Impact of Liver Disease After the Fontan Operation

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Liver disease is being reported with increased frequency in survivors of the Fontan operation. The clinical impact of structural hepatic abnormalities in these patients remains largely unknown. We sought to assess if, and how, cardiologists are screening for hepatic disease in these patients to evaluate for clinical or laboratory correlates of structural hepatic disease and determine the prevalence and clinical impact of such disease. Retrospective data analysis from tertiary institutions was performed. Hepatic imaging studies and serology performed over the last decade were reviewed and clinical and laboratory correlates of structural hepatic alterations on liver imaging or biopsy were sought. Outcomes were determined. In this cohort study, 53 of 60 adult survivors (88%) underwent hepatic imaging with computed tomography, magnetic resonance imaging, or ultrasound with a median number of 2 (0 to 10) studies over the past decade. The frequency of hepatic imaging varied widely with 70% of patients undergoing serial studies. Cirrhosis with or without abnormal hepatic nodules was seen in 29 of 53 patients (55%) at 18.4 ± 5.6 years after the Fontan procedure. Adverse hepatic-related outcome occurred in 22% of the entire patient cohort and was unrelated to time from Fontan operation. In conclusion, there exists significant variability in the type and timing of testing for hepatic complications after the Fontan procedure. Structural hepatic alterations are common and can be associated with significant morbidity and mortality. Routine imaging, and serologic evaluation, is recommended in all Fontan survivors. © 2015 Elsevier Inc. All rights reserved. **(Am J Cardiol 2015;115:249−252)**

Hepatic cirrhosis after Fontan palliation for single ventricle cardiac anatomy has been well described in small patient cohorts.[1−5] The evolution of anatomical hepatic derangements in these patients remains ill-defined thereby making it difficult to know whom to screen and how often.[4−6] We sought to characterize the frequency and modalities of hepatic screening used for evaluation of these patients and identify the type, severity, prevalence, and clinical impact of anatomic and physiologic hepatic derangements present. We also sought to assess for laboratory or clinical correlates of cirrhosis or other significant hepatic pathology in an adult cohort of patients surviving the Fontan procedure.

Methods

An institutional review board approved review of data on all patients evaluated during the past 10 years who had undergone the Fontan procedure in childhood and survived to ≥18 years was performed. Serologic and clinical correlates of "significant" hepatic pathology were assessed for. Significant hepatic pathology was defined as the presence of advanced fibrosis, cirrhosis, hepatocellular carcinoma, hepatic adenomatosis, or dysplastic hepatic nodules on imaging and biopsy. This definition was chosen as it was believed that these particular findings, in contrast to isolated portal hypertension and/or early fibrotic changes, carried significant potential to alter long-term outcome. The presence or absence of protein losing enteropathy (defined by an elevated stool α-1 antitrypsin and associated hypoalbuminemia) was recorded. Cardiac catheterization data were recorded if performed within 1 year of imaging and/or biopsy evaluation for cirrhosis. Data from routine outpatient laboratory evaluation performed in adolescence and adulthood were reviewed. Testing was performed at the discretion of the primary cardiologist. The frequency and absolute number of times routine outpatient testing was performed were recorded. Values from routine out-patient testing performed at or near the time of hepatic imaging were recorded for the purposes of data analysis. International normalized ratio values were not recorded as most patients were on warfarin therapy. Several scores found to be predictive of hepatic fibrosis in other patient populations[7−9] were calculated including aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio,[7] APRI (AST to platelet ratio)[8] and FIB-4 score (age × AST/platelet count × ALT).[9]

Evaluation for liver pathology was performed at the discretion of the primary cardiologist. Imaging of the liver was performed through ultrasound with Doppler, dual phase computed tomography with contrast, or magnetic resonance imaging. Liver biopsy was performed at the discretion of the hepatologist involved in the patient's care and was triggered

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See page 252 for disclosure information.

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Table 1
Demographic data for the entire patient cohort

Clinical Variable	N=60
Male/female	31/29
Age at last follow-up (years)	28 (18-43)
Age at Fontan (months)	66 (14-324)
Type of Fontan	
Extra cardiac conduit	20 (33%)
Lateral Tunnel	20 (33%)
Atriopulmonary connection	14 (23%)
Bjork modification of atriopulmonary connection	6 (10%)
Atrial arrhythmias	29 (48%)
Pacemaker	24 (40%)
Asplenia	12 (20%)
Protein Losing Enteropathy	13 (22%)
Peak Oxygen consumption (ml/kg/min ± SD)	60.8 ± 12.8

Table 2
Liver imaging per patient (N=53)

Maximal severity of Liver Disease On Imaging	Number of patients
No hepatic abnormalities	4 (7%)
Congestion only	20 (38%)
Cirrhosis without nodules	19 (36%)
Cirrhosis with nodules	10 (19%)

by imaging findings consistent with cirrhosis and progressive serologic abnormalities, suspicious hepatic mass, or consideration of cardiac transplantation.

