Acoustic Radiation Force Impulse Imaging of Myocardial Performance

by

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering in the Graduate School of Duke University

2009
ABSTRACT

(Biomedical Engineering)

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Abstract

Cardiovascular disease is the leading cause of death for developed countries, including the United States. In order to diagnose and detect certain cardiac diseases, it is necessary to assess myocardial performance and function. One mechanical property that has been shown to reflect myocardial performance is myocardial stiffness. Acoustic radiation force impulse (ARFI) imaging has been demonstrated to be capable of visualizing variations in local stiffness within soft tissue.

In this thesis, the initial investigations into the visualization of myocardial performance with ARFI imaging are presented. In vivo ARFI images were acquired with a linear array placed on exposed canine hearts. When co-registered with the electrocardiogram (ECG), ARFI images of the heart reflected the expected changes in myocardial stiffness through the cardiac cycle. With the implementation of a quadratic motion filter, motion artifacts within the ARFI images were reduced to below 1.5 \( \mu \text{m} \) at all points of the cardiac cycle. The inclusion of pre-excitation displacement estimates in the quadratic motion filter further reduced physiological motion artifacts at all points of the cardiac cycle to below 0.5 \( \mu \text{m} \).

In order for cardiac ARFI imaging to more quantitatively assess myocardial performance, novel ARFI imaging sequences and methods were developed to address challenges specifically related to cardiac imaging. These improvements provided finer sampling and improved spatial and temporal resolution within the ARFI images. In vivo epicardial ARFI images of an ovine heart were formed using these sequences, and the quality and utility of the resultant ARFI-induced displacement curves were
examined.

*In vivo* cardiac ARFI images were formed of *canine* left ventricular free walls while the hearts were externally paced by one of two electrodes positioned epicardially on either side of the imaging plane. Directions and speeds of myocardial stiffness propagation were measured within the ARFI imaging field of view. In all images, the myocardial stiffness waves were seen to be traveling away from the stimulating electrode. The stiffness propagation velocities were also shown to be consistent with propagation velocities measured from elastography and tissue velocity imaging as well as the local epicardial ECG.

ARFI-induced displacement curves of an *ovine* heart were formed and temporally registered with left ventricular pressure and volume measurements. From these plots, the synchronization of myocardial stiffening and relaxation with the four phases (isovolumic contraction, ejection, isovolumic relaxation, and filling) of the cardiac cycle was determined. These ARFI imaging sequences were also used to correlate changes in left ventricular performance with changes in myocardial stiffness. These preliminary results indicated that changes in the ARFI imaging-derived stiffnesses were consistent with those predicted by current, clinically accepted theories of myocardial performance and function.

These results demonstrate the ability of ARFI imaging to visualize changes in myocardial stiffness through the cardiac cycle and its feasibility to provide clinically useful insight into myocardial performance.
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Chapter 1

Introduction

Extensive research has been devoted to the quantification of myocardial performance for the detection and diagnosis of a variety of cardiac diseases. The primary focus of these studies has been to track the changes in elastic properties of the myocardium at specific points of the cardiac cycle and correlating them with the performance of the heart [15, 50, 114, 117]. The clinically accepted method for the measurement of myocardial performance utilizes an elasticity metric known as elastance [13, 69, 96]. Similar to a stress-strain relationship, yielding stiffness, myocardial elastance is measured from the pressure-volume (PV) relation within the left ventricle, with shifts in these PV relations indicative of changes in left ventricular function and therefore myocardial performance. Previous investigations into PV analysis have demonstrated its potential in providing measurements of myocardial performance and function, however the underlying simplifications and assumptions in tissue geometry and distribution of loads within the heart lend them susceptible to artifacts [13, 33, 105].

Another relatively new technique for the assessment of tissue elasticity is with acoustic radiation force impulse (ARFI) imaging. ARFI imaging measures tissue responses by using radiation force from long pulses to impart localized displacements in order to gain insight into the local viscoelastic properties of soft tissue in vivo and in vitro [71, 73]. Additionally, ARFI imaging has been shown to be clinically useful
in a variety of applications including: breast, cardiovascular, hepatic, and urological imaging [18, 21, 44, 100, 119].

As ARFI imaging induces and tracks small, sub-millimeter displacements, a primary determinant in image quality is the separation of these ARFI-induced displacements from any natural, physiological motion also present within the acquisitions. As a result, the formation of high quality, high resolution cardiac ARFI images faces unique challenges from other applications, as *in vivo* images must be formed within a beating heart where substantial and complex physiological motion is present. Accordingly, novel ARFI imaging pulse sequences, image processing methods, and motion filtering techniques that specifically address the need to continuously sample images through the cardiac cycle in the presence of significant cardiac motion are necessary. In this thesis, preliminary research into these ARFI imaging developments and the application of ARFI imaging to interrogate myocardial stiffness through the cardiac cycle are investigated. The relevance of these ARFI images to the assessment of left ventricular function and overall myocardial performance is also presented and compared with other clinically accepted measurements.

The thesis is organized as follows: Chapter 2 provides a background to the fundamentals of ultrasonic imaging, acoustic radiation force, and ARFI imaging. Additionally, the physiology of the heart and the cardiac cycle and their relevance to this thesis are provided. Chapter 3 presents initial investigations into cardiac ARFI imaging and the *in vivo* visualization of myocardial stiffness through the cardiac cycle. Chapter 4 describes ARFI imaging sequence modifications and improved motion filtering techniques that were designed for repeated sampling within a rapidly moving environment, such as the heart. Chapter 5 presents research utilizing these new sequences to observe local electromechanical stiffness propagation and calculate propagation velocities within a ventricularly paced heart. These results were
compared with propagation velocities calculated from elastography, tissue velocity imaging, and the local electrocardiogram (ECG). Chapter 6 presents another application of these new ARFI imaging sequences and methods that samples myocardial stiffness across multiple heartbeats in order to observe changes in left ventricular function and myocardial performance. Throughout all studies, sequences with radiation force pulse amplitudes set to zero were acquired to measure physiological motion artifacts within the ARFI images. Finally, Chapter 7 discusses the implications of these investigations and presents the ongoing and future work derived from this research.
Chapter 2

Background

2.1 Ultrasonic Imaging

Ultrasonic imaging operates by transmitting high frequency (1-25 MHz) acoustic pulses into soft tissue. Acoustic waves are generated by electrically exciting piezoelectric materials within a transducer to generate pressure waveforms. An array of transducer elements with the appropriate transmit delays is used to focus these acoustic waves to a specific depth or location within the region of interest. These acoustic waves are scattered and reflected within the medium due to acoustic impedance mismatches. Acoustic impedance, $Z$ (rayl), is defined by the following equation:

$$Z = \rho c = \sqrt{\rho K} \quad (2.1)$$

where $\rho$ is the material density ($kg/m^3$), $c$ is the speed of sound ($m/s$) through the material, and $K$ is the bulk modulus ($N/m^2$). The piezoelectric elements within the transducer are also used to record the returning echoes and convert them into electrical waveforms, where dynamic delay times on each received echo are used to beamform the signals into a single voltage trace through time, measured after transmission of the acoustic pulse. The envelope of the single waveform reveals
the acoustic impedance mismatches encountered by the acoustic wave along the propagation path. A simple conversion from time to depth is performed by scaling time with the propagation velocity of sound through the body and halving it in order to account for the round trip traveling distance. The speed of sound in the body is assumed to be a constant value of 1540 m/s, however studies have shown this value to vary depending on the types of tissue [3, 38]. The transmit/receive location is then electronically translated or steered across the transducer aperture in order to interrogate the entire field of view and create a two-dimensional brightness-mode (B-mode) image.

2.2 Acoustic Radiation Force

2.2.1 Radiation Force

Acoustic radiation force is applied to absorbing or reflecting targets in the propagation path of an acoustic wave. This phenomenon is caused by a transfer of momentum from the acoustic wave to the propagation medium. The radiation force \( F(\vec{r}, t) \) generated by a propagating acoustic wave is given by [79, 106]:

\[
F(\vec{r}, t) = \frac{2\alpha I(\vec{r}, t)}{c},
\]

where \( I(\vec{r}, t) \) is the local time-averaged acoustic intensity \((W/cm^2)\), \( \alpha \) is the attenuation coefficient \((Np/cm)\), and \( c \) is the speed of sound \((m/s)\). This equation models a homogeneous, isotropic, viscous, and dissipative medium and is derived from a combination of several physical equations describing dynamic motion, momentum, and conservation of mass. From these equations, the following equality relating pressure, density, and velocity \((p, \rho, \vec{v})\) can be formed:

5
\[
\frac{\partial (\rho \vec{v})}{\partial t} + \vec{v} \nabla \cdot (\rho \vec{v}) + \rho \vec{v} \cdot \nabla \vec{v} = -\nabla p + \left[ \mu' + \frac{4}{3} \mu \right] \nabla \nabla \cdot \vec{v} - \mu \nabla \times \nabla \times \vec{v} \quad (2.3)
\]

where \(\mu\) and \(\mu'\) are the shear and bulk viscosity coefficients for the fluid. By performing a time-average analysis through an integer number of transmit cycles, grouping the second order terms, and balancing the linear momentum equation, the following equation can be formed:

\[
-\vec{F} = \rho \langle \vec{v}_1 \nabla \cdot \vec{v}_1 + \vec{v}_1 \cdot \nabla \vec{v}_1 \rangle \quad (2.4)
\]

where \(\vec{v}_1\) is the first order particle velocity. Assuming plane wave propagation, which is valid at the focus, this velocity can be approximated by the following equation:

\[
\vec{v}_1 = v_0 e^{-\alpha z} \cos(\omega t - kz) \hat{z} \quad (2.5)
\]

which represents an attenuating propagating plane wave in the \(\hat{z}\) direction with a velocity amplitude \((v_0)\). Substitution of this equation into equation 2.4 and the evaluation of the time average function yield the following equation:

\[
\vec{F} = -2\rho \left\langle v_1 \frac{dv_1}{dz} \right\rangle \hat{z} = \rho \alpha v_0^2 e^{-2\alpha z} \hat{z} \quad (2.6)
\]

Due to plane wave assumptions, the force and velocity of the wave also are related by the acoustic impedance of the medium as mentioned earlier in equation 2.1. Using this relation and the attenuating plane wave velocity approximation described in equation 2.5, the time averaged intensity \((I)\) can be shown to equal:

\[
I = \frac{\rho c v_0^2 e^{-2\alpha z}}{2} \quad (2.7)
\]
A simple rearrangement of terms and substitution of force from equation 2.6 yield the relation described in equation 2.2. Therefore, the absorption of focused, high intensity acoustic beams generates acoustic radiation forces as described in the previous equations. This force, in turn, can be used to create distributions of stress within tissues where the resulting deformations provide insight into the elasticity and geometric structure of the material.

2.2.2 ARFI Imaging

Acoustic radiation force impulse (ARFI) imaging uses long (10-100 µs) acoustic pulses to generate radiation force and excite localized regions in soft tissue [73, 75]. Within regions of interest where all the values in equation 2.2 are relatively similar, radiation force, and therefore stress, can also be considered uniform. With uniform stress, the displacement images can be interpreted as a direct reflection of stiffness because the material’s elastic modulus and deflection under a given load are inversely related. As a result, ARFI imaging tracks tissue responses to the radiation force in order to determine the local stiffness of soft tissue within the region of interest [71,76].

Current methods of ARFI imaging do not utilize known values of radiation force, given the unknown characteristics of the tissue. As a result, stress cannot be calculated, and current realizations of ARFI imaging do not provide a quantitative measurement of elastic modulus. Nevertheless, relative differences in stiffness between tissues are evident, and there is good agreement between structures in matched conventional B-mode and ARFI images. Alternative methods of radiation force imaging have measured shear wave propagation velocities to determine a material’s shear modulus, which can be converted to an elastic modulus depending on tissue geometry and other underlying assumptions [8, 74, 81, 82, 98].

Along each lateral location, the ARFI imaging pulse sequence consists of at least
one reference line, one radiation force pulse line, and several consecutive tracking lines. The initial lines are used to establish the initial tissue position and serve as a reference for measuring subsequent displacements. The radiation force pulse is then fired along the same line to induce small displacements within the tissue. These displacements, \( d(t) \), are estimated through a given axial range, \( M \), by recording echoes from consecutive tracking lines at high pulse repetition frequencies and correlating them with the echoes from the initial reference line (\( t=0 \)) with the following phase shift estimation algorithm [48]:

\[
d(t) = \frac{c}{4\pi f_c} \cdot \text{arctan} \left( \frac{\sum_{m=0}^{M-1} Q(m,0) \sum_{m=0}^{M-1} I(m,t) - \sum_{m=0}^{M-1} I(m,0) \sum_{m=0}^{M-1} Q(m,t)}{\sum_{m=0}^{M-1} I(m,0) \sum_{m=0}^{M-1} I(m,t) - \sum_{m=0}^{M-1} Q(m,0) \sum_{m=0}^{M-1} Q(m,t)} \right)
\] (2.8)

where \( c \) is the speed of sound through the medium and \( f_c \) is the center frequency of the B-mode acoustic waveform, and the quadrature demodulated data (I/Q) is acquired by trigonometric quadrature demodulation of the radiofrequency data or direct sampling from the scanner itself. As axial displacements are measured by determining the phase shift of the signal, the estimated lags are limited to within \( \pm 180^\circ \) (a half wavelength in either direction). Tissue displacements surpassing these limits alias as the estimates wrap about the origin. To correct for this error, displacement discontinuities through time greater than half a wavelength within the data can be found and shifted a complete wavelength in the opposite direction.

Investigations of cardiac ARFI imaging have demonstrated it to be an effective modality for use in monitoring of radiofrequency ablations [24, 44]. These studies used electrocardiogram (ECG) gated acquisitions, where a single ARFI image per heartbeat was acquired. Accordingly, a sequence of ARFI images will provide further
insight into the changing mechanical stiffness of the myocardium. ARFI imaging has been shown to be capable of visualizing changes in the stiffness of skeletal muscle fibers under various contractile loads [72]. Recent advances in ARFI imaging beam sequencing and parallel-receive imaging have shortened acquisition times and lessened transducer heating to a point where continuous ARFI imaging acquisitions can be executed at high frame rates [16]. Additionally, studies into rapid motion tracking of ARFI-induced displacements have demonstrated the viability of real-time processing and display of ARFI images [91]. As ARFI imaging produces its own tissue deformation, it is less affected by the non-uniform stress distribution within the heart. Therefore, with the potential to provide continuous myocardial stiffness estimates through the entire cardiac cycle, we hypothesize ARFI imaging to be better suited to measure the dynamic changes in myocardial stiffness through the heartbeat than current clinically available methods.

2.3 Physiological Motion

In order to form ARFI images of the heart that reflect myocardial stiffness, tissue displacements induced by the radiation force pulse must be distinguished from the natural physiological motion of the heart. Interpolation-based motion filters have been developed to remove such motion artifacts. The fundamental assumption of these motion filters is that changes in physiological motion occur on a slower time scale than the duration of the entire response of the tissue to the radiation force pulse. Therefore, physiological motion can be modeled with piecewise functions and removed from the measured displacements.

The linear motion filter is the most commonly used motion filter for ARFI imaging and operates on a pixel-by-pixel basis by assuming that the tissue does not
accelerate within individual tracking intervals of the ARFI imaging sequences. As a result, physiological motion can be approximated by fitting a linear regression through the origin and a displacement estimate made after an end-time threshold where the tissue is assumed to have fully recovered from the ARFI excitation, and any measured displacements are the result of physiological motion only. This regression is then subtracted from displacement estimates made throughout the entire tracking interval. Studies have shown this filter to be effective in removing motion artifacts within ARFI imaging in myriad applications, including cardiac ARFI images taken at diastole [44].

