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***In Vivo* Open- and Closed-chest Measurements of Left-Ventricular Myocardial Viscoelasticity using Lamb wave Dispersion Ultrasound Vibrometry (LDUV): A Feasibility Study**

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Abstract

Diastolic dysfunction causes close to half of congestive heart failures and is associated with increased stiffness in left-ventricular myocardium. A clinical tool capable of measuring viscoelasticity of the myocardium could be beneficial in clinical settings. We used Lamb wave Dispersion Ultrasound Vibrometry (LDUV) for assessing the feasibility of making *in vivo* non-invasive measurements of myocardial elasticity and viscosity in pigs. *In vivo* open-chest measurements of myocardial elasticity and viscosity obtained using a Fourier space based analysis of Lamb wave dispersion are reported. The approach was used to perform ECG-gated transthoracic *in vivo* measurements of group velocity, elasticity and viscosity throughout a single heart cycle. Group velocity, elasticity and viscosity in the frequency range 50–500 Hz increased from diastole to systole, consistent with contraction and relaxation of the myocardium. Systolic group velocity, elasticity and viscosity were 5.0 m/s, 19.1 kPa, 6.8 Pa·s, respectively. In diastole, the measured group velocity, elasticity and viscosity were 1.5 m/s, 5.1 kPa and 3.2 Pa·s, respectively.

INTRODUCTION

Diastolic dysfunction is the inability of the left ventricle (LV) to supply sufficient stroke volumes under normal physiological filling pressures and causes close to 50% of congestive heart failures [1, 2]. Diastolic dysfunction is associated with stiffening of the left-ventricular myocardium, diagnosis of which relies on catheterization and echocardiography [3]. A clinical tool capable of quantifying mechanical properties of the left-ventricular myocardium noninvasively would be beneficial in evaluating diastolic function.

Changes in myocardial stiffness due to pathophysiology have prompted efforts towards producing imaging techniques for characterizing myocardial stiffness. Positron emission tomography, x-ray computed tomography (CT) and magnetic resonance imaging (MRI) have offered approaches for qualitative assessment of cardiac function by employing various

contrast agents to track myocardial motion [4–10]. Pulsed Doppler tissue imaging provides good time resolution of the Doppler signal that allows for reliable estimates of tissue displacement, velocity and acceleration, but has a poor spatial resolution and cannot differentiate different layers of the ventricular wall [11]. Strain rate imaging has also been used to assess cardiac function [12–16]. Konofagou, *et al.* developed an ultrasound-based myocardial elastography technique that uses intrinsic motion of the heart to produce a two-dimensional *in vivo* strain map of the myocardium [17–20]. This technique showed promising results at detecting infarcted tissue in mice at both high temporal and spatial resolution. Acoustic Radiation Force Imaging (ARFI) study of *in vivo* open-chest canine hearts reports the variation in motion amplitude through the heart cycle [21]. ARFI imaging of ablated cardiac tissue showed higher stiffness and less motion than the surrounding normal tissue [22, 23]. Such techniques are sufficient for detecting acute disorders (i.e., myocardial infarction) because of the contrast provided by the healthy tissue present in the background. Diffuse disorders such as diastolic dysfunction result in stiffening of the entire left ventricle and require quantitative measures of myocardial stiffness. Because the Young's modulus of elasticity is the ratio of stress and strain, the information of both parameters is necessary for quantitative characterization of mechanical properties of the myocardium.

In the last two decades, the fields of ultrasound and magnetic resonance elastography [24–29] have offered various methods to characterize myocardial elasticity. Intrinsic tissue motion, focused acoustic radiation force or a mechanical actuator are used as a source of mechanical waves, and the pulse-echo ultrasound or magnetic resonance imaging to track the deformation. The shear wave velocity (c_s) is directly related to the shear modulus of elasticity (μ) through $\mu = c_s^2 \rho$, where ρ is the tissue density. The wave-based methods provide quantitative evaluation of material properties because the wave equation can be solved locally and does not depend on knowing the input stress distribution.

Sack *et al.* investigated the change of shear wave amplitude in the human heart through the cardiac cycle using MRE and reported a diastole/systole amplitude ratio of about 2.5 and stiffness ratio of 37.7, consistent with the notion that the LV myocardium is softer in diastole than in systole [30, 31]. In another study involving 50 patients, Sack *et al.* demonstrated that the shear wave amplitude relates to relaxation abnormalities in patients with diastolic dysfunction [32]. In another MRE study, Kolipaka *et al.* measured changes in transverse wave velocity through a heart cycle *in vivo* in open chest pigs. This model-based approach assumes that the transverse wave velocity is the same as the shear wave velocity and reports elasticity (μ) increase from 6 kPa (diastole) to 10 kPa (systole) [33, 34]. These MRE techniques measure wave velocity at only a single frequency and therefore ignore tissue viscosity.

