Liver Disease in Patients After the Fontan Operation

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We reviewed records of all patients with an initial Fontan operation or revision from 1973 to 2012 at our institution (n = 1,138); 195 patients had postoperative liver data available. Cirrhosis was identified by histopathology or characteristic findings on imaging with an associated diagnosis of cirrhosis by a hepatologist. Of 195 patients with biopsy or imaging, 10-, 20-, and 30-year freedom from cirrhosis was 99%, 94%, and 57%, respectively. There were 40 of 195 patients (21%) diagnosed with cirrhosis (mean age at Fontan 10.7 ± 8 years). On multivariate analysis, hypoplastic left heart syndrome was associated with increased risk of cirrhosis (n = 2 of 16, p = 0.0133), whereas preoperative sinus rhythm was protective (p = 0.009). Survival after diagnosis of cirrhosis was 57% and 35%, at 1, and 5 years, respectively. The cause of death was known for 9 patients (5 multiorgan failure, 2 liver failure, and 2 heart failure). In conclusion, there is an incremental occurrence of cirrhosis after the Fontan, which should be considered when designing follow-up protocols for patients after Fontan operation. **(Am J Cardiol 2016;117:456−460)**

Since its introduction in 1968, the Fontan operation has been used for the palliation of patients with a single ventricle.[1] The procedure has undergone many modifications.[2−4] Numerous late complications after Fontan operation have been reported including arrhythmias, heart failure, protein losing enteropathy, and hepatic dysfunction.[5] In patients after Fontan operation, increased central venous pressure and subsequent passive venous congestion have been associated with increased hepatic complications and overall mortality.[6−11] However, it is unclear if any specific factors increase the risk of developing hepatic dysfunction, creating a challenge in identifying patients needing close follow-up. The hepatic dysfunction created by vascular congestion has demonstrated a level of reversibility,[12,13] providing a possible role for early cardiac transplantation for susceptible patients. In this study, we examined our institution's experience with hepatic dysfunction and cirrhosis in patients who had a Fontan operation.

Methods

In this institutional review board−approved single-center retrospective study, we reviewed the records of all patients (n = 1,138) who had their initial Fontan operation or Fontan revision at the Mayo Clinic from October 1973 to June 2012. Information regarding demographic, anatomic, preoperative, operative, and postoperative variables was abstracted into a secure electronic patient database. This database included information regarding preoperative and postoperative echocardiograms, cardiac catheterizations, electrocardiograms, Holter/event monitors, liver imaging, and surgical data. In addition, a medical questionnaire was mailed to all patients not known to be dead at the time of the study (n = 723). Nonresponders received second and third questionnaires. If the subsequent questionnaires were not returned or completed, an attempt was made to contact the patients by telephone. The overall survey response rate was 42% (305 of 723).

Data were available in the form of blood tests (aspartate aminotransferase, alanine aminotransferase, or bilirubin), liver ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance elastography (MRE), or liver biopsy. Cirrhosis was diagnosed based on either (1) histopathologic diagnosis on biopsy or autopsy or (2) correlation of imaging findings (radiologic interpretation of liver cirrhosis on CT, MRI, MRE, or liver ultrasound) with clinical evaluation by a hepatologist with experience caring for Fontan patients (P.S.K). Patients were excluded from this analysis if they had evidence of viral hepatitis, alcoholic liver disease, or had a diagnosis of cirrhosis before their initial Fontan operation.

Statistical analysis was performed using the date of the Fontan operation as time = 0. All deaths were considered in the survival analysis, irrespective if they occurred intraoperatively, during immediate postoperative hospitalization, or after hospital discharge. Kaplan-Meier curves were derived to calculate 10-, 20-, and 30-year freedom from cirrhosis. Cox regression models were used to find univariate and multivariate predictors of being diagnosed with cirrhosis. The multivariate model considered univariately significant variables ($p < 0.05$) with model selection using the stepwise method. All statistical tests were 2 sided with the alpha level set at 0.05 for statistical significance. SAS 9.3 was used for the analysis (SAS Institute, Cary, North Carolina).

The cutoffs for discrete variables used in univariate and multivariate analyses were defined as follows: preoperative

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See page 459 for disclosure information.

