Published in final edited form as:

IEEE Trans Med Imaging. 2013 December ; 32(12): 2299–2310. doi:10.1109/TMI.2013.2280903.

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

Pengfei Song^{1,3} [Student Member, IEEE], Heng Zhao¹ [Member, IEEE], Matthew W. Urban¹ [Member, IEEE], Armando Manduca¹ [Member, IEEE], Sorin V. Pislaru², Randall R. Kinnick¹, Cristina Pislaru¹, James F. Greenleaf¹ [Life Fellow, IEEE], and Shigao Chen¹ [Member, IEEE]

¹Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN

²Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN

³Mayo Graduate School, Mayo Clinic College of Medicine, Rochester, MN

Abstract

Ultrasound tissue harmonic imaging is widely used to improve ultrasound B-mode imaging quality thanks to its effectiveness in suppressing imaging artifacts associated with ultrasound reverberation, phase aberration, and clutter noise. In ultrasound shear wave elastography (SWE), because the shear wave motion signal is extracted from the ultrasound signal, these noise sources can significantly deteriorate the shear wave motion tracking process and consequently result in noisy and biased shear wave motion detection. This situation is exacerbated in *in vivo* SWE applications such as heart, liver, and kidney. This paper, therefore, investigated the possibility of implementing harmonic imaging, specifically pulse-inversion harmonic imaging, in shear wave tracking, with the hypothesis that harmonic imaging can improve shear wave motion detection based on the same principles that apply to general harmonic B-mode imaging. We first designed an experiment with a gelatin phantom covered by an excised piece of pork belly and show that harmonic imaging can significantly improve shear wave motion detection by producing less underestimated shear wave motion and more consistent shear wave speed measurements than fundamental imaging. Then, a transthoracic heart experiment on a freshly sacrificed pig showed that harmonic imaging could robustly track the shear wave motion and give consistent shear wave speed measurements while fundamental imaging could not. Finally, an *in vivo* transthoracic study of seven healthy volunteers showed that the proposed harmonic imaging tracking sequence could provide consistent estimates of the left ventricular myocardium stiffness in end-diastole with a general success rate of 80% and a success rate of 93.3% when excluding the subject with Body Mass Index (BMI) higher than 25. These promising results indicate that pulse-inversion harmonic imaging can significantly improve shear wave motion tracking and thus potentially facilitate more robust assessment of tissue elasticity by SWE.

Keywords

Harmonic imaging; shear wave elastography; acoustic radiation force; pulse inversion; *in vivo* human heart; transthoracic scanning; diastolic left ventricle stiffness

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 [25, 26]. 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 minutes 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.

MATERIALS AND METHODS

A. Shear Wave Tracking Sequence with Pulse-inversion Harmonic Imaging

A Verasonics ultrasound system (Verasonics Inc., Redmond, WA) and a phased array P4-2 (Philips Healthcare, Andover, MA) 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 μ s. 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 = 2 MHz, pulse duration = 2 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 $\approx$ 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 set to improve SNR and maintain an effective PRF equivalent to that of the harmonic sequence, as shown in Fig. 1(b). The in-phase/quadrature (IQ) data of consecutive frames was used to estimate axial particle velocity (V_z) caused by shear wave propagation. The one-dimensional autocorrelation method [32] was used to calculate V_z .

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 signal, a linear array (L7-4,

Philips Healthcare, Andover, MA) 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 = 4.09MHz, push duration = 600 μ s), 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 at 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 phantom/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 part A of this section). 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 minutes 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 part C of this section) 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 1Hz 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 the Results session.

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 through 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.