Electromechanical wave imaging is a method for quantifying elasticity of the myocardium by recording intrinsic motion of the heart due to electromechanical waves caused by physiological motion and current propagation [35–38]. The motion is acquired using successive radiofrequency frames and the Fourier analysis of the signal estimates the wave velocities at several frequencies between 80 and 250 Hz with the values ranging from 0.44 to 5 m/s. This technique has shown promising results in obtaining high frame rate cardiac

elastography measurements in anesthetized mice [39], but is limited to the areas of the heart with sufficient amplitude of intrinsic motion.

The shear wave elasticity imaging (SWEI) [40] technique was used to track mechanical waves due to radiation force in the left-ventricular myocardium of an open chest dog at several positions and depths in the LV free wall and reported speeds ranging from 0.82 to 2.65 m/s [41, 42]. A similar method, supersonic shear imaging (SSI) [43], uses focused acoustic radiation force to generate mechanical waves in tissue by moving the source of vibration at a supersonic speed along the line of excitation, creating a wave front. The waves are imaged at high frame rates and various inversion algorithms are used to estimate the shear wave velocity and tissue elasticity. SSI was used to study changes in group velocity and elasticity throughout the heart cycle in open chest ovine LV myocardium [41, 42]. The average group velocities in systole and diastole were 4.8 ± 1.4 m/s and 1.45 ± 0.32 m/s along the long axis, and 6.2 ± 1.9 m/s and 1.85 ± 0.22 m/s along the short axis. This corresponds to changes in the shear modulus of elasticity (μ) from ~ 2 to ~ 30 kPa between diastole and systole, respectively [41].

An intracardiac echocardiography (ICE) probe was used by Hollender et al. [44] to perform acoustic radiation force driven shear wave velocimetry from within the right ventricle of *in-vivo* swine hearts through the cardiac cycle. Group velocity variations for 6 different specimens were 4.09 ± 1.03 m/s and 2.05 ± 0.63 m/s in systole and diastole, respectively. The shear modulus of elasticity in systole and diastole varies between 16.59 ± 9.83 kPa and 2.82 ± 2.03 kPa. Likewise, four pigs with focal infarctions in the apical intraventricular septum (IVS) and/or left ventricular free wall (LVFW) were imaged with ICE and compared to control pigs. After comparing similar views of the septum, the authors report variation, but no significant differences between the spared regions of the infarcted pigs and those of the control.

Most tissues, including the myocardium, are inherently viscoelastic [45, 46]. Measurements of both elasticity and viscosity are necessary in order to fully characterize mechanical properties of the myocardium, a concept often ignored in both MRE and shear wave ultrasound elastography methods.

Schmeling, *et al.*, reported an increase in LV myocardial viscosity during diastole due to occlusion of the left anterior descending coronary artery in not reperfused animals, and return of the viscosity to the baseline in reperfused animals [47]. While the elasticity increased in the ischemic region, the viscosity increased in both ischemic and nonischemic regions of the LV wall. These results suggest that changes in tissue perfusion could affect the long-term mechanical properties in the tissue. In addition, application of an elastic model to characterize an inherently viscoelastic material biases the estimates of material elasticity as the elastic component has to describe behavior of the tissue that is due to both the elasticity and viscosity [48].

Kanai, *et al.*, [49, 50] used a highly sensitive ultrasound-based method to measure elasticity and viscosity of the myocardial septum *in vivo*. The elasticity values were estimated at 24–30 kPa and did not change as a function of aortic valve closure. The viscosity decreased

rapidly from 400 Pa·s to 70 Pa·s over 18 ms after aortic valve closure. This method uses closure of the aortic valve as the source of vibration and does not require an external source of vibration.

