Liver health in adults with Fontan circulation: A multicenter cross-sectional study

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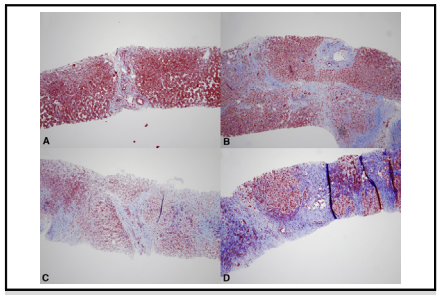
ABSTRACT

Objectives: Liver disease is an important contributor to morbidity and mortality in patients after Fontan surgery. There has been no large-scale survey of liver health in this population. We sought to explore the prevalence and predictors of liver disease in a multicenter cohort of adults with Fontan physiology.

Methods: Subjects were recruited from 6 adult congenital heart centers. Demographics; clinical history; and laboratory, imaging, and histopathology data were obtained.

Results: Of 241 subjects (median age 25.8 years [11.8-59.4], median time since Fontan 20.3 years [5.4-34.5]), more than 94% of those who underwent testing (208 of 221) had at least 1 abnormal liver-related finding. All hepatic imaging (n = 54) and liver histology (n = 68) was abnormal. Subjects with abnormal laboratory values had higher sinusoidal fibrosis stage (2 vs 1, $P = .007$) and higher portal fibrosis stage (3 vs 1, $P = .003$) compared with those with all normal values. Low albumin correlated with lower sinusoidal fibrosis stage (1 vs 2; $P = .02$) and portal fibrosis stage (0 vs 3, $P = .002$); no other liver studies correlated with fibrosis. Regenerative nodules were seen on 33% of histology specimens.

Conclusions: Regardless of modality, findings of liver disease are common among adults with Fontan circulation, even those appearing clinically well. Cirrhosis is present in up to one-third of subjects. Correlations between hepatic fibrosis stage and clinical history or findings on noninvasive testing are few. Further research is needed to identify patients at risk for more severe liver disease and to determine the best methods for assessing liver health in this population. (J Thorac Cardiovasc Surg 2016;■:1-9)



Hepatic fibrosis, present in nearly all cases, ranges from mild (A) to cirrhotic (D).

Central Message

Evidence of liver disease can be found in nearly all patients with Fontan circulation, but its clinical significance remains incompletely understood.

Perspective

As more people with Fontan circulation survive into adulthood, dysfunction of other organ systems has become apparent. In this first multicenter study of adults with Fontan circulation, evidence of liver disease is seen almost universally, but few correlations with clinical features are found. Clinicians caring for patients with Fontan circulation should include assessment of the liver as part of routine surveillance.

CONG

The development of the Fontan procedure was a major milestone in the management of patients with functionally univentricular hearts.[1] The rerouting of systemic venous blood directly into the pulmonary circulation results in near normalization of systemic oxygen saturation and ventricular volume load. With current techniques, 15-year survival after the Fontan operation approaches 95%.[2] Long term, however, compromised ventricular preload

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Abbreviations and Acronyms

AARCC = Alliance for Adult Research in Congenital Cardiology
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CT = computerized tomography
GGT = gamma glutamyl transpeptidase
HCC = hepatocellular carcinoma
INR = international normalized ratio
IQR = interquartile range
LLN = lower limit of normal
MELD-XI = model for end-stage liver disease, excluding INR
MRI = magnetic resonance imaging
NAFLD = nonalcoholic fatty liver disease
PA = pulmonary artery
PLE = protein-losing enteropathy
RA = right atrium
RV = right ventricle
ULN = upper limit of normal

and increased ventricular afterload and central venous pressures lead invariably to complications that may include arrhythmias, congestive heart failure, renal insufficiency, plastic bronchitis, protein-losing enteropathy (PLE), and liver disease.[3]

Liver disease has received much attention in recent years as more patients with Fontan circulation enter adulthood and as its impact on long-term morbidity in this population has become apparent.[4] Increasingly frequent reports of hepatocellular carcinoma (HCC) among patients with Fontan physiology have raised particular concern.[5] Studies detailing the prevalence of liver disease in patients with Fontan circulation have been restricted to single-center reports consisting of small numbers of patients[6-10] or with a short period of follow-up.[11-13] In addition, few have included histopathologic data, which is still considered the ''gold standard'' for diagnosis of hepatic fibrosis. Biochemical markers of liver disease and hepatic imaging data are more readily available for patients with Fontan circulation but may not accurately reflect the histological changes that are present on biopsy.[7-10] As such, the prevalence of liver disease and the factors that contribute to more significant liver involvement remain incompletely understood.

