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Three-Dimensional Shear Wave Elastography on Conventional Ultrasound Scanners with External Vibration

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Abstract

Two-dimensional (2-D) ultrasound shear wave elastography (SWE) has been widely used for soft tissue properties assessment. Given that shear waves propagate in three dimensions (3-D), extending SWE from 2-D to 3-D is important for comprehensive and accurate stiffness measurement. However, implementation of 3-D SWE on a conventional ultrasound scanner is challenging due to the low volume rate (tens of Hertz) associated with limited parallel receive capability of the scanner's hardware beamformer. Therefore, we developed an external mechanical vibration-based 3-D SWE technique allowing robust 3-D shear wave tracking and speed reconstruction for conventional scanners. The aliased shear wave signal detected with a sub-Nyquist sampling frequency was corrected by leveraging the cyclic nature of the sinusoidal shear wave generated by the external vibrator. Shear wave signals from different sub-volumes were aligned in temporal direction to correct time delays from sequential pulse-echo events, followed by 3-D speed reconstruction using a 3-D local frequency estimation algorithm. The technique was validated on liver fibrosis phantoms with different stiffness, showing good correlation ($r = 0.99$, $p < 0.001$) with values measured from a state-of-the-art SWE system (GE LOGIQ E9). The phantoms with different stiffnesses can be well-differentiated regardless of the external vibrator position, indicating the feasibility of the 3-D SWE with regard to different shear wave propagation scenarios. Finally, shear wave speed calculated by the 3-D method correlated well with magnetic resonance elastography performed on human liver ($r = 0.93$, $p = 0.02$), demonstrating the *in vivo* feasibility. The proposed technique relies on low volume rate imaging and can be implemented on

the widely available clinical ultrasound scanners, facilitating its clinical translation to improve liver fibrosis evaluation.

Introduction

Ultrasound shear wave elastography (SWE) techniques have been widely used to assess soft tissue mechanical properties by measuring the speed of propagating shear waves, where the shear waves are typically generated either externally by a mechanical vibrator or shaker, or internally by acoustic radiation force (ARF) [1–12]. The shear wave speed is directly associated with the shear modulus, and thus, the elasticity or stiffness of the soft tissue, which is considered a strong biomarker of tissue health. Ultrasound SWE techniques have been successfully applied to facilitate evaluation, diagnosis, and monitoring of various diseases, such as breast tumors, thyroid nodules, musculoskeletal diseases, liver fibrosis, and cirrhosis [8, 13–16]. Specifically, SWE techniques have been shown to provide measurements that are well correlated with liver fibrosis stages, indicating the effectiveness of shear wave speed measurement in disease identification [7, 17–19].

Despite its usefulness, most SWE techniques are two-dimensional (2-D), while shear wave propagation through tissue inherently occurs in three dimensions (3-D). Therefore, imaging of the shear wave in 3-D may facilitate more accurate shear wave speed estimation and better quantification of tissue stiffness. In addition, 3-D SWE would also provide a more comprehensive evaluation of the targeted tissue in a 3-D field-of-view (FOV), reducing the risk of sampling error by 2-D imaging, especially for heterogeneous tissues. Therefore, extension of SWE techniques from 2-D to 3-D is desirable. However, one critical challenge of implementing 3-D shear wave imaging (SWI) is that for most current clinical ultrasound scanners the ultrasound volume rate is limited to the level of several tens of Hertz (Hz) due to the low parallel receive capability of hardware-based beamformers. Low volume rate remains a critical hurdle for tracking fast propagating shear waves and reconstructing shear wave speed distribution accurately. In state-of-the-art studies, Gennisson *et al.* and Provost *et al.* proposed implementing 3-D SWI based on ultrafast volumetric imaging via 3-D coherent plane-wave compounding, which can achieve volume rates of thousands of volumes per second [20, 21]. Despite its excellent performance in shear wave tracking, the ultrafast volumetric imaging relies on a 1024-channel ultrasound system with software-based beamforming capability, which is generally unavailable in the majority of clinical scanners and limits its implementation to these systems. Wang *et al.* addressed this challenge by transmitting and receiving tracking beams at a small sub-volume with a very high pulse-repetition-frequency (PRF) for a certain period of time before moving to the next sub-volume; this allowed the shear waves to be effectively tracked within each tissue sub-volume [22, 23]. The pushing beam had to be repeated with a separate spherical transducer each time while tracking beams were moved to the next sub-volume. In this way, shear wave propagation can be synthetically reconstructed in a full 3-D volume, but at the cost of longer data acquisition time, which is disadvantageous when tissue motion is present. While these 3-D ARF-based SWE techniques are promising, their imaging penetration can still be limited *in vivo* due to significant attenuation of the ARF deep into the tissue [19]. The maximum depth at which shear waves can be generated and tracked accurately and precisely

by ARF on most of the ultrasound systems is between 6 – 8 cm, which may not be sufficient for imaging deeper liver tissue (> 8 cm), especially in patients with obesity [19]. This can be more severe in steatotic liver with higher ultrasound attenuation.

Because an external vibrator or shaker can generate shear waves that can be delivered deep into tissue beyond the capability of ARF-based methods, they have been used in 2-D SWE for liver fibrosis staging, even in obese patients [15, 24, 25]. However, 2-D imaging of the 3-D propagating shear wave generated by external vibration can lead to shear wave speed overestimation due to the out-of-plane shear wave motion when the vibration source is placed outside the 2-D imaging plane [15, 24]. In a more recent study, Zeng *et al.* used an external vibrator to generate sinusoidal shear waves for SWE for liver fibrosis assessment, and applied a sub-sector based scanning sequence similar to color power angiography to achieve sufficiently high PRF for each sub-sector to support better shear wave detection [26, 27]. Shear wave speed was then reconstructed for the entire 3-D volume using a 3-D local frequency estimation (LFE) algorithm [26, 27]. However, a relatively long data acquisition time was needed to allow sequential sector-by-sector data to be completed to cover the 3-D volume, requiring the patient to breath-hold for about 10 seconds.

To address the challenge of low volume rate that is inadequate for 3-D SWI, we propose an external vibration-based SWE technique that allows sampling of sinusoidal shear waves with sub-Nyquist sampling frequency (volume rate) and robust rejection of intrinsic tissue motion. The proposed technique is based on a conventional volumetric imaging sequence with a relatively low volume rate (tens of Hertz), in which the Nyquist frequency (sampling frequency/2) is typically lower than the shear wave frequency, and thus results in aliasing of the detected shear wave signal. However, analogue to the principle of MRE, because of the periodic nature of the sinusoidal harmonic shear wave signal, the aliasing artifact can be corrected by phase-shifting the shear wave signals detected at different vibration cycles to reconstruct a non-aliased shear wave signal. Here, we demonstrate the 3-D SWE technique on liver fibrosis phantoms with different stiffness, and validate the measurements with the state-of-the-art 2-D SWE method on a clinical scanner (GE LOGIQ E9). We will show the robustness of the proposed 3-D SWI under different shear wave propagation scenarios by randomly changing the position of vibration sources. Finally, a proof-of-concept study on a small number of patient livers will demonstrate the *in vivo* feasibility with validation by magnetic resonance elastography (MRE) [28]. With external harmonic vibration, improved imaging penetration compared to the ARF-based SWE methods can be achieved for deeper shear wave imaging for liver tissue. By relying on low volume rate ultrasound imaging, the proposed technique will also be easier to implement on widely available clinical ultrasound scanners, and may provide a convenient method for screening and frequent follow-up of liver fibrosis.

