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● *Original Contribution*

FULL-FIELD-OF-VIEW TIME-HARMONIC ELASTOGRAPHY OF THE NATIVE KIDNEY

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Abstract—The purpose of this study was to analyze full-field-of-view maps of renal shear wave speed (SWS) measured by time-harmonic elastography (THE) in healthy volunteers in terms of reproducibility, regional variation and physiologic effects. The kidneys of 37 healthy volunteers were investigated by multifrequency THE. The complete renal parenchyma, as well as cortex and medulla, was analyzed. A subgroup was investigated to test reproducibility (n = 3). Significant differences between SWS in cortex, medulla and full parenchyma were observed (2.10 ± 0.17, 1.35 ± 0.11 and 1.71 ± 0.16 m/s, all *p* values < 0.001) with mean intra-volunteer standard deviations of repeated measurements of 0.04 m/s (1.6%), 0.06 m/s (4.0%) and 0.08 m/s (4.5%), respectively. No effects of kidney anatomy, age, body mass index, blood pressure and heart rate on SWS were observed. THE allows generation of full-field-of-view SWS maps of native kidneys with high reproducibility. (E-mail: heiko.tzschaetzsch@charite.de)

Key Words: **Time-harmonic elastography, Ultrasound elastography, Ultrasound, Native kidney, Cortex, Medulla, Multifrequency vibration, Tissue mechanical parameters, Renal stiffness, Shear wave speed.**

INTRODUCTION

The kidneys lie in a relatively deep, retroperitoneal position within the abdominal cavity. Their central role is elimination of waste products from the blood, and they have a key function in regulating electrolytes, acid–base homeostasis, blood pressure and red blood cells (Eladari et al. 2012; Nagami and Kraut 2010; Velez 2009). The structural and functional integrity of renal tissue is essential to human life. Loss of kidney function is usually detected by blood tests and calculation of the unspecific estimated glomerular filtration rate (eGFR) (Levey et al. 2009); however, these tests provide no information on the underlying pathophysiology. Biopsies are required to examine structural changes and confirm suspected causes. A major disadvantage of biopsies is their invasive nature, with complications like bleeding. It is not clear when a biopsy should be obtained, and its benefits outweigh the risks (Corapi et al. 2012; Haas et al. 2000; Preuss et al. 2017; Whittier and Korbet 2004). Therefore, current research focuses on identifying non-invasive diagnostic methods for detecting structural changes and guiding therapeutic decisions.

Since the introduction of ultrasound elastography (USE) in 1991 (Ophir et al. 1991; Parker et al. 1990), USE methods have gained attention as being sensitive to structural soft tissue changes in the presence of disease (Bamber et al. 2013). Quantitative renal ultrasound elastography of the native kidney has been investigated in a few studies based on either acoustic radiation force impulse (ARFI) quantification (Alan et al. 2017; Asano et al. 2014; Bob et al. 2014, 2015; Bota et al. 2015; Goya et al. 2015; Guo et al. 2013; Hassan et al. 2016; Takata et al. 2016; Yu et al. 2014) or supersonic shear imaging (SSI) (Arda et al. 2011; Peng et al. 2017; Samir et al. 2015). However, there are partially conflicting reports on the relative shear wave speeds (SWSs) of the renal cortex and medulla in the literature (Asano et al. 2014; Peng et al. 2017).

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A major challenge in renal elastography is the position of the native kidneys deep inside the body. Current elastography methods are limited in their ability to test deep tissues. ARFI-based methods have been reported to be limited to a depth of the target anatomy of 7 cm (Cosgrove et al. 2013). Another limitation of both methods is that stiffness in terms of SWS is measured in a small area or even as a point measurement only, resulting in small field-of-view elastograms. In contrast, elastography based on time-harmonic continuous vibrations at low audible frequencies can, in principle, reach deeper tissue and generate full-field-of-view elastograms (Parker 2011; Taylor et al. 2000). Time-harmonic elastography (THE) has recently been reported to measure shear wave speed within the entire B-mode view up to 13 cm in depth (Tzschätzsch et al. 2016b).

The aim of this study was to provide reference data on *in vivo* renal SWS (in m/s), in the frequency range 27 to 56 Hz, with a focus on local variation in renal SWS, data reproducibility and possible effects of physiologic parameters. To this end, we (i) generated full-field-of-view elastograms of both native kidneys in a large group of healthy volunteers, (ii) provided reference values of normal renal SWS in different subregions for future clinical studies and (iii) defined possible physiologic confounders to improve the accuracy of *in vivo* stiffness measurements in the native kidney.

