Improved Shear Wave Motion Detection Using Pulse-Inversion Harmonic Imaging With a Phased Array Transducer

Pengfei Song, Student Member, IEEE, Heng Zhao, Member, IEEE, Matthew W. Urban, Member, IEEE, Armando Manduca, Member, IEEE, Sorin V. Pislaru, Randall R. Kinnick, Cristina Pislaru, James F. Greenleaf, Life Fellow, IEEE, and Shigao Chen*, Member, IEEE

Abstract—Ultrasound tissue harmonic imaging has emerged as a standard B-mode imaging technique thanks to its dramatic improvement of ultrasound radio-frequency (RF) signal shift between frames in deep tissues such as heart, liver, and kidney, the ultrasound image quality [21]–[24]. Harmonic imaging provides better spatial and contrast resolution and suffers less from noise sources such as phase aberration and ultrasound reverberation noise) ultrasound signals still re-

Index Terms—Acoustic radiation force, diastolic left ventricle stiffness, harmonic imaging, in vivo human heart, pulse-inversion, shear wave elastography, transthoracic scanning.

I. INTRODUCTION

ULTRASOUND shear wave elastography (SWE) assesses tissue elasticity by remotely inducing shear waves into the tissue with acoustic radiation force and measuring shear wave propagation speed [1]. Robust shear wave motion detection is essential in producing reliable shear elasticity measurements for SWE. shear wave motion is obtained by estimating the amount of ultrasound radio-frequency (RF) signal shift between frames taken at different time instants, therefore the quality of ultrasound signal is an important factor in determining the robustness of shear wave motion detection [2]. For in vivo applications in deep tissues such as heart, liver, and kidney, the ultrasound signal is heavily contaminated by various sources of noise and shear wave motion is weak due to significant attenuation of the acoustic radiation force, so shear wave motion detection can be very challenging [3]–[8]. To address these issues, many efforts have been made to improve shear wave generation [5], [9]–[11], develop more robust shear wave motion calculation techniques [2], [12]–[14], investigate better methods of shear wave speed measurement [5], [15]–[18], and increase the signal-to-noise ratio (SNR) of the ultrasound signal [19], [20]. While the field of SWE has been greatly advanced by these works, the issue of noise-contaminated (e.g., clutter noise, phase aberration noise, and ultrasound reverberation noise) ultrasound signals still remains unsolved and applications such as closed-chest cardiac elasticity imaging still largely remain as unfulfilled goals for SWE.

Tissue harmonic imaging has emerged as a standard B-mode imaging technique thanks to its dramatic improvement of ultrasound image quality [21]–[24]. Harmonic imaging provides better spatial and contrast resolution and suffers less from noise sources such as phase aberration and ultrasound reverberation
Among various harmonic imaging techniques, pulse-inversion harmonic imaging adds echoes from phase-inverted transmission pulses to cancel odd numbered harmonic components and double even numbered harmonic components, which is often preferred due to improved SNR of the second harmonic [27]–[29]. Recently, Doherty et al. showed that for acoustic radiation force impulse (ARFI) imaging, pulse-inversion harmonic imaging improved the displacement tracking by reducing jitter and enhancing feature detection [30]. For SWE, however, there has been no report on using the harmonic imaging to track shear wave propagation. In this paper, we propose to implement pulse-inversion harmonic imaging in ultrasound SWE to track shear wave motion with phase-inverted and high frame-rate diverging beam pulses. The hypothesis of this work is that compared to fundamental shear wave tracking, harmonic shear wave tracking is advantageous in obtaining more robust shear wave motion estimation under the presence of severe ultrasound signal noise.

In this paper, we first describe a phantom study with a gelatin phantom covered by an excised section of pork belly to systematically compare the performance of shear wave motion tracking using either the fundamental or harmonic ultrasound signal. We then conducted another experiment further comparing the two imaging methods on a closed-chest pig heart within the first 35 min after sacrifice. Lastly, we conducted an in vivo heart study using the proposed method to estimate the diastolic left ventricular wall stiffness in seven healthy volunteers with transthoracic ultrasound. We close the paper with discussion and conclusions.