Materials and Methods

1. Experimental setup

A General Electric (GE) Vivid E95 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 4V-D volume phased array transducer was used to perform volumetric ultrasound scanning in this study. As shown in Fig.1, the full image volume was

divided into 5×9 scanning sub-volumes, indexed as $V_{11}, V_{12}, V_{13} \dots, V_{21}, V_{22} \dots, V_{59}$, where the first subscript number indicates the index of the rows of the sub-volumes, and the second subscript number indicates the index of columns of the sub-volumes. For each pulse-echo cycle, an ultrasound wide-beam was transmitted to cover a single sub-volume (an example of a single sub-volume region is indicated by the yellow lines in Fig. 1), and 8×8 lines were obtained by parallel receive beamforming for each sub-volume. Once the transmit and receive event was done for one sub-volume, it moved to next sub-volume with a PRF of 4000 Hz in a sequential order as: $V_{11} \rightarrow V_{12} \rightarrow V_{13} \rightarrow \dots \rightarrow V_{21} \rightarrow V_{22} \rightarrow \dots \rightarrow V_{59}$. Therefore, a total of 45 pulse-echo events were conducted sequentially to reconstruct one entire volumetric frame, which included 40×72 lines. The effective volume rate was 88.9 Hz, with an image depth of about 11 cm, and opening angles of 57.5° and 36.7° in azimuth and elevational directions, respectively. The ultrasound was transmitted at 3.7 MHz. For each data acquisition, 52 volumetric beam-formed in-phase/quadrature (IQ) data were collected, corresponding to a scanning time of 0.58 s for the given volume rate.

For the phantom study, four shear wave liver fibrosis phantoms (Model 039, CIRS Inc., Norfolk, VA) with reported Young's moduli of 3.5 kPa, 10 kPa, 25 kPa, and 45 kPa, mimicking different stages of liver fibrosis, were utilized to validate the proposed 3-D SWI technique. The nominal shear wave speeds for the four phantoms are 1.08 m/s, 1.83 m/s, 2.89 m/s, and 3.87 m/s, respectively, obtained according to the reported Young's moduli by the manufacturer. An external mechanical shaker (LDS Model V203, Brüel and Kjær North America, Norcross, GA, USA) was driven by a sinusoidal signal from a function generator (Agilent 33250A, Agilent Technologies, Inc., Santa Clara, CA), generating a continuous mechanical vibration at a frequency of 60 Hz, as shown in Fig. 2. The sinusoidal signal from the function generator was amplified by an amplifier (Crown D150A, Crown Audio, Inc., Elkhart, IN) before being delivered to the shaker. During data acquisition, real-time ultrasound B-mode imaging was used for guiding imaging plane selection. There was no synchronization between the ultrasound system and vibration system for the current setup. The shaker was manually turned on to generate shear wave propagating inside the phantom. After a few seconds to allow reaching the steady-state vibration, the 3-D ultrasound shear wave imaging sequence was manually started, and the volumetric IQ data were acquired and saved in the hard-drive of the ultrasound system for post-processing. To test the repeatability of the 3-D SWE regarding source position of the shear wave field, the shaker was randomly placed at three different positions on top of the phantom. For each position, the acquisition was repeated five times; each included 52 volumetric frames of IQ data (corresponding to about 0.58 s for the given volume rate). As a reference, the phantoms were measured with a GE LOGIQ E9 scanner (GE Healthcare, Wauwatosa, WI) using the 2-D SWE mode with a 9L linear array transducer (induced shear wave frequency was in the range of 100 Hz – 500 Hz). Results were compared with the proposed 3-D method.

For the *in vivo* study, a loudspeaker (Zebra NWX-1044, Nippon America, FL) embedded as part of the examination bed was used to generate harmonic shear waves. The *in vivo* setup is similar to that presented in Zhao et al. [15]. The loudspeaker was driven by an amplified sinusoidal signal from the same function generator used in the phantom study. The vibration frequency was set at 60 Hz, consistent with the vibration frequency for MRE. During scanning, patients were supine with their right side slightly elevated and the back (lower rib

cage) closely coupled with the loudspeaker to allow effective delivery of harmonic shear waves into the liver. Real-time B-mode imaging from an intercostal imaging view was used for probe position guidance. Once the desired imaging plane was localized, the sonographer turned on the vibrator for a few seconds to achieve steady-state vibration, after which the patient was asked to hold a breath before data acquisition was started. The same acquisition was repeated five times for each patient, each containing 52 volumetric frames of IQ data (corresponding to about 0.58 s of scanning time). In this study, 5 patients undergoing clinical hepatic MRE were recruited and scanned on the same day under an institutional review board approved imaging protocol. Written informed consent was obtained from each patient. The MRE results, as analyzed by physicians following standardized clinical practice, were used as a reference standard to validate the proposed 3-D method.

2. Principle of shear wave reconstruction with low ultrasound volumetric frame rate

Harmonic shear waves were detected using a sub-Nyquist sampling rate (i.e., low volumetric frame rate). Figure 3 is a schematic of the frequency spectrum of a shear wave signal that appears at a certain frequency (i.e., the external vibration frequency), as indicated by f_0 . The Nyquist frequency f_N is equal to half of the sampling frequency f_s (i.e., the volumetric frame rate), assuming the underlying physiologic tissue motion has a maximum frequency of f_t , as indicated by the arrow. If the Nyquist frequency f_N is greater than the shear wave frequency f_0 , then the volumetric frame rate is sufficient for shear wave signal detection, and a highpass or bandpass filter with a low cutoff frequency that is higher than the underlying tissue motion frequency f_t can be applied to remove the underlying tissue motion and extract the shear wave motion, as indicated in Fig. 3a.

When the Nyquist frequency f_N is lower than the shear wave frequency f_0 , which is the case for 3-D volumetric imaging, aliasing will occur and the shear wave signal will appear at an aliased frequency f_a , where $f_a = |Kf_s - f_0|$, $K = 0, \pm 1, \pm 2 \dots$, as indicated in Fig. 3b. If f_a overlaps with the tissue frequency, then the shear wave signal becomes inseparable from underlying tissue motion and cannot be recovered. By careful selection of the sampling frequency f_s and shear wave frequency f_0 , the aliased frequency component can be positioned on the frequency spectrum so that it does not overlap with the underlying tissue motion frequency f_t , as indicated in Fig. 3b. Then a highpass or bandpass filter can be used to remove the tissue motion component from the aliased frequency spectrum.

For a given sampling frequency f_s and the number of temporal shear wave samples N , the phases of these shear wave samples are given by:

$$\phi_{sw}(i) = 2\pi \frac{f_0}{f_s} i, \quad \text{for } i = 1, 2, \dots, N. \quad (1)$$

Using the phase information, the non-aliased shear wave signals can be reconstructed based on the periodic nature of harmonic shear waves. In this method, the detected shear wave samples are reordered based on the phase of each shear wave sample. The phase-shifted signal is given by:

$$\varnothing_{shifted}(j) = S\{mod(\varnothing_{sw}(i), 2\pi)\}, \quad for\ i = 1, 2, \dots, N \quad (2)$$

where mod calculates the remainder of the detected shear wave phase $\varnothing_{sw}(i)$ and 2π , S is the sorting operation that sorts the remainder phase in ascending order, and j is the new index of the sorted and phase-shifted signal.