RESULTS

A. Ex Vivo Pork Belly/Gelatin Phantom Experiment

Figure 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. Figure 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_{ZMAX}) for each plot in Fig. 3. The V_{ZMAX} 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:

$$C_s = \frac{\Delta x}{\Delta t} \tan(\theta) \quad (1)$$

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

$$\tan(\theta) = N_x / N_t \quad (2)$$

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

$$\begin{aligned} N_x &= x_t / \Delta x \\ N_t &= t_t / \Delta t \end{aligned} \quad (3)$$

and

$$C_s = x_t / t_t \quad (4)$$

where x_t is the actual shear wave propagation distance and t_t is the shear wave propagation duration, one can easily derive to Eq. (1) by substituting Eqs. (3) and (4) into (2).

The same analyses were performed on all the harmonic sequence data and fundamental sequence data. The V_{ZMAX} 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:

$$SNR = \frac{\bar{x}}{\sigma} \quad (5)$$

where $\bar{x}$ and σ are the mean and standard deviation values of the V_ZMAX 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_ZMAX 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_ZMAX using the harmonic sequence is over 6 times greater than the mean V_ZMAX found using the fundamental sequence. Moreover, the V_ZMAX found using the harmonic sequence is biased low by 37.2% compared to the ground truth value, while the V_ZMAX found using the fundamental sequence is biased low by 90%: almost a 3-fold less underestimation by the harmonic sequence than the fundamental. There is also an almost 2-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 Eq. (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 ± 0.03 m/s, which is in good agreement with the diastolic myocardium stiffness measurements of pig hearts in [7, 35, 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 the Methods section, 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 $-x$ 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 transthoracically by acoustic radiation force. Previous *in vivo* and closed-chest tests have only been done in pigs [37].

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 3-fold less underestimation of shear wave motion, 2-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, 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 non-moving 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 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) 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. Figure 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 *MI* 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 two-dimensional 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.

CONCLUSIONS

This paper demonstrated the implementation of pulse-inversion harmonic imaging in ultrasound shear wave elastography (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 6 out of 7 healthy volunteers. These

promising results indicate that pulse-inversion harmonic imaging can be used for improving shear wave motion detection for shear wave imaging.

ACKNOWLEDGMENTS

This work was supported by NIH grants EB002167, DK082408, and DK092255, and by Mayo CTSA grant UL1TR000135. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH. The authors thank Steve Krage for his assistance on the pig experiment.

