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● *Original Contribution*

TWO-DIMENSIONAL TIME-HARMONIC ELASTOGRAPHY OF THE HUMAN LIVER AND SPLEEN

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Abstract—Measurement of shear wave speed of the liver and spleen by elastography is an established diagnostic procedure for the detection of hepatic fibrosis, portal hypertension and esophageal varices. However, current elastography systems are limited by the size and penetration depth of elastographic windows. In this study, 2D time-harmonic elastography is proposed for generating full field-of-view shear wave speed maps in great depth. Two-dimensional time-harmonic elastography uses external harmonic stimulation at multiple frequencies to create compound shear wave speed maps. The method is tested in a phantom with soft and stiff inclusions and used for elastography of the liver and spleen in 13 asymptomatic volunteers. Each volunteer was scanned twice to determine the sensitivity of the method to physiologic variations: first, after 2 h of fasting, and a second time, 15 min after drinking 1 L of water. The wave speed maps of the phantom clearly identified the soft and stiff inclusions, yielding values that were consistent with those from magnetic resonance elastography. *In vivo* wave speed values were 1.49 ± 0.11 m/s for the liver and 2.03 ± 0.15 m/s for the spleen in a lower-frequency band centered at 40 Hz and 3.15 ± 0.30 m/s for the spleen in a higher-frequency band centered at 120 Hz. After water intake, wave speed values increased by 6% in the liver ($p = 0.002$) and decreased in the spleen by 4% ($p = 0.021$, low-frequency band) and 6% ($p = 0.0002$, high-frequency band), suggesting the high sensitivity of the method to altered blood flow and perfusion pressure. Two-dimensional time-harmonic elastography of the liver and spleen is a promising method for measuring tissue stiffness at different states of blood flow and perfusion in a large tissue window and at great penetration depth. (E-mail: ingolf.sack@charite.de) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **2D ultrasound elastography, Time-harmonic elastography, Multifrequency vibration, Liver, Spleen, Blood perfusion.**

INTRODUCTION

Ultrasound-based elastography is widely used for the clinical diagnosis of diseases in various abdominal organs. In the liver, tissue stiffness is directly correlated with the grade of fibrosis (Cosgrove et al. 2013; Van Beers et al. 2015). Liver fibrosis can cause portal hypertension, splenomegaly, spleen fibrosis and esophageal varices, and all of these complications are associated with poor prognosis and increased mortality. Determination of liver and spleen stiffness can contribute information to the diagnosis of portal hypertension and esophageal varices (Singh et al. 2014).

Different methods have been employed to measure liver stiffness including transient elastography (TE) (Sandrin et al. 2002), acoustic radiation force impulse imaging (Nightingale et al. 2002), shear wave elasticity imaging (SWEI) (Sarvazyan et al. 1998) and supersonic shear wave imaging (SSI) (Bercoff et al. 2004). All of these methods can reliably detect liver fibrosis, but are limited in their capability to analyze larger regions farther away from the body surface. For example, a depth limit of 8 cm has been reported for SSI (Bamber et al. 2013), whereas TE is normally limited to 7 cm below the skin (Arda et al. 2013). In obese patients, the liver volume that can be assessed with these techniques is reduced dramatically, and TE has high failure rates in the presence of ascites (Cosgrove et al. 2013). In addition, small

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elastograms represent only a fraction of the whole organ, which limits the diagnostic accuracy of elastography in the assessment of disseminated disease.

Time-harmonic shear waves in the low-frequency range (<100 Hz) can reach deeper tissue throughout the body (Venkatesh et al. 2013). This technique, originally introduced as sonoelastography (Parker 2011; Yamakoshi et al. 1990), has recently been implemented for liver examinations in larger tissue windows using single-frequency (Zhao et al. 2014) or multifrequency (Tzschätzsch et al. 2014) external vibrations. However, these implementations are either limited in window size and penetration depth or measured averaged values along profiles. Nevertheless, promising results have been reported for the detection of fibrosis (Tzschätzsch et al. 2015; Zhao et al. 2014), as well as for capturing small but significant physiologic variations in liver stiffness caused by fasting or water ingestion (Ipek-Ugay et al. 2016).