METHODS

Patients

In this prospective study we examined both kidneys in 37 healthy volunteers using 2-D THE. The volunteer characteristics are given in Table 1 (and Supplementary Table A1, online only, available at https://doi.org/j.ultrasmedbio.2018.01.007). The study was approved by the institutional ethics board, and informed consent was obtained. Exclusion criteria were past history of chronic kidney disease, hydronephrosis, persistent urinary disorders, infection, polycystic kidney, infarction and malignancy. All volunteers were investigated after 2 h of not drinking or eating.

To assess the reproducibility of the method, a subgroup of 3 healthy volunteers underwent serial examination of both kidneys on 5 consecutive days.

Table 1. Volunteer characteristics

Characteristic	Mean ± standard deviation (range)
No. of volunteers	37; 17 female, 20 male
Age (y)	35 ± 11 (21–64)
Body mass index (kg/m^2)	22 ± 3 (17–30)
Blood pressure (mm Hg)	
Systolic	125 ± 12 (104–162)
Diastolic	81 ± 9 (59–111)
Resistive index	
Right	0.59 ± 0.04 (0.49–0.67)
Left	0.59 ± 0.04 (0.50–0.65)
Heart rate (bpm)	66 ± 9 (21–64)
Kidney region of interest depth (cm)	8.7 ± 1.0 (6.8–11.6)
Kidney length (cm)	10.2 ± 0.8 (8.7–11.8)
Parenchymal thickness (cm)	1.7 ± 0.2 (1.2–2.2)
Cortical shear wave speed (m/s)	2.10 ± 0.17 (1.83–2.53)
Medullary shear wave speed (m/s)	1.35 ± 0.11 (1.16–1.62)
Parenchymal shear wave speed (m/s)	1.71 ± 0.16 (1.40–2.14)

In vivo *time-harmonic elastography*

Time-harmonic ultrasound elastography with 2-D elastogram display was introduced in Tzschätzsch (et al. 2016b). In brief, the setup consists of a vibration bed for shear wave excitation, an ultrasound device for shear wave acquisition and an elastography PC for shear wave evaluation and imaging (Fig. 1).

A clinical ultrasound device (SonixMDP, Ultrasonix, Scottsdale AZ, USA) with a 2.5-MHz convex transducer (C5-2/60) was used for anatomic guidance and shear wave acquisition. Shear waves were generated using a vibration bed with an integrated loudspeaker providing multifrequency waveforms of six superimposed frequencies (27, 33, 39, 44, 50 and 56 Hz). Volunteers were examined in supine position with the kidneys directly above the loudspeaker. Because of the low frequency of the vibration, the shear waves penetrated the entire abdominal cavity. Ultrasound raw data were acquired using an ultrasound device over 1 s with a usual frame rate of 80 Hz. The acquired data were continuously transferred to the elastography PC for direct data processing and visualization.

Shear wave post-processing was performed by calculating axial tissue displacement, decomposition of six measured vibration frequencies *via* Fourier transformation and controlled aliasing and application of the *k*-MDEV

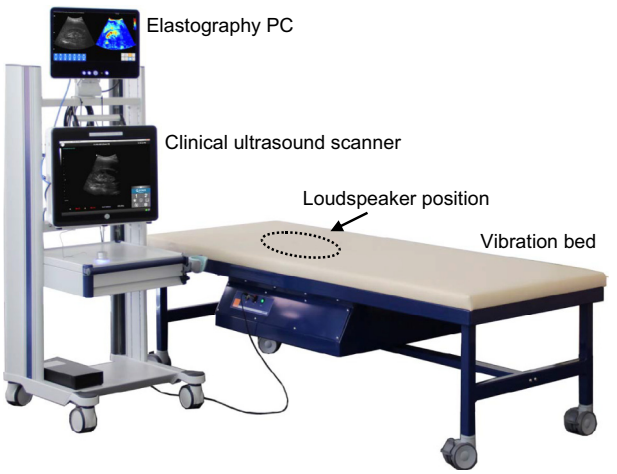

Fig. 1. Setup for time-harmonic ultrasound elastography: vibration bed with the integrated loudspeaker for shear wave excitation, clinical ultrasound scanner for shear wave acquisition and elastography PC for shear wave evaluation.