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Table 1
Patient demographics

Characteristic	All Fontan Patients (N = 1,138)	Patients with liver data (N = 195)	Patients with Cirrhosis (N = 40)
Female	456 (40%)	88 (45%)	16 (40%)
Age at Operation	10.2 ± 8.3	9.6 ± 9.2	10.7 ± 8
Type of Fontan operation			
Atriopulmonary connection	619 (54%)	96 (49%)	22 (55%)
Lateral tunnel	290 (25%)	46 (24%)	9 (22%)
Extracardiac conduit	134 (12%)	44 (22%)*	5 (13%)
Other type of Fontan	95 (9%)	9 (5%)	4 (10%)
Preoperative anatomy			
Tricuspid Atresia	310 (27%)	57 (29%)	13 (33%)
Double Inlet Left Ventricle	292 (26%)	40 (21%)	11 (28%)
Asplenia/Heterotaxy	78 (7%)	16 (8%)	4 (10%)
Pulmonary Atresia/Intact Septum	62 (5%)	16 (8%)*	2 (5%)
Hypoplastic Left Heart Syndrome	27 (2%)	16 (8%)	2 (5%)
Mean post-bypass left atrial pressure (mmHg)	9.6 ± 3.2	8.9 ± 2.8	9.1 ± 3
Mean post-bypass Fontan pressure (mmHg)	17.4 ± 3.1	16.9 ± 2.6	17.1 ± 2.9
Post-Fontan Ejection Fraction (%)	49.5 ± 10.3	51 ± 10	54 ± 8.1
Most recent Ejection Fraction (%)	47.1 ± 13.4	50.6 ± 9.8	52 ± 13.5
Most recent Systemic Ventricle End-Diastolic Pressure (mmHg)	11 ± 4.3	10.7 ± 4.1	12.3 ± 4.4
Average New York Heart Association Functional Class (1-4)	1.83 ± 0.8	1.98 ± 0.9	2 ± 1
Protein-Losing Enteropathy	111 (9.7%)	33 (17%)*	7 (18%)
Documented arrhythmia	522 (46%)	141 (72%)*	34 (85%)*

* Denotes values that are statistically different from All Fontan Patients ($p < 0.05$).

pulmonary artery pressures (>15 mm Hg), pulmonary arteriolar resistance (>3 U × m^2), ventricular end-diastolic pressure (>12 mm Hg), post-bypass Fontan pressures (>20 mm Hg), and chest tube duration (>21 days). Bypass times and post-bypass left atrial pressures were analyzed as continuous variables. The complete set of variables evaluated for their association with survival and functional status of survivors are listed in Supplementary Table 1.

Results

Overall, 1,138 patients had their initial Fontan or Fontan revision operation at our institution, with a mean duration of follow-up of 14.3 ± 9.5 years (median 14.1 years). Clinical follow-up of liver function and associated imaging were available for 195 patients with an average duration of follow-up of 20.6 ± 8.1 years (median 22 years). Demographics of this cohort are described in Table 1. In comparison with all Fontan patients, there was a higher proportion of patients with extracardiac conduits, initial lesion of pulmonary atresia with intact ventricular septum, history of arrhythmia, or history of PLE in patients with liver imaging available ($p < 0.05$). There were no other significant differences between the liver follow-up and the overall Fontan cohort. In long-term follow-up, there were no significant differences in cardiac function in the form of ejection fraction or systemic ventricle end-diastolic pressure, or in functional class between the groups.

For the 195 patients with available liver data, the mean age at Fontan operation was 9.6 ± 9.2 years with a range of 7 months to 53 years; 40 of 195 patients (21%) had a fenestration performed at the time of the operation, with most of the fenestrations being performed after 1995. At

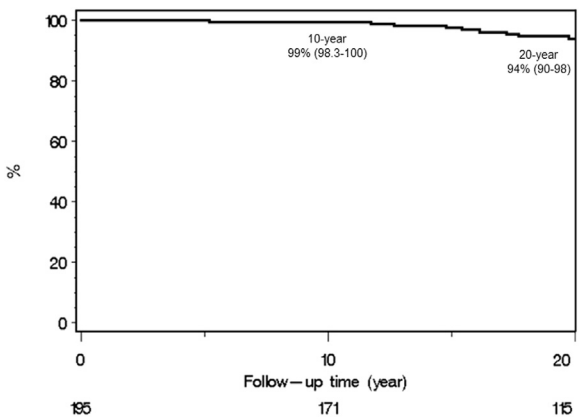

Figure 1. Kaplan-Meier curve of freedom from developing cirrhosis in 195 patients with liver data after Fontan. There is an incremental incidence of cirrhosis with freedom from cirrhosis of 99% (98.3-100) in 171 patients at 10 years and 94% (90-98) in 115 patients at 20 years.

most recent follow-up, 150 of 195 patients (77%) were alive and 45 (23%) were known to be dead. Liver biochemical tests were available for all 195 patients; there were no significant differences in aspartate aminotransferase, alanine aminotransferase, total bilirubin, or direct bilirubin levels between patients who did or did not develop cirrhosis; 24 of 195 patients (12%) had a liver biopsy (3 of 24 postmortem), of which 23 (96%) were abnormal; 152 of 195 patients (78%) had a liver ultrasound, of which 86 (57%) were noted to be abnormal; 25 of 195 patients (30%) had a liver MRI (72% abnormal), 33 of 195 (17%) had a CT of the liver (91% abnormal), and 33 of 195 (17%) had an MRE of the liver (79% abnormal) with 81 of 195 (42%) having at least