A key to idealized recovery of shear wave signal is to choose a combination of f_s and f_0 to achieve evenly-distributed sampling phases. The following minimization problem can be used to determine the optimal combination of f_s and f_0 , as:

$$\underset{f_s, f_0}{\operatorname{argmin}} \left\{ \left| \varnothing_{shifted}(f_s, f_0, i) - 2\pi \frac{i-1}{N} \right| \right\}, \quad for\ i = 1, 2, \dots, N \quad (3)$$

where $\varnothing_{shifted}$ is the phase of the shear wave sample after phase-shifting, and $2\pi \frac{i-1}{N}$ is the idealized, evenly-distributed phase over N samples. For this study, estimations of 50 shear wave samples (i.e., $N=50$) from the acquired ultrasound volumetric frames were used. When the harmonic shear wave frequency is 60 Hz, a sampling frequency of 89.1 Hz would be ideal to achieve an even sampling of the full shear wave cycle for $N=50$, as illustrated in Fig. 4. Fig. 4a shows the detected aliased shear wave samples given a simulated harmonic shear wave at 60 Hz with a sampling rate of 89.1 Hz, and Fig. 4b shows the recovered phase-shifted shear wave signal according to (2). The new sampling rate of the recovered signal is given by $Nf_0 = 3000$ Hz in Fig. 4b. However, when the choice of f_s and f_0 does not minimize the above equation, the phase of the shear wave will not be evenly sampled over one cycle. This will happen when it is challenging to change f_s to an exact optimal value derived from the above equation, which leads to a phase mismatch at each time point. In this study, the achievable volume rate by the ultrasound system that is closest to 89.1 Hz is 88.9 Hz, leading to mismatched phases and a distorted shear wave signal, as shown in Fig. 4c (black line). To correct for this mismatch at each time point, the phase of the shear wave signal can be finely-adjusted at each time point using a Hilbert transform-based phase-shifting method as follows:

$$SW_{adjusted}(i) = \operatorname{real}\{ \operatorname{analytic}[SW_{shifted}(i)] \cdot e^{j\Delta\theta(i)} \}, \quad for\ i = 1, 2, \dots, N \quad (4)$$

where $\operatorname{analytic}[SW_{shifted}(i)]$ indicates the calculation of the analytic signal of the phase-shifted shear wave $SW_{shifted}(i)$ (i.e.,

$\operatorname{analytic}[SW_{shifted}(i)] = SW_{shifted}(i) + j \cdot \mathcal{H}[SW_{shifted}(i)]$, where $\mathcal{H}$ indicates Hilbert transform). The real is taking the real part of the signal, and $\Delta\theta(i)$ is the phase difference between the idealized and detected phases for each sample (i.e.,

$\Delta\theta(i) = 2\pi \frac{i-1}{N} - \varnothing_{shifted}(i)$). The signal $SW_{adjusted}(i)$ indicates the finely-adjusted shear wave signal. After applying such fine-adjustment a more accurate match to the ideal shear wave signal can be obtained, as indicated by the blue line in Fig. 4c.

3. 3-D shear wave elastography

Inter-frame particle motion induced by the shear wave was estimated using a 1-D autocorrelation method [29] based on the IQ data for the whole 3-D volume. A nine-pixel spatial window (equal to 6.8 ultrasound wavelengths) along the axial direction was used for averaging in the autocorrelation calculation, and a 5×5 pixel spatial median filter (equal to 3.8 ultrasound wavelengths in the axial direction and spanning an angle of 4° in the lateral direction) was used to remove noise from the resulting shear wave signal. Inter-frame particle motion of a sinusoidal shear wave signal is also a sinusoidal signal with the same frequency, which is used for the subsequent processing for SWE. An 8th-order Butterworth bandpass filter with cutoffs of 26 Hz and 31 Hz was applied to preserve the aliased shear wave signal and remove the tissue motion components. The non-aliased shear wave signal was then reconstructed by reordering the aliased shear wave samples using the order determined by (2). A fine-adjustment followed, compensating for the phase mismatch and producing a more accurate reconstruction of the non-aliased shear wave signal, which was then smoothed by setting high-frequency components (> 120 Hz) to be zeros in frequency domain, to remove spurious noise. To align the shear wave signals from different sub-volumes, the phases of the harmonic shear wave signals were shifted according to the time delays between different sub-volumes. More specifically, the aligned shear wave signals within each sub-volume can be obtained by:

$$\widehat{SW_{m,n}}(t) = \mathcal{F}^{-1} \left\{ \mathcal{F}[SW_{m,n}(t)] \cdot e^{\frac{j\omega[(m-1) \cdot 9 + n - 1]}{PRF}} \right\}, \quad (5)$$

where $\widehat{SW_{m,n}}(t)$ indicates the aligned shear wave signals of the sub-volume V_{mn} , here m and n represent the row index and column index of the sub-volumes. $SW_{m,n}(t)$ represents the shear wave signals before alignment. $\mathcal{F}$ and $\mathcal{F}^{-1}$ denote Fourier transform and inverse Fourier transform operators, respectively. To suppress the global probe or tissue motion, which is essential for shear wave speed estimation with LFE, the shear wave data was first mirrored in all three spatial dimensions to minimize boundary discontinuity [30]. Then the DC component was rejected and an 8th-order Butterworth bandpass filter was applied in the spatial frequency domain to exclude shear waves propagating less than 0.01 m/s or more than 10 m/s, which should still preserve the full biological range of shear wave speeds in human liver tissue [19, 30]. After 3-D scan conversion, a 3rd-order Butterworth bandpass filter was then applied to the wave data to remove spatial wavelengths corresponding to shear wave speeds outside a predetermined physiological range of 0.5 to 6.0 m/s [19]. The 3-D LFE was then applied to the filtered shear wave data to estimate the local spatial wavelength [31–34]. This method utilizes a bank of 6 spatial frequency filters with half-octave scaling of the center frequency for each frequency band, and the ratio of the filtered signals provides an estimation of instantaneous spatial frequencies [24, 31]. An additional weighting term was applied to the estimation method to compensate for changes in shear wave signal amplitudes [34]. Given the vibration frequency is known, the spatial wavelength at each volumetric pixel can then be converted to shear wave speed using $c_s = f_0 \lambda$, where f_0 is the vibration frequency, and λ is the estimated spatial wavelength. Manual segmentation was done on multiple axial-azimuth 2-D planes to generate multiple 2-D regions-of-interest (ROIs). The 2-D ROIs were then linearly interpolated along the elevational direction to

produce 3-D ROIs, from which the mean shear wave speed was calculated for each dataset. There were five volumetric datasets acquired for each phantom per vibration position or per patient, providing five measurements of shear wave speed each, and unless otherwise stated, the final measured shear wave speed values were shown as mean $\pm$ standard deviation (SD) of the five measurements. Differences of measurements among different vibration positions or among different methods were analyzed using a non-parametric Wilcoxon rank-sum test. Pearson's correlation coefficient was calculated to evaluate the correlation of shear wave speeds between 3-D SWE and MRE methods for the *in vivo* patients, and a p -value < 0.05 was considered indicative statistical significance.