2.3.1 Decorrelation and Jitter

The Cramer-Rao lower bound states that the minimum error (jitter) associated with time delay estimators as:

\[
\sigma = \sqrt{\frac{3}{2f_c^3\pi^2T(B^3 + 12B)} \left( \frac{1}{\rho^2} \left( 1 + \frac{1}{SNR^2} \right)^2 - 1 \right)}
\]  

(2.9)

where \(T\) is the kernel size, \(f_c\) is the center frequency, \(B\) is the fractional bandwidth, \(SNR\) is the signal to noise ratio, and \(\rho\) is the correlation coefficient [112]. When imaging stationary targets, these jitter levels are normally small (0.2-1 \(\mu m\)) and well below typical ARFI-induced displacement magnitudes. However, in the presence of physiological motion, there is a greater likelihood for signal decorrelation, and therefore the resultant ARFI images are formed with increased jitter. The presence of jitter also negatively affects motion filter performance, as jitter in displacement estimates leads to misapproximation and greater uncertainty in the physiological motion regressions. As a result, in environments with increased physiological motion and signal decorrelation, motion artifacts are difficult to remove and compromise the
integrity of ARFI images [25]. This is a significant concern in cardiac ARFI imaging where the heart beats in a vigorous and complex manner.

2.4 Myocardial Physiology

2.4.1 The Cardiac Cycle

Figure 2.1: Diagrams of left ventricular function. (a) A Wiggers diagram shows variations in chamber pressures and the four phases of the cardiac cycle: (1) isovolumic contraction, (2) ejection, (3) isovolumic relaxation, and (4) filling. The phases are separated by mitral and aortic valve openings and closures and determined by differences in pressures between the left ventricle and left atrium or aorta. (b) A parametric plotting of left ventricular pressure and volume produces a rectangular loop with each side corresponding to an individual phase. A single heartbeat progresses in a counterclockwise manner and forms a complete loop.

The cardiac cycle is divided into four distinct phases: isovolumic contraction, ejection, isovolumic relaxation, and filling [49]. Filling encompasses both passive filling due to the natural relaxation of the ventricles and active filling due to atrial contraction. These four phases are separated by the openings and closures of the mitral and aortic valves, and therefore reflect the differences in pressures of the left
ventricle and left atrium or aorta. For example, when the aortic pressure exceeds the left ventricular pressure, the aortic valve closes and marks the end of ejection and the beginning of isovolumic relaxation. Although myocardial contraction is stimulated by an electrical action potential in the heart, these four phases cannot all be registered with specific events in the electrocardiogram. A Wiggers diagram, demonstrating the relations between left atrial, left ventricular, and aortic pressures with the four phases of the cardiac cycle and the global electrocardiogram is shown in Figure 2.1a [45].

When left ventricular pressure is parametrically plotted against left ventricular volume, a rectangular loop proceeding in a counterclockwise manner is obtained. Each side is associated with one of the four phases and the corners pertain to valve openings and closures. An individual heartbeat correlates to the passage of a single complete loop. From this parametric plot, left ventricular pressures during ejection and filling can be seen to be relatively isobaric. An example of a single pressure-volume (PV) loop with the four phases of the cardiac cycle is shown in Figure 2.1b.

Several studies have correlated shifts in the position and shape of the entire PV loop with the performance of the heart [35, 69, 111]. For example, an upward, rightward shift of the entire PV loop may reflect the presence of myocardial ischemia or infarction. However, these methods are qualitative assessments of myocardial performance and thus a metric known as myocardial elastance has been developed to help quantify myocardial performance.

### 2.4.2 Pressure-Volume Analysis

Myocardial elastance \( \text{mmHg/cm}^3 \) is a metric of elasticity, akin to stiffness, and calculated via pressure-volume analysis. However, rather than determining the stress-strain relation, elastance is measured through the pressure-volume relationship
Figure 2.2: Parametric pressure-volume analysis of myocardial elastance by calculating the end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR). The pressure-volume relationship for a typical heartbeat progresses in a counterclockwise manner and exhibits a rectangular shape with isovolumic contraction/relaxation and isobaric ejection/filling. ESPVR and EDPVR are calculated by incrementally changing either variable while tracking the subsequent changes within the pressure-volume loops. A curve is fitted to the upper-left and lower-right most points, which correspond to end-systole and end-diastole. The slopes of these curves represent the end-systolic and end-diastolic elastances.

and is derived from parametric analysis of PV loops. The upper-left most point of each PV loop corresponds with aortic valve closure and marks the end of systole. Similarly, the bottom-right most point of the PV loop corresponds with mitral valve closure and marks end-dia-stole.

Myocardial elastances are measured by incrementally varying either left ventricular pressure or volume and recording the subsequent changes to the pressure-volume loops [15, 52, 69]. The pressure-volume data recorded at end-systole and end-diastole reflect the end-systolic and end-diastolic pressure-volume relation (ESPVR and EDPVR), respectively. Elastances are defined to be the slope of a linear function fitted to these PV relations. At end-diastole, the pressure-volume relation is non-linear and studies have shown an exponential function to better fit the data at this point. As a result, end-diastolic elastances are typically approximated with exponential
functions, with the instantaneous slope of the exponential at the end-diastolic left ventricular pressure correlating to an exact value for the end-diastolic elastance. A graphical demonstration of PV analysis is shown in Figure 2.2 [13].

### 2.4.3 Cellular Physiology

During contraction, an electric action potential activates sodium/potassium exchange between the sarcomere and extracellular matrix, resulting in the depolarization of the cell. Voltage dependent calcium channels are then activated, allowing calcium to enter the sarcomere. This, in turn, then triggers the rapid release of additional calcium ions from within the sarcoplasmic reticulum of the myocardial fibers. This onrush of calcium then binds with troponin C, freeing it from the myosin filament’s binding sites and allowing actin-myosin cross bridges to form. These cross bridges are then broken and reformed down successive binding sites along each filament allowing them to slide against each other, thereby shortening the myocardial fiber length. As the overlap between the actin and myosin filaments increases, more and more binding sites are available to be formed and continue fiber shortening. Throughout many of these processes, including the actin-myosin cycle, adenosine triphosphate (ATP) is used [49]. During relaxation, calcium is released from troponin C and taken back into the sarcoplasmic reticulum. The actin-myosin cross bridges also detach, and the myocardial fiber returns to its rest length. As is the case in contraction, ATP is required throughout relaxation and is used for each of the processes mentioned previously [4, 49, 123].

As both contraction and relaxation consist of a series of energy consuming cellular processes, the impediment or restriction of any of these processes will result in decreased myocardial contractility. The duration and rate of these cellular processes also determine the extent of myocardial contraction/relaxation [123]. For example,
the effects of myocardial ischemia, where the supply of oxygenated blood to the heart is obstructed, can be observed by a decrease in myocardial contractility within the affected myocytes.

The extent of myocardial contraction/relaxation is also reflected by the stiffness of the muscle. Although several cellular mechanisms contribute to myocardial stiffness, the formation of actin-myosin cross bridges is widely accepted as the primary determinant in the increase myocardial stiffness during contraction, with the greater number of cross bridges resulting in increased stiffness [67,77]. As a result, several methods have been developed that use myocardial stiffness as a measure for myocardial contractility and function as well as the determinant for cardiac disorders including systolic and diastolic heart failure. Many of these studies have utilized echocardiography and ultrasonic imaging to obtain their myocardial stiffness estimates [62,88].
Chapter 3

In vivo ARFI imaging of myocardial stiffness

The work presented in this chapter was published in the following manuscript:


3.1 Introduction

In addition to displaying cardiac anatomy, various medical imaging modalities provide information related to myocardial function. PET, CT, MRI and echocardiography have all demonstrated capabilities in assessing myocardial function by measuring perfusion of contrast agents into and out of the intercellular space of cardiac tissue [32,55,58,61,118]. However, the potential complications with the use of contrast agents as well as the cost of these imaging modalities are limiting factors for their widespread clinical application.

Echocardiography displays real-time images of the heart that provide insight into anatomy and function. Through Doppler and other methods, the velocity of blood and cardiac tissue can also be measured. Advanced signal and image processing
methods, such as acoustic integrated backscatter, tissue Doppler, and automated calculation of cardiac chamber volumes, have been used to evaluate the performance of the heart and determine cardiac irregularities [31, 80, 103, 115]. However, correlating changes in these parameters to myocardial function becomes difficult as they could be biased by several additional factors, including myocardial fiber orientation, plane of imaging, and tissue depth, that also have been observed to vary during a heartbeat [6, 41, 66]. Additionally, these measurements are often hindered by poor signal to noise ratio (SNR) and large variability between subjects and acquisitions.

An important parameter that reflects cardiac function is myocardial stiffness. Several studies have associated increased myocardial stiffness with diastolic heart failure [10, 50, 122]. Stiffness has also been shown to vary with infarcted, ischemic, and ablated tissue. Stiffness is measured by determining the elastic relationship between stress and strain within tissue. The calculation of stress within the heart is difficult as there currently is not a direct, non-invasive method to measure the radial and circumferential forces encountered by the myocardium. Conversely, strain is easier to quantify as it can be calculated through image-based algorithms that track tissue motion. One method to measure strain is through a temporal integration of strain rate, which can be measured from the difference in tissue velocities at two points within the myocardium [40, 92]. Another method to measure strain is from the spatial gradient of tissue displacements. Several imaging modalities utilize motion tracking to calculate tissue displacements. Tagged MRI has been used to measure three-dimensional cardiac motion, though the prolonged acquisition times leave this method susceptible to artifact due to patient and respiratory motion [65]. Echocardiography has been used extensively to track myocardial deformation [2, 17], though the relative inaccessibility and depth of the heart limit the accuracy of these measurements.
Images of strain and strain rate have been used to correlate reduced myocardial deformation with weaker heart contraction and reduced cardiac output. These methods have shown promise in the detection of ischemic or infarcted myocardium [31, 63, 92]. However, without measuring stress, these images are vulnerable to misinterpretation as observed variations could be due to the intrinsic non-uniform deformation of the heart.

Another method of imaging stiffness is through acoustic radiation force impulse (ARFI) imaging. Investigations in cardiac ARFI imaging have demonstrated it to be an effective modality for use in monitoring of radiofrequency ablations [24, 44]. These studies used electrocardiogram (ECG) gated acquisitions, where a single ARFI image per heartbeat is acquired. We hypothesize that a sequence of ARFI images will provide further insight into the changing mechanical stiffness of the myocardium. ARFI imaging has been shown to be capable of visualizing changes in the stiffness of muscle fibers under various contractile loads [72]. Recent advances in ARFI beam sequencing and parallel-receive imaging have shortened acquisition times and lessened transducer heating to a point where continuous ARFI imaging acquisitions can be executed at high frame rates [16]. Additionally, studies into rapid motion tracking of ARFI-induced displacements have demonstrated the viability of real-time processing and display of ARFI images [91]. In this chapter, we present preliminary in vivo investigations of real-time ARFI imaging of the heart through the cardiac cycle.
3.2 Methods

3.2.1 Imaging Methods

The Siemens (Siemens Medical Solutions, USA, Ultrasound Division, Issaquah, WA) SONOLINE Antares™ ultrasound scanner was used with the VF10-5 probe. The 192 element, linear array formed B-mode and ARFI images at a center frequency of 6.67 MHz. Traditional B-mode images were formed across a 38 mm lateral field of view and with a line density of 6.7 lines per millimeter. In-phase (I) and quadrature (Q) signals from the received echoes were recorded via the Siemens Ultrasonic Research Interface™. During acquisition, the corresponding ECG was also recorded.

Along each lateral location, the ARFI imaging pulse sequence consisted of one reference line, one radiation force pulse line, and several consecutive tracking lines. The first line was used to establish the initial tissue position and served as a reference for measuring subsequent displacements. The pushing beam (45 µs pulse length) was then fired along the same line to induce small displacements within the tissue. These displacements were estimated by recording echoes from thirteen consecutive tracking lines at a pulse repetition frequency (PRF) of 3 kHz and correlating them with the echoes from the initial reference line with a phase shift estimation algorithm [48]. The reference and tracking lines used conventional B-mode pulses, 1-2 cycles long. Previous studies have shown the axial and lateral resolution of ARFI images to be comparable to B-mode images obtained under similar imaging conditions.

3.2.2 Three-line M-mode ARFI imaging

To examine specific regions of tissue at a high sampling frequency, three-line M-mode ARFI images were acquired. These sequences consisted of consecutively
transmitted radiation force pulses at three lateral positions spaced 9.5 mm apart. Repeated tracking lines were then recorded by multiplexing the tracking location through each of the three transmit beams. The acquisition time for the entire sequence was 5.9 ms. In order to limit tissue and transducer heating, three-line M-mode ARFI imaging sequences in these experiments were executed for three seconds (across 4-5 heartbeats) at a sampling rate of 40 Hz.

3.2.3 Two-dimensional ARFI Imaging

Two-dimensional ARFI images were formed across a 14 mm lateral field of view at a line density of 3.6 lines per millimeter. Much like the three-line M-mode sequences, these two-dimensional ARFI imaging sequences consisted of consecutive radiation force pulses transmitted at three lateral locations spaced one third of the lateral field of view apart. Multiplexed tracking lines, consisting of four parallel-receive lines centered around each of the three transmit locations, were recorded for 4.28 ms with a PRF per single location of 3.0 kHz. The entire sequence was then electronically translated across the field of view to form a complete two-dimensional image. Single frame ARFI images were formed by displaying the measured tissue displacements 1.3 ms after cessation of the radiation force pulse. These displacement images were spatially median filtered with a 0.3 mm (axial) x 0.7 mm (lateral) kernel.

The sequence interrogated the entire 14 mm field of view using twelve radiation force pulses for a total acquisition time of 24 ms. Conventional ARFI imaging sequences without parallel-receive and multiplexing methods would have required 288 ms and 48 radiation force pulses for the same field of view. Again, to limit long-term tissue and transducer heating, 2-D ARFI images in these experiments were acquired for three seconds at a frame rate of 10 Hz.
3.2.4 Displacement Estimation

Axial displacements were calculated by using a phase shift estimation algorithm [48]. As the displacements are measured by determining the phase shift of the signal, the lags estimated are limited to within $\pm 180^\circ$ (a half wavelength in either direction). Tissue displacements surpassing these limits alias as the estimates wrap about the origin. To correct for this error, large displacement discontinuities through time greater than half a wavelength within the data were found and shifted a complete wavelength in the opposite direction.

3.2.5 Physiological Motion Filters

Interpolation-based motion filters approximate physiological motion using displacement estimates made during periods within the ARFI imaging acquisitions where the ARFI-induced displacements are assumed to be negligible. These periods correspond to times of the reference line, before the transmission of the excitation pulse, and after an end-time threshold where the tissue is assumed to have recovered from the ARFI excitation. Displacements estimated when ARFI-induced displacements are still present bias the motion filter. A least squares regression is used to fit an analytic function to these data and then interpolate and remove physiological displacements through the entire ARFI imaging acquisition.

For most applications of ARFI imaging, a linear regression is fit to these data. The linear motion filter assumes constant velocities and therefore zero tissue accelerations within the ARFI imaging tracking interval. However, the linear motion filter is a rudimentary approximation of physiological motion and cannot account for complex displacement profiles as well as displacement estimation errors arising from out-of-beam motion and signal decorrelation [19]. Additionally, displacement
estimates with low SNR are likely to bias physiological motion interpolations. As a result, a linear approximation of cardiac motion is insufficient, and a more sophisticated filter is needed to better approximate this motion at all points of the cardiac cycle. The following subsection provides a description for a higher-order, quadratic motion filter used for cardiac ARFI imaging. A graphical representation for the linear and quadratic motion filters is shown in Figure 3.1.

**Quadratic Motion Filter**

The quadratic motion filter assumes that tissue acceleration arising from physiological motion is constant, but not necessarily zero, within the time intervals of the radiation force pulses. Thus, at any point inside the region of interest, a second-order polynomial can be used to approximate the physiological displacements, $d(t)$, measured within the ARFI images:

$$d(t) = c_1 t^2 + c_2 t + c_3 \quad (3.1)$$

The initial reference line is defined as the origin, and all displacements are estimated with respect to windowed echoes from that line. Evaluating the polynomial at that point yields:

$$d(0) = c_3 = 0 \quad (3.2)$$

$c_1$ and $c_2$ are found with a least squares regression to the displacement data. This regression is calculated using displacements measured after a thresholded time ($t_{thresh}$) when the tissue is assumed to have fully recovered from the radiation force excitation. This time must be short enough so that the assumption of constant
Figure 3.1: Graphical representation of the linear and quadratic interpolation-based motion filters. ARFI imaging displacement estimates (diamond plots) include ARFI-induced tissue displacements along with physiological cardiac motion. Both filters approximate physiological motion with an analytic function that passes through the origin (starred point) and is determined by a least squares regression of a subset of displacement estimates (solid circle points) that are believed to be a result of physiological motion only. Within the ARFI imaging sequences, these displacement estimates are made after an end-time threshold (dotted line), where the tissue is assumed to have recovered from the radiation force excitation (dashed line). (a) The traditional linear motion filter fits a line through the origin and a single displacement estimate at that end-time threshold. (b) A quadratic motion filter approximates physiological motion with a parabola through the origin and all displacement estimates recorded after the end-time threshold. (c) The resulting motion filtered displacement curves from the linear (circle plot) and quadratic (triangle plot) motion filters are shown with the true ARFI-induced displacement curve (solid line).