REFERENCES

- [1]. Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound Med. Biol.* Nov.1998 24:1419–35. [PubMed: 10385964]
- [2]. Pinton GF, Dahl JJ, Trahey GE. Rapid tracking of small displacements with ultrasound. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Jun.2006 53:1103–17.
- [3]. Varghese T, Bilgen M, Ophir J. Phase aberration effects in elastography. *Ultrasound Med. Biol.* Jun.2001 27:819–27. [PubMed: 11516542]
- [4]. Shi, Y.; Xie, H.; Shamdassani, V.; Fraser, J.; Robert, J-L.; Zhou, S.; Urban, MW.; Chen, S.; Greenleaf, JF. IEEE International Ultrasonics Symposium. Orlando, FL: 2011. Phase aberration in shear wave dispersion ultrasound vibrometry.
- [5]. Palmeri ML, Wang MH, Dahl JJ, Frinkley KD, Nightingale KR. Quantifying hepatic shear modulus in vivo using acoustic radiation force. *Ultrasound Med. Biol.* Apr.2008 34:546–58. [PubMed: 18222031]
- [6]. Couade M, Pernot M, Messas E, Bel A, Ba M, Hagege A, Fink M, Tanter M. In vivo quantitative mapping of myocardial stiffening and transmural anisotropy during the cardiac cycle. *IEEE Trans. Med. Imag.* Feb.2011 30:295–305.
- [7]. Hollender PJ, Wolf PD, Goswami R, Trahey GE. Intracardiac echocardiography measurement of dynamic myocardial stiffness with shear wave velocimetry. *Ultrasound Med. Biol.* Jul.2012 38:1271–83. [PubMed: 22579544]
- [8]. Amador C, Urban MW, Chen S, Greenleaf JF. Shearwave dispersion ultrasound vibrometry (SDUV) on swine kidney. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Dec.2011 58:2608–19.
- [9]. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Apr.2004 51:396–409.
- [10]. Song P, Zhao H, Manduca A, Urban MW, Greenleaf JF, Chen S. Comb-push ultrasound shear elastography (CUSE): a novel method for two-dimensional shear elasticity imaging of soft tissues. *IEEE Trans. Med. Imag.* Sep.2012 31:1821–32.
- [11]. Song P, Urban MW, Manduca A, Zhao H, Greenleaf JF, Chen S. Comb-Push Ultrasound Shear Elastography (CUSE) With Various Ultrasound Push Beams. *IEEE Trans. Med. Imag.* Aug.2013 32:1435–47.
- [12]. Viola F, Walker WF. A spline-based algorithm for continuous time-delay estimation using sampled data. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Jan.2005 52:80–93.
- [13]. Mauldin FW Jr. Viola F, Walker WF. Complex principal components for robust motion estimation. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Nov.2010 57:2437–49.
- [14]. Luo J, Konofagou E. A fast normalized cross-correlation calculation method for motion estimation. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Jun.2010 57:1347–57.
- [15]. McLaughlin J, Renzi D. Using level set based inversion of arrival times to recover shear wave speed in transient elastography and supersonic imaging. *Inverse Problems.* Apr.2006 22:707–725.
- [16]. Tanter M, Bercoff J, Athanasiou A, Deffieux T, Gennisson JL, Montaldo G, Muller M, Tardivon A, Fink M. Quantitative assessment of breast lesion viscoelasticity: Initial clinical results using supersonic shear imaging. *Ultrasound Med. Biol.* Sep.2008 34:1373–1386. [PubMed: 18395961]
- [17]. Rouze NC, Wang MH, Palmeri ML, Nightingale KR. Robust estimation of time-of-flight shear wave speed using a radon sum transformation. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Dec.2010 57:2662–70.