Results

1. Phantom study

Figure 5a shows a detected shear wave signal from the 10 kPa phantom at a sub-Nyquist sampling rate of 88.9 Hz. The frequency spectrum indicates the aliased shear wave frequency f_a at around 28.5 Hz for the given vibration frequency (60 Hz, aliased shear wave images are shown in Supplemental Video 1). After anti-aliasing correction via phase shifting and fine adjustment, the corrected shear wave signal is shown in Fig. 5b, with a sufficiently high sampling rate (2991.7 Hz) for 50 shear wave samples given within one vibration cycle. Spurious noise present in the corrected shear wave signal (Fig. 5b), which may be introduced by motion estimation error, can be rejected via suppressing high-frequency components to produce a smoother shear wave signal, as shown in Fig. 5c (corresponding aliasing-corrected shear wave images are depicted in Supplemental Video 2).

Due to the zone-by-zone scanning sequence, inherent time delays of shear wave signals exist between different sub-volumes, leading to discontinuities in the shear wave field (indicated in Fig. 6a and Supplemental Video 2). The discontinuity can be more pronounced when viewed along the axial-elevation imaging plane (Fig. 6a, second column, side view) and the azimuth-elevation plane (Fig. 6a, third column, top view), and needs to be corrected for accurate shear wave tracking over the 3-D FOV. By phase-shifting in the temporal direction for the given time delays, the shear waves from different sub-volumes can be largely aligned (shown in Fig. 6b and Supplemental Video 3). The aligned 3-D shear wave data was then scan-converted (Fig. 7) for shear wave speed estimation via LFE.

Figure 8a shows the shear wave speed images for the corresponding volumetric planes reconstructed with 3-D LFE, revealing a homogeneous speed distribution over the FOV, which is expected for the given homogeneous liver fibrosis phantom (10 kPa). The velocities for the three 2-D planes (axial-azimuth, axial-elevation, and azimuth-elevation) are 1.55 ± 0.01 m/s, 1.50 ± 0.14 m/s, and 1.52 ± 0.11 m/s, respectively. Here the velocities were calculated as mean $\pm$ SD of the pixels inside the black rectangles indicated in Fig. 8b. The bottom regions with large speed variations were outside the edge of the phantom (seen in the B-mode images in Supplemental Fig. S1) and excluded from the analysis. As a comparison, shear wave speed estimations using 2-D LFE [24] on each of the three 2-D image planes are shown in Fig. 8b, indicating a larger speed value and a larger measurement variation (1.73 ± 0.13 m/s, 1.75 ± 0.18 m/s, and 1.86 ± 0.29 m/s for the three planes, respectively). Due to the 3-D nature of the shear wave propagation and the unknown position of the shear wave

source, it is difficult to align a 2-D image plane to maintain in-plane shear wave propagation. Thus, shear wave speed tends to be overestimated using 2-D imaging because of the out-of-plane shear wave propagation generated by the external vibration sources outside the 2-D image plane, indicating the necessity of 3-D shear wave tracking for accurate speed reconstruction.

Figure 9a shows representative volumetric frames of shear wave motion for the four different liver fibrosis phantoms (refer to Supplemental videos 4 to 7 for dynamic shear wave propagation), revealing a changing spatial wavelength with varying stiffness. The corresponding 3-D reconstructions of shear wave speed are depicted in Fig. 9b, showing a relatively homogenous speed distribution inside the phantom tissue for each of the different stiffnesses. To evaluate the reproducibility of the proposed technique when changing the shear wave propagation direction or shear wave source location, the shear wave speed was measured with the vibration source randomly placed at three different positions for each phantom (as shown Fig. 9c and summarized in Table I). Statistically significant but very small differences of shear wave speed measurements were found for the three random vibration source positions for three of the four phantoms, as detailed in Table I. Specifically, the variations of shear wave measurements (indicated by SD) among vibration source positions are smaller than 0.06 m/s, and the maximum difference of shear wave speed among vibration positions is ranging from 0.003 m/s to 0.13 m/s. There are statistically significant differences of shear wave speeds between the four phantoms ($p < 0.0001$), indicating that the four phantoms can be well-differentiated with the 3-D SWE method.

Phantom shear wave speeds were also measured using the ARF-based SWE method with a GE LOGIQ E9 scanner [12]. The results are summarized and compared in Fig. 9d and Table II. The shear wave speeds measured with the proposed 3-D method are shown as mean $\pm$ SD of the 5 repeated measurements from vibration position 1 as indicated in Table I, while the values measured using the GE LOGIQ E9 scanner are shown as mean $\pm$ SD of five repeated measurements for each phantom. A significant correlation was found between shear wave speed measurements by the 3-D SWE and LOGIQ E9 methods ($r = 0.9993$, 95% confidence interval: 0.9672–1.0000, $p < 0.001$, with a linear relationship of $SWV_{3D\ SWE} = 0.73SWV_{LOGIQ\ E9} + 0.38$). The relative differences of shear wave speeds for the four phantoms estimated by the 3-D SWE and LOGIQ E9 are 13.3 %, –5.0 %, –11.1 %, –16.4 %, respectively, all with statistical significance ($p < 0.05$). As shown in Table II, both the shear wave speed measurements from the LOGIQ E9 and the 3-D SWE methods are tended to be lower than the nominal values reported by the manufacturer. Relative differences of shear wave speeds between 3-D SWE method and nominal values are –5.4 %, –17.4 %, –25.0 %, –23.7 % for the four phantoms, respectively, and –16.7 %, –12.9 %, –15.6 %, –8.9 % between LOGIQ E9 and nominal values for the four phantoms, respectively. Similarly, a significant correlation was shown between shear wave speed measurements by the 3-D SWE method and the nominal values ($r = 0.9970$, 95% confidence interval: 0.8574–0.9999, $p < 0.01$, with a linear relationship of $SWV_{3D\ SWE} = 0.67SWV_{Nominal} + 0.29$), and between shear wave speeds by LOGIQ E9 and the nominal values ($r = 0.9976$, 95% confidence interval: 0.8877–1.000, $p < 0.01$, with a linear relationship of $SWV_{LOGIQ\ E9} = 0.9976SWV_{Nominal} - 0.12$).

In this study, a vibration frequency of 60 Hz was initially chosen to be consistent with MRE for the *in vivo* validation. Variation of the vibration frequency is considered for the phantom study in Fig. 10, which shows the 3-D shear wave speed measurements with the proposed method at three different vibration frequencies (40 Hz, 60 Hz, and 80 Hz) in the four phantoms. The same signal processing method as proposed was applied to all of the different vibration frequency data to reconstruct oversampled shear wave signals for robust 3-D SWE, including the data utilizing the 40 Hz vibration frequency. In general, the shear wave speeds estimated from different vibration frequencies are similar for each phantom, showing an increasing trend with the phantom stiffness. The maximum differences of shear wave speeds among different vibration frequencies are 0.10 m/s, 0.02 m/s, 0.04 m/s and 0.5 m/s for the four phantoms, respectively. For the stiffest phantom (45 kPa), however, a significantly lower shear wave speed was observed at 40 Hz vibration frequency, as indicated by the blue bar for phantom 4 in Fig. 10.