II. MATERIALS AND METHODS

A. Shear Wave Tracking Sequence With Pulse-Inversion Harmonic Imaging

A Verasonics ultrasound system (Verasonics Inc., Redmond, WA, USA) and a phased array P4-2 (Philips Healthcare, Andover, MA, USA) with 64 elements and center frequency of 2.5 MHz were used for shear wave generation and detection. For shear wave generation, all 64 elements were excited to transmit a single focused ultrasound push beam with center frequency of 2 MHz and push duration of 800 μs. For SWE, however, all 64 elements were excited to transmit a single focused ultrasound push beam with center frequency of 2 MHz and push duration of 800 μs. For the harmonic sequence, after transmitting the push beams, the Verasonics system immediately switched to flash imaging mode with excitation of all 64 elements and emitted phase-inverted pulses (center frequency MHz, pulse duration cycles) at a pulse repetition frequency (PRF) of 7.69 kHz, as shown in Fig. 1(a). For each pair of the phase-inverted pulses, a positive pulse is first transmitted and the backscattered data are received; then a negative pulse with 180° phase shift is transmitted, and the backscattered data from that transmission are received and added to the data backscattered from the positive pulse transmission. The PRF is thus effectively reduced by a factor of 2 after the summation (final effective PRF ≈ 3.85 kHz). A diverging beam with the focal depth at the virtual apex of the P4-2 (~28 mm from the probe surface) was used in this study due to improved performance in the far field when compared to transmitting plane waves [31]. The focal depth of the diverging beam was adjusted to ~288 mm for more concentrated energy delivery to enhance harmonic generation in the ex vivo pig and in vivo human study. For the fundamental
sequence, the transmitting frequency was also centered at 2 MHz, with the same PRF as in the harmonic sequence. Every two frames were then averaged to form a fundamental frame. In an additional calibration experiment, the P4-2 did not transmit detection pulses while the L7-4 detected the shear waves, which was used as ground truth in this experiment.

**B. Ex Vivo Pork Belly/Gelatin Phantom Experiment**

To compare the performance of shear wave motion detection between the fundamental and harmonic sequences, an experiment was designed in which a gelatin phantom (9% gelatin, 10% glycerol, and 1% cellulose) was covered with a piece of excised pork belly and the ultrasound probe was placed on top of the excised tissue section, as shown in Fig. 2. A fresh piece of pork belly with a thickness of about 2.5 cm was used to simulate the body wall for evaluation of in vivo shear wave detection. The pork belly section had clearly delineated layers including skin, muscle, and subcutaneous fat. A thin layer of distilled water was poured between the pork belly and the phantom surface to ensure good acoustic coupling. In this experiment, in order to obtain a ground truth of shear wave velocity, a linear array (L7-4, Philips Healthcare, Andover, MA, USA) was operated by one Verasonics machine (Verasonics1) to produce shear waves from the bottom of the phantom (a hole was cut in the container’s bottom) so that both the push beam and detect beam of the L7-4 were not affected by the pork belly and thus the shear wave signal obtained from L7-4 could be used as ground truth. The phased array P4-2 was operated by a second Verasonics machine (Verasonics2) to track shear wave motions produced by the L7-4 from the top of the phantom. The two probes were carefully aligned without the phantom and pork belly and then the P4-2 was translated upwards by the mechanical stage [Fig. 2(a)] so that the alignment was maintained throughout the translation. The imaging sequence is shown in Fig. 2(b): Verasonics1 drove the L7-4 to emit a push pulse (center frequency = 4.09 MHz, push duration = 600 μs), after which a trigger signal was sent to Verasonics2 to initiate the shear wave detection pulses by the P4-2. The same setup was used for both the fundamental and harmonic detection sequences. To obtain the ground truth signal from L7-4, a separate sequence with the L7-4 detecting its own shear waves was conducted without the detection pulses from the P4-2. To test repeatability, five measurements through five different locations of the pork belly were made for both the fundamental and the harmonic sequences. To perform this repeatability test, the position of the probes was maintained and the pork belly was moved.