- [18]. Wang MH, Palmeri ML, Rotemberg VM, Rouze NC, Nightingale KR. Improving the robustness of time-of-flight based shear wave speed reconstruction methods using RANSAC in human liver in vivo. *Ultrasound Med. Biol.* May.2010 36:802–13. [PubMed: 20381950]
- [19]. Montaldo G, Tanter M, Bercoff J, Benech N, Fink M. Coherent plane-wave compounding for very high frame rate ultrasonography and transient elastography. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Mar.2009 56:489–506.
- [20]. Tanter M, Bercoff J, Sandrin L, Fink M. Ultrafast compound imaging for 2-D motion vector estimation: application to transient elastography. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Oct.2002 49:1363–74.
- [21]. Shapiro RS, Wagreich J, Parsons RB, Stancato-Pasik A, Yeh HC, Lao R. Tissue harmonic imaging sonography: evaluation of image quality compared with conventional sonography. *AJR Am. J. Roentgenol.* Nov.1998 171:1203–6. [PubMed: 9798848]
- [22]. Thomas JD, Rubin DN. Tissue harmonic imaging: why does it work? *J. Am. Soc. Echocardiogr.* Aug.1998 11:803–8. [PubMed: 9719092]
- [23]. Tranquart F, Grenier N, Eder V, Pourcelot L. Clinical use of ultrasound tissue harmonic imaging. *Ultrasound Med. Biol.* Jul.1999 25:889–894. [PubMed: 10461715]
- [24]. Averkiou MA. Tissue Harmonic Imaging. in *IEEE International Ultrasonics Symposium.* 2000:1563–1572.
- [25]. Christopher T. Finite amplitude distortion-based inhomogeneous pulse echo ultrasonic imaging. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* 1997; 44:125–39.
- [26]. Ward B, Baker AC, Humphrey VF. Nonlinear propagation applied to the improvement of resolution in diagnostic medical ultrasound. *J. Acoust. Soc. Amer.* Jan.1997 101:143–54. [PubMed: 9000731]
- [27]. Simpson DH, Chin CT, Burns PN. Pulse inversion Doppler: a new method for detecting nonlinear echoes from microbubble contrast agents. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* 1999; 46:372–82.
- [28]. Ma Q, Ma Y, Gong X, Zhang D. Improvement of tissue harmonic imaging using the pulse-inversion technique. *Ultrasound Med. Biol.* Jul.2005 31:889–94. [PubMed: 15972194]
- [29]. Hwang J-J, Simpson DH. Two pulse technique for ultrasonic harmonic imaging. *US patent.* 1999; 5:951–478.
- [30]. Doherty, JR.; Dahl, JJ.; Trahey, GE. *IEEE International Ultrasonics Symposium.* Dresden, Germany: 2012. A harmonic tracking method for acoustic radiation force impulse (ARFI) imaging.
- [31]. Hasegawa H, Kanai H. High-frame-rate echocardiography using diverging transmit beams and parallel receive beamforming. *J. Med. Ultrason.* Jul.2011 38:129–140.
- [32]. Kasai C, Namekawa K, Koyano A, Omoto R. Real-Time Two-Dimensional Blood-Flow Imaging Using an Auto-Correlation Technique. *IEEE Trans. Son. Ultrason.* 1985; 32:458–464.
- [33]. Herman BA, Harris GR. Models and regulatory considerations for transient temperature rise during diagnostic ultrasound pulses. *Ultrasound Med. Biol.* Sep.2002 28:1217–24. [PubMed: 12401393]
- [34]. Urban MW, Greenleaf JF. Use of the Radon transform for estimation of shear wave speed. *J. Acoust. Soc. Amer.* 2012; 132:1982–1982.
- [35]. Urban MW, Pislaru C, Nenadic IZ, Kinnick RR, Greenleaf JF. Measurement of viscoelastic properties of in vivo swine myocardium using lamb wave dispersion ultrasound vibrometry (LDUV). *IEEE Trans. Med. Imag.* Feb.2013 32:247–61.
- [36]. Pislaru C, Urban MW, Nenadic I, Greenleaf JF. Shearwave dispersion ultrasound vibrometry applied to in vivo myocardium. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009; 2009:2891–4. [PubMed: 19964051]
- [37]. Nenadic, IZ.; Urban, MW.; Pislaru, C.; Bernal, M.; Greenleaf, JF. *IEEE International Ultrasonics Symposium.* Orlando, FL: 2011. In vivo open and closed chest measurements of myocardial viscoelasticity through a heart cycle using Lamb Wave Dispersion Ultrasound Vibrometry (LDUV); p. 17-20.

- [38]. McAleavey SA, Nightingale KR, Trahey GE. Estimates of echo correlation and measurement bias in acoustic radiation force impulse imaging. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Jun.2003 50:631–41.
- [39]. Urban MW, Chen S, Greenleaf J. Harmonic motion detection in a vibrating scattering medium. *IEEE Trans. Ultrason. Ferroelectr., Freq. Contr.* Sep.2008 55:1956–74.
- [40]. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief.* Jan.2012 :1–8.

Figure 1.

Pulse-inversion harmonic imaging sequence (a) and fundamental sequence (b) for shear wave motion tracking. (a) Phase-inverted pulses were emitted with certain pulse repetition frequency (PRF). Every two frames were then added to obtain harmonic frames with an effective frame rate of PRF/2. (b) Pulses with identical phases were emitted with the same PRF as in harmonics for the fundamental sequence. Every two frames were then averaged to form a fundamental frame set with the same effective frame rate as of the harmonic sequence.

Figure 2.

(a) Picture of the *ex vivo* pork belly/gelatin phantom experiment setup. (b) Pulse sequences for the two Verasonics systems used for the push and detection of the shear waves. 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.

Figure 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 5 different locations of the phantom/pork belly. Lower row: shear wave motions tracked by the fundamental sequence at the same 5 locations as in HI. All plots use the same color scale with units of mm/s.