Our group has developed Lamb wave Dispersion Ultrasound Vibrometry (LDUV), an ultrasound method for quantifying mechanical properties of biological tissues and soft solids with plate-like geometry [51]. LDUV uses focused acoustic radiation force or a mechanical actuator to excite harmonic cylindrical anti-symmetric Lamb waves in a plate-shaped medium and a pulse-echo transducer to track the motion as a function of time and distance. For harmonic excitations the shear wave phase delay has a linear variation in respect to the distance from the excitation point. This is calculated by taking a Fourier transform at each location and extraction the phase shift for each frequency and then performing a regression of the phase with respect to distance for estimation of the phase velocity [51–53]. In impulse excitation, a Fourier-based method is used to obtain Lamb wave velocities at multiple frequencies. Change in Lamb wave velocity as a function of frequency (Lamb wave dispersion) is measured in the range 50–500 Hz and the Lamb wave dispersion equation is fitted to the Lamb wave dispersion velocities to estimate elasticity and viscosity of the medium. Our group has validated the use of LDUV to quantify elasticity and viscosity of soft materials by comparing the LDUV results to those obtained using an independent method [54], and reported LDUV measurements in excised porcine LV free wall myocardium. Studies from our group have also investigated the viscoelastic change between normal and infarcted myocardium. The authors reported highly abnormal shear elasticity and viscosity measurements, mainly during diastole, for infarcted hearts compared to normal [55].

In vivo application of LDUV with a mechanical actuator (shaker) in an open chest pig has also been reported [56, 57]. *In vivo* Shaker-LDUV requires placement and vibration of a metal rod attached to the shaker on the surface of the exposed porcine LV myocardium. This method excites Rayleigh (surface), so Rayleigh wave Dispersion Ultrasound Vibrometry (RDUV) was developed [58]. Conceptually, the difference between LDUV and RDUV is solely in the method of excitation and the set of equations used to describe the tissue motion (Lamb versus Rayleigh waves). However, in [58] we demonstrated that Lamb and Rayleigh waves converge in the myocardium above a certain cut-off frequency (usually around 100 Hz) that depends on elasticity, viscosity and thickness of the free wall [51], which allows us to use either set of the equations to measure viscoelasticity.

Transthoracic application of the LDUV would require use of acoustic radiation force to excite Lamb-Rayleigh waves in the beating heart and pulse-echo ultrasound to track the waves. The Lamb-Rayleigh convergence allows us to quantify myocardial viscoelasticity by focusing acoustic radiation force on the highly reflective epicardial surface as opposed to the middle of the free wall which could prove to be difficult due to physiological motion. Focusing acoustic radiation force on the epicardial surface would also increase the radiation force [59]. In addition, an extension of RDUV theory resulted in a simple relationship between the Lamb, Rayleigh and shear wave dispersion velocities that allows us to bypass the complexity of Lamb and Rayleigh dispersion fitting [60]. More recently, our group has

demonstrated improvements in detecting wave propagation in the LV myocardium using harmonic imaging [61, 62, 63].

In this paper, we report the use of LDUV/RDUV technique for *in vivo* measurements of elasticity and viscosity of the porcine LV free wall myocardium in open- and closed-chest settings. Studies comparing Lamb wave dispersion obtained using monochromatic shaker excitation and a single element pulse-echo transducer and Lamb wave dispersion obtained with a linear array transducer that focuses acoustic radiation force to produce transient Lamb waves and switches elements to track the motion are also reported. The array transducer was used to quantify elasticity and viscosity of the pig heart in systole and diastole in an open chest *in vivo* setting. The technique was then used for *in vivo* transthoracic measurements of group velocity, elasticity and viscosity throughout a heart cycle in porcine LV myocardium.

METHODS

Principles of Lamb wave Dispersion Ultrasound Vibrometry

Lamb wave Dispersion Ultrasound Vibrometry (LDUV) is an ultrasound-based method for quantifying viscoelasticity of organs with plate-like geometry [64]. In its basic application, LDUV uses a mechanical shaker or focuses ultrasound to excite harmonic Lamb waves in the medium of interest and pulse-echo ultrasound to measure the change in phase ($\phi = \phi_2 - \phi_1$) as function of propagation distance (r), or the phase gradient. The phase gradient is used to compute the velocity of the Lamb wave (c_L) at the given frequency (f) using $c_L(f) = 2\pi f^{-1} \phi$. The phase velocity is measured at several frequencies in the range 50–500 Hz to obtain the velocity versus frequency diagram (Lamb wave velocity dispersion). The anti-symmetric Lamb wave dispersion equation for a viscoelastic plate submerged in an incompressible fluid of density similar to that of the medium (1) is fitted to the dispersion data to calculate myocardial elasticity (μ_1) and viscosity (μ_2):