Physiological tissue acceleration remains valid yet sufficiently long to ensure displacements measured after this threshold do not include any ARFI-induced tissue displacements. Previous investigations into cardiac ARFI imaging have shown that myocardial tissue recovery occurs within 2-3 ms after cessation of the radiation force.
pulse [24]. By applying a quadratic regression to a limited subset of times ($t_s$) and measured displacements ($d_s$), where $t_s > t_{\text{thresh}}$, the coefficients ($c_1$ and $c_2$) are found to be:

$$
\begin{bmatrix}
  c_1 \\
  c_2
\end{bmatrix}
= \frac{1}{\sum_s t_s^4 \cdot \sum_s t_s^2 - (\sum_s t_s^3)^2}
\begin{bmatrix}
  \sum_s t_s^2 \cdot \sum_s t_s^2 d_s - \sum_s t_s^3 \cdot \sum_s t_s d_s \\
  - \sum_s t_s^3 \cdot \sum_s t_s^2 d_s + \sum_s t_s^4 \cdot \sum_s t_s d_s
\end{bmatrix}
$$

(3.3)

Excluding the origin, these coefficients can be determined with only two data points beyond the threshold time. The curve (Equation 3.1) is then subtracted from the entire displacement profile and the residual displacements are considered the tissue responses to the radiation force excitation. The quadratic motion filter operates on a pixel-by-pixel basis and calculates these coefficients at every spatial location based on displacements measured at each point.

### 3.2.6 Experimental Procedure

The beating hearts of two canine subjects were imaged in this study, as approved by the Institutional Animal Care and Use Committee at Duke University conforming to the Research Animal Use Guidelines of the American Heart Association. Both animals weighed approximately 20 kg. The chest was opened for reasons unrelated to this study. A Parker Laboratories (Fairfield, NJ) Aquaflex ultrasonically transparent 5 mm standoff pad was placed between the heart and the transducer. The imaging probe was held in place by hand while attempting to maintain a fixed imaging plane for each acquisition.

With canine heart rates above 100 beats per minute, it was questionable if subtle ARFI-induced displacements could be measured in the presence of vigorous cardiac
motion. Therefore, the effectiveness of the quadratic motion filter in estimating and removing cardiac motion was first examined.

To assess potential physiological cardiac motion artifacts, three-line M-mode ARFI images of the left ventricular free wall were acquired at a 1.5 cm focus. Passive ARFI imaging sequences, where the radiation force pulse transmit voltage was zero, were acquired. As these sequences provided no external excitation to the tissue, displacements within the images represent cardiac motion artifacts. The quadratic motion filter with a time threshold of 2.97 ms was used to approximate cardiac motion. Five points, one reference and four post-threshold lines, were used to determine the motion filter coefficients in Equation 3.3. The displacement profile was subtracted from the initial displacement estimates to produce a residual displacement plot. Along each of the three M-mode lines, the average residual displacements, which were measured 0.66 ms after cessation of the radiation force pulse within a 3.9 mm axial window at a constant depth of 1.1 cm, were plotted through time and matched with the corresponding ECG. These plots were used to evaluate the expected levels of motion artifact within ARFI images at various points of the cardiac cycle.

Active three-line M-mode ARFI imaging sequences, now including a 45 μs radiation force excitation pulse, were then acquired. The same quadratic motion filter was applied to the measured displacements. The resulting filtered displacements, which were measured 0.66 ms after cessation of the radiation force pulse within a 3.9 cm axial window at constant depth of 1.1 cm, were plotted with the corresponding ECG.

The transducer was placed on the right side of the heart and parallel to its long axis. From this viewing angle, the field of view contained both the right atrium and right ventricle. Two-dimensional B-mode and ARFI images, focused on the septum at a depth of 2.0 cm, were acquired for 3 seconds at a sampling rate of 10 Hz. By
holding the transducer in this manner, the full expansion of the atria and ventricles was restricted. Displacements within the septum in both chambers were examined and tracked through the entire cardiac cycle.

A Cardiac Pathways (Sunnyvale, CA) radiofrequency ablation device with a Boston Scientific (Natick, MA) SteeroCath catheter was used to perform a 20 Watt, 120 second ablation on the epicardial surface of the free wall of the left ventricle. The ablation site was manually irrigated with 0.9% saline. Following the ablation, a visibly discolored lesion was present that moved with the heart but would not be expected to contract nor change in mechanical stiffness through the cardiac cycle. The 5 mm standoff pad was placed on the heart and the transducer was centered directly over the ablation lesion. Two-dimensional B-mode and ARFI images were acquired with the transducer focused at 1.5 cm.

With the heart in normal sinus rhythm, multibeat synthesis was used to create tissue displacement plots through the cardiac cycle by sorting the 30 ARFI images with their relative times of acquisition between QRS complexes. Tissue displacements were plotted at two points within the myocardium (one in the center of the lesion; another in non-ablated myocardium). The two plots were compared to track myocardial stiffness through the cardiac cycle.

To quantify physiological motion artifacts within the ARFI images of the lesion, 3-line M-mode ARFI imaging sequences were acquired with the center M-mode line positioned directly over the lesion. The two outer M-mode lines were positioned over healthy, non-ablated tissue. Three-line M-mode ARFI images were acquired with and without radiation force pulse excitations and matched with the corresponding ECG trace. The sequences were focused at a depth of 1.5 cm, while the points of interest were shifted towards the epicardial surface such that the center point would be inside the lesion. As the points of interest were shallow to the transmit focus, the
maximum displacement and tissue recovery times associated with these points would occur later in time than at points around the focus [85]. As a result, displacements plots were made 1.3 ms after cessation of the radiation force pulse while the threshold time was set at 3.30 ms. With this time threshold, the four points were used to determine the motion filter coefficients in Equation 3.3. Displacements measured within the center beam were then compared to displacements measured from the two outer beams.

3.3 Results

The B-mode image of the left ventricle with marked locations of the three M-mode ARFI lines is shown in Figure 3.2a. The three points of interest are marked on the B-mode image. The residual motion filtered displacement plots from a zero excitation pulse amplitude sequence are shown in Figure 3.2c. The physiological tissue motion measured at the same time (0.66 ms) after cessation of the radiation force pulse is shown in Figure 3.2b. Ideally, the filtered displacements would be zero, indicating complete filtering of cardiac motion, however, as the cardiac motion increases and becomes more complex, the quadratic approximation of cardiac motion becomes less accurate and the tracking of local tissue motion, on which the filter is based, becomes noisier. As a result, displacement artifacts arise.

The three residual displacement curves have similar magnitudes and profiles, with a $0.19 \pm 0.26 \mu m$ average absolute residual displacement. When matched with the ECG in Figure 3.2d, the maximum absolute residual displacements of approximately $1.5 \mu m$ can be observed to occur around the QRS complexes. Physiologically, these points correspond to ventricular systole and myocardial contraction. Large physio-
Figure 3.2: Matched B-mode image and plots from the three-line M-mode ARFI imaging acquisitions of a healthy left ventricular free wall. The B-mode image (a) shows the left ventricle, with vertical lines indicating the lateral locations of the three M-mode lines. The points of interest for the subsequent plots are also marked by their respective shapes within the B-mode image. With zero pulse amplitude excitation, motion filtered displacements (c) measured 0.66 ms after cessation of the radiation force pulse show residual artifacts with an average absolute displacement of $0.19 \pm 0.26 \mu m$. The estimated physiological motion (b) measured at the same time show the greatest residual displacements occur with large tissue motion. The ECG (d) shows that these points coincide with ventricular systole. When the sequences were acquired with a 45 $\mu s$ excitation pulse and matched with its corresponding ECG (g), ARFI induced tissue displacements (f) show cyclic patterns with the minimum and maximum displacements measured during systole and late diastole, respectively. Physiological motion estimates (e) are comparable to those previously measured, suggesting that the levels of artifact within the displacements plots should also be similar.

Physiological motion estimates measured at these points of the cardiac cycle suggest that greater tissue motion increases the uncertainty and error in the motion filter. The motion artifacts measured in passive ARFI imaging sequences can be used to predict the levels of bias and error in subsequent ARFI imaging acquisitions of the left ventricle. Tissue displacements measured for active ARFI imaging acquisitions that include excitation pulses must be greater than these residual displacements in order to assure that they are due to variations in myocardial stiffness and not an artifact of cardiac motion.

The motion filtered displacement plots from the active three-line M-mode ARFI
imaging sequence that included high intensity excitation pulses are shown in Figure 3.2f. The three displacement plots have similar profiles and magnitudes, suggesting that ventricular myocardial stiffness and its variations through the cardiac cycle are relatively uniform. The plots show cyclic displacements with the differences between maximum and minimum displacements from each of the three lines greater than 12 µm. Tissue displacements at all three positions fall below 5 µm during systole, reflecting the fact that the ventricular myocardium has stiffened as it contracts. At these points of the cardiac cycle, the average minimum systolic displacement is 3.96 ± 1.16 µm. After the T-wave, the heart is in ventricular diastole as the ventricles relax and become more compliant. Accordingly, tissue displacements for all three lines rise to their maximum values, above 15 µm. The average maximum diastolic displacement is 19.75 ± 2.97 µm. The average ratio between maximum diastolic to minimum systolic displacements is 5.3:1. Physiological motion estimates, shown in Figure 3.2e, have similar magnitudes though fewer spikes than measured in the previous passive ARFI imaging acquisition. Thus, the levels of physiological motion artifact are likely to be comparable to those measured in the preceding null excitation acquisition.

Two-dimensional ARFI images of the septum, formed across a 14 mm lateral field of view and a line density of 3.6 lines per millimeter, were acquired for three seconds at a frame rate of 10 Hz. Each image utilized twelve 45 µs radiation force pulses to interrogate the entire field of view. Two frames of matched B-mode and ARFI images at atrial and ventricular systole are shown in Figure 3.3. The right atrium (RA), right ventricle (RV) and tricuspid valve (TV) are labeled in the B-mode images in Figure 3.3a and c. The relative times of acquisition of the images are marked by the two vertical lines on the ECG in Figure 3.3e. The B-mode image acquired during
Figure 3.3: Matched B-mode and ARFI images of the right side of the heart and its global ECG (e). The images were focused at 2.0 cm on the septum. The right atrium (RA) is located on the left, and the right ventricle (RV) is on the right. The B-mode image of the heart during atrial systole (a) is shown with an open tricuspid valve (TV). The corresponding ARFI image (b) suggests the atrial myocardium has stiffened as displacements ($\mu$m away from the transducer) within the atrial septum are low. Meanwhile, tissue displacements are higher within the ventricular septum, suggesting that it is more compliant. The B-mode image of the heart during ventricular systole (c) shows that the TV has closed, preventing blood to flow back into the RA as the ventricles contract and atria relax. The ARFI image (d) reflects this trend as the stiffer ventricular septum displaces less than the more compliant atrial septum.
atrial systole (Figure 3.3a) shows that the tricuspid valve has opened as the atria are contracting and blood is flowing into the ventricles. In Figure 3.3b, the corresponding ARFI image suggests that the atrial septum is stiffer than the ventricular septum as the tissue displacements in the ventricular septum ($\sim 8 \mu m$) are higher than those measured within the atrial septum ($\sim 2 \mu m$). Again, the difference in displacements between the two chambers is greater than the residual displacements measured in sequences without excitation pulses.

After the QRS complex, ventricular contraction is apparent within the B-mode image in Figure 3.3c as the tricuspid valve has closed. The ventricular septum has stiffened as the ventricles expunge blood out of heart. Meanwhile, the atrial septum has become more compliant as the heart is also at atrial diastole. The corresponding ARFI image (Figure 3.3d) reflects this trend as the displacements within the ventricular septum are small, while tissue displacements within the atrial septum have increased. The difference in myocardial stiffness between the two chambers is comparable to what is observed during atrial systole.

Matched two-dimensional B-mode and ARFI images of the left ventricular free wall with a stiffer lesion on the epicardial surface at four points of the cardiac cycle are shown in Figure 3.4. The four B-mode images show a section of the myocardium changing thickness as the heart beats, however provide little indication into the presence of a stiffer lesion. Conversely, the ARFI images show a hemispherical region of decreased displacement on the proximal surface of the tissue.

In all four ARFI images, displacements within the lesion are low and remain low throughout the cardiac cycle. This suggests that the lesion is functionally inactive and does not change in stiffness as the ventricles contract/relax. In contrast, tissue displacements of non-ablated myocardium surrounding the lesion are higher.
Figure 3.4: B-mode and ARFI images of the left ventricular free wall at various points of the cardiac cycle with a lesion on its epicardial surface. When matched to the ECG (e), the images corresponded to: (a) atrial systole, (b) atrial diastole, (c) ventricular systole, and (d) cardiac diastole. All four ARFI images show displacements (µm away from the transducer) within the lesion are low and remain low during the entire heartbeat. In the surrounding healthy myocardium, tissue displacements vary through the cardiac cycle. During ventricular systole, displacements are small indicating the myocardium has stiffened as it contracts. Using multibeat synthesis, displacement plots of points inside and outside the lesion (f) reflect this trend as there are little variations in tissue displacements inside the lesion. Outside the lesion, the displacements rise above 8 µm during diastole, and are below 4 µm during systole.
and vary through the cardiac cycle. During ventricular systole (Figure 3.4c), the
displacements within healthy tissue decrease as the myocardium stiffens and fall
to a level where it is difficult to distinguish the hemispherical lesion from the sur-
rounding non-ablated myocardium. The lesion is best visualized within the ARFI
images during ventricular diastole (Figure 3.4a), when the healthy myocardium is
most compliant. ARFI images of the left ventricular free wall in transition between
systole and diastole are shown in Figure 3.4b and d.

Displacement plots at two selected points within the myocardium created via
multibeat synthesis are shown in Figure 3.4f. The two selected regions of interest
span a 1.7 mm x 1.7 mm window, and their positions are marked by their respective shapes in the four B-mode images. From these plots, the cyclic variation in
tissue stiffness within healthy cardiac tissue becomes more apparent. After the QRS
complex, tissue displacements within untreated tissue drop sharply. From contrac-
tion through repolarization, the average displacement for the region of healthy left
ventricular myocardium was \(2.76 \pm 0.28 \mu m\). Inside the lesion, the average displace-
ments during this segment of the ECG was \(2.23 \pm 0.25 \mu m\). Displacements within
healthy myocardium gradually rise above \(8 \mu m\) after the T wave. After ventricu-
lar repolarization but before ventricular contraction, the average displacements in
healthy and ablated tissue were \(8.43 \pm 0.79 \mu m\) and \(3.54 \pm 0.48 \mu m\), respectively.

To assess the levels of motion artifact within these images, three-line M-mode
ARFI images were acquired. The B-mode image and three-line M-mode ARFI-
induced displacement plots are shown in Figure 3.5. The positions of the three
displacement plots are marked by their respective shapes in the B-mode image in
Figure 3.5a. With the zero radiation force pulse amplitude sequences, the motion
filtered displacements are shown in Figure 3.5c. The three plots are similar in shape
Figure 3.5: Matched B-mode and three-line M-mode ARFI-induced displacement plots of the left ventricular free wall with a laterally centered lesion on the proximal surface created via radiofrequency ablation. The motion filtered displacement plots 1.3 ms after cessation of the radiation force pulse from a zero pulse amplitude sequence (c) show small residual displacements with little variances between the center line and the outer two lines that do not contain the lesion. The motion filtered displacement plots from a sequence containing excitation pulses (f) show cyclic variations in tissue displacements that correspond to the myocardial stiffening during the cardiac cycle. The displacements inside the lesions, however, do not rise above 1.5 µm. During ventricular diastole, displacements on the two outer lines within healthy myocardium are greater as they rise above 4.0 µm. The estimated physiological motion plots (b and e) show reduced tissue motion as the points of interest are now closer to the transducer.

and magnitude and provide little evidence to differentiate the center line containing the lesion from the other two. The largest residual displacements still occur around systole. The average absolute residual displacement of the three lines is $0.18 \pm 0.24 \mu m$ and similar to displacements measured in the previous M-mode acquisition (Figure 3.2c). The physiological motion estimates (Figure 3.5b) show a significant reduction in cardiac motion, compared to the previous acquisition. This is likely due to the fact that the regions of interest are at shallower depths, which move less than deeper regions of tissue, relative to the in-contact transducer.

