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Ultrasonic characterization of the nonlinear properties of canine livers by measuring shear wave speed and axial strain with increasing portal venous pressure

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ABSTRACT

Elevated hepatic venous pressure is the primary source of complications in advancing liver disease. Ultrasound imaging is ideal for potential noninvasive hepatic pressure measurements as it is widely used for liver imaging. Specifically, ultrasound based stiffness measures may be useful for clinically monitoring pressure, but the mechanism by which liver stiffness increases with hepatic pressure has not been well characterized. This study is designed to elucidate the nonlinear properties of the liver during pressurization by measuring both hepatic shear wave speed (SWS) and strain with increasing pressure. Tissue deformation during hepatic pressurization was tracked in 8 canine livers using successively acquired 3-D B-mode volumes and compared with concurrently measured SWS. When portal venous pressure was increased from clinically normal (0–5 mmHg) to pressures representing highly diseased states at 20 mmHg, the liver was observed to expand with axial strain measures up to 10%. At the same time, SWS estimates were observed to increase from 1.5–2 m/s at 0–5 mmHg (baseline) to 3.25–3.5 m/s at 20 mmHg.

1. Introduction

Increasing portal venous pressure (PVP) is one of the hallmarks of advancing liver disease and contributes to leading causes of death and morbidity from cirrhosis, such as variceal hemorrhage (Ripoll et al., 2007; Gulzar et al., 2009; Sharara and Rockey, 2001). Increasing pressure in the portal vein, which is the primary source of blood flow to the liver, is typically referred to as elevated hepatic or PVP. Monitoring hemodynamic response to therapies for reducing hepatic pressure through use of hepatic venous pressure gradient (HVPG) measurement has proven effective in prolonging life, but is expensive and invasive (Imperiale, 2003). Ultrasound imaging has been widely used for imaging the liver and gallbladder (Wu, 2008) and therefore is ideal for potential noninvasive hepatic pressure measurements. Duplex Doppler ultrasonography has been previously proposed for HVPG estimation (Yang, 2007; Zironi et al., 1992; Wu, 2008) and has shown a clear relationship between quantitative results and esophageal varices development (Bolondi and Gaiani, 1994). However, this method is not sufficiently accurate or reproducible between observers for implementation in clinical practice for HVPG quantification (Bolondi et al., 1991; Vries et al., 1991; Vizzutti et al., 2008). Ultrasound and MRI-based estimates of liver stiffness have been reported to increase with hepatic pressure (Millonig et al., 2010; Vizzutti et al., 2008; Bureau et al., 2008; Robic et al., 2011; Yin et al., 2011), suggesting that stiffness-based approaches may provide the basis for a noninvasive and inexpensive approach toward characterizing portal vein pressure in the clinic. These include splenic stiffness measurements (Takuma et al., in press; Nedredal et al., 2011) and direct liver stiffness measures (Robic et al., 2011; Han et al., 2012).

The major challenge to noninvasive stiffness-based metrics for characterizing hepatic pressure in vivo is that estimates of hepatic stiffness are also known to increase from a SWS of 1–1.5 m/s for normal livers to 3.5–5 m/s to with advanced fibrosis stage (Takuma et al., in press; Robic et al., 2011; Palmeri et al., 2011; Friedrich-Rust et al., 2008; Yoneda et al., 2008; Bavu et al., 2011; Crespo et al., 2012; Schlosser et al., 2009). While splenic stiffness has also been observed to increase with esophageal varices risk and PVP, splenic stiffness is also increased from baseline in patients with cirrhosis and without high levels of esophageal varices risk (Takuma et al., in press). Thus, a better understanding of the mechanisms by which hepatic pressure modulates estimates of liver stiffness could provide information needed to distinguish

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increasing hepatic pressure from advancing fibrosis stage. We have previously reported the nonlinear hyperelastic behavior of the liver as PVP increases (Rotemberg et al., 2012). In this work, an experiment was designed to simultaneously measure changes in hepatic strain and stiffness with increasing hepatic pressure in excised canine livers.

2. Background

This work primarily focuses on the potential applications of nonlinear characterization of the liver using shear wave speed (SWS) metrics toward noninvasive hepatic pressure characterization. Nonlinear properties of the liver have previously been explored for the purpose of computational surgery guidance (Jordan et al., 2009) and modeling car accident injury (Brunon et al., 2010) as well as development of power law based models for soft tissues (Nicolle et al., 2010). Nonlinear mechanical property evaluation of soft tissues such as the liver often requires information about corresponding stress and strain at particular time points. In the pressurized liver, because the geometry is so complicated, it is not feasible to translate the PVP directly into a stress without many simplifying assumptions. However, it is of clinical interest for potential applications of noninvasive pressure characterization to characterize the nonlinear mechanical properties that determine the increase in liver stiffness corresponding to PVP increases. The experiments described herein are inspired by acoustoelasticity experiments in that they generate estimates of SWS and applied strain (Gennisson et al., 2007; Shams et al., 2011), but novel in that both the applied strain and the resulting SWS increase are measured using ultrasonic metrics in response to an unknown applied stress in the form of PVP.

3. Methods

3.1. Experimental animals

Experimental excised canine livers were obtained through cooperation with the Duke University Vivarium and euthanasia was achieved within the guidelines provided by the Duke Institutional Animal Care and Use Committee. Imaging was performed within 2 h of excision and 3 mL of heparin were administered prior to euthanasia in 7 of the 8 cases to reduce coagulation effects.