In this study, we introduce 2D time-harmonic elastography (THE) for obtaining elastograms covering the full field of view at depths up to 13 cm beneath the skin. The method requires an external vibration device incorporated into the patient bed, but can otherwise be integrated into a clinical B-mode ultrasound scanner with a standard frame rate of 80 Hz. Two-dimensional THE will be tested in phantoms and *in vivo* for examining the liver and spleen in asymptomatic volunteers, once after 2 h of fasting and a second time after drinking of 1 L of water. With this study design, we aim to reproduce the previously discovered sensitivity of 1D THE to vascular flow and perfusion in the liver (Ipek-Ugay et al. 2016) and to investigate this effect for the first time in the spleen.

METHODS

Two-dimensional THE was investigated in phantom experiments and *in vivo* examinations of the liver and spleen of 10 asymptomatic volunteers.

Phantom preparation

A cubic phantom with a mass of approximately 3 kg was prepared from a mixture of water with 0.6% agar–agar (Fluka Chemie, Buchs, Germany). After solidification, two 2 cm diameter horizontal cylinders were punched out and filled with 0.4% and 0.8% agar-in-water solution. Microcrystalline cellulose (Euro OTC Pharma, Bönen, Germany) at a concentration of 0.5% was added to ensure echogenicity. The shear wave speeds of the matrix, the soft inclusion and the stiff inclusion were 1.84, 0.88 and 2.81 m/s, respectively, according to magnetic resonance elastography (MRE) experiments of samples of the same material and in the same frequency range as used in the phantom. The phantom was investigated by 2D THE in a lower- and a higher-frequency range using the same setup as for examination of the volunteers.

Volunteers

The study was approved by the institutional ethics board. Written informed consent was obtained from all volunteers before study participation. The 13 asymptomatic volunteers (10 male, 3 female) had a mean age of 36 y (standard deviation [SD]: 10 y, range: 25–55 y) and a mean body mass index of 22.9 (SD: 2.8, range: 18–27). In each subject, the liver and spleen were examined in a lower-frequency range (40 Hz center frequency). Additionally, we used a higher-frequency range (120 Hz center frequency) for elastography of the spleen to test whether the greater stiffness and smaller diameter of the spleen favor the use of higher vibration frequencies as compared with the standard frequency range used for examining the softer and larger liver. Details regarding the applied vibration frequencies are given below. The entire examination was performed twice in each volunteer, once after 2 h of fasting and a second time 15 min after intake of 1 L of water. Both the liver and spleen were investigated through intercostal windows in expiratory breath hold. To test the reproducibility of the method, the liver protocol was applied in one volunteer under fasting conditions on five different days. On each day, the volunteer was scanned in three sessions within a total of 15 min. Between sessions, the volunteer was asked to stand up and walk a few meters.

Shear wave generation

For shear wave generation, a patient bed with integrated loudspeaker as detailed in Tzschätzsch et al. (2015) was used (Fig. 1). Volunteers were examined in the supine position with the abdominal region directly above the loudspeaker. For tissue stimulation in the lower-frequency range, a multiharmonic waveform was designed, which was composed of six frequencies (f = 27, 33, 39, 44, 50 and 56 Hz) and approximately covered the range of frequencies applied in previous studies of the liver (Guo et al. 2015; Ipek-Ugay et al. 2016; Tzschätzsch et al. 2014, 2015). As explained later, these frequencies were chosen based on the concept of controlled aliasing. To account for higher attenuation with increasing frequency, we increased the amplitudes of the vibration signals by the empirical function exp(f/16 Hz) similar to Guo et al. (2015), Ipek-Ugay et al. (2016) and Tzschätzsch et al. (2014, 2015). For higher-frequency stimulation of the spleen, a superposition of three frequencies of f = 107, 119 and 136 Hz was used. As in the lower-frequency range, the choice of frequencies was made based on the Nyquist theorem applied to undersampled oscillations. In this