The displacement plots from the three-line M-mode ARFI imaging acquisition that included high intensity excitation pulses focused at 1.5 cm are shown in Figure 3.5f. The overall differences in maximum and minimum tissue displacements are also
less than the previous three-line M-mode acquisition. As the radiation force pulses were focused at a greater depth than the regions of interest, the observed ARFI-induced displacements are also less. From this plot, it also can be observed that the two outer plots have a similar cyclic pattern with a systolic and diastolic displacement difference greater than 3 \( \mu m \). For the center M-mode line containing the lesion, a cyclic variation of displacements remains present, though the displacements are much lower than measured in the two outer lines. The maximum displacements reaches only 1.5 \( \mu m \) during diastole while the differences between systolic and diastolic displacements are below 1 \( \mu m \). During systole, displacements inside the lesion are similar to those measured within the two outer M-mode lines, indicating that the lesion is of comparable stiffness to the contracted myocardium. However, the reduced diastolic displacements and lower levels of residual cardiac motion artifacts affirm that the measured displacements are the result of the differing mechanical properties between the heart and ablated tissue.

3.4 Discussion and Conclusions

Passive three-line M-mode ARFI imaging acquisitions do not excite the tissue. Therefore, the ideal motion-filtered residual displacements for these sequences are zero, indicating the complete removal of cardiac motion. Residual displacements that are measured within the passive ARFI images are a metric for the performance of the motion filters and reflect the levels of noise and bias expected during active ARFI imaging. More effective motion filters are currently being investigated to further reduce cardiac motion artifacts. As these motion filters are used to approximate the measured cardiac motion, they will not remove displacement artifacts caused by errors in tracking the tissue motion. Several factors, including out of beam
motion and tissue shearing/rotation, introduce error into the displacement estimates. More accurate displacement estimators, such as normalized cross-correlation [91], could provide better estimates of the displacements and therefore would be less susceptible to motion artifacts; however, the additional computational expense of these estimators must be considered for real-time applications.

Tissue displacements measured within the active three-line M-mode ARFI sequences, as seen in Figure 2e, are less than 5 µm during ventricular systole, reflecting the fact that the ventricular myocardium has stiffened during contraction. After the T-wave, the heart enters cardiac diastole, and the ventricles become more compliant. Accordingly, tissue displacements at this point of the cardiac cycle are above 10 µm and at their maximum values. The difference between systolic and diastolic ARFI-induced displacements exceeds the measured residual displacements from the previous null excitation sequence. Therefore, observed variations in tissue displacements likely reflect changes in myocardial stiffness and not artifacts resulting from cardiac motion.

The three-line M-mode plots show mean measured displacements at a fixed axial depth in order to maintain a specific region of interest where the radiation force magnitude is believed to be constant. However, changes in any of the three variables from Equation 2.2 that determine radiation force magnitude will bias the measured displacements. Therefore, a degree of uncertainty is present when making stiffness comparisons as some of the differences in displacements could be due to variable radiation force magnitudes. Also, by fixing the imaging plane, the same section of the myocardium is not interrogated. As a result, spatial variations in stiffness with tissue depth will introduce errors in the displacement plots.

Large variations among displacement estimates result in a large margin of uncertainty in the stiffness ratio, particularly because the smaller systolic displacement
is the denominator term. In this study, the stiffness ratios are calculated only for regions of interest with large tissue displacements and therefore larger signal to noise ratio (SNR). Systolic displacements at the depth of the epicardial lesion were too small to calculate accurate stiffness ratios. In the displacements plots shown in Figure 2e, the regions of interest are close to the transmit focus of the radiation force pulse, and therefore the measured tissue displacements are higher. The 5.3:1 stiffness ratio for this region is comparable to the stiffness ratios measured in other studies. Jalil et al. used indirect measurements of left ventricular pressure and weight and assumed spherical geometry to determine stress/strain relations within the heart [46]. The measured end-systolic to end-diastolic stiffness ratio from this method was 4.2:1. Jegger et al. used PV analysis to derive an end-systolic to end-diastolic ratio of 13.2:1 [47].

The two-dimensional ARFI images of the heart show the changes in local stiffness of the heart through the cardiac cycle. The ARFI images from the right side of the heart show the staggered atrioventricular contraction of the heart at the appropriate times during the ECG. ARFI images taken at four distinct points of the cardiac cycle also reflect the changes in myocardial stiffness as the muscle contracts and relaxes. The ARFI image acquired during diastole indicates that the untreated tissue has become more compliant as the displacements within those regions of myocardium are large. At this point, the lesion becomes most apparent within the ARFI images because the differences in myocardial stiffness between the lesion and surrounding tissue are at their greatest. During systole, tissue displacements within the untreated tissue are small, indicating that the tissue stiffened. In fact, tissue displacements are reduced to a level where it is difficult to distinguish the semicircular lesion from the surrounding untreated tissue.

The displacement versus time plot created from multibeat synthesis of untreated
tissue shows myocardial stiffness changes throughout the cardiac cycle. The plot suggests that myocardial stiffening occurs quickly, as tissue displacement falls sharply from its peak value. Myocardial relaxation appears to be a more gradual process, as the slope returning to maximum diastolic displacement is shallower. This pattern reflects the rapid spread of electrical excitation that drives myocardial contraction and the gradual, more diffuse repolarization during relaxation [39].

During the active three-line M-mode ARFI imaging acquisition of the lesion, a cyclic pattern is observed in all three displacement traces, as seen in Figure 2c. However, one would not expect the displacements within ablated tissue to vary. One explanation for these observed cyclical variations is that the transducer was not placed directly over the ablation site and the cross section of the lesion within this image is not of fully ablated tissue. It is also possible that the ablated tissue was stiffened by the contraction of the surrounding normal tissue. Nevertheless, the fact that the plot from the middle M-mode line has reduced displacements compared to those of the two outer lines suggests that a lesion is present. The B-mode images provide no such indication.

In order to create a real-time clinical system, further development is necessary. To be less invasive, ARFI images must be formed without exposing the heart. One viable option is to expand these methods to transducers better suited for cardiac imaging, such as phased array transthoracic, transesophageal (TEE) and intracardiac (ICE) echocardiography probes. The reduced output power from the smaller arrays associated with TEE and ICE must be addressed. Investigations into abdominal ARFI imaging have suggested that transthoracic ARFI imaging with a handheld array would be capable of producing measurable displacements at the depth of the heart [22]. However, the same factors that limit the applications of standard echocardiography, including restricted viewing angles and increased depth, will limit
transthoracic ARFI imaging.

Thermal safety concerns related to tissue and transducer heating due to ARFI imaging also need to be addressed for clinical acceptance. Finite element modeling of tissue heating associated with ARFI imaging has shown that the temperature increase from a single image is moderately low. However, heat accumulation during extended ARFI imaging is a concern [26, 84]. In these experiments, the sampling rates were restricted to 10 Hz for 2-D ARFI imaging and 40 Hz for M-mode ARFI imaging, while acquisition times were limited to only three seconds. The maximum temperature rise of the transducer face for these sequences was measured to be approximately 4°C. Extended acquisition and higher sampling rates would further increase this value and could possibly cause thermal damage to the tissue. One possible solution is to reduce the radiation force amplitude, which in turn, would reduce tissue and transducer heating. However, a reduction of radiation force pulse amplitude would also result in reduced displacements within the ARFI images. A decrease in the signal (tissue displacements) within the ARFI images is acceptable so long as the noise can also be reduced, thereby preserving the SNR. This can be accomplished by improving the displacement estimators and motion filters as previously discussed.

We have presented preliminary results and demonstrated the feasibility of real-time cardiac ARFI imaging. The plots and images presented in the chapter show cyclic displacement curves that reflect the changing mechanical properties of the heart through the cardiac cycle. The observed increases of myocardial stiffness within the ARFI images can be correlated to myocardial contraction and the systolic periods of the ECG. Also, realtime ARFI imaging was capable of visualizing a RFA created lesion and show that it is functionally inactive during a heartbeat. These results demonstrate the clinical utility of realtime cardiac ARFI imaging.
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Chapter 4

ARFI imaging sequence modifications

4.1 Introduction

A fundamental concern in acoustic radiation force impulse (ARFI) imaging is the removal of displacements external to those caused by the ARFI excitation, which are typically small (∼10 µm). The primary sources of these external displacements are associated with motion from the transducer and the presence of physiological motion within the regions of interest. Transducer motion can be minimized by stabilizing the probe with either a steady hand or an apparatus that holds the probe static against the heart through the acquisition. However, ARFI imaging in the presence of moderate to great physiological motion requires more sophisticated measures.

The main sources of physiological motion in vivo are associated with respiratory and cardiovascular motion. Accordingly, the applications of ARFI imaging most affected by physiological motion are within abdominal and cardiovascular ARFI imaging. Within a single breath, the thoracic diaphragm can displace up to 4 cm, causing the entire abdomen to displace with it [110]. This is particularly a concern in hepatic ARFI imaging where abdominal motion is principally normal to the correlation (axial) dimension. As a result, this motion contributes to pulse-to-pulse
decorrelation and motion artifacts that are difficult to remove [22,25]. In cardiovascular ARFI imaging, physiological motion is caused by myocardial contraction and the pulsatile flow of blood. Vascular distention due to blood flow and changes in blood pressure are typically small, with the maximum distention of larger vessels approximately 1 mm, and vary from vessel to vessel [7]. Meanwhile, the heart produces perhaps the most complex and considerable physiological motion within the body, with myocardial velocities exceeding 3 cm/s during ejection and filling [37,65,95].

For single image acquisitions, breath holds and gating off the electrocardiogram (ECG) are used to help minimize these motion artifacts in vivo. Additionally, interpolation-based motion filters have been developed to approximate and remove motion artifacts. These measures have proven to be effective in removing motion artifacts in virtually every application of ARFI imaging [18,20,44,107]. However, when continuously sampling ARFI images within a rapidly moving environment, imaging sequence advancements and modifications that maintain image quality while increasing the sampling capability are necessary. Also, the thermal exposure to the subject and the transducer due to repeated transmissions of the radiation force pulse must be considered [26,83].

Typical acquisition times for traditional two-dimensional (2-D) ARFI images are approximately 200 ms, corresponding to a maximum sampling rate of 5 Hz. These long acquisition times allow for greater variability in tissue velocities within the acquisition and increase the likelihood for spatial artifacts within the images. As a result, initial investigations into cardiac ARFI imaging utilized parallel-receive and multiplexed imaging to shorten acquisition times and reduce thermal exposure to both the transducer and tissue and yielded 2-D ARFI images of a beating heart sampled at 10 Hz [11,16,43]. To further increase sampling rates, spatial sampling was sacrificed and ARFI excitations were transmitted at three spatial locations only.
These three-line M-mode ARFI images were sampled at 40 Hz.

In order to further increase the applicability of ARFI imaging, additional improvements to the imaging sequences are needed to provide finer sampling with better spatial and temporal resolution and interbeam consistency so that more detailed information can be gleaned from the ARFI images and displacement data. We present new ARFI imaging sequences, designed to image rapidly moving and changing myocardium. These sequencing advancements include: pre-excitation tracking, parallel-transmit excitation, parallel-transmit tracking, ECG-gating, and multibeat synthesis. The significance and relevance of these new sequences to cardiac ARFI imaging are demonstrated.

4.2 Methods

4.2.1 Imaging Methods

A more detailed description of ARFI imaging sequences is provided by Nightingale et al [73]. Imaging acquisitions were performed with the Siemens SONOLINE Antares™ ultrasound scanner (Siemens Medical Solutions, USA, Ultrasound Division, Issaquah, WA) and a VF10-5, linear ultrasound transducer. All images were formed at a center frequency of 6.67 MHz and acquired using the Siemens Ultra-sonic Research Interface™ to record in-phase (I) and quadrature (Q) data from the received echoes.

All in vivo cardiac images were formed epicardially with the transducer placed directly on the heart. A vacuum apparatus was constructed to better maintain a single imaging plane within the heart. This apparatus employed suction to position the transducer over a fixed location on the epicardial surface of the heart and kept
Figure 4.1: Vacuum apparatus for epicardial imaging. A linear array transducer is inserted into the apparatus with an opening for the transducer face. A 1 cm thick ultrasonically transparent standoff pad is also inserted into the opening to couple the transducer face with the tissue. A vacuum pump is connected to the apparatus, which produces suction at small openings on the face of the apparatus that surround the transducer. As a result, the apparatus is capable of stabilizing the transducer over a fixed position atop the epicardial surface of the heart.

the transducer a constant 1.0 cm distance away from the heart while holding an ultrasonically transparent standoff pad between the two. A diagram of this transducer/vacuum apparatus is shown in Figure 4.1.

4.2.2 Displacement estimation

Displacements were estimated from the I/Q data using a phase shift estimation algorithm [48]. To correct for phase wrapping and aliasing errors from this algorithm, displacement discontinuities through all times that were greater than half of a wavelength within the data were shifted a full wavelength in the opposite direction. Physiological motion filters were used to separate ARFI-induced displacements from the natural cardiac motion of a heartbeat. Two-dimensional ARFI images and ARFI-induced displacement curves were generated by taking displacements measured at specific times after cessation of the radiation force pulse for each lateral
location. Two-dimensional ARFI images were also median filtered using a 0.9 mm x 0.9 mm kernel. ARFI-induced displacement curves were low-pass filtered with a 5.8 ms mean filter.

4.2.3 Physiological Motion Filters

Interpolation-based quadratic motion filter

For cardiac ARFI imaging, an interpolation-based quadratic motion filter was used to approximate and remove physiological motion artifacts. Traditional quadratic motion filtering operates by interpolating physiological motion based on the reference line and displacement estimates after an end-time threshold, where the tissue is assumed to have fully recovered from the ARFI excitation. A comprehensive description of this quadratic motion filter is detailed in Chapter 3. Previous studies into cardiac ARFI imaging have used interpolation-based quadratic motion filters to effectively reduce physiological motion artifacts to below 1 µm through the entire cardiac cycle [44]. These studies have also observed that at points of greater cardiac motion, such as during ejection or filling, physiological motion artifacts also increased. A likely cause for these increased artifacts is the error in displacement estimates that are used in the motion filter. By including more accurate displacement estimates that better reflect physiological motion, the performance of the filter likely can be improved. A novel method of including pre-excitation displacement estimates in the physiological motion filter to further reduce cardiac motion artifacts is presented.
Figure 4.2: Graphical representation of the interpolation-based quadratic motion filter with the inclusion of pre-excitation displacement estimates. (a) ARFI imaging displacement estimates (circle plot) include ARFI-induced tissue displacements along with physiological cardiac motion. A quadratic function (dash-dotted line) passing through the origin (starred point) is fit to a subset of displacement estimates (solid circle points) taken before transmission of the radiation force pulse (dashed line) and after an end-time threshold (dotted line). This quadratic function is then subtracted from the data at all times to obtain (b) the motion-filtered ARFI-induced displacement and recovery profile (square plot).

Pre-excitation displacement estimation

As interpolation-based motion filters are biased by displacements that include tissue motion resulting from the application of radiation force, displacement estimates made at later tracking times and intervals are used. Consequently, there is greater time for the tissue to move off axis in both the lateral and elevational dimensions, and these data are more likely to decorrelate from the initial reference line. The Cramer-Rao lower bound indicates that the minimum displacement estimate error (jitter) associated with time-delay estimators is inversely related to the correlation coefficient [112]. Therefore, displacements at these later time steps are likely to have increased jitter and error within the ARFI images. As interpolation-based motion filters rely on these data to approximate physiological motion, any error within the displacement estimates will transfer to the motion filter and therefore the ARFI
Conversely, displacement estimates at earlier time steps are likely to have higher correlation coefficients and smaller jitter as the tissue has less time to move out of the tracking beam. As a result, new ARFI imaging sequences were developed that included multiple tracking lines directly preceding the reference line. As these tracking lines are recorded before transmission of the ARFI excitation, their displacements also provide an estimate of physiological motion in the absence of any ARFI-induced motion and can therefore be used in the motion filter. Additionally, the effectiveness of the physiological motion filter is likely to improve, as these pre-excitation tracking lines are closer in time to the reference line. A graphical representation of the quadratic motion filter including pre-excitation displacement estimates is shown in Figure 4.2.