**C. Ex Vivo Closed-Chest Heart Experiment**

To further compare the performance of shear wave tracking by harmonic imaging and fundamental imaging, we conducted an experiment on a freshly sacrificed pig to image the stiffness of the left ventricular myocardium through the intact chest. The absence of breathing and cardiac motion allowed us to compare the performance of fundamental detection and harmonic detection under the same conditions while simulating in vivo shear wave measurements in heart. A pig weighing 44.6 kg was anesthetized by Telazol-xylazine, and then was injected with 4.5 cc of heparin for anticoagulation, followed by 10 cc of Fatal-Plus solution for euthanasia. After death, ultrasound B-mode imaging was used as guidance to locate the left ventricular wall with a short-axis view, after which the P4-2 probe was fixed at the chest surface using a clamp. A 48 scan-line B-mode imaging scheme provided by the Verasonics was used to improve the quality of the B-mode image, which is called “Guidance B-mode” hereinafter. The phased array P4-2 was used to both produce and track shear waves with the fundamental sequence and harmonic sequence (as introduced in Section II-A). The ultrasound push beam was focused at the anterior wall of the left ventricle, which was about 34 mm away from the probe surface. Five trials were done for both the harmonic sequence and the fundamental sequence, at the same fixed position. The entire experiment finished within 35 min after the death of the pig.

**D. In Vivo Human Heart Study in Healthy Volunteers**

To test the feasibility of using the proposed harmonic shear wave tracking sequence for in vivo studies, we recruited seven healthy volunteers to produce and track shear waves in the heart from a transthoracic approach with the phased array P4-2 (same push and detection setup as in Section II-C) and measure the shear wave propagation speed in end-diastole. The experiment protocol was approved by the Mayo Clinic Institutional Review Board and written informed consent was obtained prior to scanning. The experiment was conducted under the guidance
of a cardiologist who also performed the ultrasound scan on the volunteers. The left ventricle was imaged using a short-axis view. The harmonic imaging sequence was combined with the same Guidance B-mode imaging sequence used in the ex vivo pig study so that real-time B-mode imaging could be used as a guide to select the imaging plane for shear waves, locate the focal depth of the ultrasound push beam, and trigger the shear wave imaging sequence in a real-time fashion. The Verasonics system was synchronized with the ECG signal from the subject in order to produce and track shear wave motion in end-diastole. Because the Guidance B-mode imaging sequence uses 48 scan lines which requires much longer data acquisition time and the shear wave imaging sequence has to be precisely triggered by the ECG signal, the Guidance B-mode sequence could not be integrated into the shear wave imaging sequence. Thus, the Guidance B-mode images were not synchronized with the ECG signal (i.e., the Guidance B-mode images were not necessarily acquired at end-diastole). Nevertheless, each shear wave imaging sequence saved one Guidance B-mode image which can be used as offline data analysis references.

The mechanical index (MI) and spatial peak time average intensity (I_{SPTA}) regulated by the Food and Drug Administration (FDA) were measured for all the ultrasound beams used in this study. Both MI and I_{SPTA} were derated at a rate of 0.3 dB/cm/MHz and the measured values were summarized in Table I. For succinctness, the experiment is not described here and one can refer to [10] for details. The frame rate used for I_{SPTA} calculation was 1 Hz for the shear wave detection beams and the push beams, and 16 Hz for the Guidance B-mode beam. All values used in this study are under the FDA regulatory limits of 1.90 and 720 mW/cm² for the MI_{0.3} and I_{SPTA,0.3}, respectively [33]. Note that for depths shallower than 45 mm, the push beam pulse width modulation (PWM) was reduced to as low as 27% to avoid exceeding the MI limit (the output power of the Verasonics transmit waveform is regulated using PWM and can be varied to obtain acoustic output levels that meet FDA regulatory limits), which significantly reduced the power of the push beam and consequently the amplitude of the shear waves. This results in poor shear wave generation in the anterior left ventricular wall which typically locates at depths shallower than 45 mm, as will be discussed in Section III.

Due to breathing and cardiac motion, it cannot be guaranteed that each acquisition was made in the same part of the myocardium through the same path of the fat and muscle layers. Therefore, a comparison with fundamental detection was not done here, because it was difficult to control these confounding factors for a fair comparison.

