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● *Technical Note*

ULTRASOUND SHEAR WAVE ELASTOGRAPHY AS A MEASURE OF PORCINE HEPATIC DISEASE IN RIGHT HEART DYSFUNCTION: A PILOT STUDY

Jessie J. Hu,* M. Yasir Qureshi,* Matthew W. Urban,† Rondell Graham,‡ Meng Yin,† Saji Oommen,§ Kimberly A. Holst,¶ Sarah Edgerton,§ Luiz Vasconcelos,‖ Ivan Nenadic,‖ Frank Cetta*,# and for the Wanek Program Pre-clinical Pipeline

* Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota, USA; † Division of Radiology Research, Mayo Clinic, Rochester, Minnesota, USA; ‡ Division of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota, USA; § Wanek Program for Hypoplastic Left Heart Syndrome, Mayo Clinic, Rochester, Minnesota, USA; ¶ Department of Cardiothoracic Surgery, Mayo Clinic, Rochester, Minnesota, USA; ‖ Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA; and # Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA

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Abstract—Patients with congenital heart disease with a pressure-overloaded right ventricle can develop liver disease and would benefit from non-invasive diagnostic modalities such as ultrasound shear wave elastography (US SWE). We sought to investigate the ability of US SWE to measure dynamic changes in liver stiffness with an acute fluid bolus in an animal model. Three piglets underwent surgical intervention to create a pressure-overloaded right ventricle and, 12 wk later, underwent US SWE, both pre- and post-intravenous infusion of a saline bolus. Ultrasound measures of shear modulus, velocity and attenuation were taken to characterize hepatic mechanical properties. Liver stiffness exhibited a dynamic component that increased after fluid bolus, although not reaching statistical significance with our small sample size, and these changes were greater in more diseased livers. US SWE may provide a promising non-invasive method for assessing dynamic changes in hydration status and degree of liver disease. (E-mail: Cetta.Frank@mayo.edu) Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine and Biology.

Key Words: **Ultrasound shear wave elastography, Congenital heart disease, Pigs, Liver stiffness, Liver disease, Fontan operation.**

INTRODUCTION

Liver disease has become an increasing problem in patients with congenital heart disease and, specifically, those with functional single-ventricle physiology. These patients usually have definitive palliation with a Fontan operation at 3 to 4 years of age. Decades after the Fontan operation, these patients face many challenges. Fontan-associated liver disease (FALD) is a relatively recent discovery and limits long-term survival for these patients (Pundi et al. 2016). Initially, the liver has venous congestion, which can progress to fibrosis and later to cirrhosis. Survival after the diagnosis of cirrhosis is approximately 57% at 1 year and 35% at 5 years (Pundi et al. 2016). Most concerning is the late complication of hepatocellular carcinoma. Routine laboratory markers of liver disease become abnormal only with advanced disease. Percutaneous liver biopsy has been advocated for definitive diagnosis of FALD. Several surveillance protocols for FALD have been published and some recommend liver biopsy in all patients at 10 years after Fontan (Rychik et al. 2012). Liver biopsy is invasive and has poor patient acceptance and a complication rate of 3%. In addition, the sensitivity of liver biopsy with heterogeneous liver findings is unclear and is subject to sampling error (Janes and Lindor 1993). Therefore, accurate, reproducible and non-invasive means of assessing liver disease in patients with congenital heart disease are needed.

Abdominal ultrasonography has previously been described predominantly as a tool for detecting signs of cirrhosis, such as a nodular liver surface with increased echogenicity and irregular borders; however, in patients after Fontan, these signs may be seen even without

Address correspondence to: Frank Cetta, MD, Division of Pediatric Cardiology and Department of Cardiovascular Medicine, Gonda 6335, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: Cetta.Frank@mayo.edu

cirrhosis (Hilscher et al. 2017). Doppler waveform changes have been described in patients after Fontan; however, the utility of this technique is unclear (Wu et al. 2011). In patients who have undergone Fontan operation, imaging studies such as ultrasound shear wave elastography (US SWE) could be valuable non-invasive tools for evaluation of hepatic dysfunction but have not yet been reliably validated. US elastography techniques include transient elastography (TE) and shear wave elastography. More literature exists for transient elastography, which has a sensitivity and specificity of diagnosing liver cirrhosis of 81% and 88%, respectively (Geng et al. 2016). However, the disadvantages of TE are that it does not produce anatomic images, so the precise location of the measurements is not known, and it is available only on a dedicated non-imaging device manufactured by a single manufacturer (Fibroscan, Echosens), whereas SWE is available on conventional ultrasound scanners (Serai et al. 2017).