Cirrhosis was defined on biopsy using the Metavir grading system[3] or in those patients without biopsy, as computed tomography or magnetic resonance imaging findings of parenchymal heterogeneity with irregular undulating liver margins, and caudate hypertrophy with or without enhancing nodules.[3] Hepatic imaging was assigned a score out of 4 with[1] representing no identified hepatic abnormalities,[2] minor changes believed to represent congestion or early fibrosis,[3] consistent with cirrhosis and[4] cirrhotic changes with enhancing nodules. Patients with a score of 3 or 4 were deemed to have cirrhosis whereas those with a lesser score were said to not have cirrhosis unless there was evidence to the contrary on liver biopsy. Frequency of an adverse hepatic outcome was calculated and defined as clinically symptomatic synthetic hepatic dysfunction including gastrointestinal pathology with bleeding requiring treatment, hepatic encephalopathy defined as altered level of consciousness in association with an elevated ammonia level, hepatocellular carcinoma or adenomatosis, hepatorenal syndrome in the face of normal systolic function, or progressive change in dysplastic hepatic nodules required listing for liver transplant in association with listing for cardiac transplant.

Statistical analysis was conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Continuous data were expressed as means with SDs or medians with ranges as appropriate and categorical data were tabulated. A 2-sided p value of <0.05 was considered statistically significant. Demographic, clinical, and serologic variables for those patients with versus without significant liver pathology and those patients with versus without adverse clinical outcome were compared using a chi-square test for dichotomous or categorical variables and *t* test or Wilcoxon rank sum for continuous variables depending on their normality. Correlates of cirrhosis, and the presence of adverse clinical outcome were sought using a logistic regression model and odds ratios calculated. Using a logistic regression model, the area under the curve was determined to calculate the sensitivity and specificity of each laboratory test.

Results

Sixty adult patients who had undergone the Fontan procedure during childhood, and who were evaluated as adults in either a pediatric cardiology clinic or adult congenital cardiology clinic within the last 10 years, were identified. Clinical characteristics of the patient cohort are outlined in Table 1. At the time of last follow-up, 45 (75%) were alive without listing for heart transplantation, 1 alive awaiting heart transplantation, 3 (5%) alive and awaiting combined heart and liver transplantation, 6 (10%) alive after heart transplantation, and 5 (8%) deceased. Age at death was 24 ± 5 years. Of the 53 (88%) patients who underwent hepatic imaging for evaluation of cirrhosis (Table 2), initial hepatic imaging was performed at 24 ± 7 years occurring 18 ± 5 years after the Fontan procedure. Serial imaging was performed in 37 patients (70%). Patients underwent a median of 2 (0 to 10) studies during adolescence and adulthood. Patients with a normal initial study were less likely to undergo repeat imaging (33% vs 75%, $p = 0.003$). Of the 8 patients who had a normal first study and underwent repeat study, 4 (50%) had new abnormalities on repeat imaging 2.8 (1 to 10) years later. Of the 29 patients undergoing serial imaging who had abnormal findings on first study, 25 (86%) had new abnormalities on repeat scan 2 (1 to 7) years later. Comparing those patients who underwent hepatic imaging ($n = 53$) versus those that did not ($n = 7$), evaluation with hepatic imaging was not related to current age (25 ± 5 vs 26 ± 6, $p = 0.6$), age at Fontan procedure (7 ± 6 vs 6 ± 4 years, $p = 0.8$), interval from Fontan procedure (20 ± 6 vs 21 ± 5 years, $p = 0.8$), type of Fontan procedure (modern day vs atriopulmonary connection 69% vs 66%, $p = 0.4$), clinical symptoms, or presence of an abnormal liver function test (70% vs 57%, $p = 0.4$) but was related to whether the patient was seen in a pediatric cardiology versus adult congenital cardiology clinic (48% vs 100%, $p = 0.001$). Liver biopsy was performed in 19 of the 35 (54%) patients noted to have cirrhosis on imaging and demonstrated Metavir F1 stage (no fibrosis) in 0, F1 to F2 stage (portal fibrosis and/or bridging fibrosis with few septae) in 4 (21%), F3 stage (bridging fibrosis with many septae) in 4 (21%), and F4 stage (cirrhosis) in 11 (58%). Esophagogastroduodenoscopy was performed in 23 patients, with findings of varices in 10 (43%), erosive gastric or duodenal ulcers in 5 (26%), and hepatic gastropathy or duodenopathy without ulcers in 9 (39%). Outpatient laboratory evaluation as defined herein was performed a median of 5 (1 to 20) times per patient over the past 10 years. Routine testing in everyone included a comprehensive metabolic panel with assessment of AST, ALT, alkaline phosphatase, protein, and albumin. In addition, 29 (48%)