3.2. Evaluation of hepatic changes with pressurization

The experiments described were designed to compare changes in hepatic deformation and stiffness estimates with increasing PVP. Eight excised canine livers were investigated. After the canine liver was removed, the hepatic artery, hepatic vein, and portal vein were cannulated and the hepatic artery and vein were closed. In all livers, super glue (Loctite® Westlake, OH) was used to seal any observed defects in the liver capsule due to the liver extraction (all defects were <2 mm). The liver was then placed in a heparinized saline bath for 5 min to remove remaining air in the liver. We attempted to mitigate the effects of included air, saline leakage, and clotting, because all could contribute to decreased observed strain and stiffness response to increasing hepatic pressure.

Increasing PVP was achieved by attachment of the portal vein to a variable height saline reservoir as described in (Rotemberg et al., 2012). A diagram of the experimental setup is shown in Fig. 1.

In order to characterize hepatic expansion, the livers were allowed to expand in a heparinized saline bath throughout the experiment. Liver pressure was increased stepwise from 0 to 20 mmHg with pressurization steps at 0.5–5 mmHg in magnitude as measured using a handheld digital manometer (SPER Scientific, Ltd., resolution=0.075 mmHg) attached to the portal vein cannulation setup. During each pressurization step, 3-D B-mode datasets were acquired using a Siemens Acuson SC2000™ scanner and 4Z1c matrix array ((Frey and Chiao, 2008) Siemens Healthcare, Mountain View, CA, USA). The 3-D B-mode volumes were acquired with a frame rate of 0.1 Hz for up to 4 min over a $2\times1.2\times1.2$ cm^3 volume located 5–7 cm axially away from the transducer.

Fig. 2 shows a single A-line through time from the 4-D dataset acquired for one pressurization increment. After each pressurization step, 6 SWS datasets were acquired with a separate system as described below from the region corresponding to that in which the 3-D B-mode acquisition occurred.

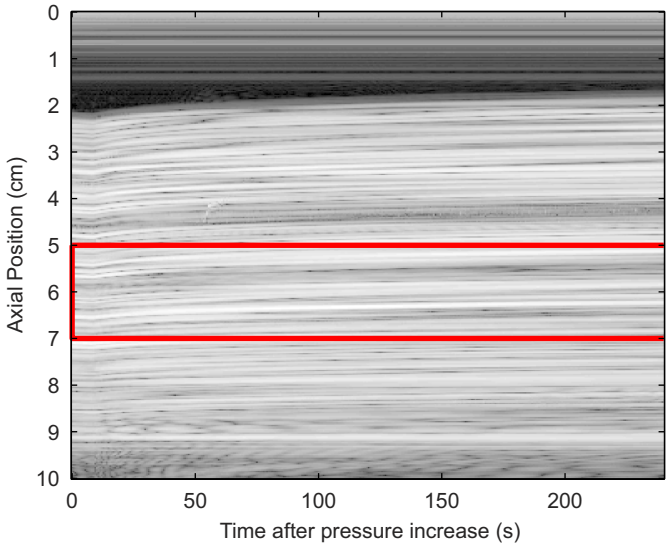

Fig. 2. Example of data acquired in a pressurization increment between 17 and 18 mmHg PVP in one excised canine liver. One axial A-line through the center of the volume interrogated is shown through time after pressure increase. Expansion is observed in the growth of the brighter region, which represents the liver. The red lines represent the axial extent of the 3-D region of interest over which strain was computed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

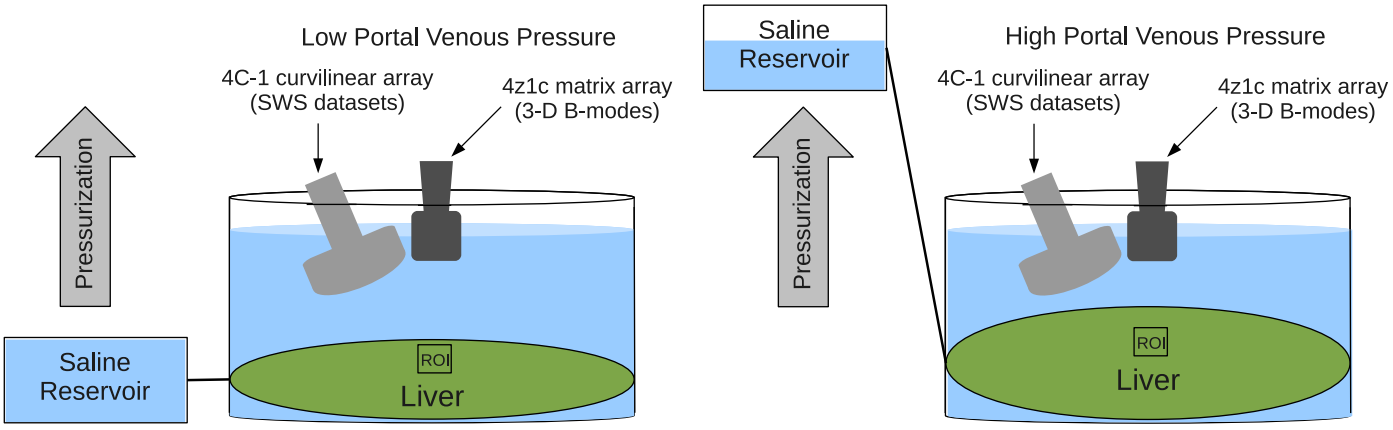

Fig. 1. Diagram of the hepatic pressurization and monitoring setup.