Ultrasound SWE has been emerging as a possible imaging modality to examine hepatic stiffness, which is used as a surrogate for hepatic fibrosis (Hilscher et al. 2017). One study examined the effect of the Fontan operation on liver stiffness in 18 children and revealed a significant increase in liver stiffness immediately post-surgery and at the 5- to 7-month follow-up (DiPaola et al. 2017). Kutty et al. compared 41 patients with Fontan physiology with controls and found that they had higher hepatic stiffness on US SWE, and this stiffness correlated with higher ventricular end-diastolic pressure and pulmonary artery wedge pressure during hemodynamic catheterization and increased hepatic fibrosis (Kutty et al. 2014). Another study reported an excellent correlation between US SWE and biopsy findings of acute rejection in transplanted livers (Nenadic et al. 2017).

Tissue stiffness, however, may have two components: a static component reflecting the intrinsic properties of the liver parenchyma and a dynamic component reflecting hemodynamic effects of changes in extracellular fluid. These properties have been observed in liver magnetic resonance elastography (MRE) studies. Multiple studies have reported on the use of MRE in quantitatively assessing the mechanical properties of the liver (Asbach et al. 2008; Huwart et al. 2006). MRE liver stiffness indices correlate with progressive fibrosis and portal hypertension and vary differently with respect to the cause of portal hypertension (i.e., congestion or cirrhosis) (Yin et al. 2017). In addition to examining static changes from progressive liver disease, however, studies on MRE have also examined dynamic changes in liver disease. In patients with biopsy-proven hepatic fibrosis, MRE has revealed that hepatic stiffness will increase more after a liquid meal as compared with healthy controls (Yin et al. 2011). Yin et al. (2013), using a disease-free porcine model, reported significantly increased shear stiffness of the liver on MRE after a fluid bolus.

To our knowledge, US SWE has mostly been used to examine static, parenchymal changes and has only examined dynamic hepatic changes in an *ex vivo* model. Rotemberg et al. (2013) found, in excised canine livers, that hepatic shear wave speed and strain increased with increases in portal venous pressure. The aim of this study was to investigate the influence of dynamic, acute fluid status changes on the measurements of shear stiffness with US SWE in a pressure-overloaded, congested liver in an *in vivo* model. In this study, we utilized shear wave modulus to characterize elastic mechanical properties of the tissue, as well as shear wave phase velocity and attenuation to measure viscoelastic mechanical properties. Juvenile pigs were utilized in this study because their growth would theoretically parallel hemodynamic changes that occur in young children with congenital heart disease.

METHODS

Animal preparation

After approval of the study by our Institutional Animal Care and Use Committee, four piglets (Landrace/Large White) at approximately 4−6 wk of age underwent surgical banding of the main pulmonary artery to simulate a pressure overload-induced right heart dysfunction model. A right ventriculotomy was also performed to inflict additional myocardial injury to augment right heart failure. At approximately 16 wk of age (12 wk after pulmonary artery band placement), the pigs (31.0−48.8 kg) underwent US SWE imaging. All animals were strictly fasted 12 h prior to imaging to establish uniform intravascular volume status. Anesthesia consisted of 1%−3% isoflurane, and animals were intubated and not moving during the scans. Baseline liver US SWE results were obtained. The animals then received a 20 mL/kg intravenous bolus of normal saline after which a repeat liver US SWE was performed. Approximately 1 wk after the US SWE exam series, the pigs were euthanized and necropsy was performed.

US SWE acquisition

A General Electric Logiq E9 (General Electric Healthcare, Wauwatosa, WI) with a C1-6 curvilinear array (General Electric Healthcare) was used for making SWE measurements. The Society of Radiologists in Ultrasound Consensus Conference Statement (Barr et al. 2015) was not specifically consulted for this study; however best practices in ongoing liver studies with the Department of Radiology at Mayo Clinic were utilized and adapted to the pigs. The pig was placed