2. In vivo study

Analogous to Fig. 5 for the phantom study, a representative shear wave signal detected from an *in vivo* patient liver is shown in Fig. 11. Different from the phantom study, physiologic tissue motion is inherently present *in vivo* that can contaminate the detected shear wave signal. For the given sampling frequency and vibration frequency, the tissue motion frequency f_t and aliased shear wave frequency f_a can be well separated in the frequency spectrum. Thus, the tissue motion can be suppressed by using a bandpass filter to extract the clean shear wave signal (Fig. 11b). Similar to the phantom study, anti-aliasing correction was then performed by phase shifting, fine adjustment, and smoothing to recover a non-aliased shear wave signal (Fig. 11c).

Representative volumetric frames of the B-mode imaging, shear wave motion, and shear wave speed reconstruction for this *in vivo* liver are shown in Fig. 12. Well-developed shear wave motion was observed deep in the liver tissue (Fig. 12b, and a video of the shear wave motion can be found in Supplemental Video 8), indicating an effective delivery of the shear wave using the experimental setup. The 3-D shear wave speed map was reconstructed based on the 3-D propagating shear wave data via 3-D LFE (Fig. 12c), and an averaged shear wave speed from five repeated measurements for each patient was calculated and compared with results measured with MRE (Fig. 13). The shear wave speed provided by MRE was converted from the reported shear modulus μ based on $\mu = \rho v^2$, where ρ is the mass density of liver tissue, which is assumed to be 1000 kg/m³, and v is the shear wave speed. A significant correlation of the shear wave speed measurement was found between MRE and the proposed 3-D SWI method for the 5 patients ($r = 0.93$, 95% confidence interval: 0.239–0.995, $p = 0.02$).

Discussion

In this study, a 3-D SWI method based on external vibration was proposed and validated in liver fibrosis phantoms and in human livers *in vivo*. The proposed method addressed the challenge of low ultrasound volume rate that is inadequate for shear wave detection by leveraging the periodic nature of a harmonic shear wave, allowing shear wave sampling with

sub-Nyquist sample frequency (volumetric frame rate). We demonstrated that the shear wave propagation could be recovered in 3-D, and 3-D shear wave speed can be accurately reconstructed using the proposed method. For the phantom study, a good correlation was found between the measured shear wave speeds by the proposed 3-D SWE method and the 2-D ARF-based SWE (GE LE 9). The *in vivo* cases also demonstrated a strong correlation of shear wave speed measurements by the proposed 3-D method and MRE, showing the *in vivo* feasibility of the proposed technique. Both the phantoms and *in vivo* results indicated the capability of shear wave speed measurement with a penetration depth of up to 10 cm, which is beyond the capability of the ARF-based methods; thus, the 3-D SWI method may allow accurate evaluation and monitoring of liver fibrosis in obese patients. Furthermore, the proposed method was developed based on a conventional clinical scanner operating at relatively low volumetric frame rates, making our method convenient to use. With only an external vibrator required for harmonic shear wave generation, it is inexpensive and shows great potential for clinical translation.

Three-dimensional shear wave detection can not only provide more comprehensive tissue characteristics covering a 3-D FOV to avoid sampling error, but also allow more accurate shear wave speed reconstruction compared with external vibration-based 2-D SWI. For the ARF-based SWE technique, the push beam and the detection beams are typically in the same 2-D plane, and thus the shear wave is in general propagating in-plane. Therefore, the 2-D ARF-based SWE technique does not generally suffer from the out-of-plane estimation bias. Different from the 2-D ARF-based method, investigators have shown that 2-D SWE with external vibration methods can be easily biased due to the out-of-plane shear wave propagation generated by the vibration source outside the 2-D imaging plane [15, 24]. In this study, because the shear wave source is unknown and shear waves can propagate in any direction in 3-D, out-of-plane shear wave propagation is inevitable for any 2-D plane, which will lead to a larger spatial wavelength appearing in the 2-D image plane. Therefore, the resulting 2-D shear wave speed will tend to be overestimated, which is validated in Fig. 8. However, by applying 3-D LFE on the 3-D propagating shear wave data, the spatial wavelength can be estimated more accurately; thus, the shear wave speed bias can be easily mitigated. It should be noted that shear wave speeds, either estimated by the 3-D SWE method or by the 2-D ARF-based method using LOGIQ E9, tended to be underestimated when compared with the nominal values reported by the manufacturer. The underestimation of the shear wave speeds, however, is consistent with the measurements in previously published papers on the same phantoms [24, 35, 36]. J. Racedo et al. reported shear wave speeds of 0.90 m/s, 1.6 m/s, 2.42 m/s and 3.46 m/s for the four phantoms, respectively [36]; D. Mellema et al. reported shear wave speeds of 1.74 ± 0.16 m/s, 2.43 ± 0.13 m/s, 3.51 ± 0.19 m/s using a 2-D external vibration technique and 1.63 ± 0.05 m/s, 2.46 ± 0.06 m/s, 3.56 ± 0.12 m/s using LOGIQ E9 for the last three phantoms, respectively [24]; and P. Kijanka et al. reported values below 1.64 m/s, 2.44 m/s, 3.50 m/s for the last three phantoms, respectively, as compared with the nominal values of 1.08 m/s, 1.83 m/s, 2.89 m/s, and 3.87 m/s [35]. Therefore, we assumed that there might be unknown biases for the reported nominal values for these four phantoms used in these studies. Because of this concern we used the state-of-the-art ARF-based method as the validation. Nevertheless, strong correlations were found among the 3-D SWE method, 2-D ARF-based method, and the

reported nominal values ($r > 0.99$, $p < 0.01$). We further validated the proposed 3-D technique by changing the position of vibration source to generate shear wave fields with different propagation directions. Similar shear wave speed measurements were shown (Fig. 9c), indicating the feasibility of the proposed technique with respect to varying shear wave propagation scenarios, and revealing the advantage of 3-D measurement over 2-D methods. Therefore, shear wave propagation direction and source position are not limited for the proposed method, which is particularly beneficial for *in vivo* applications where shear wave propagation direction can vary.

