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● *Original Contribution*

TIME HARMONIC ELASTOGRAPHY REVEALS SENSITIVITY OF LIVER STIFFNESS TO WATER INGESTION

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Abstract—The aim of the study was to test the sensitivity of liver stiffness (LS) measured by time harmonic elastography in large tissue windows to water uptake and post-prandial effects. Each subject gave written informed consent to participate in this institutional review board-approved prospective study. LS was measured by time harmonic elastography in 10 healthy volunteers pre- and post-prandially, as well as before, directly after and 2 h after drinking water. The LS–time function during water intake was measured in 14 scans over 3 h in five volunteers. LS increased by 10% ($p = 0.0015$) post-prandially and by 11% ($p = 0.0024$) after pure water ingestion, and decreased to normal values after 2 h. LS was lower after overnight fasting than after 2-h fasting (3%, $p = 0.04$). Over the time course, LS increased to post-water peak values 15 min after drinking 0.25 L water and remained unaffected by further ingestion of water. In conclusion, our study indicates that LS measured by time harmonic elastography represents an effective-medium property sensitive to physiologic changes in vascular load of the liver. (E-mail: ingolf.sack@charite.de) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Liver stiffness, Time harmonic elastography, Water uptake, Prandial effects, Hepatic vasculature, Blood volume.**

INTRODUCTION

Liver stiffness measurements by elastography have become a viable method to detect non-invasively structural changes in liver tissue resulting from various pathologic conditions such as hepatitis, steatosis and fibrosis (Bota et al. 2013; Fabrellas et al. 2013; Loomba et al. 2014; Martinez et al. 2012; Myers et al. 2012). In particular, the well-established link between LS and fibrosis motivates the clinical use of elastography based on sonography (such as transient elastography [TE] [Sandrin et al. 2003] or acoustic radiation force imaging [ARFI] [Palmeri et al. 2011]) or magnetic resonance elastography (MRE) (Asbach et al. 2010; Huwart et al. 2007; Venkatesh and Ehman 2015).

Despite the success of elastography in hepatologic examinations, there are still limitations concerning the assessment of mechanical properties in large tissue windows of the liver, as well as the detection of mild degrees of hepatic fibrosis (Tzschatzsch et al. 2014; 2015; Zhao et al. 2014). Furthermore, it remains to be explored which components of liver tissue contribute to the macroscopic response of LS in different dynamic regimes of TE, ARFI or MRE. Research in this area has revealed the influence of the collagen network, fat content, micro-fluid flow and vasculature on the liver's gross mechanical properties (Hirsch et al. 2014; Mazza et al. 2007; Parker 2015; Reiter et al. 2014).

For example, multi-scalar fluid–solid interactions communicate fluid properties such as volume, pressure and viscosity into the effective medium LS parameter as measured by elastography (Parker 2015). For this reason, LS is reduced by decompression of the liver in patients with an increased hepatic venous pressure gradient after receiving an intrahepatic shunt (Guo et al. 2015). Interestingly, sensitivity of LS to the intrahepatic venous pressure gradient was observed by

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multi-frequency MRE in the dynamic range of 30 to 60 Hz, whereas no sensitivity was reported when transient-based elastography methods were used (Berzigotti et al. 2013; Gao et al. 2012).

We therefore use time harmonic elastography (THE) by ultrasound, which operates in the frequency range of multifrequency MRE, to investigate the influence of water ingestion on LS. The THE method used to determine LS was recently introduced (Tzschatzsch et al. 2014; 2015) for examination of larger portions of the liver, especially in patients with ascites and obesity. THE combines continuous harmonic tissue stimulation by a vibrating patient bed with a standard clinical ultrasound scanner.

The purpose of this study was to test the sensitivity of THE-measured LS to physiologic effects related to an altered vascular load of the liver after water uptake. This knowledge provides a reference for the development of LS as a clinical marker sensitive to portal hypertension. Moreover, characterization of potential confounders of LS could increase the accuracy of hepatic elastography in many applications.