4.2.4 Parallel-transmit imaging

Cardiac ARFI imaging sequences in previous studies have utilized multiplexed ARFI imaging to shorten acquisition times [11, 44]. Multiplexed ARFI imaging consecutively transmits radiation force pulses through multiple locations, thereby sacrificing temporal resolution for increased lateral interrogation. However, for higher-energy and longer excitation pulses, a gradual weakening in successive excitation pulses is typically encountered. As a result, a degree of inter-beam radiation force variability between the multiplexed lines is present, thereby making precise comparisons between ARFI imaging M-mode lines difficult. To address this issue, a new technique of parallel-transmit excitation is employed, where ARFI excitation pulses are simultaneously transmitted along multiple lateral locations through the use of non-overlapping apertures.

In order to perform parallel-transmit excitations, the lateral spacings between
the multiple transmit locations must be sufficiently large to accommodate the desired F/#s and transmit foci. However, these spacings are also limited by the size of the transducer aperture. As a result, parallel-transmit excitation is most applicable when using large, linear array transducers and at shallow transmit foci. Thus, parallel-transmit excitation can be implemented when imaging superficial organs and structures including the thyroid or breast. Parallel-transmit excitation can also be used for epicardial imaging, as lateral separations between M-mode lines in previous epicardial ARFI imaging studies were approximately 1 cm and focused no deeper than 2.0 cm [44]. In contrast, parallel-transmit excitation is nearly impossible to implement on phased array probes, which have limited aperture sizes, and impractical for most transthoracic and abdominal applications, where images are typically formed while focused at great depths.

With large lateral spacings for parallel-transmit excitation, conventional B-mode transmit pulses, which usually use larger F/#s and smaller transmit apertures than ARFI excitations, can also be generated in parallel and focused about each lateral location without overlapping apertures. Therefore, parallel-transmit can be implemented for the tracking lines. The parallel-receive lines can then be centered about each M-mode line, and they can simultaneously record echoes along these lateral locations. As a result, displacement estimates can be sampled at each tracking location in parallel and without the need for multiplexing. By not having to multiplex tracking lines, the data can be sampled at tracking pulse repetition frequencies (PRFs) commonly associated with traditional ARFI imaging (9.1 kHz). As the actual displacement time and recovery of the tissue are naturally unaffected, the maximum ARFI imaging sampling rate of the M-mode sequences does not increase with parallel-transmit imaging.

Parallel-transmit tracking is designed to be an alternative to multiplexed imaging;
however, it does not have the benefits of shortening acquisition times and sampling rates associated with multiplexed imaging. This is inconsequential in M-mode ARFI imaging, as acquisition times and sampling rates are dictated by thermal safety limitations. For 2-D ARFI imaging, shortening acquisition times remains a priority, and therefore multiplexed imaging remains implemented for those sequences.

4.2.5 New ARFI Imaging Sequences

Three-line M-mode ARFI imaging

Three-line M-mode ARFI imaging sequences are used to record myocardial stiffness through the entire cardiac cycle at high temporal sampling frequencies. As myocardial tissue has been observed to recover from an ARFI excitation within 2-3 ms, the maximum sampling rates for these sequences can exceed 300 Hz. However, in order to limit tissue and transducer heating, M-mode ARFI lines are sampled at considerably lower frequencies. The three-line M-mode images and plots presented in this chapter were acquired at a sampling rate of 120 Hz.

Parallel-transmit excitation and tracking was implemented for these sequences to simultaneously transmit radiation force pulses and track displacements at multiple lateral locations. With a transmit F/# of 1.5 and focus of 1.5 cm, the M-mode lines were spaced 1.31 cm apart, laterally, to assure the transmit apertures did not overlap.

Traditional M-mode lines were also recorded at each lateral location at a sampling rate of 480 Hz during these acquisitions. From these data, incremental axial displacements were calculated using the same phase-shift estimation algorithm used to estimate axial displacements in ARFI imaging. Tissue velocities were then obtained by multiplying these incremental axial displacements by the traditional M-
mode imaging sampling frequency. B-mode images were also acquired within these sequences at a sampling rate of 30 Hz. Although not performed in this study, these B-mode images could be used to measure clinically relevant metrics of cardiac imaging, such as chamber volumes, wall thicknesses, and 2-D velocities, for comparative purposes.

**ECG-gated extended three-line M-mode ARFI imaging**

In order to observe transient changes of the heart across multiple heartbeats, ECG-gated extended three-line M-mode ARFI imaging sequences were developed. These sequences were derived from the three-line M-mode ARFI imaging sequences described in the previous section. Parallel-transmit excitation and tracking were implemented, and the lateral spacing for the three M-mode lines was 1.07 cm. The sequences were focused at 1.5 cm with a transmit F/# of 1.5.

The ARFI imaging PRF was reduced to extend the acquisition time. At these lower sampling rates, 2-D B-mode images could also be acquired. To further prolong these acquisitions, the sequences were ECG-gated to record data for every other heartbeat. In total, twenty-four 2-D B-mode and M-mode ARFI imaging frames were acquired on every other heartbeat across seventeen beats. For a resting heart rate of 60 beats per minute (bpm), this would correspond to an imaging frame rate of 24 Hz.

**ECG-gated two-dimensional ARFI imaging**

ECG-gated two-dimensional ARFI imaging sequences were also developed. These sequences were based on the extended three-line M-mode ARFI imaging sequences as described in the previous section; however, through multiple consecutive heartbeats, the lateral locations of the three M-modes lines were electronically translated across a
Figure 4.3: Graphical depiction of an ECG-gated two-dimensional ARFI imaging sequence. Across nine consecutive heartbeats, M-mode ARFI images were repeatedly sampled at twelve lateral locations, multiplexed in quatrains about three excitations regions, and separated one-third of the field of view apart. On successive heartbeats, the excitation and tracking locations were then electronically translated across the field of view. At the end of the acquisition, multibeat synthesis was used to reconstruct a sequence of two-dimensional ARFI images through a single cardiac cycle.

...
made along twelve lateral locations from each individual ARFI-excitation transmit. The ARFI imaging sequences repeatedly interrogated these twelve locations at ARFI imaging PRFs that were determined by the heart rate. In total, twenty ARFI imaging frames were acquired within a single cardiac cycle.

The process was electronically translated to span a 24.7 mm lateral field of view, with a line density of 3.3 lines per millimeter. Each successive ensemble of twelve tracking lines was ECG-gated to a separate heartbeat. In total, the entire sequence of images was formed across nine heartbeats and interrogated 108 individual lateral locations. Multibeat synthesis was then used to reconstruct 2-D ARFI images of the heart through a single cardiac cycle. A diagram of this sequence is presented in Figure 4.3.

4.3 Experimental Procedure

4.3.1 Parallel-transmit imaging evaluation

A CIRS (Norfolk, VA) homogeneous tissue-mimicking phantom was imaged with three-line M-mode ARFI imaging sequences, which utilized either multiplexed imaging or parallel-transmit imaging. Single-line M-mode ARFI images centered about each of the lateral locations were also acquired. The transmit foci and transmit F/#s were the same in all acquisitions. As the stiffness of the phantom was constant, the displacement and recovery profiles of the phantom in response to a single excitation pulse were compared between the three sequences. Each M-mode sequence acquired data for 1 s at an ARFI imaging PRF of 120 Hz. Repeated sampling within each acquisition was used for statistical analysis.
In vivo ARFI imaging of an ovine subject

A thoracotomy was performed and the pericardium was cut away to expose the left side of the heart. Pacing electrodes were sewn onto the left atrium, near the sinoatrial node, and onto the left ventricular free wall, near the apex. As a result, the heart could be paced at heart rates above the normal sinus rhythm from either the atria or ventricles. The transducer/vacuum apparatus was then centered atop the left ventricular free wall and oriented along the long axis of the heart. With this orientation, the left side of the image was closer to the base of the heart, and the right side was closer to the apex and the ventricular pacing wire. Various images while the heart was paced from either electrode were then formed. In order to register the images with the cardiac cycle, the global ECG was recorded along with the power supply voltage of the scanner for each imaging acquisition. The voltage of the pacing generator was also recorded.

Physiological Motion Filter Performance Analysis

While pacing from the left ventricle, a passive (zero-amplitude radiation force pulse) 2-D ARFI image of the heart was acquired at systole. The ARFI imaging sequence utilized parallel-receive and multiplexed imaging. However, as the sequences were passive acquisitions, there was no need to parallel transmit any ARFI excitation. Displacement data were filtered using the quadratic motion filter with and without including pre-excitation displacement estimates. An end-time threshold of 3.75 ms was used in both cases. Using displacement estimates recorded only after the null excitation, two points of data beyond this end-time threshold were applied to the motion filter. A single displacement estimate, measured one tracking pulse repetition interval (PRI) before the reference line, was then added to the quadratic
motion filter. The absolute residual 2-D ARFI images from both filters were then compared.

The performance of the quadratic motion filter through the entire cardiac cycle was then characterized using passive single-line M-mode ARFI imaging sequences. Again, displacement data were filtered using the quadratic motion filter with and without inclusion of pre-excitation displacement estimates. With a higher tracking PRF than the 2-D sequences, six displacement estimates after the same end-time threshold were available for use in the quadratic motion filter. Three pre-excitation displacement estimates were then added to the motion filter for comparison. From each filter, the average absolute ARFI-induced displacement curves through the entire thickness of the myocardium were calculated.

4.3.2 *In vivo* ARFI imaging

While pacing from the left ventricle, the heart was imaged with active three-line M-mode ARFI imaging sequences. The ARFI imaging sequence utilized parallel-transmit excitation/tracking and was focused at an axial depth of 1.5 cm. The resulting ARFI-induced displacement curves were examined for uniformity in the displacement estimates through each lateral location and the entire cardiac cycle.

ECG-gated two-dimensional ARFI imaging sequences of the heart were then acquired. Again, the images were focused at a 1.5 cm axial depth. The spatial uniformity within each reconstructed 2-D ARFI image was examined. An average ARFI-induced displacement curve was also calculated to assess the spatial variability of this new sequence through the cardiac cycle.

The pacing source was then switched to the atrial electrode, and the heart was allowed to adjust to this new pacing location. Surgical tape was then wrapped around the superior and inferior venae cavae. ECG-gated extended three-line M-mode ARFI
images of the heart were then acquired while occluding venous flow returning to the right atrium with surgical tape. As a result, ARFI-induced displacement curves of the heart under decreasing preloads were obtained. The displacement curves were inspected across multiple heartbeats for any changes that could be attributed to the decrease in preload.

4.4 Results

4.4.1 Parallel-transmit imaging evaluation

Three-line M-mode ARFI imaging acquisitions of a homogeneous phantom are shown in Figure 4.4. As the sequences were designed for myocardial imaging, the total tracking time was insufficient to record the full displacement and recovery profile of the more compliant phantom. As a result, the displacement estimates were not motion filtered. Normalized displacements taken within a 1.9 mm axial kernel about the transmit focus and 0.66 ms after cessation of the radiation force pulse from each acquisition are shown in Figure 4.4b. From this plot, the effects of multiplexing become apparent as a gradual left-to-right drop can be seen in the normalized displacements taken from the multiplexed acquisitions. Conversely, good agreement can be seen between the superimposed single-line M-mode and parallel-transmit acquisitions.

The averaged displacement profiles within a 1.9 mm kernel about the transmit focus for the multiplexed, parallel-transmit, and superimposed single-line M-mode acquisitions are shown in Figure 4.4c-e, respectively. The regions of interest and lateral locations of these displacement profiles are shown in the B-mode image in Figure 4.4a. The loss of temporal resolution due to multiplexed imaging is evident
Figure 4.4: Three-line M-mode ARFI imaging of a homogeneous phantom. (a) The B-mode image marks the lateral locations and regions of interest for each M-mode line by their respective shapes. (b) Normalized displacements at the first commonly recorded tracking time (dashed line) shows good agreement between the superimposed single M-mode line acquisitions (red trace) and the three-line parallel-transmit excitation/tracking M-mode acquisition (green trace). Due to power supply limitations, the corollary three-line multiplexed M-mode imaging acquisition (blue trace) exhibits a progressive left-to-right drop in the normalized displacements. The benefit of parallel-transmit excitation/tracking can be seen within the displacement profiles of each acquisition. (c) The multiplexed acquisition is more sparsely sampled and cannot begin tracking displacements until much later in time than the other two sequences. A disadvantage of parallel-transmit excitation is a reduction of overall pushing strength and can be observed by a reduction in the magnitudes of (d) the ARFI-induced displacement profiles from the parallel-transmit ARFI excitation sequence. Within a stationary homogeneous phantom, (e) the superposition of single-line M-mode acquisitions produces displacement profiles with the highest displacement magnitudes and the finest temporal sampling.

within the less sampled displacement plots in Figure 4.4c. Additionally, the overall reduction in transmit power due to parallel-transmit excitation can be observed, as the ARFI-induced displacement profiles in Figure 4.4d are smaller than the other two sequences.
4.4.2 *In vivo* ARFI imaging

**Physiological Motion Filter Performance Analysis**

The improvement due to the inclusion of pre-excitation displacement estimates for the quadratic motion filter is demonstrated in the 2-D ARFI images Figure 4.5. The matched B-mode image taken at this point of the cardiac cycle is shown in Figure 4.5a. The relative time of acquisition within the cardiac cycle is marked by the solid vertical line in Figure 4.5d and can be seen to be coincident with the QRS complex and ventricular systole. At this point of the cardiac cycle, the heart is contracting and there is considerable and complex physiological motion within the heart. The dashed vertical lines within the ECG plot indicate the application times of the pacing stimulus. The quadratic motion filtered images, taken 0.66 ms after cessation of the zero-amplitude excitation pulse, without and with pre-excitation displacement estimates, are shown in Figure 4.5b-c, respectively. Ideally, these images would be zero, indicating the complete removal of cardiac motion artifacts. Although this is not the case, the advantages in including pre-excitation displacement estimates in the motion filter are evident within the images as the residual displacements are reduced and more uniform in Figure 4.5c.

Average motion filtered absolute residual displacement plots from a passive, single-line M-mode ARFI imaging acquisition of an *ovine* left ventricular free wall *in vivo* is shown in Figure 4.6. The lateral location and region of interest of the M-mode displacement plots are marked in the corresponding B-mode image, shown in Figure 4.6a. Figure 4.6b displays residual displacement plots taken 0.71 ms after cessation of the null radiation force pulse and after application of the quadratic motion filter with and without including pre-excitation displacement estimates. The matched global ECG is shown in Figure 4.6b, below the ARFI-induced displacement
Figure 4.5: In vivo two-dimensional ARFI imaging demonstration of the improvement of the quadratic motion filter by including pre-excitation displacement estimates. From a passive ARFI imaging acquisition, absolute residual displacement images ($\mu m$), taken 0.66 ms after cessation of the zero-amplitude radiation force pulse, were formed at systole. The relative time within the cardiac cycle of the image acquisition is marked on (d) the matched ECG by the solid vertical line. The dashed vertical lines within this plot indicate the times of application of the external stimulating pulse. (a) The B-mode image shows a section of left ventricular myocardium located near the apex. By motion filtering with displacement estimates taken only after the end-time threshold, (b) the residual displacement ARFI image contains considerable physiological motion artifacts, as an appreciable amount of the image is non-zero. By including pre-excitation displacement estimates in the quadratic motion filter, physiological motion artifacts are markedly reduced, as (c) the corresponding residual displacement ARFI image has become more uniform and closer to zero.
Figure 4.6: Average residual displacements within an *in vivo* single line M-mode ARFI image of the left ventricular free wall. The lateral position and region of interest of the M-mode ARFI line are marked within (a) the matched B-mode image. After motion filtering, (b) the average absolute residual displacement plots indicate that the inclusion of pre-excitation displacements (triangle points) better estimates physiological motion at systole than motion filtering with only post-excitation displacement estimates (circle points). The performances of the motion filters at diastole are comparable. The matched global electrocardiogram is shown below.

