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Hepatic stiffness in the bidirectional cavopulmonary circulation: The Liver Adult-Pediatric-Congenital-Heart-Disease Dysfunction Study group

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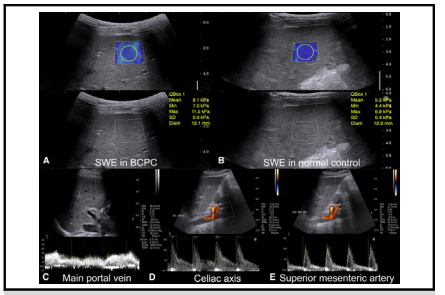
ABSTRACT

Objectives: We hypothesized that hepatic injury in single-ventricle CHD has origins that predate the Fontan operation. We aimed to measure hepatic stiffness using ultrasound and shear wave elastography (SWE) in a bidirectional cavopulmonary connection (BCPC) cohort.

Methods: Subjects were prospectively recruited for real-time, hepatic, ultrasound-SWE for hepatic stiffness (kPa) and echocardiography. Doppler velocities, a velocity-time integral, flow volume, and resistive index, pulsatility index, and acceleration index were measured in celiac and superior mesenteric arteries, and in the main portal vein (MPV). Comparisons were made among subjects who had BCPC, subjects who were healthy, and a cohort of patients who had undergone the Fontan procedure.

Results: Forty subjects (20 patients who had BCPC; 20 age- and gender-matched control subjects) were studied. The hepatic stiffness in BCPC was elevated, compared with that in control subjects (7.2 vs 5.7 kPa; $P = .039$). Patients who had BCPC had significantly higher celiac artery resistive index (0.9 vs 0.8; $P = .002$); pulsatility index (2.2 vs 1.7; $P = .002$); and systolic-diastolic flow ratio (10.1 vs 5.9; $P = .002$), whereas the superior mesenteric artery acceleration index (796 vs 1419 mL/min in control subjects; $P = .04$) was lower. An elevated resistive index (0.42 vs 0.29; $P = .002$) and pulsatility index (0.55 vs 0.35; $P = .001$) were seen in MPV, whereas MPV flow was reduced (137.3 vs 215.7 mL/min in control subjects; $P = .036$). A significant correlation was found for hepatic stiffness with right atrial pressure obtained at catheterization ($P = .002$). Comparison with patients who underwent the Fontan procedure showed patients who had BCPC had lower hepatic stiffness (7.2 vs 15.6 kPa; $P < .001$).

Conclusions: Hepatic stiffness is increased with BCPC physiology, and this finding raises concerns that hepatopathology in palliated, single-ventricle CHD is not exclusively attributable to Fontan physiology. Hepatic stiffness measurements using SWE are feasible in this young population, and the technique shows promise as a means for monitoring disease progression. (J Thorac Cardiovasc Surg 2016;151:678-84)



Hepatic elastography and Doppler in BCPC.

Central Message

Hepatic stiffness is increased with bidirectional cavopulmonary connection physiology.

Perspective

Hepatopathology in palliated single-ventricle CHD may not be attributable to exclusively Fontan physiology. Hepatic stiffness measurements using shear wave elastography is feasible in this young population, and the technique shows promise as a means for monitoring disease progression.

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The bidirectional cavopulmonary connection (BCPC) is a palliative procedure for single-ventricle congenital heart disease (CHD), typically performed on patients aged 3 to 6 months, to provide adequate prograde pulmonary blood flow until Fontan palliation is accomplished 3 to 4 years later. The procedure consists of an end-to-side connection

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Abbreviations and Acronyms
BCPC = bidirectional cavopulmonary connection
CHD = congenital heart disease
MPV = main portal vein
SWE = shear wave elastography

between the superior vena cava and the undivided right pulmonary artery, and flow from the heart into the pulmonary arteries is interrupted in most patients.

Unfortunately, hepatic abnormalities after the Fontan operation are common[1-5]; these include markedly higher risk for nonalcoholic cirrhosis.[6] Progressive hepatic failure and even hepatocellular carcinoma has occurred in these young patients.[1,5,7,8] The pathologic changes in the liver after a Fontan operation consist of sinusoidal dilatation and fibrosis. These changes are presumably related to high venous pressures from high resistance to hepatic venous drainage, also called "hepatic afterload," but hypoxemia and diminished cardiac output may be important factors in pathogenesis.[2,9,10]

The clinical importance of liver disease in single-ventricle CHD is recognized increasingly. However, very little is known about the origin and progression of liver fibrosis in this population. Hepatic failure in single-ventricle heart disease patients influences surgical choices, including Fontan revision, heart transplantation, and heart-liver transplantation, so noninvasive means for evaluating the liver in single-ventricle CHD are of great interest.

