Impact of hemodynamics and fluid energetics on liver fibrosis after Fontan operation

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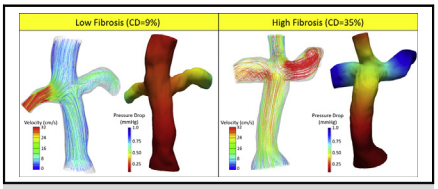
ABSTRACT

Objective: The staged Fontan procedure has shown promising short-term outcomes in patients with single ventricles. However, Fontan-associated liver disease is a marked problem as patients age. The purpose of this study is to investigate the relationship between hemodynamics and liver fibrosis in patients undergoing the Fontan.

Methods: A total of 33 patients undergoing the Fontan with liver fibrosis were included in this study. Cardiac magnetic resonance and phase-contrast cardiac magnetic resonance data, as well as catheterization measurements and liver biopsies, were obtained for each patient. Computational fluid dynamic simulations were performed to quantify total cavopulmonary connection hemodynamics using patient-specific anatomies and blood flow waveforms reconstructed from cardiac magnetic resonance data. Collagen deposition (as a measure of liver fibrosis) was quantified by digital image analysis of Sirius Red stained slides. Statistical analyses were performed to investigate potential relationships between liver fibrosis and Fontan hemodynamics.

Results: Liver fibrosis was found to be related to global metrics (inferior vena cava flow, ventricle power output) rather than to local total cavopulmonary connection hemodynamics and efficiency. Indexed inferior vena cava flow showed a significant, positive correlation with liver fibrosis (rho = 0.624, $P < .001$). Upper and lower Sirius Red tertile comparisons showed a significant difference in indexed inferior vena cava flow ($P = .008$).

Conclusions: Significant increases in inferior vena cava flow consistent with fibrosis induced arterialization and ventricular power output suggest a burden being placed on the single ventricle from liver fibrosis. Local total cavopulmonary connection flow dynamics do not seem to influence the degree of fibrosis. Favorable total cavopulmonary connection hemodynamics may not be enough to overcome the power shortage and elevated venous pressures inherent to a Fontan circulation. (J Thorac Cardiovasc Surg 2018;156:267-75)



Velocity and pressure fields for low and high FALD.

Central Message

Liver fibrosis in patients with single ventricles after the Fontan is related to increased IVC flow and ventricular power output rather than local TCPC hemodynamics.

Perspective

The degree of liver fibrosis is independent of TCPC hemodynamics in patients with single ventricles with Fontan circulation. Increased IVC flow is associated with increased liver fibrosis, possibly related to hepatic arterialization, and may add a chronic volume load to the single ventricle. Superior TCPC performance may not be enough to overcome the power shortage and elevated pressures inherent to a Fontan.

See Editorial Commentary page 276.

The current surgical treatment strategy for single ventricle reconstruction leads to a Fontan palliation with passive blood flow to the lungs through a total cavopulmonary connection (TCPC). Inherent physiologic differences exist between a biventricular circulatory system and a Fontan circulation, including elevated central venous pressure (CVP) and relatively diminished cardiac output (CO), as well as a

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Abbreviations and Acronyms
BSA = body surface area
CFD = computational fluid dynamics
CMR = cardiac magnetic resonance
CO = cardiac output
CVP = central venous pressure
EDV = end-diastolic volume
FALD = Fontan-associated liver disease
IVC = inferior vena cava
LPA = left pulmonary artery
PL = power loss
TCPC = total cavopulmonary connection

myriad of additional features, including the potential for ventricular dysfunction, increased vascular impedance, and venous congestion.[1-4] As these unique patients survive into early adulthood, numerous long-term complications are commonly recognized, such as poor growth and development, lymphatic insufficiency manifest as protein losing enteropathy, plastic bronchitis, and liver fibrosis.[3,5-8]

Fontan-associated liver disease (FALD) is a well-documented complication that may have its roots in genetic, biochemical, and hemodynamic origins. Liver insult also may occur at birth (hypoxia and hypoperfusion), during the various perioperative states (Norwood, bidirectional Glenn and Fontan surgeries), and throughout the chronic condition of elevated CVP and relatively diminished CO.[5] Regardless of cause, FALD is now recognized as "universal" and likely a progressive process affecting all Fontan survivors.[6]

With the goal of determining specific causes and risk factors of FALD, previous studies have investigated relationships among biochemical markers, comorbidities, cardiac morphology, demographics, hemodynamics, and hepatic fibrosis using a variety of liver assessment techniques and scores.[6,8-11] Several biochemical markers show significant correlations in specific studies, as do duration of existence with a Fontan circulation and some hemodynamic measures such as hepatic wedge pressure.[8,10-12] These correlations are moderate at best and often vary between studies, likely because of variability in patient cohort, sample size, and fibrosis quantification methodology.