### III. Results

#### A. Ex Vivo Pork Belly/Gelatin Phantom Experiment

Fig. 3 shows the plots of the shear wave particle velocity signal (V_Z) at the focal depth of the focused push beam of the L7-4 for both the harmonic imaging (HI) sequence and the fundamental sequence at five different locations of the phantom/pork belly. Fig. 3 also shows the B-mode images reconstructed by the detection beams (named Detection B-mode hereinafter) for both the fundamental and harmonic sequences, and the shear wave generation and analysis regions. Both the harmonic and fundamental sequences could detect discernible shear wave motions. However, the amplitude of the shear waves tracked by the harmonic sequence is consistently higher than that tracked by the fundamental sequence. Moreover, the shear waves tracked by the harmonic sequence are also better delineated than with the fundamental sequence.

To quantitatively compare the performance of the harmonic and fundamental sequences, we first measured the maximum shear wave particle velocity (V_Z\_MAX) for each plot in Fig. 3. The V_Z\_MAX was measured for the shear waves propagating in the −x direction and +x direction separately. We then used a Radon transform to convert the plots of shear wave motion signal into sinograms from which the shear wave speed (c_s) can be calculated [17], [34]. For example, Fig. 4(a) shows the plot of the shear wave motion produced and tracked by the L7-4 probe (the ground truth signal). Fig. 4(b) shows the sinogram of Fig. 4(a) with an angular resolution of 0.18° obtained from the MATLAB function “radon.m”. There are two peaks in the sinogram corresponding to the two shear waves in Fig. 4(a): the peak around 21° corresponds to the shear wave going toward the +x direction; the peak around 159° corresponds to the shear wave going toward the −x direction. These peak sinogram angles can be converted to shear wave speed (c_s) by

\[
c_s = \frac{\Delta x}{\Delta t} \tan(\theta)
\]

where \(\Delta x\) and \(\Delta t\) are the pixel sizes along the x and t directions [Fig. 4(a)]; and \(\theta\) is the peak sinogram angle. The derivation of (1) is shown in Fig. 4(a): the peak sinogram angle \(\theta\) is indicated as the angle between the shear wave trajectory and the horizontal direction, which is given by

\[
tan(\theta) = N_x/N_t
\]
Fig. 3. Plots of the shear wave particle velocity signal at the focal depth of the push beam. Upper row: B-mode images reconstructed by the harmonic and fundamental detection beam sequences. The red dashed boxes indicate the shear wave generation and analysis regions. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). The green dashed box indicates the area of pork belly. Middle row: shear wave motion tracked by the harmonic imaging (HI) sequence at five different locations of the phantom/pork belly. Lower row: shear wave motions tracked by the fundamental sequence at the same five locations as in HI. All plots use the same color scale with units of mm/s.

Fig. 4. (a) Plot of the shear wave particle velocity signal produced and tracked by the L7-4 probe. The black dashed lines indicate the shear wave propagation trajectories. $N_x$ and $N_t$ are the number of pixels of the shear wave trajectory along $t$ and $x$ directions, respectively. (b) Radon transform of (a). The values are normalized by the length of the projection vector $X_x$. The black arrows indicate the positions of the peak sinogram values.

where $N_x$ and $N_t$ are the number of pixels of the shear wave trajectory along the $x$ and $t$ dimensions, respectively. Given

$$N_x = x_t/\Delta x \quad (3)$$

$$N_t = t_x/\Delta t \quad (4)$$

where $x_t$ is the actual shear wave propagation distance and $t_x$ is the shear wave propagation duration, one can easily derive to

$$r_x = x_t/t_x \quad (1)$$

by substituting (3) and (4) into (2).
TABLE II

<table>
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<th>Methods</th>
<th>Parameters</th>
<th>Position 1</th>
<th>Position 2</th>
<th>Position 3</th>
<th>Position 4</th>
<th>Position 5</th>
<th>Mean</th>
<th>Std.</th>
<th>SNR</th>
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<td>L7-4 (ground truth)</td>
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<td>68.6</td>
<td>77.2</td>
<td>60.0</td>
<td>55.3</td>
<td>60.2</td>
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<td>2.22</td>
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<td>38.1</td>
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<td>59.0</td>
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<td></td>
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<td>2.27</td>
<td>2.17</td>
<td>2.25</td>
<td>2.27</td>
</tr>
<tr>
<td>Fundamental sequence</td>
<td>$V_Z\text{MAX (mm/s)}$</td>
<td>7.20</td>
<td>4.70</td>
<td>10.5</td>
<td>5.56</td>
<td>4.27</td>
<td>4.92</td>
<td>11.2</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>$c_s$ (m/s)</td>
<td>2.13</td>
<td>2.03</td>
<td>3.42</td>
<td>2.18</td>
<td>2.06</td>
<td>2.10</td>
<td>2.13</td>
<td>2.10</td>
</tr>
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</table>