$$4k_L^3 \beta \cosh(k_L h) \sinh(\beta h) - (k_s^2 - 2k_L^2)^2 \sinh(k_L h) \cosh(\beta h) = k_s^4 \cosh(k_L h) \cosh(\beta h), \quad (1)$$

where $k_L = \omega/c_L$ is the Lamb wave number, ω is the angular frequency, c_L is the frequency dependent Lamb wave velocity, $k_s = \omega \sqrt{\rho_m/\mu}$ is the shear wave number, $\beta = \sqrt{k_L^2 - k_s^2}$, ρ_m is the density of the sample and h is the half-thickness of the sample. Here, the frequency response of the free wall is assumed to obey the Voigt model so that the calculated shear modulus (μ) can be decomposed in terms of the elastic (μ_1) and viscous (μ_2) components so that $\mu = \mu_1 + j\omega\mu_2$ [51]. We have validated the LDUV technique in our laboratory for gelatin and urethane rubber phantoms with an embedded sphere method [64]. In addition, viscoelasticity measurements in gelatin phantoms, excised porcine myocardium and spleen samples obtained using LDUV are in excellent agreement with those obtained using MRE [64, 65].

Fourier-space Dispersion Analysis

Harmonic vibration excites a single frequency (f) wave whose velocity (c) can be estimated by measuring the phase gradient (ϕ) as a function of distance (r) at that given frequency

via $c = 2\pi f / \phi$. Impulse excitation allows one to extract multiple phase velocities from a single push. It is important to note that the impulse propagates at a group velocity that is different from the velocities of individual frequency phase velocities. Because dispersion diagrams consist of phase velocities, so it is important to extract the phase velocities at each frequency from the impulse displacement data. We performed a two-dimensional discrete fast Fourier transform (2D FFT) on the displacement versus time data due to an impulse using (2):

$$U_z(k, f) = \sum_{m=-\infty}^{+\infty} \sum_{n=-\infty}^{+\infty} u_z(x, t) e^{-j2\pi(kmx + fnt)}, \quad (2)$$

where $u_z(x, t)$ is the motion of the heart wall perpendicular to the excitation beam (z -axis) as a function of distance from the excitation beam (x) and time (t) (Figure 1) [66]. Here, k is the wave number and f is the temporal frequency of the wave. The coordinates of the k -space are the wave number ($1/\lambda$) and the frequency (f), and since the wave velocity $c = \lambda f$ one can calculate the phase velocity of each pixel in the k -space by dividing the frequency coordinate by the wave number coordinate [66, 67]. For acoustic radiation force applications the excitation beam is commonly referred as push beam, whereas the tissue motion is captured by the detection beam.

Water Tank Lamb wave Dispersion Ultrasound Vibrometry (LDUV) Experimental Set Up

The phantoms were used to compare measurements of Lamb wave dispersion obtained using the traditional mechanical shaker LDUV method that uses harmonic excitation (harmonic LDUV) and the single transducer focused ultrasound LDUV method that uses impulse excitation (impulse LDUV). The experimental setup for these studies is shown in Figure 2. Excised pig LV free wall myocardium sample was embedded in a gelatin mixture (80% water, 10% glycerol, 10% 300 Bloom gelatin, all by volume and 10 g/L potassium sorbate preservative, all manufactured by Sigma-Aldrich, St. Louis, MO) inside a plastic container with a cut out bottom to allow ultrasound transducer access. The pig heart was obtained at a local butcher shop and was frozen overnight 24 hours before the experiment. The container was placed on a metal stand inside a water tank. The gelatin was contained to the edges of the phantom to avoid mechanical coupling (Figure 2). A glass rod coupled with a mechanical shaker (V203, Ling Dynamic Systems Limited, Hertfordshire, UK) was glued to the hole bored through the thickness of the samples (Figure 2a). Four sinusoidal cycles were used to drive the shaker at different frequencies ranging from 40 to 500 Hz, within the range of optimal operation of the shaker, which does not vibrate with high amplitude at frequencies above 500 Hz. A 5 MHz L7-4 transducer pulse-echo transducer (Philips Healthcare, Andover, MA) operating at 4 kHz was used to track the motion along the axis parallel to the glass rod (z -axis) at 31 points, 0.5 mm apart along the line of wave propagation (x -axis). Cross-spectral analysis was used to calculate the phase at each point away from the excitation and the phase gradient was used to estimate the Lamb wave velocity at each frequency [64]. For each frequency, the Lamb wave velocity was measured at 10 different depths 1 mm apart in the z -axis. The mean and standard deviation of the velocities at each frequency was calculated.

