:515-21.
43. Narkewicz MR, Sondheimer HM, Ziegler JW, et al. Hepatic dysfunction following the Fontan procedure. *J Pediatr Gastroenterol Nutr* 2003;36:352-7.
44. Rydberg A, Wiklund U, Rask P, Hornsten R. Serial assessment of variability in heart rate in children with the Fontan circulation. *Cardiol Young* 2005;15:498-503.