*Std. denotes standard deviation

The same analyses were performed on all the harmonic sequence data and fundamental sequence data. The $V_Z\text{MAX}$ and shear wave speeds $c_s$ were recorded, as shown in Table II. The signal-to-noise ratio (SNR) of the shear wave signal was also calculated. The SNR is given by

$$\text{SNR} = \frac{\bar{x}}{\sigma}$$

where $\bar{x}$ and $\sigma$ are the mean and standard deviation values of the $V_Z\text{MAX}$ measurements. Table II also shows the values measured by the L7-4 probe, which were regarded as ground truth in this study.

From Table II, compared to the mean $V_Z\text{MAX}$ value measured by the L7-4, both the harmonic sequence and the fundamental sequence provided significant underestimates of the shear wave peak motion due to the presence of the pork belly as the noise source. However, the mean $V_Z\text{MAX}$ using the harmonic sequence is over six times greater than the mean $V_Z\text{MAX}$ found using the fundamental sequence. Moreover, the $V_Z\text{MAX}$ found using the harmonic sequence is biased low by 37.2% compared to the ground truth value, while the $V_Z\text{MAX}$ found using the fundamental sequence is biased low by 90%; almost a three-fold less underestimation by the harmonic sequence than the fundamental. There is also an almost two-fold increase of shear wave signal SNR using the harmonic sequence instead of the fundamental sequence. For the shear wave speed calculation, the harmonic sequence provided more consistent shear wave speed measurements than the fundamental sequence, evidenced by a 1.78% standard error (given by the ratio of standard deviation to mean) of the harmonic sequence compared to an 18.8% standard error of the fundamental sequence. These results all together indicate a significant improvement of shear wave motion tracking by the harmonic sequence.

B. Ex Vivo Closed-Chest Heart Experiment

Shear wave motion at the focal depth of the ultrasound push beam as well as the B-mode images indicating the location of shear wave generation and analysis are shown in Fig. 5. The top row of Fig. 5 shows the relationship between the Guidance B-mode imaging area and the shear wave detection beam area. This same imaging set up was used for the in vivo human heart study in the next session. The middle row of Fig. 5 shows the shear wave motion detected by the harmonic imaging sequence and the bottom row shows the shear wave motion detected by the fundamental sequence. One can see that the harmonic sequence consistently tracked a propagating shear wave with clear boundaries for all five trials, while the fundamental sequence could not. The same Radon transform method as used in the previous section was used to estimate shear wave speed using the plots in Fig. 5. A shear wave speed limit of 0.5–10 m/s [6] was set by restricting the searching range of the Radon transform angle as in (4) so that estimates beyond the limit would be rejected. The results are summarized in Table III. In accordance with the observations from Fig. 5, harmonic imaging could provide consistent measurement of shear wave speed while the fundamental sequence failed due to the absence of detected shear wave motion. The mean and standard deviation value of the shear wave speeds measured by the harmonic sequence is $1.19 \pm 0.03$ m/s, which is in good agreement with the diastolic myocardium stiffness measurements of pig hearts in [7], [35], and [36]. The clutter noise in the heart severely contaminated the fundamental pulses and consequently deteriorated the shear wave signal. The harmonic pulses, however, are less vulnerable to such clutter noise and thus could provide more robust shear wave motion estimates compared to the fundamental pulses.