An impulse contains multiple frequency components up to the inverse of the time length of the impulse. This allows one to extract many phase velocities from a single impulse push. In addition, this process allows for quicker data acquisition. LDUV has been implemented on a Verasonics V-1 system (Verasonics, Redmond, WA), a programmable ultrasound research platform with multiple independent transmit and receive channels [68]. For the excised myocardium, a linear array transducer with a higher center frequency for a better spatial resolution. A linear array L7-4 transducer with a center frequency of 5 MHz (Philips Healthcare, Andover, MA) excites and tracks mechanical waves in the region of interest by transmitting and detecting with a single probe. The transmitter can produce long tonebursts necessary for radiation force with sustained high power. In this study, the length of the impulse was 400 μ s. The waveform is not windowed in time. The acquired data is stored and processed off-line. Verasonics (VSX) detect mode operated at 5 MHz with frame rates of 4 kHz, allowing high resolution motion detection. We refer to this data acquisition approach as impulse LDUV.

Lamb wave dispersion measurements obtained with impulse LDUV were compared to the harmonic LDUV measurements in the excised pig myocardium phantom. Cross-spectral analysis of the detect beams was used to estimate the tissue motion (Figure 2b) [69]. The Fourier-space (k-space) analysis method of the average tissue motion through thickness was used to calculate the Lamb wave dispersion velocities in the frequency range 50–1000 Hz.

In Vivo Animal Studies

An open-chest (thoracotomy) and a closed-chest (transthoracic) protocol approved by the Mayo Clinic Institutional Animal Care and Use Committee were used for *in vivo* studies of Lamb wave propagation in pig hearts. For the *in vivo* acquisitions, a curved array transducer with a lower center frequency was used to provide higher acoustic radiation force at the deeper depths. Additionally, the shear wave bandwidth can change as a function of acoustic radiation force duration and geometry. The curved array will produce an acoustic radiation force push with a larger spatial distribution that may reduce the shear wave bandwidth [70]. A C4-2 curved linear array transducer (Philips Healthcare, Andover, MA) with a center frequency of 3.3 MHz was used to excite 1 ms long impulse with sustained high power in the myocardium and to track the wave propagation using a flash imaging mode scheme with pixels on the order of tenths of millimetres and frame rate of 4 kHz. Although both harmonic and impulse methods are consistent in phantom studies, the harmonic method is not suitable for closed chest studies. When the vibration originates on the surface of the body, the resulting waves are not isolated to the ultrasound imaging plane. As a result, out-of-plane motion can cause bias in measured wave speeds [71]. The transducer was wrapped in latex filled with ultrasound gel. Wave excitation from the VSX probe was triggered by the electrocardiographic (ECG) R-wave and the data were acquired every 50 ms for 600 ms to capture an entire heart cycle. The k-space analysis method was used to obtain the Lamb wave dispersion velocities. Equation (1) was fit to the dispersion data to estimate myocardial elasticity and viscosity throughout the heart cycle. Group velocity was measured using a time-to-peak (TTP) algorithm, by performing a linear regression over the calculated TTP displacement at sequential lateral positions [72]. The heart cycle can generally be divided into systole and diastole. Systole is the phase of the cycle during which the ventricles

contract and pumps the blood into the pulmonary artery and aorta. Diastole is the phase of the heart cycle during which the ventricles relax to allow blood flow from the atria.

RESULTS

Figure 3 shows the comparison between Lamb wave velocities obtained using the harmonic and impulse LDUV methods. Fourier analysis of the rightward propagating wave was used to calculate the wave dispersion due to impulse LDUV excitation. Fig. 3(a) shows a displacement image of impulse propagation in the excised LV myocardium. 2D-FFT of the displacement image gives the k-space of the displacement (Fig. 3(b)) where the x -axis represents frequency and the y -axis the inverse wavelength ($1/\lambda$). The lowest order mode of propagation is the A_0 Lamb wave mode and it has the highest energy. The phase velocity at each frequency is calculated by finding the maximum amplitude values for each frequency in k-space, recognizing that the wave velocity $c = \lambda f$ and dividing the frequency coordinate (f) by the wave number ($1/\lambda$) coordinate for each maxima [66]. For example, the k-space maximum at 300 Hz corresponds to the wave number ($1/\lambda$) of approximately 100 m^{-1} , as shown in Fig. 3(b). Thus the phase velocity at 300 Hz is around 3 m/s, as shown in Fig. 3(c). This process was repeated for frequencies 0–1000 Hz to obtain the dispersion curve shown in blue in Figure 3(c). LDUV measurements of the Lamb wave dispersion in an excised pig myocardium obtained using the shaker method is shown in red for comparison. The harmonic LDUV method was used to estimate the Lamb wave velocity at multiple frequencies for each millimeter of the sample thickness. The mean and standard deviation of Lamb wave velocity through sample thickness is reported.