...plot. The ARFI-induced displacements indicate that the greatest residual displacements occurred at systole and about the QRS complex. However, by including pre-excitation displacement estimates in the quadratic motion filter, these systolic residual displacements are considerably reduced and physiological motion artifacts are seen to be below 0.2 $\mu$m throughout the entire cardiac cycle. The performances of the motion filters through diastole are comparable, with each filter reducing cardiac motion artifacts to below 0.15 $\mu$m.

ARFI imaging sequence demonstration

Three-line M-mode ARFI images of an *ovine* left ventricular free wall are shown in Figure 4.7. The corresponding B-mode image with the lateral positions and region of interest is shown in Figure 4.7a. With the matched ECG shown below in Figure
Figure 4.7: Three-line M-mode ARFI images of an externally paced ovine left ventricular free wall. The lateral positions and regions of interest are marked by their respective shapes within (a) the corresponding B-mode image. With this acquisition, (b) parallel ARFI-induced displacement curves and (c) mid-myocardial tissue velocities can be calculated simultaneously at three lateral locations. (d) The matched global ECG is shown below, and the application of the pacing stimulus is marked by the dashed vertical lines. Diastolic ARFI-induced displacements at all three curves are comparable due to the implementation of parallel-transmit excitation. The displacement and tissue velocity plots indicate that there is sufficient temporal resolution within these sequences to extract systolic phase delays between the three lateral locations.

4.7d, Figure 4.7b-c demonstrates the capabilities of the imaging sequence to produce three-line ARFI-induced displacement curves, averaged within a 1.9 mm axial kernel about the transmit focus, and average tissue velocity curves, within a 1.9 mm axial kernel at the mid-myocardium. A benefit of parallel-transmit excitation can be seen in Figure 4.7b, as the three ARFI-induced displacement estimates made at late diastole are similar, indicating nearly uniform diastolic elasticities within the regions of interest. Myocardial contraction is apparent within these plots, with a sharp drop in ARFI-induced displacements and a rise in tissue velocity magnitudes at systole and shortly after application of the stimulating pulse (dashed vertical lines). Additionally, asynchronous relaxation is apparent within each image as the rightmost M-mode lines (triangle plot) are dissimilar in both ARFI and tissue velocity plots.
Figure 4.8: A single (a) B-mode and (b) ARFI image frame from an ECG-gated two-dimensional ARFI imaging acquisition of an externally paced ovine left ventricle. The point of the cardiac cycle at which this specific frame was acquired is marked by the starred point in (c) the ARFI-induced displacement curve and the matched global ECG below. The ARFI-induced displacement curve was calculated by spatially averaging displacements (µm away from the transducer) measured within the region of interest, as marked on the B-mode image by the two horizontal lines. Error bars within the plot indicate that images are relatively homogeneous, with spatial variations in ARFI-induced displacement ranging from 2-4 µm.

A single matched B-mode and ARFI image frame, reconstructed from an ECG-gated 2-D ARFI imaging sequence, is shown in Figure 4.8. The spatial continuity
within the B-mode image in Figure 4.8a suggests that the behavior of the heart was widely stable and repeatable across the nine heartbeats of the acquisition. The ARFI image in Figure 4.8b, taken right at the onset of ventricular systole, shows a region of myocardium with relatively uniform ARFI-induced displacements and little indication of a multiplexing artifact which would be manifested as discontinuities within each third of the image. The exact point of acquisition within the cardiac cycle of the selected B-mode and ARFI images is marked in Figure 4.8c by the starred points in the ARFI-induced displacement curve and its matched global ECG. The ARFI-induced displacement curve can be observed to resemble the ones generated with the three-line M-mode imaging sequences. The error bars within this displacement plot correspond to the lateral variability within a region of interest centered about the transmit focus (1.5 cm), as marked by the two horizontal lines in the B-mode image in Figure 4.8a. These error bars indicate that the stiffness of the tissue was relatively uniform through the entire cardiac cycle.

ECG-gated extended three-line M-mode ARFI images of a left ventricle free wall while occluding the superior and inferior venae cavae are shown in 4.9. The matched B-mode image, with the lateral positions and regions of interest of the three M-mode lines, is shown in Figure 4.9a. ARFI-induced displacements were averaged within a 3.8 mm axial kernel, starting from the epicardial surface. In Figure 4.9b, with the matched ECG below, a beat-to-beat analysis of the center M-mode line indicates that the end-diastolic ARFI-induced displacements increased during the occlusions, and therefore the myocardium was more compliant at diastole due to the decrease in preload. The end-systolic displacements remained relatively constant and therefore suggested the end-systolic stiffness was unaffected by changes in preload. As the heart was atrially paced during this acquisition, a pacing artifact (rather than a normal P-wave) is present within the ECG at the beginning of each beat and atrial
Figure 4.9: ECG-gated extended three-line M-mode ARFI image of a left ventricular free wall during venal caval occlusions. The lateral locations and regions of interest are marked within (a) the corresponding B-mode image. With the matched global ECG below, (b) the ARFI-induced displacement curve of the center lateral location shows diastolic displacements increased, indicating a decrease in diastolic stiffness as the preload decreases. The end-systolic displacements remained unchanged, suggesting that the end-systolic stiffness was preload independent. This trend can also be observed within the individual ARFI-induced displacement plots between the first (circle plots) and last (triangle plots) heartbeats for the (c) left, (d) center, and (e) right lateral locations.

Individual inspections of the first and last heartbeats for the left, center, and right lateral locations, shown in Figure 4.9c-e, respectively, corroborate these results.
4.5 Discussion and Conclusions

Between the three methods of three-line M-mode imaging presented in this chapter, the superposition of the three single-line M-mode acquisitions of a homogeneous phantom produced the best-sampled images with the greatest ARFI-induced displacements. However, a clinical realization of this sequence would require ECG-gating and multibeat synthesis in order to temporally register the M-mode lines. Although parallel-transmit excitation reduced the effective pushing strength at each individual excitation, the uniformity of the push and ability to track displacements in parallel allow in vivo interbeam comparisons of local myocardial elasticities. Also, by tracking in parallel without multiplexing, there was greater flexibility in frame selection and for parametric analyses of the data. Finer temporal sampling also provided additional displacement estimates for the physiological motion filters and therefore could help further reduce motion artifacts within the images.

Perhaps the most advantageous effect of parallel-transmit excitation was that displacements could be tracked more immediately after cessation of the radiation force pulse. As a result, the sequences were capable of observing the initial response of the tissue to the radiation force pulse. This benefit can be seen within the displacement and recovery profiles in Figure 4.4b, as the multiplexed sequences were only able to track the homogeneous phantom in recovery, and therefore the true maximum displacement was not observed.

The parallel-transmit sequences did not exactly reproduce the same displacement and recovery profiles at each of the three M-mode lines. However, as similar displacement and recovery profile variations were also observed within the superimposed single-line M-mode acquisitions, it is likely that these differences were caused by factors external to the ARFI imaging sequences, possibly pertaining to variability.
related to the transducer and the local elasticities within the phantom.

By sequencing pre-excitation tracking lines, the interpolation-based motion filters were able to more effectively remove physiological cardiac motion artifacts from the ARFI images. The three-line M-mode image in Figure 4.6b demonstrates that average absolute residual displacement artifacts were below 0.35 µm through the entire cardiac cycle. With diastolic ARFI-induced tissue displacements above 10 µm in all active ARFI imaging acquisitions, we believe that these levels of motion artifacts are sufficiently low to make accurate stiffness comparisons within the ARFI image. In the 2-D ARFI image in Figure 4.5, the levels of motion artifact are satisfactorily low in the proximal regions of the myocardium that are more relevant to epicardial ARFI imaging. However, significant levels of residual displacement are present in the distal portions of the 2-D ARFI image. This increase in error at depth can likely be attributed to the vacuum apparatus. As the apparatus held the transducer over a fixed region of myocardium, the transducer was able to move in unison with the epicardium. As a result, regions of myocardium proximal to the vacuum apparatus and transducer would appear more stationary within the images, and therefore contain smaller amounts of physiological motion and motion artifacts.

Several studies have investigated electromechanical propagation within the heart as a potential non-invasive method to track the propagation of the local electrocardiogram [27, 90]. The potential of ARFI imaging to track a corollary electromechanical wave of stiffness is demonstrated in Figures 4.7 and 4.8. The ARFI imaging sequences associated with these figures are capable of observing variations within the local tissue elasticities with sufficient temporal resolution to estimate timing delays between the ARFI-induced displacement curves at each lateral location. This is apparent within the ARFI-induced displacement plots, as myocardial stiffening within the right M-mode line (triangle plots) appears to lead the other two. With
the right side of the image proximal to the pacing wires, this result may reflect the propagation of mechanical stiffness across the field of view and away from the pacing source.

Stiffness propagation may also be extrapolated from the two-dimensional ARFI imaging sequences, where the additional spatial information may provide complementary data to the three-line M-mode images. Although variations within the two-dimensional images can be attributed to many sources, one possible contributor to the error bars in Figure 4.8c is timing differences within the field of view associated with a propagating stiffness wave. Further investigations with the ARFI imaging sequences described in this chapter are warranted to investigate the feasibility of ARFI imaging in measuring stiffness and electromechanical propagation through the heart.

Previous 2-D ARFI imaging sequences involved the acquisition of multiple 2-D ARFI images at low sampling rates (10 Hz) across 4-5 heartbeats. These images were then rearranged based on their relative times of acquisition within the cardiac cycle to form a sequence of ARFI images of a single heartbeat [44]. A consequence of this method is that the effective PRFs between each frame were variable. Additionally, this sequence of ARFI images provided no temporal continuity. As a result, calculations into the amount and rates of myocardial stiffening and relaxation were problematic. In contrast, as the new sequences gated the acquisitions into three-line M-mode sub-images, the ARFI-induced displacement estimates at each individual lateral location were regularly sampled at constant PRFs and came from a single heartbeat.

ECG-gated extended three-line M-mode ARFI imaging sequences were designed to investigate the feasibility of ARFI imaging-based measurement of myocardial function and performance. The ARFI-induced displacement plots demonstrate the
capabilities of this new sequence to track gradual, beat-to-beat changes in myocardial elasticity through multiple heartbeats. As a result, the transient changes in myocardial stiffness under various loads and operating conditions can be recorded. The three M-mode lines also provide spatial sensitivity not available with pressure-volume analysis, the current clinically accepted method for measuring left ventricular function.

The sequences developed in this chapter provide ARFI-induced displacement curves which reflect myocardial stiffnesses. However, the fundamental challenge of quantitatively relating ARFI-induced displacements to myocardial stiffness remains. Propagation velocities, stiffness ratios and normalized rates of stiffening can be extracted from these data without knowing the exact displacement-to-stiffness conversion. However, as both diastolic and systolic stiffnesses can be variable, the widespread clinical utility of these metrics remains uncertain. Investigations into shear wave elasticity (SWEI) and shear wave velocimetry have produced quantitative measures of elasticity that could also be applied to cardiac imaging [8, 59, 64, 87, 99]. However, these imaging modalities rely on the propagation of slower traveling (1-4 m/s), mechanical waves and may not be suited for dynamic environments such as the heart.

Further, although the new ARFI imaging sequences have been designed specifically for epicardial ARFI imaging, the exact precision and accuracy needed to accomplish the proposed future investigations are yet unknown and likely to be high. Additional sequence development and procedure modifications are necessary to address these concerns. Also, as physiological motion artifacts are principal impairments to ARFI imaging, refinement and optimization of the motion filters that remove these artifacts are necessary.

Novel ARFI imaging sequences were developed for epicardial imaging investiga-
tions. These sequences utilized parallel-receive acquisition, parallel-transmit excitation, parallel-transmit tracking, ECG-gating, multibeat synthesis, and multiplexing to form quality ARFI images at all points of cardiac cycle. The resultant ARFI-induced displacement curves provided new information into myocardial elasticity with high temporal and spatial resolution previously not available. Additionally, the accuracy of ARFI-induced displacement estimation was improved. With these new sequences and the improved ARFI images, various quantitative applications of cardiac ARFI imaging can be investigated.

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Chapter 5

ARFI imaging of myocardial stiffness propagation

5.1 Introduction

A major determinant of cardiac function is the precise coordination of the electrical action potential through the heart [51, 54, 97]. Cardiac arrhythmias arise when there is improper electrical conductance within the heart, resulting in asynchronous cardiac function. Although much information about these arrhythmias can be gleaned by analyzing the global electrocardiogram (ECG), localizing specific aberrant pathways that cause arrhythmias is achieved primarily by determining the electrical propagation paths of the local ECG. Current clinical methods that determine the local electrical propagation involve the introduction of invasive intracardiac catheters and electrodes that measure the endocardial ECG directly. As a result, many studies have investigated non-invasive alternatives for measurement of electrical propagation within the heart. However, where measurements of the local electrocardiogram are made directly, non-invasive alternatives have focused on tracking motion-based changes within the heart that result from the electrical action potential and therefore propagate along the same paths.

Faris, et al. utilized tagged magnetic resonance imaging (MRI) to calculate three
dimensional strains within canine hearts and observed a mechanical wave following the electrical activation propagation with an approximately 25 ms delay between the two [27]. Pernot, et al. applied ultrasonic motion tracking algorithms to observe a mechanical wave that propagated through the interventricular septum at systole within murine hearts and measured a mechanical propagation velocity that was comparable to velocities measured for electrical action potential propagation [90]. Rappaport, et al. also utilized ultrasound-measured tissue motion within a two-dimensional imaging plane in ovine hearts and demonstrated that the measured mechanical activation and propagation reflected its electrical homologue [93].

These methods have shown promise as potential non-invasive alternatives to measure electrical propagation, however a degree of uncertainty arises due to several additional factors that influence cardiac motion. In addition to the electrical conductance, a point of observable motion within the B-mode images is also dependent upon various myocardial properties including the load, heart rate, and chamber volumes. Consequently, describing the propagation of tissue motion as solely following from electrical propagation is problematic.

Another mechanical property that could possibly be used to track electrical propagation within the heart is myocardial stiffness. Although myocardial stiffness is related to several cellular mechanisms, the formation of the actin-myosin cross bridges has been shown to be a determinant in the increase of myocardial stiffness during contraction, with greater number of cross bridges causing in increased stiffness [67]. Therefore, as cross-bridge formation is stimulated by the electrical action potential, we expect myocardial stiffness to follow the electrical activation propagation paths.

Current clinical gold standards for myocardial stiffness measure a corollary value known as elastance. Elastances, however, provide a global estimate of left ventricular stiffness, as a whole, and consequently cannot be used to determine local
electrical/mechanical defects [13,69]. In Chapter 3, initial investigations into cardiac acoustic radiation force impulse (ARFI) imaging have demonstrated it to be capable of visualizing changes in local myocardial stiffnesses through the entire cardiac cycle, with rapid increases in left ventricular stiffness coincident with the QRS complex and ventricular systole. Accordingly, we have evaluated ARFI imaging as a modality to observe myocardial stiffness propagation within the heart. From Chapter 4, we have generated ARFI imaging sequences that utilize ECG gating and multi-beat synthesis to produce cardiac ARFI images with high temporal and spatial resolution. In this chapter, the preliminary work in the application of these sequences to visualize the propagation of mechanical stiffness waves within an externally paced left ventricle is presented.

### 5.2 Methods

#### 5.2.1 Imaging Methods

For these experiments, the Siemens SONOLINE Antares™ ultrasound scanner (Siemens Medical Solutions, USA, Ultrasound Division, Issaquah, WA) was used with a VF10-5 linear handheld array. All B-mode and ARFI imaging sequences were acquired using the Siemens Ultrasonic Research Interface™ to record in-phase (I) and quadrature (Q) signals from the received echoes. Each image was formed at a center frequency of 6.67 MHz and an F/# of 1.5. The ARFI-excitation pulse was also transmitted using a 6.67 MHz center frequency. Conventional B-mode images were formed across a 38 mm lateral field of view and with a line density of 6.7 lines per millimeter. Both B-mode and ARFI imaging acquisitions utilized the advances of parallel-receive imaging, as previously described [11,16,44]. A description of
traditional ARFI imaging sequences is provided by Nightingale, et al [73].