C. In Vivo Human Heart Study in Healthy Volunteers

A total of five measurements were made out of five cardiac cycles in each volunteer (one acquisition per cardiac cycle). The left ventricular wall was located under the short-axis view in Guidance B-mode imaging (Fig. 6) and then the focal point of the ultrasound push beam was set either at the anterior or posterior left ventricular wall. Due to the reduced PWM level required by the $MI$ limit at depths shallower than 45 mm as discussed in Section II, no discernible shear waves could be produced at the anterior left ventricular wall. Therefore, only the posterior left ventricular wall was scanned in this study. The shear wave motions at the focal depth of the five trials for volunteers 1, 2, 3, 4, 6, and 7 are plotted in Fig. 6 (volunteer 5 was not plotted because no shear waves could be detected).
which shows that the harmonic image could consistently detect discernible shear wave motions. The Radon transform method was again used to estimate shear wave speed from the plots in Fig. 6, with shear wave speed limit of 0.5–10 m/s [6]. The reconstructed shear wave speed trajectories calculated by the Radon transform were also plotted in Fig. 6. Note that in trial 3 for volunteer 1 and trial 4 for volunteer 6, the Radon transform method misfit one branch of the shear wave. The fit would have been better had the data been truncated along the time direction (e.g., only analyzing the shear wave towards $-\chi$ direction from 0 to 3 ms for trial 3 of volunteer 1). However, in this study, we used the same temporal window size for both branches of shear waves to maintain consistency in the analysis. The shear wave speed measurements together with the mean and standard deviation values for all the tests are summarized in Table IV. Table IV also shows the Body Mass Index (BMI) of each volunteer. From Table IV, in general, 56 out of 70 measurements provided shear wave speed estimates that were within the speed limit, corresponding to a success rate of 80%; the success rate was 93.3% (56 out of 60 trials) when excluding volunteer 6 whose BMI exceeds 25. The overall mean shear wave speed of these 56 measurements is 1.56 m/s, with a standard deviation of 0.36 m/s, which shows good agreement to the diastolic left ventricle stiffness measurement in sheep [6] and pigs [7], [36]. The ratio of the standard deviation to the mean value varies from 8.6% (volunteer 2) to 30.3% (volunteer 1) for all the subjects, with a mean value of 18.6%. These results showed that the harmonic imaging sequence provided consistent measurements of shear wave speed in diastolic left ventricular myocardium. This is, to our knowledge, the first reported shear wave speed measurements of the left ventricular myocardium stiffness on in vivo, closed-chest human subjects with shear waves induced

### Table III

<table>
<thead>
<tr>
<th>Shear Wave Speed ($c_s$) Measurements of the Left Ventricular Wall in an Ex Vivo Closed-Chest Pig</th>
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<table>
<thead>
<tr>
<th></th>
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<tr>
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<tr>
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<tr>
<td>Mean</td>
<td>1.19</td>
<td>0.03</td>
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</table>

*Std. denotes standard deviation
Fig. 6. Plots of the shear wave particle velocity signals transthoracically produced and tracked by the harmonic sequence in \textit{in vivo} human heart under diastole for the seven recruited volunteers. The left-most column shows the Guidance B-mode images of the short-axis view of the left ventricle, with red dashed boxes indicating the shear wave generation and analysis regions. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). Shear wave motion data of the seven volunteers are shown in each row of the plot. The black dashed lines indicate the angles of shear wave propagation obtained by the Radon transform. The failed shear wave speed measurements (not within the 0.5–10 m/s range) were not plotted. Results of volunteer 5 are not shown because no discernible shear waves could be detected.
transthoracically by acoustic radiation force. Previous in vivo and closed-chest tests have only been done in pigs [37].

IV. DISCUSSION

This paper investigated the implementation of pulse-inversion harmonic imaging for the task of shear wave tracking in ultrasound shear wave elastography, with the hypothesis that harmonic imaging can improve shear wave motion tracking in the presence of severe noise sources based on the principles that apply to general ultrasound B-mode imaging. The ex vivo pork belly phantom experiment showed significant improvement of shear wave tracking by the harmonic imaging sequence, indicated by an almost three-fold less underestimation of shear wave motion, two-fold increase of shear wave SNR, and more consistent shear wave speed calculation than the fundamental sequence. The experiment on an ex vivo closed-chest pig further demonstrated this improvement by showing that harmonic imaging could consistently track the shear wave motion and provide robust shear wave speed estimates while the fundamental sequence completely failed. Finally, the in vivo human heart study proves the feasibility of implementing the proposed harmonic tracking technique in in vivo applications.