Following the validation of the impulse LDUV against the harmonic LDUV method (previously validated against gold standard in [64]), the impulse LDUV was applied *in vivo* in anesthetized pigs. An image of wave displacement as a function of time and distance in an open chest *in vivo* LV porcine myocardium is shown in Figure 4.

The rightward propagating wave (bottom wing) is used to calculate the phase velocity dispersion as shown in Figs. 5(a)–(c). The Lamb wave dispersion Eq. (1) (blue in Fig. 5(c)) was fitted to the phase velocities (red in Fig. 5(c)) to estimate elasticity (μ_1) and viscosity (μ_2) of the myocardium. The ECG signal was used to trigger the system to make measurements in systole and diastole. Estimates of elasticity (μ_1) and viscosity (μ_2) in an open-chest pig were made in systole and diastole and are summarized in Figure 6.

Figure 7(a) shows ECG R-wave gated transthoracic measurements of changes in group velocity through a heart cycle in the LV free wall myocardium. The average and standard deviation values of the group velocities of the rightward and leftward propagating waves were averaged over three acquisitions. The ECG recording is shown in Fig. 7(b) for reference. The Fourier-space dispersion analysis method was used to obtain the Lamb wave dispersion curves throughout a heart cycle. The Lamb wave dispersion equation (1) was fit to the dispersion data to estimate LV elasticity (μ_1) and viscosity (μ_2). The values of elasticity (μ_1) and viscosity (μ_2) through a single heart cycle are shown in Figs. 7(d) and (e). Table I compares the values of elasticity and viscosity of the myocardium obtained using transthoracic impulse LDUV with values obtained by other groups.

DISCUSSION

Most elastography techniques assume that the tissue is purely elastic, and relate the wave velocity (c) directly to the elastic modulus (μ) of the tissue via $\mu = \rho c^2$, where ρ is the tissue mass density (close to that of water). However, all biological tissues are inherently viscoelastic and ignoring the viscous component not only biases the velocity-derived estimates of elasticity but also fails to report a potentially important tissue parameter. In addition, disregarding tissue viscosity masks potentially complex pathophysiological changes that manifest in structural changes affecting both elasticity and viscosity by grouping the two terms under the elasticity parameter. Reperfused myocardium, for example, does not present statistically significant changes in elasticity during systole, conversely, it shows significantly higher viscosity when compared to normal myocardium [55].

Elastography techniques that relate the measured velocity (c_s) to the shear modulus (μ) via $\mu = c_s^2 \rho$ (ρ being tissue density) also assume that the propagating wave is the shear wave in within the bulk of tissue, away from the organ edges. In essence, this simple relationship ignores potential boundary affects. In boundary sensitive organs whose geometry resembles plates, such as the myocardium, cornea, tendons, and bladder wall, the shear and compressional waves due to the acoustic impulse interfere to form Lamb waves [64, 73, 74]. The relationship between the Lamb wave velocity and the shear modulus is different than the corresponding relationship for the shear wave velocity mentioned above because the Lamb wave velocity also depends on the elasticity of the surrounding media and the thickness of the structure. Hence, additional theory must be derived in order to relate the observed Lamb wave velocity to the shear modulus of elasticity. In addition, plate-like elastic media display the phenomenon called geometric dispersion in which the Lamb wave velocity varies as a function of excitation frequency. Using the Lamb wave theory, a mathematical model is derived that describes the relationship between the Lamb wave velocities at different frequencies and the shear modulus of elasticity and viscosity (equation 1) [64, 73, 74]. In practice, it is possible to excite Lamb waves in plate-like organs by using an impulsive acoustic radiation force [64, 73, 74]. An impulsive acoustic radiation force consists of multiple frequencies, where each frequency component may propagate at a different velocity. Therefore, one can estimate myocardial elasticity and viscosity by fitting the analytically derived Lamb wave model to the Lamb wave velocities measured at multiple frequencies (Lamb wave dispersion).

