Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–7, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.01.002

● *Technical Note*

WHAT DO WE KNOW ABOUT SHEAR WAVE DISPERSION IN NORMAL AND STEATOTIC LIVERS?

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(*Received* 12 *August* 2014; *revised* 29 *December* 2014; *in final form* 11 *January* 2015)

Abstract—A number of new approaches to measure the viscoelastic properties of the liver are now available to clinicians, many involving shear waves. However, we are at an early stage in understanding the physical processes that govern shear wave propagation in normal liver, with more unknowns added when pathologies such as steatosis are present. This technical note focuses on what is known about the characterization of normal and steatotic (or fatty) livers, with a particular focus on dispersion. Some studies in phantoms and mouse livers support the hypothesis that, starting with a normal liver, increasing accumulations of micro- and macrosteatosis will increase the lossy viscoelastic properties of shear waves in a medium. This results in an increased dispersion (or slope) of shear wave speed and attenuation in the steatotic livers. Theoretical and empirical findings across a number of studies are summarized.
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Key Words: **Liver, Ultrasound, Shear waves, Dispersion, Steatosis, Magnetic resonance elastography.**

INTRODUCTION

The accumulation of fat in the liver has important clinical consequences and is growing in prevalence. For example, non-alcoholic fatty liver disease (NAFLD) is an emerging national health problem, with an estimated prevalence of 23%–33.6% (Angulo 2002; Lam and Younossi 2010; Schreuder et al. 2008; Wanless and Lentz 1990). NAFLD is actually a higher risk factor for cardiovascular mortality and malignancy than for liver-related mortality (Ong et al. 2008). The risk factors for NAFLD (obesity and insulin resistance/type 2 diabetes) are increasing dramatically, and the incidences of NAFLD and NASH (non-alcoholic steatohepatitis) are rising proportionately. A significant fraction of people with NASH—between 20% and 40%—will develop progressive liver fibrosis (Dyson et al. 2014), leading to cirrhosis and increased risk of hepatocellular carcinoma.

Currently the only methods for quantitative measurement of steatosis are liver biopsy, which is invasive with concomitant patient risk, and magnetic resonance imaging (MRI), which is expensive and not widely available. Thus, there is need for a non-invasive and readily available method to quantify hepatic fat, which is a biomarker for hepatic disease and the metabolic syndrome. Most recent elastographic research and clinical studies have focused on liver fibrosis staging, which can be performed with several U.S. Food and Drug Administration-approved MRI and ultrasound imaging systems. In addition, transient elastography, which has no imaging component, is performed with the FibroScan instrument (Echosens, Paris, France) (Sandrin et al. 2003). Numerous studies have reported promising results for characterization of later-stage fibrosis (Bavu et al. 2011; Boursier et al. 2010; Huwart et al. 2008; Muller et al. 2009; Palmeri et al. 2008; Yin et al. 2007). The effect of steatosis on high-grade fibrosis measurement is not yet clear (Ferraioli et al. 2012). Compared with a larger body of studies of shear wave speed and fibrosis, relatively few studies have examined frequency-dependent shear wave properties, related to dispersion or viscoelastic models (Asbach et al. 2008; Bavu et al. 2011; Deffieux et al. 2015; Friedrich-Rust et al. 2009; Huwart et al. 2007; Klatt et al. 2007; Nightingale et al. 2013; Salameh et al. 2007; Wang et al. 2009). Nonetheless, there are some preliminary observations that can be made about dispersion measurements from lean and steatotic livers. Some theoretical considerations and then experimental

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results from the literature and across a number of different species and measurement techniques are presented in the next two sections.

THEORY

Theoretical basis

In an isotropic elastic medium, it can be shown that a rotational or shear wave can propagate with a speed $c_s = \sqrt{\mu/\rho}$, where μ is the shear modulus, and ρ is the density (Graff 1975). This equation is widely used in the field of elastography to connect an observed wave speed with the presumed tissue shear modulus and the related Young's modulus, assuming a nearly incompressible tissue with a density close to unity.