There are several possible explanations why harmonic imaging works better than fundamental imaging for shear wave tracking. First, harmonic imaging suffers significantly less from phase aberration than fundamental imaging, as explained in [22] and [24]. Under the presence of phase aberration, such as the pork belly and the chest walls of the pig and human, the inhomogeneous distribution of ultrasound speed can significantly disturb the ultrasound RF signal and misregister the position of the scatterers. This can cause a partial volume effect in which echoes from the moving and nonmoving scatterers are mixed and the overall effect is a “smearing” of the sharp and high shear wave motion such that what is detected is blurred and low shear wave motion. Because harmonic imaging is less affected by phase aberration, this “smearing” effect is less pronounced than fundamental imaging, evidenced by the observations from the pork belly experiment in which the underestimation of motion is much less by the harmonics than the fundamental. A second possible reason is the finer resolution cell and weaker side lobes for the harmonic component compared with the fundamental. This can help ameliorate the partial volume effect as proposed in the first reason because harmonic imaging is capable of examining a smaller and finer cell of scatterer motion [38], [39]. Another reason is based on the fact that in general, harmonic imaging is effective in suppressing clutter noise, especially for cardiac applications where the heart wall is usually contaminated by heavy clutter noise [23]. The clutter noise can completely ruin the fundamental ultrasound RF signal and cause failure of the shear wave motion detection, as observed in the heart experiment on the ex vivo closed-chest pig. Harmonic imaging, however, suffers less from clutter noise and thus could still provide robust shear wave tracking and shear wave speed estimate.

An alternative approach of doing harmonic imaging is to filter the fundamental signal to extract a harmonic signal at twice the frequency of the fundamental, which is named filter-based harmonic imaging. When receiving at the center frequency of the transmission frequency (e.g., 2 MHz in this study), the filter-based harmonic imaging method requires a minimum of 200% receiving bandwidth to avoid cutting off the second harmonic signal at 4 MHz. The Verasonics system used in this study, however, imposes a default input band-pass filter with a bandwidth of 128% to filter the backscattered RF signal and suppress noise, significantly lower than the required 200% bandwidth. Therefore, it is difficult to extract a reliable second harmonic signal directly from the fundamental signal and perform the filter-based harmonic imaging approach, due to the limitation of Verasonics. Harmonic imaging on the Verasonics is achieved by setting the receiving center frequency to the frequency of the harmonics such that the harmonic signal can pass the input band-pass filter. In other words, Verasonics can perform one of the fundamental and harmonic imaging, but not both at the same time.

For the proposed harmonic imaging shear wave detection method, there is a tradeoff between the detection frame rate and harmonic excitation. If one were to use a focused beam as in conventional B-mode imaging to excite more harmonics, the frame rate would have to be sacrificed because line-by-line scanning is required to track shear wave propagation. If one were to use a high frame rate diverging beam as used in this study to provide sufficient frame rate for shear wave tracking, the harmonic excitation would have to be compromised due to

<table>
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<th>Table IV</th>
<th>SHEAR WAVE SPEED $c_{s}$ MEASUREMENTS OF THE LEFT VENTRICULAR WALL IN END-DIASTOLE</th>
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*Std. denotes standard deviation
**Vol. denotes volunteer
the dispersed distribution of the acoustic energy. To compare the harmonic excitation among different types of detection beams, we used a CIRS elasticity homogeneous phantom (CIRS Inc., Norfolk, VA, USA) and three different types of detection beams to excite the harmonics: a focused beam with a focal depth of 45 mm (regarded as the beam used in conventional B-mode imaging); the narrow diverging beam with a focal depth of -288 mm used in the ex vivo pig study and in vivo human study; and the wide diverging beam with a focal depth of -28 mm used in the pork belly phantom study. All beam configurations were the same for the three types of beams except for the focal depth. The frequency spectrum of the RF signal is plotted in Fig. 7. Fig. 7 indicates that the narrow diverging beam was able to excite comparable amount of harmonics to the focused beam in the shallow and deep fields, while the focused beam could excite significantly more harmonics than both diverging beams around its focal depth where the energy was mostly concentrated. The narrow diverging beam produces more consistent amount of harmonics through all depths compared to the other two beams. Meanwhile Table I shows that the narrow diverging beam has an $M_I$ of 1.51, which corresponds to a 2.14 MPa negative pressure given a 2 MHz transmission frequency. Therefore, the intensity of the diverging beam used in this study was strong enough to excite sufficient harmonics for shear wave detection purposes while preserving a high frame rate of several kilohertz.