An area left mostly untouched by these previous studies is the use of detailed cardiac magnetic resonance (CMR)–derived flow dynamics and computational fluid dynamics (CFD) to assess and correlate local Fontan flows and energetics with liver fibrosis. Individual vessel flow rates could provide new information regarding factors not seen in previous studies using more global flow metrics. Investigating the energetics of the Fontan pathway and the TCPC may offer insights into surgical optimization and novel design as a method to potentially combat liver fibrosis.

To contribute to the understanding of FALD and its causes, we combine CMR, CFD, cardiac catheterization, and liver biopsy data to investigate potential relationships between hepatic fibrosis and Fontan hemodynamics. In this study, we investigated detailed CMR-derived flow dynamics and TCPC energetics as potential risk factors for hepatic fibrosis. We hypothesize that the extent of hepatic fibrosis is associated with poor Fontan hemodynamics.

MATERIAL AND METHODS

Patient Cohort

A total of 33 patients with single ventricles after Fontan completion were studied with concurrent CMR, cardiac catheterization, and liver biopsy. All subjects were evaluated as part of an institutional recommended clinical care protocol for elective comprehensive assessment who are more than 10 years from their Fontan operation.[5] Indication for assessment was institutional recommendation for comprehensive surveillance and not for any specific signs or symptoms of Fontan circulatory failure. No subject had any clinical signs or symptoms of hepatic dysfunction. This study cohort of 33 is a subset of a larger cohort of 67 patients who had catheterization and liver biopsy performed. Inclusion in the current cohort required that the cardiac catheterization, magnetic resonance imaging, and liver biopsy were all performed within a 6-month period. In most cases, CMR was obtained just before catheterization, and liver biopsy was performed immediately after catheterization. Demographic data including age, gender, body surface area (BSA), Fontan type, and Fontan duration were obtained for each patient. Fontan duration is defined as the time between the Fontan surgery and data collection. All patient data were obtained from the Children's Hospital of Philadelphia and collected under Institutional Review Board approval (12-009791) with written informed consent.

Magnetic Resonance Imaging Acquisition

All CMR scans were performed with a Siemens 1.5 T magnetic resonance imaging system (Siemens Medical Solutions, Malvern, Pa). Patients were scanned supine, head first in the scanner with electrocardiogram leads placed. After localizers were obtained, a stack of contiguous, static, diastolic steady-state free precession images were obtained from the diaphragm to thoracic inlet to assess anatomy and provide inputs for CFD modeling. Slice thickness was generally 4 to 5 mm, and in-plane resolution was 1.2 × 1.2 mm.

Through-plane, retrospectively gated, phase-contrast magnetic resonance was used to assess flows in the cavae, branch pulmonary arteries, and pulmonary veins, and across the aortic valve. Inferior vena cava (IVC) flow was measured supra-hepatic. Velocity encoding was generally 150 cm/sec for the aorta and 60 cm/sec for the other vessels. Slice thickness was generally 4 to 5 mm with in-plane resolution of 1.25 × 1.25 mm. The number of phases was a function of the heart rate similar to the cines and ranged from 20 to 30.

Global ventricular function was calculated from cine images of the ventricular short axis. Endocardial and epicardial borders were semiautomatically traced, and ventricular volumes were determined by multiplying the slice thickness with the segmented area. Slice volume was integrated along the ventricular longitudinal axis using Simpson's rule to extract the total volume of the ventricle in a cardiac phase. This method was applied at end diastole and end systole to calculate end-diastolic volume (EDV) and end-systolic volume, respectively. Stroke volume and ejection fraction were calculated as the EDV/end-systolic volume and stroke volume/EDV, respectively.

Catheterization Protocol

All subjects were in a fasting state for 8 hours before the catheterization, as per institutional policy. The use of light sedation, deep sedation, or