For the phantom study, the proposed 3-D SWI and the GE LOGIQ E9 ARF-based method showed a similar trend of increasing shear wave speed with increasing tissue stiffness (Fig. 9d). However, the 3-D shear wave speeds tended to be slightly lower than the 2-D ARF-based measurements. This may have resulted from the limited ultrasound FOV compared with the relatively large wavelength of the shear wave, especially for the stiffer phantom, as shown in Fig. 9a, resulting in underestimation of the LFE due to the boundary effects [33]. The underestimation can be more pronounced at the top regions of the image volume close to the probe, where the ROI size is very limited compared with the spatial wavelength of the shear wave, as evident in Fig. 9a and 9b. To mitigate these, a higher vibration frequency may be utilized but at the cost of shear wave penetration. In this study, we also demonstrated the feasibility of using a different vibration frequency other than 60 Hz in the phantoms, as indicated in Fig. 10. It should be noted that for the stiffest phantom (45 kPa), a lower shear wave speed was shown at a lower vibration frequency, especially for the 40 Hz vibration frequency (indicated by the blue bar in Fig. 10). Because the wavelength of the shear wave increases as frequency decreases, in the case of the stiffest phantom it becomes of the order of the FOV size, thus resulting in further underestimation of the shear wave. A potential way to alleviate the underestimation due to the large spatial wavelength is to increase the size of FOV. For example, for each subvolume in this study, a wider ultrasound beam may be utilized to cover a larger tissue volume so as to increase the overall FOV while maintaining the same volumetric frame rate. In the future, the FOV may even be adaptively scaled by the vibration frequency to avoid the underestimation effect when applying different vibration frequencies in 3-D SWE. The large wavelength associated with low vibration frequency will also lead to lower spatial resolution of the SWE. At high vibration frequency (e.g., 80 Hz), the aliased frequency f_a may be too low (e.g., in this case $f_a = 8.9$ Hz) to allow successful tissue motion suppression when applying the technique *in vivo*. In this case, a larger volumetric frame rate will be required when the tissue motion is present. Therefore, a tradeoff exists between vibration frequency, volumetric frame rate, FOV, SWE spatial resolution, penetration, and reconstruction accuracy. According to the results of the current study, a vibration frequency of 60 Hz with a volumetric frame rate of 88.9 Hz provides a fair balance between spatial wavelength and tissue motion suppression, and was shown to be capable of showing differences in shear wave speed among phantoms with different stiffness, and resulted in a very high correlation with MRE measurement *in vivo*. A vibration frequency of 60 Hz is also consistent with that of MRE used in the current study, and should be able to provide sufficient spatial resolution for evaluating liver fibrosis given its diffuse disease nature.

We further demonstrated the feasibility of *in vivo* liver measurement in patients with liver fibrosis by the proposed method with MRE as a gold standard. Unlike the phantom experiment, tissue motion or probe motion is inevitable *in vivo*. The proposed 3-D SWE technique can only be valid when the tissue motion and aliased shear wave signal are separable. When the tissue motion frequency and aliased shear wave frequency f_a are overlapping in the frequency spectrum, the shear wave signal contains interference and cannot be perfectly recovered, which is a limitation of the proposed technique. For the given vibration frequency and volumetric frame rate considered in this study, the aliased shear wave signals were positioned at around 30 Hz; thus, tissue components below 30 Hz could be easily suppressed by a highpass or bandpass filter. Based on our current *in vivo* patient data, the major frequency components of tissue motion are within 20 Hz, as shown in Fig. 11a (right column), where the interference with the aliased shear wave signal at around 30 Hz can be considered minimal. However, it should be noted that patients were asked to hold their breath during data acquisition to minimize tissue motion. One advantage of the proposed technique is that it only requires a relatively short acquisition time of about 0.58 s, during which a breath-hold can be easily done for most of the patients. Our results also indicated a robust rejection of tissue motion and recovery of shear wave signal, as shown in Fig. 11. A high correlation of shear wave measurement between the proposed and MRE methods was shown, indicating the potential of the proposed method to be a convenient and robust tool for liver fibrosis staging. However, the low number of patients in the current study is a limitation of the *in vivo* study. A larger patient sample would be required to further validate the clinical value of 3-D SWE. In this study, the phantoms were assumed to be elastic and the viscosity effect was ignored, which might be another reason leading to the discrepancy between shear wave speed measurements among different methods. From analysis of dispersion measured in these phantoms using ARF-based methods (not shown), it was found that the dispersion is small and so viscosity can be considered minimal (< 0.76 Pa·s). Nevertheless, the shear wave speed can be frequency-dependent with the presence of tissue viscosity, which should be taken into account in future studies when different vibration frequencies are used especially for *in vivo* liver tissue [11, 35, 37, 38]. Furthermore, viscosity is another valuable parameter, 3-D measurement of which may be beneficial for a more comprehensive evaluation of liver tissue, which is left for future investigation.

Conclusions

A 3-D SWE technique was proposed, based on external mechanical vibration for a conventional ultrasound scanner working at low volume rate, to provide 3-D SWI and robust 3-D shear wave speed reconstruction. The proposed technique overcame the challenge of low ultrasound volume rate for fast shear wave detection by leveraging the periodic nature of harmonic shear waves generated by an external vibrator. The technique was validated in liver fibrosis phantoms compared using a state-of-the-art 2-D SWE ultrasound system. *In vivo* feasibility was demonstrated in human livers using MRE as a reference standard. This method allows accurate shear wave speed measurement at low ultrasound volume rates or frame rates, has better imaging penetration than the ARF-based SWE, can overcome the limitation of out-of-plane shear wave propagation for 2-D SWE, and can be easily

implemented on a clinical ultrasound scanner, showing great potential to be a convenient and robust imaging technique for liver fibrosis staging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. Bercoff J, Tanter M, and Fink M, "Supersonic shear imaging: A new technique for soft tissue elasticity mapping," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 51, no. 4, pp. 396–409, 4 2004. [PubMed: 15139541]
- [2]. Nightingale K, McAleavey S, and Trahey G, "Shear-wave generation using acoustic radiation force: In vivo and ex vivo results," *Ultrasound Med. Biol.*, vol. 29, no. 12, pp. 1715–1723, 12 2003. [PubMed: 14698339]
- [3]. Parker KJ, Dooley MM, and Rubens DJ, "Imaging the elastic properties of tissue: the 20 year perspective," *Phys. Med. Biol.*, vol. 56, no. 1, pp. R1–R29, 1 2011. [PubMed: 21119234]
- [4]. Sandrin L, Tanter M, Catheline S, and Fink M, "Shear modulus imaging with 2-D transient elastography," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 49, no. 4, pp. 426–435, 4 2002. [PubMed: 11989698]
- [5]. Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, and Emelianov SY, "Shear wave elasticity imaging: A new ultrasonic technology of medical diagnostics," *Ultrasound Med. Biol.*, vol. 24, no. 9, pp. 1419–1435, 11 1998. [PubMed: 10385964]
- [6]. Tanter M, Bercoff J, Sandrin L, and Fink M, "Ultrafast compound imaging for 2-D motion vector estimation: Application to transient elastography," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 49, no. 10, pp. 1363–1374, 10 2002. [PubMed: 12403138]
- [7]. Bavu E et al., "Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis c virus patients," *Ultrasound Med. Biol.*, vol. 37, no. 9, pp. 1361–1373, 9 2011. [PubMed: 21775051]
- [8]. Muller M, Gennisson JL, Defieux T, Tanter M, and Fink M, "Quantitative viscoelasticity mapping of human liver using supersonic shear imaging: preliminary in vivo feasibility study," *Ultrasound Med. Biol.*, vol. 35, no. 2, pp. 219–229, 2 2009. [PubMed: 19081665]
- [9]. Palmeri ML, Wang MH, Dahl JJ, Frinkley KD, and Nightingale KR, "Quantifying hepatic shear modulus in vivo using acoustic radiation force," *Ultrasound Med. Biol.*, vol. 34, no. 4, pp. 546–558, 4 2008. [PubMed: 18222031]
- [10]. Song PF, Zhao H, Manduca A, Urban MW, Greenleaf JF, and Chen SG, "Comb-Push Ultrasound Shear Elastography (CUSE): A Novel Method for Two-Dimensional Shear Elasticity Imaging of Soft Tissues," *IEEE Trans. Med. Imaging*, vol. 31, no. 9, pp. 1821–1832, 9 2012. [PubMed: 22736690]
- [11]. Chen SG et al., "Shearwave Dispersion Ultrasound Vibrometry (SDUV) for Measuring Tissue Elasticity and Viscosity," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 56, no. 1, pp. 55–62, 1 2009. [PubMed: 19213632]
- [12]. Song PF et al., "Two-Dimensional Shear-Wave Elastography on Conventional Ultrasound Scanners With Time-Aligned Sequential Tracking (TAST) and Comb-Push Ultrasound Shear Elastography (CUSE)," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 62, no. 2, pp. 290–302, 2 2015. [PubMed: 25643079]