Another phenomenon of the impulsive wave propagation in a dispersive medium is the group velocity of the impulse, which is equal to the phase velocity of the frequency with the highest energy. The group velocity is calculated directly by estimating the impulse propagation as a function of time and distance and does not require the knowledge of myocardial thickness, but in the case of the Lamb waves it is not explicitly related to the shear modulus of the plate-like medium. Taking a two-dimensional Fast Fourier Transform (2D FFT) of the impulse propagation with respect to time and space results in the k-space from which the velocities at each frequency (dispersion data) within the impulse can be calculated. While this is more computationally expensive and requires better signal to noise

ratio, the Lamb wave dispersion equation can be fit to the dispersion data to estimate myocardial elasticity and viscosity.

Estimates of myocardial elasticity (μ_1) and viscosity (μ_2) in the septum of a beating human heart in the frequency range 10 – 90 Hz were reported by Kanai [49] with the values $\mu_1 = 30$ kPa and $\mu_2 = 70\text{--}400$ Pa·s. *In vivo* MRE measurements of myocardial elasticity in open chest pigs report the values in the range 5–10 kPa [33]. Couade *et al.* [41] reported similar *in vivo* measurements in open chest sheep hearts with the elasticity ranging from 2.17 kPa to 38.7 kPa throughout the heart cycle. The LDUV-shaker estimates of elasticity (μ_1) and viscosity (μ_2) changing from $\mu_1 = 5.1$ kPa and $\mu_2 = 3.2$ Pa·s in diastole to $\mu_1 = 19.1$ kPa and $\mu_2 = 6.8$ Pa·s in systole are within the range of the values reported by most of the groups, except for the values of μ_2 reported by Kanai [49]. A more detailed parametric study of the effects of elasticity and viscosity on the Lamb wave velocity has been previously reported by our group [55, 57].

In vivo open-chest studies show that the group velocity increases from diastole to systole, consistent with the relaxation and contraction of the myocardium (Table I). The open chest studies show a change in group velocity from around 1.5 m/s in diastole to around 4.5 m/s in systole (not shown).

Kanai, *et al.*, [49, 50] used a highly sensitive ultrasound method to measure elasticity and viscosity of the myocardial septum *in vivo*. The elasticity values were estimated at 24–30 kPa and did not change as a function of aortic valve closure. The viscosity estimates decreased rapidly from 400 Pa·s to 70 Pa·s over 18 ms after aortic valve closure. In addition to these large changes in measured viscosity of the myocardium, this method estimates myocardial elasticity and viscosity in the septum and around the aortic valve in the frequency range 10–90 Hz.

In vivo transthoracic measurements of elasticity (μ_1) and viscosity (μ_2) in Figure 7(d) and 7(e) follow the phase of change in group velocity in Figure 7(c). Group velocity changed from around 1.5 m/s in diastole to around 5 m/s in systole (Figure 7(c)). Leftward and rightward propagating waves follow the same general pattern and are fairly similar. The values of elasticity (μ_1) increased from ~ 2 to ~ 8 kPa, while the values of viscosity (μ_2) increased from ~ 2 to ~ 12 Pa·s from diastole to systole. These changes are similar to those observed in open-chest studies reported in Table I. The R wave precedes the increase in group velocity by about 100 ms, consistent with the delay between the ventricular depolarization and ventricular contraction. The increase in group velocity at 550 ms could be attributed to the atrial kick (Figure 7(b)). The R wave after 600 ms would support this hypothesis.

Our velocity values compare well with the those reported in [49]: 1 – 6 m/s (Diastolic – Systolic) in the range 10 – 90 Hz, [33]: 2.2 – 3.2 m/s at 80 Hz, [41]: 1.45 – 6.2 m/s along the short axis of the heart in the frequency range 100 – 400 Hz and [64]: where they found a mean velocity of 1.56 m/s with a standard deviation of 0.36 m/s in end-diastole. The measurements range also agrees with [55]: mean velocity of about 1.5 – 3.1 m/s at 100 Hz and with [57]: 1.5 – 3 m/s at 100 Hz. These encouraging results provide a stepping stone for

further research aimed at producing a clinical tool capable of transthoracic estimates of elasticity and viscosity of the myocardium.

This study included two animals total: one for the open-chest and one for the closed-chest studies. In both animals, the measurements were made at a single location throughout the heart cycle. As such, the results reported in this paper serve as a proof of concept as they demonstrate the ability to measure shear wave elasticity and viscosity in live animals at several points through the heart cycle. For the purpose of these studies, we treated the myocardium as a homogenous medium in order to simplify the analysis. Myocardial anisotropy might be an important concept, the study of which is beyond the scope of this study.