Figure 4.

(a) Plot of the shear wave particle velocity (V_z) signal produced and tracked by the L7-4 probe. The black dashed lines indicate the shear wave propagation trajectories. N_t and N_x 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_p . The black arrows indicate the positions of the peak sinogram values.

Figure 5.

Plots of the shear wave particle velocity signal at the focal depth of the push beam in the left ventricular wall of an *ex vivo* close-chest pig. Upper row: Guidance B-mode images and Detection B-mode images of the left ventricular wall for both the harmonic imaging sequence (HI) and fundamental sequence. The regions indicated by the green dashed boxes are the shear wave detection region by the high PRF diverging beam. The red dashed boxes on the Detection B-mode images indicate the shear wave analysis region. Shear wave signal was averaged along depth direction within the region (region thickness = 2.7 mm). Middle row: shear wave motions tracked by the HI sequence out of 5 trials at a fixed position. Lower row: shear wave motions tracked by the fundamental sequence out of 5 trials at the same fixed position as in the HI sequence. All plots are on the same color scale with units of mm/s.

Figure 6.

Plots of the shear wave particle velocity signals transthoracically produced and tracked by the harmonic sequence in *in vivo* human heart under diastole for the seven recruited volunteers. The leftmost 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.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 7.

Plots of the frequency spectrum of three types of ultrasound beams at three depths. Ten cycles of radio-frequency (RF) signal backscattered from the CIRS phantom were Fourier transformed to obtain the spectrum. The focused beam stands for the conventional B-mode imaging beam which was focused at 45 mm. The narrow diverging beam is the diverging beam focused at -288 mm used in the *ex vivo* pig study and *in vivo* human study for shear wave detection. The wide diverging beam is the diverging beam focused at -28 mm used in the pork belly phantom study for shear wave detection.

Table I

Ultrasound safety measurements of the ultrasound beams used in this study

	Guidance B-mode	Diverging beam (focused at −288 mm)	Diverging beam (focused at −28 mm)	Push beam focused at 45 mm	Push beam focused at 60 mm	Push beam focused at 65 mm	Push beam focused at 70 mm
$MI_{0.3}$	1.24	1.51	1.19	1.60	1.11	1.00	0.90
$I_{SPTA,0.3}$ (mW/cm ²)	6.8	51.7	21.3	225.5	98.6	80.1	62.6

Table II

Maximum shear wave particle velocity (V_{ZMAX}) and shear wave speed (c_s) measurements by the L7-4 probe, the harmonic sequence (by P4-2) and the fundamental sequence (by P4-2)

Methods	Parameters	Position 1	Position 2	Position 3	Position 4	Position 5	Mean	Std.*	SNR
L7-4 (ground truth)	Direction	-x	+x	-x	+x	-x	+x		
	V_{ZMAX} (mm/s)	68.6	77.2				72.9	6.1	12.0
	c_s (m/s)	2.19	2.23				2.21	0.03	
Harmonic sequence	V_{ZMAX} (mm/s)	39.3	38.1	34.3	41.8	59.0	57.7	50.9	40.8
	c_s (m/s)	2.17	2.30	2.25	2.25	2.27	2.28	2.17	2.25
Fundamental sequence	V_{ZMAX} (mm/s)	7.20	4.70	10.5	5.56	4.27	4.92	11.2	5.8
	c_s (m/s)	2.13	2.03	3.42	2.18	2.06	2.10	2.13	2.10

* Std. denotes standard deviation

Table III

Shear wave speed (c_s) measurements of the left ventricular wall in an *ex vivo* closed-chest pig

		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Mean	Std.*
HI	C_s (m/s)	1.16	1.19	1.19	1.19	1.24	1.19	0.03
Fundamental		-	-	-	-	-	-	-

* Std. denotes standard deviation

Shear wave speed (c_s) measurements of the left ventricular wall in end-diastole[illegible]

* Std. denotes standard deviation

Vol. denotes volunteer