- [13]. Athanasiou A et al., "Breast Lesions: Quantitative Elastography with Supersonic Shear Imaging-Preliminary Results," *Radiology*, vol. 256, no. 1, pp. 297–303, 7 2010. [PubMed: 20505064]
- [14]. Tanter M et al., "Quantitative assessment of breast lesion viscoelasticity: Initial clinical results using supersonic shear imaging," *Ultrasound Med. Biol.*, vol. 34, no. 9, pp. 1373–1386, 9 2008. [PubMed: 18395961]
- [15]. Zhao H et al., "External Vibration Multi-Directional Ultrasound Shearwave Elastography (EVMUSE): Application in Liver Fibrosis Staging," *IEEE Trans. Med. Imaging*, vol. 33, no. 11, pp. 2140–2148, 11 2014. [PubMed: 25020066]
- [16]. Brandenburg JE et al., "Ultrasound Elastography: The New Frontier in Direct Measurement of Muscle Stiffness," *Arch. Phys. Med. Rehabil.*, vol. 95, no. 11, pp. 2207–2219, 11 2014. [PubMed: 25064780]
- [17]. Friedrich-Rust M et al., "Liver Fibrosis in Viral Hepatitis: Noninvasive Assessment with Acoustic Radiation Force Impulse Imaging versus Transient Elastography," *Radiology*, vol. 252, no. 2, pp. 595–604, 8 2009. [PubMed: 19703889]
- [18]. Sandrin L et al., "Transient elastography: A new noninvasive method for assessment of hepatic fibrosis," *Ultrasound Med. Biol.*, vol. 29, no. 12, pp. 1705–1713, 12 2003. [PubMed: 14698338]
- [19]. Barr RG et al., "Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement," *Radiology*, vol. 276, no. 3, pp. 845–861, 9 2015. [PubMed: 26079489]
- [20]. Gennisson JL et al., "4-D Ultrafast Shear-Wave Imaging," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 62, no. 6, pp. 1059–1065, 6 2015. [PubMed: 26067040]
- [21]. Provost J et al., "3D ultrafast ultrasound imaging in vivo," *Phys. Med. Biol.*, vol. 59, no. 19, pp. L1–L13, 10 2014. [PubMed: 25207828]
- [22]. Wang M, Byram B, Palmeri M, Rouze N, and Nightingale K, "Imaging Transverse Isotropic Properties of Muscle by Monitoring Acoustic Radiation Force Induced Shear Waves Using a 2-D Matrix Ultrasound Array," *IEEE Trans. Med. Imaging*, vol. 32, no. 9, pp. 1671–1684, 9 2013. [PubMed: 23686942]
- [23]. Wang M, Byram B, Palmeri M, Rouze N, and Nightingale K, "On the Precision of Time-of-Flight Shear Wave Speed Estimation in Homogeneous Soft Solids: Initial Results Using a Matrix Array Transducer," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 60, no. 4, pp. 758–770, 4 2013. [PubMed: 23549536]
- [24]. Mellema DC et al., "Probe Oscillation Shear Elastography (PROSE): A High Frame-Rate Method for Two-Dimensional Ultrasound Shear Wave Elastography," *IEEE Trans. Med. Imaging*, vol. 35, no. 9, pp. 2098–2106, 9 2016. [PubMed: 27076352]
- [25]. Baghani A et al., "Real-Time Quantitative Elasticity Imaging of Deep Tissue Using Free-Hand Conventional Ultrasound," Berlin, Heidelberg, 2012, pp. 617–624: Springer Berlin Heidelberg.
- [26]. Zeng Q. 3D Liver Shear Wave Absolute Vibro-Elastography with an xMATRIX Array - A Healthy Volunteer Study; 2018 IEEE International Ultrasonics Symposium (IUS); 2018. 1–9.
- [27]. Zeng Q. In-Vivo Validation of 3D Multi-Frequency Liver Shear Wave Absolute Vibro-Elastography with an xMATRIX Array; 2019 IEEE International Ultrasonics Symposium (IUS); 2019. 876–879.
- [28]. Venkatesh SK, Yin M, and Ehman RL, "Magnetic resonance elastography of liver: Technique, analysis, and clinical applications," *Journal of Magnetic Resonance Imaging*, vol. 37, no. 3, pp. 544–555, 2013. [PubMed: 23423795]
- [29]. Kasai C, Namekawa K, Koyano A, and Omoto R, "Real-Time Two-Dimensional Blood Flow Imaging Using an Autocorrelation Technique," *IEEE Transactions on Sonics and Ultrasonics*, vol. 32, no. 3, pp. 458–464, 1985.
- [30]. Mellema DC et al., "Probe Oscillation Shear Wave Elastography: Initial In Vivo Results in Liver," *IEEE Trans. Med. Imaging*, vol. 37, no. 5, pp. 1214–1223, 2018. [PubMed: 29727284]
- [31]. Knutsson H, Westin C, and Granlund G, "Local multiscale frequency and bandwidth estimation," in *Proceedings of 1st International Conference on Image Processing*, 1994, vol. 1, pp. 36–40 vol.1.
- [32]. Manduca A, Muthupillai R, Rossman P, Greenleaf J, and Ehman R, *Image processing for magnetic-resonance elastography (Medical Imaging 1996)*. SPIE, 1996.

- [33]. Manduca A et al., "Magnetic resonance elastography: Non-invasive mapping of tissue elasticity," *Med. Image Anal.*, vol. 5, no. 4, pp. 237–254, 12 2001. [PubMed: 11731304]
- [34]. Sack I, Rump J, Elgeti T, Samani A, and Braun J, "MR Elastography of the Human Heart: Noninvasive Assessment of Myocardial Elasticity Changes by Shear Wave Amplitude Variations," *Magn. Reson. Med.*, vol. 61, no. 3, pp. 668–677, 3 2009. [PubMed: 19097236]
- [35]. Kijanka P and Urban MW, "Local Phase Velocity Based Imaging: A New Technique Used for Ultrasound Shear Wave Elastography," *IEEE Trans. Med. Imaging*, vol. 38, no. 4, pp. 894–908, 4 2019. [PubMed: 30296217]
- [36]. Racedo J and Urban MW, "Evaluation of Reconstruction Parameters for 2-D Comb-Push Ultrasound Shear Wave Elastography," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 66, no. 2, pp. 254–263, 2 2019. [PubMed: 30507530]
- [37]. Chen SG et al., "Assessment of Liver Viscoelasticity by Using Shear Waves Induced by Ultrasound Radiation Force," *Radiology*, vol. 266, no. 3, pp. 964–970, 3 2013. [PubMed: 23220900]
- [38]. Nightingale KR et al., "Derivation and Analysis of Viscoelastic Properties in Human Liver: Impact of Frequency on Fibrosis and Steatosis Staging," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 62, no. 1, pp. 165–175, 1 2015. [PubMed: 25585400]

Fig. 1. Schematic illustration of volumetric imaging. The full image volume consisted of 5×9 scanning sub-volumes, indexed as V_{11} , V_{12} , V_{13} ..., V_{21} , V_{22} ..., V_{59} , and for each sub-volume, 8×8 lines were obtained by parallel receive beamforming. A sequential scanning order was applied as: $V_{11} \rightarrow V_{12} \rightarrow V_{13} \rightarrow \dots \rightarrow V_{21} \rightarrow V_{22} \rightarrow \dots \rightarrow V_{59}$ to complete one full volumetric frame.