CONCLUSION

A programmable ultrasound-imaging platform was used to conduct a feasibility study to evaluate the mechanical properties of a beating left-ventricular myocardium. Group velocity changed through a heart cycle, consistent with myocardial contraction and relaxation. Lamb wave dispersion curves of a beating heart were obtained in open- and closed-chest settings and fit to estimate tissue elasticity and viscosity. Elasticity and viscosity of the myocardium increased from diastole to systole.

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Figure 1. Implementation of LDUV with an array transducer with electronically focused push (solid) and detection (dashed) beam.

Figure 2.

Experimental setup for comparing dispersion velocities in an excised pig LV myocardial free wall phantom obtained using a mechanical actuator (shaker) vibrating at multiple harmonics referred to as harmonic LDUV (a), and using a multiple array transducer that focuses radiation force (solid line) to excite an impulsive wave and track the motion (dashed line) referred to as impulse LDUV (b).

Figure 3.

Linear array impulse excitation in an excised pig LV myocardium submerged in water. (a) Impulse propagation in time and space, (b) k-space of the propagated impulse, (c) phase velocities as a function of frequency due to impulse excitation (blue) compared to the phase velocity obtained using the harmonic LDUV method (red). The harmonic LDUV method was used to estimate the Lamb wave velocity at multiple frequencies for each millimetre of the sample thickness. The mean and standard deviation of those measurements are shown in red.

Figure 4.

Image of wave displacement in an open chest *in vivo* left-ventricular free wall myocardium. Focused radiation force excites a mechanical wave at $x = 0$ and the wave propagates to the left and right from the excitation point as a function of time. The group velocity of Lamb wave propagation in the beating heart is estimated by measuring the slope of the wave propagation.

Figure 5.

Analysis of open chest pig elasticity and viscosity in systole. (a) Measured displacement of propagating wave, (b) 2D k-space of displacement, (c) Wave speed dispersion and Lamb wave dispersion fit $\mu_1 = 10.7$ kPa and $\mu_2 = 3.7$ Pa·s.

Figure 6.

Average and standard deviation of elasticity (μ_1) and viscosity (μ_2) measurements in open chest *in vivo* porcine LV myocardial during systole and diastole. Elasticity of 12.44 ± 1.3 kPa and viscosity of 3.99 ± 1.19 Pa·s during systole, and elasticity of 2.24 ± 0.54 kPa and viscosity of 3.36 ± 0.5 Pa·s during diastole.

Figure 7.

R-wave ECG gated transthoracic measurements of Lamb wave group velocity, elasticity and viscosity in a beating porcine left ventricular free wall averaged over 5–10 acquisitions.

Average group velocity (a), elasticity (c) and viscosity (d) show a similar pattern of increase in systole and decrease in diastole, consistent with the ECG signal.

Table I

Comparison of group velocity, elasticity and viscosity

Group	Region	Animal	Diastole			Systole		
			Group Velocity (m/s)	Elasticity μ_1 (kPa)	Viscosity μ_2 (Pa.s)	Group Velocity (m/s)	Elasticity μ_1 (kPa)	Viscosity μ_2 (Pa.s)
Kanai et al. [48]	IVS	Human	1.0	N.R	N.R	6.0	27.0 ± 3	235 ± 165
Couade et al. [43]	LVFW	Sheep	1.6 ± 0.47	2.17	N.R	5.75 ± 2.34	38.7	N.R
Hollender et al. [63]	IVS	Pig	2.05 ± 0.63	2.82 ± 2.03	N.R	4.09 ± 1.03	16.59 ± 9.83	N.R
Bouchard et al. [38]	LVFW	Canine	0.82	0.69	N.R	2.65	4	N.R
Pernot et al. [32]	LVFW	Rat	1.0	1.2 ± 0.1	N.R	10.0	8.4 ± 0.5	N.R
Pislaru et al. [52]	RVFW	Pig	N.R	1.7	3.2	N.R	31.0	5.0
Kolipaka et al. [29]	LV	Pig	2.2	6.03 ± 1.8	N.R	3.2	9.34 ± 1.9	N.R
Song et al. [65]	LVFW	Human	1.56	N.R	N.R	N.R	N.R	N.R
Nenadic et al.	LV	Pig	1.5	5.1	3.2	5.0	19.1	6.8

N.R = Not Reported; IVS = interventricular septum; LVFW = left ventricular free wall; RVFW = right ventricular free wall; LV = left ventricle.