All images of the heart were formed epicardially with the transducer placed directly on the heart while using the vacuum apparatus presented in Chapter 4 to better maintain a single imaging plane within the heart. Displacements were estimated using a phase shift estimation algorithm [48]. To correct for phase wrapping errors, displacement discontinuities through time greater than half of a wavelength within the data were shifted a full wavelength in the opposite direction. An interpolation-based quadratic motion filter was used to separate ARFI-induced displacements from the natural cardiac motion [44]. The sequences utilized pre-excitation tracking so that displacement estimates made before transmission of the radiation force pulse could also be used in the physiological motion filter.

ARFI-induced displacement plots were made by taking displacements measured 0.67 ms after cessation of the radiation force pulse at each lateral location. Time delay estimates between these ARFI-induced displacement curves at various lateral locations were calculated using the normalized cross-correlation method [91]. A direction and average velocity of propagation of myocardial stiffness across the field of view were then calculated based on these time delay estimates and their lateral spacings.

M-mode ARFI imaging

M-mode ARFI images were acquired to observe stiffness changes within the heart through the cardiac cycle at high sampling frequencies. These M-mode sequences are based on the three-line M-mode ARFI imaging sequences described in the previous chapters. In order to reduce long-term tissue and transducer heating, the M-mode ARFI imaging sequences acquired data for 1 second (approximately 2 heartbeats) and at a sampling rate of 120 Hz. Single-line and two-line versions of these M-mode
ARFI imaging sequences were acquired for these experiments. The lateral spacing of the two M-mode lines was 0.95 cm.

A single M-mode line was also simultaneously recorded at each ARFI imaging lateral location at a sampling rate of 480 Hz. Incremental axial displacements were calculated from these M-mode lines with the same phase-shift estimation algorithm used to estimate displacements within the ARFI images. From these data, mid-myocardial axial tissue velocities were estimated by multiplying the incremental axial displacements measured within a 0.2 cm axial kernel at a imaging depth of 2.1 cm by the M-mode frame rate. Mid-myocardial strain rates were also estimated from these data by tracking the axial positions of two points within the myocardium: one at the epicardial surface and the other at the mid-myocardium. The difference in incremental axial displacements divided by the axial distance between the two points was taken to be the mid-myocardial strain [34].

**ECG-gated two-dimensional ARFI imaging**

ECG-gated two-dimensional ARFI images, as described in the previous chapter, were used in this study. As the hearts were externally paced for these experiments, the sequences were triggered using the pacing electrode stimulus rather than the global ECG. ARFI-induced displacements were measured at each lateral location at an ARFI imaging PRF of 65 Hz. In total, twenty-five ARFI imaging frames were acquired within a single cardiac cycle. The full 2-D image spanned a 24.7 mm lateral field of view with a line density of 3.3 lines per millimeter.

**Physiological Motion Filter**

Physiological motion artifacts were removed from all ARFI images using the interpolation-based quadratic motion filter. For the two-line M-mode ARFI imaging
sequences, an end-time threshold was 2.80 ms, and 0.33 ms of displacement data both before transmission of the excitation pulse and after the end-time threshold, corresponding to four pre-excitation and four post-excitation displacement estimates, were used in the motion filter. The ECG-gated 2-D ARFI images were motion filtered using two pre-excitation displacement estimates within a 0.66 ms tracking interval and four post-excitation displacement estimates within a 1.32 ms tracking interval and after a 3.1 ms end-time threshold.

5.2.2 Experimental Methods

The epicardial propagation of the electrical action potential was measured by recording the local electrocardiograms on the epicardial surface of the heart. An electrode plaque was developed with 112 probes spanning a 3 cm x 3 cm active aperture. With the plaque held in place by hand, the local electrocardiograms were recorded at each electrode at a sampling frequency of 3 kHz and band-pass filtered with cutoff frequencies of 0.5 Hz and 1000 Hz. Electrical action potential propagation was measured by tracking the peak negative voltage measured at each point. Averaging through multiple heartbeats, the direction and lateral propagation velocities across the plaque were determined using a least squares regression of the times of these negative peaks and locations of each electrode. The velocity component across the face of the electrode plaque was taken as the lateral electrical propagation velocity.

5.2.3 Experimental Procedure

The beating heart of two canine subjects, weighing approximately 30 kg and with heart rates above 80 beats per minute (bpm), were imaged for these experiments as
approved by the Institutional Animal Care and Use Committee at Duke University and conforming to the Research Animal Use Guidelines of the American Heart Association. A left thoracotomy was performed to expose the left side of the heart so that the transducer/vacuum apparatus could be centered over the left ventricular free wall and along the long axis of the heart. The transducer was also positioned such that the left side of the image was towards the base of the heart, while the right side of the image was closer to the apex.

For both subjects, two stimulating electrodes were sutured onto the epicardium such that they were positioned laterally on either side of the transducer and in line with the imaging plane. The heart was externally paced by one of the two electrodes at heart rates above the normal sinus rhythm of the animal. As a result, depending on which electrode was used to pace the heart, an electrical action potential could be made to propagate across the field of view from either base to apex (left to right) or apex to base (right to left). Throughout these experiments, the pacing site was alternated between these two electrodes while allowing the heart sufficient time to adjust to the pacing location before acquiring data. A diagram of the experimental setup is shown in Figure 5.1.

Passive, two-line M-mode ARFI images of the left ventricular free wall were acquired for both subjects. These ARFI images were also acquired while pacing from either electrode. The average absolute residual displacements, measured 0.67 ms after cessation of the radiation force pulse, were estimated across multiple heartbeats to examine the effectiveness of the physiological motion filter. The residual displacement plots were also inspected for indications of electromechanical propagation between the two lateral locations.

Active two-line M-mode ARFI images that included 45 $\mu$s excitation pulses were acquired for the first canine subject while pacing the heart from either stimulating
Figure 5.1: Graphical representation diagramming the experimental setup. An exposed and externally paced canine heart is imaged with a transducer/vacuum apparatus placed directly on the left ventricular free wall. ECG-gated B-mode and ARFI images, the voltage from the power supply of the ultrasound scanner, global ECG, and stimulating pulse waveforms were simultaneously recorded and temporally registered. The procedure was performed while pacing on either side of the transducer. The transducer/vacuum apparatus was then removed and replaced with a 112-electrode electrophysiology plaque. The procedure was then repeated while recording the local epicardial potentials.

electrode. An average time delay between the two M-mode tissue displacement curves was estimated through the cardiac cycle with the normalized cross correlation method [91]. The time delay between the displacement curves was used to calculated
A direction and velocity of propagation of myocardial stiffness.

A comparison between the propagations of myocardial stiffness and the electrical action potential was performed. Two-dimensional ARFI images were formed while the heart of the second canine subject was paced from the basal electrode. Time delays in lateral myocardial stiffening during systole were measured within the entire 2-D image using the lateral location most proximal to the pacing source as the reference (zero delay) curve. Least squares regression was used to determine a direction and average velocity of lateral stiffness propagation across the field of view. Next, the transducer/vacuum apparatus was removed and replaced with the electrode plaque. The local epicardial electrocardiograms were recorded within the same field of view across multiple consecutive heartbeats. The propagation of the electrical action potential was determined and a lateral propagation velocity and direction were calculated. These values were compared with the ARFI imaging-assessed direction and velocity of myocardial stiffness propagation. The process was repeated while pacing from the apical electrode.

To examine the relationship between stiffness and other metrics that have been used to determine myocardial electromechanical propagation, two-line M-mode ARFI images were formed while the heart of the second canine subject was paced from the apical electrode. Mid-myocardial ARFI-induced displacements, strain rates, and tissue velocities were calculated from this sequence. Propagation velocities were calculated by estimating the systolic time delays between the two lateral locations from each of these measurements. The transducer/vacuum apparatus was removed and replaced with the electrode plaque. The electrical propagation velocities were calculated and then compared with the three mechanical propagation velocities.
5.3 Results

As the passive, zero-amplitude radiation force pulse ARFI imaging sequences provided no external excitation to the tissue, displacements measured within the images were the result of cardiac motion only. As a result, residual displacements after motion filtering reflect cardiac motion artifacts and the expected levels of noise within subsequent ARFI images. Average absolute residual displacements through the entire thickness of the left ventricular free wall of the hearts of the two animal subjects from passive ARFI imaging acquisitions are shown in Figure 5.2. Figure 5.2a-c corresponds to the first animal, and Figure 5.2d-f corresponds to the second animal. The lateral positions and regions of interest are marked by their respective shapes within the matched B-mode images in Figure 5.2a and d. Residual displacement plots while pacing from the basal electrode are shown in Figure 5.2b and e. Residual displacement plots while pacing from the apical electrode are shown in Figure 5.2c and f. The application of the pacing stimulus is marked in each subfigure by the dashed vertical lines. From these four plots, the motion filter used in these experiments can be observed to reduce physiological motion artifacts to below 0.35 µm through the entire cardiac cycle. Physiological motion artifacts were greatest shortly after application of the pacing stimulus and corresponded to myocardial contraction and periods of increased cardiac motion. However, no direction of propagation can be observed within any of these residual displacement plots, as no clear delay is present between the two lateral locations.

The propagation of myocardial stiffness can be seen with ARFI imaging as demonstrated in Figure 5.3. The lateral locations and relative depths of the displacement plots within the M-mode ARFI images are marked by the vertical lines and their respective shapes in the corresponding B-mode image in Figure 5.3a. The
Figure 5.2: Average absolute residual displacements through multiple heartbeats from passive, two-line M-mode ARFI images within the left ventricular free walls of two animal subjects. (a and d) The corresponding B-mode images show the lateral locations marked by their respective shapes and the regions of interest. When pacing from either (b and e) the basal or (c and f) apical electrode, displacement artifacts are below 0.35 μm through the entire cardiac cycle. The times of application of the stimulating electrodes are marked in each plot by the dashed vertical lines.
Figure 5.3: Matched B-mode and active two-line M-mode ARFI images of an externally paced left ventricle. The lateral locations and regions of interest are marked with their respective shapes within (a) the B-mode image. Pacing electrodes were positioned on either side of the lateral field of view. The times when the myocardium was stimulated by the pacing electrodes are marked by the dashed vertical lines within the ARFI-induced displacement plots. Displacements measured from the active M-mode ARFI imaging sequences show cyclic curves with a phase difference that is dependent on the location of the pacing electrode. When pacing from (b) the left, myocardial stiffening at the left lateral location (circle plot) leads the right (triangle plot). When pacing from (c) the right, the reverse trend is seen and myocardial stiffening at the right lateral location now leads the left.

motion filtered displacement plots of the active two-line M-mode ARFI imaging acquisitions are shown in Figure 5.3b-c. The application times of the pacing electrodes are marked by the dashed vertical lines within each displacement plot. As the ARFI
imaging sequences included high-intensity excitation pulses, these displacement plots included both tissue displacements responding to the application of radiation force as well as physiological cardiac motion artifacts comparable to those previously measured in Figure 5.2c and e. Both plots show myocardial stiffening and relaxation occurring earlier for the M-mode line proximal to the excitation source. When pacing near the base (Figure 5.3b), the M-mode line on the left side of the image can be observed to lead the M-mode line on the right. When pacing near the apex (Figure 5.3c), the reverse trend can be seen as the M-mode line on the right side of the image now leads the left. Using the normalized cross-correlation method, the average time delay between the two M-mode ARFI lines was estimated to be $18.6 \pm 12.8$ ms when paced from the base, and $-20.0 \pm 15.8$ ms when paced from the apex. These delays corresponded to average propagation velocities between the M-mode lines of 0.52 m/s and -0.50 m/s.

A sample time to peak negative epicardial voltage image, recorded by the 112-electrode plaque, is shown in Figure 5.4. This image has been masked at pixels with no discernible action potential. With the pacing source positioned to the right of the image, peak negative voltages can be seen to occur later in time as the distance from each electrode to the pacing source increases. As the plaque was elevationally centered about the pacing source, this action potential propagation was predominantly in the lateral dimension (right to left) with only a slight bottom to top propagation. An apparent acceleration of the action potential as it propagated away from the pacing source can also be seen within this image as differences in the time of peak negative voltage in the left side of the image were smaller than in the right side of the image.

Estimated time delays between ARFI-induced displacement curves within full 2-D ARFI imaging acquisitions are shown in Figure 5.5. The matched B-mode image
Figure 5.4: Sample time (ms after application of the pacing stimulus) to peak negative epicardial voltage along a section of canine left ventricular free wall. With the pacing electrode located near the apex and to the right of the image, an action potential can be seen to propagate across the field of view from right to left. Black-colored pixels within the image indicate electrodes where an action potential could not be measured. Average lateral propagation velocities across the field of view and for multiple consecutive heartbeats were compared with ARFI imaging-based stiffness propagation velocities.

is shown in Figure 5.5a with the region of interest marked between the two horizontal lines. Time delays were estimated while pacing externally from either (Figure 5.5b) the basal or (Figure 5.5c) the apical electrode. In each case, the lateral location most proximal to the pacing electrode was used as the reference (zero delay) line. Both time delay plots show increasing delays as the lateral locations moved farther away from the selected stimulating electrode, reflecting a mechanical stiffness wave that propagated across the field of view and away from the pacing electrode. Linear least square regressions of the data estimated average lateral propagation velocities across the field of view to be 0.72 m/s and -0.69 m/s. The corresponding epicardial action potential propagation velocities for each stimulating electrode were measured to be $0.79 \pm 0.14$ m/s and $-0.78 \pm 0.37$ m/s.
Figure 5.5: Matched B-mode and time delays between ARFI-induced tissue displacement curves and times to peak negative epicardial voltages when paced by an external source. The ARFI imaging region of interest is marked by the two horizontal lines within (a) the matched B-mode image. The lateral location most proximal to the selected pacing source was defined as the reference line and zero delay. When pacing from either (b) the left or (c) the right side of the image, time delays between the other lateral locations and that reference line were estimated using the normalized cross correlation method. These time delay plots show increasing delays as the lateral locations move farther away from the pacing source. When observing electrical propagation, a similar trend can be seen. While pacing from (d) the left or (e) the right side of the image, the time delays to peak negative voltages increased as the distance from the pacing source increased. Using a least squares linear approximation, the average propagation velocities of stiffness were measured to be $-0.69$ m/s and 0.72 m/s. The corresponding lateral propagation velocities of the epicardial action potential were measured to be $-0.78 \pm 0.37$ m/s and $0.79 \pm 0.14$ m/s.
Figure 5.6: Electromechanical propagation comparison between (a) ARFI, (b) strain rate, and (c) tissue velocity imaging with the matched (d) global ECG. The points of application of the pacing electrode are marked by the dashed vertical lines in each plot. For all three cases, the M-mode line proximal to the pacing source (triangle plot) leads the distal M-mode line (circle plot) at systole. Diastolic electromechanical propagation is less apparent, as the plots suggest reversed or nearly instantaneous propagation.
A comparison of electromechanical propagation between ARFI, strain rate, and tissue velocity imaging is shown with the matched global ECG in Figure 5.6. Electromechanical propagation at systole is evident for all three cases, as the M-mode line proximal to the pacing site (triangle plot) leads the distal M-mode line (circle plot). Using the normalized cross correlation method, average systolic propagation velocities measured with ARFI, strain rate, and tissue velocity imaging were $0.75 \pm 0.13 \text{ m/s}$, $0.73 \pm 0.10 \text{ m/s}$, and $0.76 \pm 0.04 \text{ m/s}$ respectively. The corresponding average propagation velocity of the epicardial action potential was measured with the EP plaque to be slightly faster at $0.86 \pm 0.23 \text{ m/s}$.

As the waveforms of the two M-mode lines were dissimilar through diastole, there was no clear indication of any diastolic electromechanical propagation away from the pacing source. In fact, with ARFI imaging, the distal location appeared to relax before the proximal location, indicating propagation in the reverse direction. For the strain rate and tissue velocity cases, the M-mode plots were nearly coincident at early diastole and therefore reflect physiologically unrealistic propagation velocities. As a result, diastolic propagation velocities were not measured.

### 5.4 Discussion and Conclusions

With the inclusion of pre-excitation tracking lines, the interpolation-based motion filters effectively reduced physiological cardiac motion artifacts at all points of the cardiac cycle to below $0.35 \text{ \mu m}$. With diastolic ARFI-induced tissue displacements above $4 \text{ \mu m}$ in all subsequent acquisitions, motion artifacts were sufficiently low to make accurate time delay estimates and calculate propagation velocities with ARFI imaging. The performance of the motion filters also was significantly aided by the vacuum apparatus, which steadied the transducer atop the regions of interest.
and reduced out-of-beam motion and the resultant signal decorrelation.