METHODS

The study was approved by the institutional review board (ethics committee). Written informed consent was obtained from all patients before study participation. A group of 10 healthy volunteers (mean age = 32 ± 10 y, nine males and one female, body mass index = 23.16 ± 2.57) were measured five times by THE: (i) after overnight fasting, (ii) directly after consuming a lunch of approximately 1000 kcal, (iii) after 2 h of fasting, (iv) 15 min after drinking 1.5 L of water and (v) 2 h after drinking 1.5 L of water. These measurements were made on each volunteer on two different days: measurements (i) and (ii) on day 1, and (iii)–(v) on day 2. To determine the time function of changes in LS induced by drinking water, 5 volunteers were scanned 14 times within a total period of 3 h, in the first 1.5 h of which 2 L of water (in portions of 0.25 L) was ingested.

Time harmonic elastography

The principles underlying THE of the liver were described by Tzschatzsch et al. (2012; 2014; 2015).

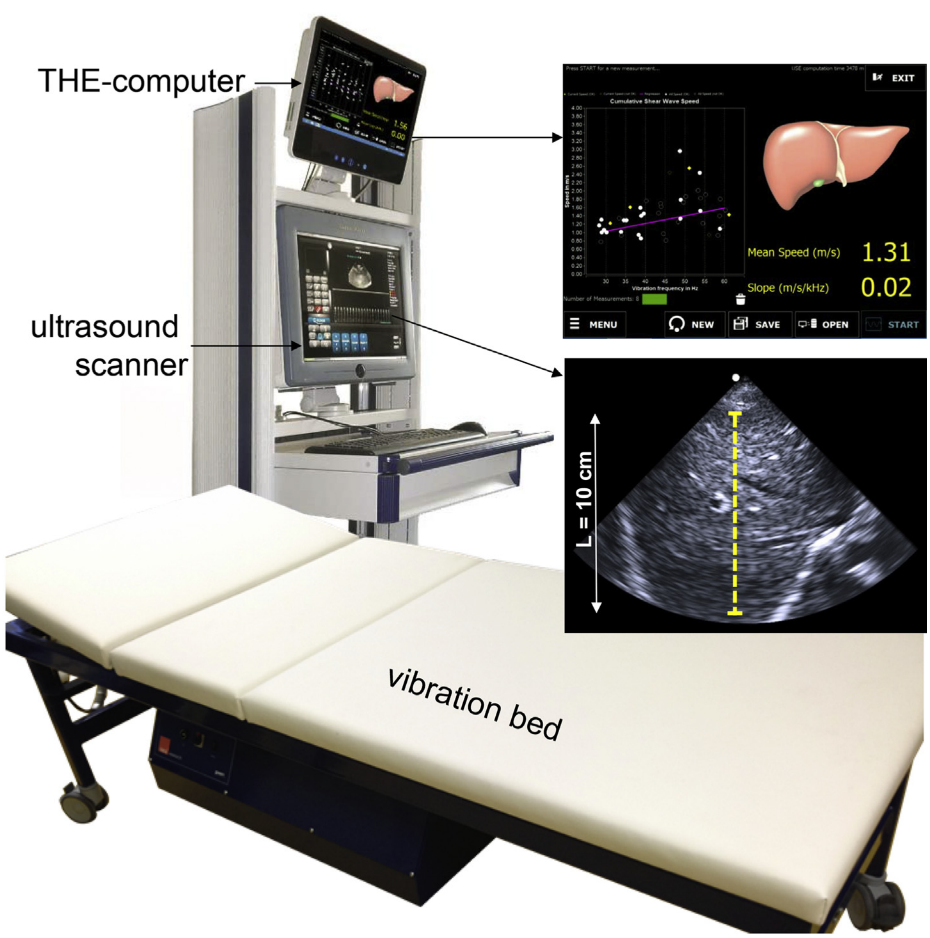

Fig. 1. Experimental setup of the time harmonic elastography (THE) system. Insets: B-mode display from the ultrasound scanner for elastography profile positioning and online display of measurement results of the THE computer.