The Liver Adult-Pediatric-Congenital-Heart-Disease-Dysfunction Study (LADS) group at our institution recently reported the feasibility of shear wave elastography (SWE) for noninvasive assessment of hepatic stiffness.[10] Analysis of SWE and ultrasound and duplex flow dynamics suggests that Fontan physiology produces sufficient elevation of hepatic afterload to result in changes in hepatic stiffness and histology.[10] After the Fontan procedure, hepatic stiffness is markedly increased; flow volume in the main portal vein is decreased; and celiac and mesenteric arterial resistive indices are higher.[10] Associations of elevated hepatic stiffness with unfavorable Fontan hemodynamics and advanced liver fibrosis are well documented.[11,12] Hepatic stiffness in a single ventricle at the BCPC palliation stage has not been reported, but may provide insights into the pathogenesis of this process.

We hypothesized that hepatic stiffness in a palliated single ventricle, as measured by ultrasound elastography, is elevated before the Fontan operation. The purpose of this study was to use SWE prospectively, to measure hepatic stiffness in infants and children who have BCPC physiology, for comparison with age- and gender-matched healthy control subjects, and with a historical cohort of patients who underwent the Fontan procedure, from our institution.[10] In addition, we sought to correlate hepatic stiffness and vascular Doppler indices with patient age, time from BCPC, and pre-BCPC cardiac catheterization hemodynamic findings.

METHODS

Study Population

This was a prospective, single-center research study, approved by an institutional review board, conducted between May 2013 and September 2014. Patients with BCPC physiology were prospectively enrolled for research liver ultrasound-SWE imaging at the time of routine outpatient clinical follow-up. Age- and gender-matched healthy volunteer infants and children (serving as a control group) were recruited in response to an advertisement asking for participation, which was placed in the institution's (of the review board) employee newsletter. Informed, written consent was obtained from the parents or legal guardians of all recruited patients and healthy subjects. Complete transthoracic echocardiograms were performed in the BCPC subjects within 3 months of liver ultrasound-SWE, using a GE Vivid E9 Ultrasound System (GE Healthcare, Milwaukee, Wis).

Hepatic Ultrasound and SWE Protocol

A comprehensive liver ultrasound examination with duplex, followed by SWE, was performed using the ultrasound-SWE system (Aixplorer, SuperSonic Imagine, Bothell, Wash), per our protocol.[10] Real-time B-mode imaging, with Doppler assessments of the celiac axis, the superior mesenteric artery, and the main portal vein (MPV) was performed. A broad-bandwidth curved transducer (SC6-1, SuperSonic Imagine) was used for generation of transient shear waves with simultaneous real-time B-mode imaging.

Quantitative viscoelasticity mapping of the liver was performed from the shear wave propagation, generating a real-time anatomic reference gray-scale image and an elastogram color map. At least 3 SWE image acquisitions were made in each study. A-single, experienced sonographer (one of the investigators) performed all acquisitions. The study was transferred to a Macintosh computer (Macbook Pro, Apple, Inc, Cupertino, Calif), for SWE quantification using the OsiriX DICOM (Digital Imaging and Communications in Medicine) review software and Q-box plug-in (OsiriX, Pixmeo Sàrl, Geneva, Switzerland). The Q-box was positioned over an area of relative homogeneous elastogram, within a zone of uniform liver parenchyma. The SWE gain (70%), Q-box diameter (12 mm), elastogram range (0-40 kPa), and depth (4-7 cm) were set to the default setting, per manufacturer recommendations. The mean elastogram value was measured, expressed in terms of Young's modulus (kPa) in the area delineated by the Q-box. The measurement was repeated 3 times, to obtain 3 independent SWE maps of the patient in the same scanning plane, and the average of the 3 independent mean elastogram values was taken as the final hepatic stiffness for each patient.

Statistical Analysis

Data are expressed as mean ± SDs with ranges. The nonpaired Student *t* test was used for comparison of patients who had BCPC with the control group and the group who underwent the Fontan procedure. Univariate least-square linear regressions of hepatic stiffness and vascular Doppler indices against patient age, body surface area, and duration of BCPC were performed. Statistical analysis was performed using Minitab 16.1 (Minitab, Inc, State College, Pa).

RESULTS

In all, 40 subjects were studied, including 20 patients who had BCPC physiology, and 20 age- and gender-matched