To gain better insight into liver health in this population and to form a basis for further prospective studies, the Alliance for Adult Research in Congenital Cardiology (AARCC) sought to document the prevalence of liver disease and its associated factors in a large, diverse group of adult patients with Fontan physiology. We hypothesized that abnormalities in liver-related serum markers, imaging studies, and histopathology are highly prevalent in this population and are likely to be more pronounced in those with more significant hemodynamic derangement or with more long-standing Fontan circulation.

METHODS

Study Design

This was a multi-institutional, cross-sectional, observational study. Subjects were patients 16 years of age or older who had undergone Fontan surgery and who presented to 1 of 6 US adult congenital heart disease (ACHD) centers for evaluation from September 2009 through April 2012. The protocol was developed by the core institution (Boston Children's Hospital, Boston, Mass) and was subsequently refined and approved by members of AARCC. Subjects were excluded if they had a history of cardiac transplantation, inherited forms of liver disease (including hereditary hemochromatosis, Wilson disease, α1-antitrypsin deficiency, and cystic fibrosis) or autoimmune hepatitis. The protocol was approved by each center's institutional review board, and written informed consent was obtained when applicable.

A suggested algorithm for comprehensive assessment of the patient with Fontan circulation, based on established care guidelines and expert consensus, was provided to all centers (Figure 1); however, each subject underwent only those studies deemed clinically indicated by the primary cardiologist. Standardized case report forms were used for data collection, which included basic demographic information, primary congenital cardiac diagnosis as designated using standardized nomenclature,[14] date of initial Fontan operation, type of initial Fontan operation, other surgical procedures performed, and current medications. Additional data were obtained within 6 months of liver biopsy, or within any 1-year period if no biopsy was performed, including hemodynamics; imaging parameters of cardiac function[15]; cardiopulmonary exercise testing; and laboratory studies, including complete blood count, basic metabolic panel, and liver function tests. For enrolled subjects who had undergone prior liver biopsy, including before 16 years of age, data collected from the 6 months before and after liver biopsy were used. Normal ranges for each center were obtained for use during data analysis.

Hepatic imaging studies included computerized tomography (CT) or magnetic resonance imaging (MRI). These were sent to the core center (Boston Children's Hospital/Brigham and Women's Hospital) in DICOM format where they were reviewed by 2 radiologists (NIS, AJH) who were blinded to all clinical data other than history of Fontan surgery. Cardiac CT and MRI studies, when available, were also reviewed by these radiologists for usable data related to liver health. Available liver biopsies were stained with hematoxylin and eosin, Masson trichrome, and reticulin stain and shipped to the core center for analysis by 2 pathologists (RDO, MEJ), blinded to all clinical data other than history of Fontan surgery. The specimens were graded semiquantitatively for a number of features according to a predetermined scoring system outlined in Table 1, including a scoring scheme for portal fibrosis modified from the METAVIR criteria to provide finer detail in cases of more advanced fibrosis.[16]

Statistical Analysis

Categorical data are presented as n (%) and continuous data are presented as median and range or median and interquartile range as indicated. Characteristics were compared between groups using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Spearman's rank correlation was used to assess the relationships between ordinal sinusoidal and portal fibrosis scores and continuous hemodynamic and laboratory variables. Sinusoidal and portal fibrosis scores were compared by clinical characteristics, imaging findings, and laboratory values based on normal ranges using the Wilcoxon rank sum test. All data analyses were performed with SAS version 9.2 for Windows (SAS Institute, Inc, Cary, NC). Unless otherwise indicated, all tests of significance are 2-sided with statistical significance judged as $P < .05$.