In the in vivo human heart study, five acquisitions were performed with one acquisition per cardiac cycle during end-diastole. Acquisitions were not performed other than at end-diastole because the motion of the heart poses two major challenges to shear wave generation and detection. First, the focal point of the push beam had to be pre-positioned onto the location of the left ventricular myocardium in end-diastole to ensure shear wave generation. The position of the left ventricular myocardium varies significantly during one cardiac cycle and thus the location of the focal point has to be changed accordingly, which is very challenging to realize in practice. Second, because heart contraction follows a complicated “twisting” motion and the ultrasound scan is 2-D in nature, the shear wave may propagate out of the imaging plane and disappear from the field-of-view. Meanwhile the bulk motion of the heart can cause decorrelation of the ultrasound signal from consecutive frames and results in poor shear wave motion estimation. In end-diastole, however, the heart is moving more slowly and it is therefore less challenging to produce and detect shear waves.

The failed test in the in vivo human heart study was on the subject with the highest BMI of 27.5, which indicates that obesity still remains as an issue with the proposed method, as with shear wave elastography in general on cardiac applications. The absence of shear waves in the failed test could be caused by significant attenuation to the ultrasound push beam and consequently weak or no shear wave production at the left ventricular wall; or by severe phase aberration and ultrasound attenuation to the harmonic detection beams which results in an unreliable shear wave motion estimate. Since one-third of adults and almost 17% of youth in the US are obese [40], the success rate of SWE with harmonic imaging on the heart could be significantly lower than 80% as reported in this paper. Nevertheless, this study showed a significant improvement of shear wave detection and the first report of the SWE application on in vivo and closed-chest human heart using the pulse-inversion harmonic imaging approach.

One limitation of this study is that the pulse-inversion harmonic imaging sequence could have been implemented in a sliding-window-sum fashion as proposed in [30] such that the original frame rate is preserved instead of reduced by a factor of 2 as in this paper. However, due to system limitations of the Verasonics, for now we could only sum the echoes in the way as in Fig. 1(a). This limitation was due to the way the Verasonics scanner was configured and was not fundamental. The current configuration of Verasonics enables online processing of the IQ data so that the operator can observe the resulting shear waves immediately after the push and detection. This setup is very convenient in practice, especially for in vivo studies. This online processing requires the sum of the RF signals from phase-inverted pulses to be done before the beamforming and IQ demodulation processes, therefore the original positive and negative frames shown in Fig. 1 are not accessible anymore and Doherty’s sliding-window-sum approach cannot be implemented. One can use the sliding-window-sum technique before the beamforming and IQ demodulation process, however the Verasonics does not support duplicate use of the same frame: e.g., once a frame A is assigned to be added to another frame B, this frame A cannot be used anymore. A potential solution is to save all the positive and negative frames and perform
offline beamforming and shear wave calculation, so that the sliding-window technique can be done without the restriction of the Verasonics system. However, this approach would disable the real-time feedback of shear wave motion information and can be very inconvenient for in vivo studies.

In this study, only the phased array transducer P4-2 was used for harmonic detection. However, the same principle can be applied to other types of ultrasound probes such as curved and linear arrays for a wide range of elasticity imaging applications. To perform the harmonic imaging appropriately, the transducer being used must have adequate bandwidth to incorporate both the fundamental and harmonic frequencies.

V. CONCLUSION

This paper demonstrated the implementation of pulse-inversion harmonic imaging in ultrasound SWE and showed significant improvement of shear wave motion tracking under the presence of severe noise sources such as phase aberration, ultrasound reverberation, and clutter noise. Harmonic shear wave tracking was shown to be able to reduce the underestimation bias of shear wave motion and improve the consistency of shear wave speed measurement in an experiment using a section of excised pork belly tissue. Harmonic imaging also provided robust shear wave tracking on an ex vivo closed-chest pig heart while conventional fundamental imaging failed. This study also showed the feasibility of using the proposed harmonic shear wave tracking method to transthoracically measure diastolic left ventricular myocardium stiffness in six out of seven healthy volunteers. These promising results indicate that pulse-inversion harmonic imaging can be used for improving shear wave motion detection for shear wave imaging.

ACKNOWLEDGMENT

The authors would like to thank S. Krage for his assistance on the pig experiment.

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