If the medium is not purely elastic, but also incorporates loss mechanisms, then an attenuation coefficient will be observed that increases with frequency, and the shear wave speed will also tend to increase with frequency. These increases with frequency are called attenuation dispersion and wave speed dispersion, respectively. The standard framework for this (Blackstock 2000; Carstensen and Parker 2014) begins with the plane wave solution for displacement, ξ,

$$\xi(x,t) = \xi_0 e^{j(\omega t - kx)} \tag{1}$$

where the wave number $k = \omega/\sqrt{\mu/\rho} = \omega/c_s$, and ω is frequency. The amplitude of the displacement ξ_0 is directly proportional to the applied surface stress. But if the wavenumber k is complex, then we can explicitly write the phase velocity and attenuation in terms of a complex shear modulus, $\mu = \mu_1 + j\mu_2$:

$$k = \beta - j\alpha = \frac{\omega}{\sqrt{\frac{\mu_1 + j\mu_2}{\rho}}} \tag{2}$$

Then,

$$\overrightarrow{\xi}(x,t) = \overrightarrow{\xi} e^{-\alpha x + j(\omega t - \beta x)} \tag{3}$$

Various models exist for the complex shear modulus; for example, in the simple Kelvin–Voigt model of a parallel spring and dashpot with viscosity η, the imaginary component μ_2 increases with frequency:

$$\mu = \mu_1 + j\omega\eta \tag{4}$$

Whereas for a linear hysteresis model, μ_2 is a constant H with respect to frequency:

$$\mu = \mu_1 + jH \tag{5}$$

Other models that may be relevant to soft tissues such as the liver are found elsewhere (Carstensen and Parker 2014; Klatt et al. 2007; Liu and Bilston 2000; Parker 2014; Zhang et al. 2007).

These various models, with the exception of linear hysteresis, predict that the complex modulus, and therefore the phase velocity, will increase with frequency, indicating a dispersive medium. Note that in a dispersive medium, the group velocity, which defines the speed of the envelope of a broadband signal, is different from the phase velocity (Fitzpatrick 2013).

Equation (2) illustrates a simple empirical fact: As the complex shear modulus μ_2 approaches zero, the imaginary part, and therefore the attenuation coefficient, approaches zero, and the wave speed becomes a constant (and independent of frequency) given by $\sqrt{\mu/\rho}$. Conversely, as the complex shear modulus increases from zero, the attenuation and wave number and phase velocity of the shear wave can increase with frequency; however, the exact form of the increase, which is the observed dispersion, depends on the nature of the loss element or the particular model used. Normal lean liver has a measurable shear wave attenuation and dispersion (data are provided in the next section), and the impact of early-stage steatosis is hypothesized to increase dispersion by the addition of a viscous material to the medium, in effect increasing μ_2 and therefore dispersion by eqns (2) and (3). However, finding the most appropriate physical model for this remains as an important research question. There is the additional possibility of attenuation losses caused by scattering from the fat-filled vacuoles in steatosis. Shear wave scattering theory is covered in Einspruch et al. (1960) and White (1958) and is complicated by mode conversion mechanisms. However, it remains to be seen how large a factor this may be in the common shear wave band of 40–1,000 Hz. Finally, it must be noted that the progression of lean liver to early-stage steatosis is marked by the accumulation of fat as macro- and microvesicles of triglycerides. This may be the simplest set of changes to model, as compared with cases with high-grade fibrosis, plus steatosis, plus other possible complications. It may be that an adequate model of dispersion from early-stage steatosis will not be adequate for a discussion of high-grade fibrotic or cirrhotic livers with steatosis.

Empirical basis

A number of different techniques and studies have been used to study steatosis in liver. In Figure 1 we attempt to plot on a common parameter space the results of a number of studies (Asbach et al. 2008; Barry et al. 2012, 2014a, 2014b; Bavu et al. 2011; Chen et al. 2009, 2013; Deffieux et al. 2009; Hah et al. 2012; Klatt et al. 2007; Muller et al. 2009; Orescanin and Insana 2010; Xie et al. 2010). All animal studies were performed in accordance with protocols approved by institutional committees on animal resources, and all human studies were performed in accordance with protocols approved