Fig. 2. Phantom study experimental setup. A shaker was fixed and driven by amplified sinusoidal signal to generate continuous shear wave delivered into the phantom tissue.

Fig. 3. Schematic illustration of the frequency spectrum of a shear wave signal (a) without and (b) with aliasing, where f_t indicates the tissue motion frequency, f_0 indicates the vibration frequency, f_a indicates the aliased shear wave frequency, and f_N represents the Nyquist frequency, which equals to half of the sampling frequency f_s (i.e., the volumetric frame rate).

Fig. 4.

(a) Detected aliased shear wave samples given a simulated harmonic shear wave at 60 Hz and a sampling frequency at 89.1 Hz. (b) Reordered aliased shear wave samples to ideally reconstruct a non-aliased shear wave signal. The new sampling rate for the reordered shear wave signal is 3000 Hz. (c) Phase-shifted shear wave signal with the presence of phase mismatch sampled at 88.9 Hz (black line), and the phase-shifted shear wave signal after fine-adjustment (blue line). The red line indicates the ideal harmonic shear wave.

Fig. 5.

(a) Detected aliased shear wave signal on a liver fibrosis phantom (10 kPa) for the given vibration frequency of 60 Hz and a sampling frequency of 88.9 Hz (left column), and the corresponding frequency spectrum (right column). (b) Reconstructed non-aliased shear wave signal (left column) from (a) via phase-shifting and fine adjustment, and the corresponding frequency spectrum (right column). (c) Non-aliased shear wave signal (left column) is smoothed by rejecting high-frequency components and preserving harmonic components at around 60 Hz (vibration frequency).

Fig. 6.

A representative volumetric frame of shear wave motion (a) before and (b) after time alignment according to three planes of view: axial-azimuth (first column), axial-elevation (second column), and azimuth-elevation at axial depth of around 7 cm (third column).

Fig. 7.

Representative volumetric frames of shear wave motion after scan conversion at three consecutive time points. First column: axial-azimuth plane, second column: axial-elevational plane, third column: azimuth-elevational plane at axial depth of around 7 cm, and fourth column: slice view for the volumetric frame.

Fig. 8.

(a) Shear wave speed images reconstructed from a single acquisition using 3-D LFE for a homogenous liver fibrosis phantom (10 kPa). (b) Shear wave speed images reconstructed from a single acquisition using 2-D LFE on the corresponding 2-D image planes. The black rectangles indicate the ROIs for averaged speed calculation for each 2-D plane. First column: axial-azimuth plane, second column: axial-elevational plane, and third column: azimuth-elevational plane at axial depth of around 7 cm.

Fig. 9.

(a) A representative volumetric frame (slice plot) of shear wave motion for each of the four liver fibrosis phantoms. (b) Corresponding 3-D reconstruction of shear wave speed from one single acquisition for the four phantoms (slice plot). (c) The vibration source was randomly placed to produce shear waves propagating in different directions with regard to the ultrasound probe; shear wave speeds were measured with the vibration source in three different positions for each of the four phantoms (Pht.). Errorbar indicates the SD of 5 repeated measurements. (d) Shear wave speed measurements of the four phantoms using the proposed 3-D shear wave imaging method (here errorbar indicates the SD of 5 repeated measurements from vibration position 1 as indicated in Table I) compared with those obtained with the GE LOGIQ E9 (here errorbar indicates the measurement SD of 5 repeated measurements) and nominal values.

Fig. 10.

Shear wave speed measurements of the four phantoms (Pht.) using the proposed 3-D shear wave imaging method with three different vibration frequencies (40 Hz, 60 Hz and 80 Hz, respectively). Errorbar indicates the SD of 5 repeated measurements for each phantom and each vibration frequency.

Fig. 11.

(a) Detected aliased shear wave signal contaminated with tissue motion from an *in vivo* patient liver (left column) and the corresponding frequency spectrum (right column). f_t indicates the underlying tissue motion frequency, and f_a indicates the aliased shear wave frequency. (b) Detected aliased shear wave signal after the suppression of tissue motion components from (a). (c) Non-aliased shear wave signal (left column) recovered from (b) via phase-shifting, fine adjustment, and noise suppression.

Fig. 12.

(a) A representative volumetric B-mode image from an *in vivo* patient liver. (b) A representative volumetric frame of shear wave motion. (c) Corresponding 3-D reconstruction of shear wave speed from the *in vivo* case. The shear wave speed is 2.35 ± 0.08 m/s measured by 3-D SWE method, while 2.19 m/s measured by MRE. First column: axial-azimuth plane, second column: axial-elevation plane, third column: azimuth-elevation plane, and fourth column: slice view for the volumetric frame.

Fig. 13.

Correlation of shear wave speed measurement using MRE and the proposed 3-D shear wave imaging methods. Errorbar indicates the SD of the 5 repeated measurements for each patient.

TABLE I

SHEAR WAVE SPEED MEASUREMENTS BY THE PROPOSED 3-D SWE TECHNIQUE IN LIVER FIBROSIS PHANTOMS WITH RANDOM VIBRATION SOURCE POSITIONS

	Phantom 1	Phantom 2	Phantom 3	Phantom 4
Position 1 (m/s)	1.08 ± 0.02	1.51 ± 0.01	2.18 ± 0.01	2.98 ± 0.02
Position 2 (m/s)	0.95 ± 0.01	1.51 ± 0.01	2.17 ± 0.02	2.92 ± 0.03
Position 3 (m/s)	1.03 ± 0.01	1.51 ± 0.01	2.16 ± 0.02	2.95 ± 0.02
SD (m/s)	0.06	0.001	0.01	0.03
Maximum difference (m/s)	0.13 [*]	0.003	0.02 [*]	0.06 [*]

SD here indicates the standard deviation of shear wave speed measurements over 3 different vibration positions. Maximum difference indicates the maximum difference of the shear wave speed measurements among vibration positions. Significant differences are denoted with asterisks (*p < 0.05, **p < 0.01).

TABLE II

NOMINAL SHEAR WAVE SPEED VALUES AND THE SHEAR WAVE SPEED VALUES MEASURE BY THE 2-D ARF-BASED SWE METHOD IN LIVER FIBROSIS PHANTOMS

	Phantom 1	Phantom 2	Phantom 3	Phantom 4
Nominal values (m/s)	1.08	1.83	2.89	3.87
LOGIQ E9 (m/s)	0.90 ± 0.00	1.59 ± 0.01	2.44 ± 0.01	3.53 ± 0.02