Two-line M-mode ARFI imaging methods estimated similar propagation velocity magnitudes between the two lateral locations when pacing from either side of the transducer. Additionally, both observed propagation directions corresponded to stiffness waves that were traveling away from the pacing source. In all M-mode ARFI-induced displacement plots, a short delay (approximately 40 ms) can be observed between the application of the electrical stimulus and the point where the ARFI-induced displacements dropped sharply and indicated the onset of myocardial stiffening. This delay was likely due to an approximate 5 mm separation between the pacing electrode and the positions of the M-mode lines and the time needed for the action potential to propagate into the regions of interest.

The two-dimensional ARFI images produced similar results to the two-line M-mode acquisitions, as the ARFI-induced displacement curves at lateral locations proximal to the pacing electrode led those measured at distal locations. Although the magnitudes of the average propagation velocities within each 2-D image were comparable to each other, they were slightly greater than estimated by the two-line M-mode ARFI imaging sequences. One likely explanation for this difference is the fact that the action potential propagation is dependent upon the underlying myocardial fiber orientation and conduction pathways. As a result, a degree of variability within the measured propagation velocities between experiments is expected and an exact reproduction of results among subjects is unrealistic.

As demonstrated in Figure 5.5, the matched average epicardial electrical propagation velocities calculated within the same field of views agreed with average stiffness propagation velocities in both direction and magnitude. The percent differences measured between these two methods for the left- and right-traveling waves, using the local electrical propagation velocities as the gold standard, were calculated to
be -8.9% and -11.5%, respectively. This agreement suggests that the propagating stiffness wave followed the propagation of the electrical action potential. However, for both traveling waves, the ARFI imaging-estimated propagation velocities were slower than those measured from the epicardial action potential. One likely explanation for this discrepancy is due to the fact that the ARFI images were focused near the mid-myocardium. As a result, with the complex geometry and structure of the heart, stiffness propagations measured at the mid-myocardium may not exactly have reflected propagation at the epicardium. Additionally, as propagation velocities were measured only in a single (lateral) dimension, any misalignment between the transducer and epicardial plaque would result in differences between these two measurements.

A closer inspection of the time delay profiles indicates that the ARFI imaging-derived delays oscillated about the average stiffness propagation velocity while the epicardial ECG accelerated as the action potential propagated away from the pacing source. This discrepancy could have been caused by many factors including motion artifacts or imprecise temporal gating and registration of the two-dimensional ARFI imaging sequences. Nevertheless, these results indicate that although ARFI imaging may not be capable of exactly inferring the electrical activation propagation path, ARFI imaging has the potential as a non-invasive method for visualizing local stiffness propagation and approximate electrical propagation within the heart.

The comparisons between ARFI, strain rate, and tissue velocity imaging indicate that electromechanical propagation is most easily observed during systole and myocardial contraction. As seen in the previous two-dimensional ARFI imaging/electrical propagation comparison, the electrical propagation velocity was estimated to be higher than any of the electromechanical measurements. Misregistration between the transducer and the plaque on the heart and the variant propa-
gation paths through the thickness of the myocardium may be the source of this discrepancy. Such non-uniform activation potential propagation has been observed in previous studies [28]. Conversely, as all three electromechanical measurements (ARFI-induced displacements, strain rates, and tissue velocities) were made within a single region of interest and during a single acquisition, the average propagation velocities could be expected to be more similar and accordingly were all within 0.03 m/s of each other.

The two-line M-mode ARFI-induced displacement plots in Figure 5.3 from the first subject display stiffness curves with one lateral location leading the other throughout the entire cardiac cycle. This is not the case with any of the mechanical plots in Figure 5.6, where there was no clear indication of a diastolic mechanical wave propagating away from the pacing electrode. All three methods suggested some degree of reversal in propagation, while the strain rate and tissue velocity plots also had dissimilar mechanical activity between the two lateral locations. Consequently, diastolic delay and propagation velocity estimation was problematic. These results likely can be explained by the passive nature of diastolic relaxation. As no subsequent action potential actively stimulates repolarization, the cellular mechanisms of diastolic repolarization occur in a less spatially coordinated manner [39]. As a result, myocardial relaxation may not follow the exact same propagation paths as during contraction. However, additional experiments are necessary to investigate this phenomenon before more definitive conclusions can be made.

As previously mentioned, all ARFI-induced displacement plots contained a brief time delay after application of the stimulating pulse to the onset of myocardial stiffening and contraction. This delay is believed to be associated with the temporal lag between the location of the pacing source and the M-mode lines. However, the same delay cannot be observed within the other electromechanical plots, as strain rates
and tissue velocities at the M-mode line proximal to the pacing source begin to fall nearly with the stimulating pulse. This apparent lack of delay could be attributed as a consequence of both strain rate and tissue velocity imaging being motion-based algorithms. As a result, these measurements are derived from observing changes in myocardial fiber lengths and thicknesses as the muscle contracts and relaxes. With this transducer orientation and by performing only 1-D (axial) tracking, myocardial strains and velocities measured within these acquisitions were predominantly due to myocardial wall thickening. However, as no one myocardial fiber can move independently of another, the strain rate and tissue velocity estimates made within these experiments were likely influenced by motion from adjacent regions that propagated through the heart at bulk wave speeds that are significantly higher than electrical propagation velocities.

ARFI imaging may experience a similar effect in the presence of bulk changes in myocardial elasticity from surrounding tissue. However, the observable delays between the application of the stimulating pulse and the onset of myocardial stiffening within the ARFI-induced displacement plots suggest that these effects occur on a smaller scale, and therefore ARFI imaging may be better suited to make high spatial resolution images of electromechanical propagation. The strain rate and tissue velocity estimates made in these experiments were calculated using rudimentary algorithms, and more sophisticated ones may be able to account for these neighboring effects and improve spatial resolution.

The research presented propagation velocities only in the lateral dimension. In order to obtain additional information and increase its applicability, two-dimensional or full three-dimensional stiffness propagation maps are preferred. Although not performed in this study, axial stiffness tracking can be achieved by selecting an appropriate ARFI-excitation F/# so that the depth of view could span the entire thick-
ness of tissue. Elevational stiffness tracking can be achieved with three-dimensional ARFI imaging. Preliminary research into 3-D ARFI imaging has been performed with promising results [30]. However, frame and sampling rates must be considered when forming ARFI images with sufficient temporal resolution necessary to predict electromechanical propagation.

Acknowledgements

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Chapter 6

ARFI imaging of myocardial performance

6.1 Introduction

Cardiovascular disease is the primary cause of death in the United States, accounting for over 800,000 deaths in 2004 [5]. Myocardial stiffness changes have been associated with virtually every form of cardiac disease. As a result, many studies have measured myocardial stiffness to determine and diagnose various forms of myocardial dysfunction or abnormalities. Several studies have shown increased stiffness to be an indication of infarcted, ischemic, and ablated myocardium [32, 42, 63, 89, 105]. Additionally, increased myocardial stiffness has been correlated with both systolic and diastolic heart failure [10, 50, 122].

Current clinically accepted methods for determining myocardial stiffness measure a corollary metric known as elastance. Myocardial elastances are derived from parametric analysis of the pressure-volume (PV) relation within the left ventricle [69]. However, elastances are measured by tracking incremental changes in the PV relation caused by an external stimulus through multiple heartbeats, thus lacking the robustness and practicality for general use. Alternative methods for measuring myocardial stiffness and elasticity have been investigated with varying degrees of
success. Elastography-based strain and strain rate imaging as well as tissue velocity or Doppler imaging have shown great promise in evaluating regional and global cardiac function [2, 17, 57, 60]. However, these methods often require finite element modeling techniques and high quality three-dimensional image data and have not found widespread clinical applications to date.

Initial investigations into cardiac acoustic radiation force impulse (ARFI) imaging were directed towards the visualization of radiofrequency ablation lesions within myocardium [24, 44]. These studies employed ARFI imaging sequences that gated acquisitions off the global electrocardiogram (ECG) to synchronize long (∼200 ms) acquisitions to late diastole and periods of the cardiac cycle where physiological motion artifacts are minimized. Also during late diastole, the myocardium was relaxed and therefore more compliant, resulting in greater ARFI-induced displacements and higher signal to noise ratios (SNRs) within the images.

In order to repeatedly form high resolution ARFI images at all points of the cardiac cycle, ARFI imaging sequence advancements were made to increase spatial and temporal resolution while mitigating thermal safety concerns [11, 16, 43]. These advancements and the resultant ARFI images have been detailed in the previous chapters of this thesis. As ARFI imaging has been shown to be capable of measuring myocardial stiffness through the cardiac cycle, beat-to-beat variations within the ARFI-induced displacement curves could provide corollary insight into myocardial performance and function. In fact, ARFI imaging may be able to provide additional information into myocardial performance over PV analysis due to its ability to continuously image local spatial variations in stiffness across many heartbeats. In this chapter, the preliminary investigations into the feasibility of ARFI imaging to measure myocardial performance are presented.
6.2 Methods

6.2.1 Imaging Methods

The Siemens SONOLINE Antares (Siemens Medical Solution, USA, Ultrasound Division, Issaquah, WA) platform was used with the VF10-5, linear handheld probe. The transducer was placed in a vacuum apparatus to minimize physiological motion artifacts within the field of view. While holding the transducer in place by hand, this vacuum apparatus helped the transducer maintain a single imaging plane through the heart during the entire cardiac cycle.

The Siemens Ultrasonic Research Interface™ was used to record in-phase (I) and quadrature (Q) data from the received echoes. The ARFI imaging acquisition sequences used in these experiments were single-line versions of the extended ECG-gated M-mode ARFI imaging acquisitions outlined in Chapter 4. With these sequences, seventeen heartbeats were interrogated on every other beat (nine total) at B-mode and ARFI imaging frame rates of twenty-four samples per beat. With a baseline heart rate of 100 beats per minute, this corresponded to a sampling rate of 40 Hz. The lateral and axial fields of view for the B-mode images were 3.8 cm and 6.0 cm, respectively. Specific ARFI imaging sequence specifications are provided in Table 6.1.

6.2.2 Displacement estimation

The I/Q data were used to estimate tissue displacements within the image using an autocorrelation phase shift estimation algorithm [48]. Displacement discontinuities within the data greater than a half wavelength (58 µm) between successive frames were considered to be aliasing errors, and all displacement estimates measured
after these temporal discontinuities were shifted a full wavelength in the opposite direction. ARFI-induced displacement curves were generated by taking displacements measured 0.71 ms after cessation of the radiation force pulse. ARFI-induced displacement curves were also temporally low-pass filtered with a mean filter using a 5.8 ms kernel.

### 6.2.3 Physiological Motion Filters

An interpolation-based quadratic motion filter was used to remove physiological motion artifacts within the displacement estimates. The quadratic motion filter used four pre-excitation displacement estimates, made within a 0.33 ms tracking interval, along with post-excitation displacement estimates made within a 0.49 ms tracking interval, and after a 3.4 ms end-time threshold. In total, ten displacement estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARFI imaging PRF</td>
<td>24 samples/beat</td>
</tr>
<tr>
<td>Tracking PRF</td>
<td>9.1 kHz</td>
</tr>
<tr>
<td>Number of pre-excitation tracking lines</td>
<td>4</td>
</tr>
<tr>
<td>Number of post-excitation tracking lines</td>
<td>37</td>
</tr>
<tr>
<td>Transmit focus</td>
<td>1.5 cm</td>
</tr>
<tr>
<td>Transmit F/#</td>
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</tr>
<tr>
<td>Frequency</td>
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</tr>
<tr>
<td>Pulse length</td>
<td>0.2 µs</td>
</tr>
<tr>
<td>Focus</td>
<td>1.5 cm</td>
</tr>
<tr>
<td>F/#</td>
<td>1.5</td>
</tr>
<tr>
<td>Frequency</td>
<td>6.67 MHz</td>
</tr>
<tr>
<td>Pulse length</td>
<td>45 µs</td>
</tr>
</tbody>
</table>
(4 pre-excitation, 6 post-excitation) were used by the quadratic motion filter to approximate and remove physiological motion artifacts within the ARFI images.

6.2.4 Left ventricular volume extrapolation

The endocardial surfaces of the left ventricle of both the left ventricular (LV) free wall and interventricular septum were detected from the B-mode images using a brightness thresholding algorithm. The number of pixels ($N$) between these two detected boundaries, scaled by the lateral and axial spacings ($dx$ and $dz$, respectively) of the B-mode image, was used to estimate the cross-sectional area of the left ventricle within the field of view. From these cross-sectional area estimates, left ventricular volumes ($V$) were extrapolated using the following equation:

$$V = \frac{4}{3\sqrt{\pi}} (N \cdot dx \cdot dz)^{\frac{3}{2}},$$

which assumes an ellipsoid left ventricular geometry and an elevational radius equaling the geometric mean of the other two radii.

6.3 Experimental Procedure

The heart of an ovine subject was imaged under an open chest preparation. A left thoracotomy was performed and the pericardium was cut away. The transducer was inserted into a vacuum apparatus and placed directly onto the left ventricular epicardium, along the long axis of the heart. A Millar Instruments (Houston, TX) pressure catheter was inserted directly into the left ventricle via a trochar puncture at the apex. A pacing wire was sewn onto the left atrium of the exposed heart, close to the sinoatrial node. This pacing wire was used to atrially pace the heart at rates
above 100 beats per minute (bpm) and above the normal sinus rhythm of the heart.

6.3.1 ARFI imaging of the cardiac cycle

The heart was paced at a specific heart rate for a minute before images were formed. B-mode and single-line M-mode ARFI images were acquired using the extended ECG-gated extended M-mode ARFI imaging sequences described in Chapter 4. These acquisitions were first performed using passive ARFI imaging sequences to determine the effectiveness of the physiological motion filter and characterize the amount of motion artifact within the ARFI images. Co-registered B-mode and active ARFI imaging sequences were acquired while simultaneously recording left ventricular pressures, the global ECG, and the stimulating pulse voltages. Averaged ARFI-induced displacements across the nine alternate heartbeats within a 3.8 mm axial kernel from the epicardial surface of the LV free wall were calculated. The error bars in the subsequent ARFI-induced displacement plots correspond to the temporal variance between heartbeats. The displacement plots were then temporally registered with the LV pressure, LV volume, and global ECG waveforms. The waveforms were examined and compared through the entire cardiac cycle.

6.3.2 ARFI imaging of left ventricular function

While still pacing atrially, baseline ECG-gated extended M-mode ARFI images of the LV free wall were acquired. Four factors that determine myocardial performance (preload, afterload, heart rate, and contractility) were independently varied, and the subsequent ARFI images were inspected for changes from the baseline measurements that could be attributed to changes in LV function. Each of the four factors was individually varied while holding the other three variables constant. Also, the heart
was given adequate time to return to a new baseline state between each experiment and new baseline ARFI-induced displacement curves were re-acquired for each case.

Heart rate was varied by increasing the pacing rate of the external stimulus from the baseline 100 bpm to 120 bpm and 150 bpm. The heart was given a minute at each heart rate to adjust before the ARFI images were acquired. To vary preload, surgical tape was placed around both superior and inferior venae cavae, close to the entrance of the right atrium. The tape was pulled upwards, thereby occluding venous flow to the right side of the heart and decreasing preload. The afterload was increased with a phenylephrine drip (10 µg/kg/min), infused intravenously. ARFI images were acquired after sufficient time was given for the drip to take effect. Finally, contractility was increased via a single intravenous injection of a bolus of calcium chloride (15 mg/kg). Again, sufficient time was given for the inotropic agent to take effect before ARFI images were acquired.

6.3.3 ARFI imaging comparison with PV analysis

Incrementally varied PV loops were formed on every other heartbeat across 17 beats (9 total) by venal caval occlusions. The upper-left most points of these loops were used to determine the end-systolic pressure volume relation (ESPVR), while the bottom-rightmost points were used to determine the end-diastolic pressure volume relation (EDPVR). Linear regressions were performed on these relations where the slopes of these regressions yielded the end-systolic and end-diastolic elastances.

The average ARFI-induced displacements for these nine heartbeats were also measured. The relative times within the cardiac cycle of end-systole and end-diastole were determined from the PV data and used to determine the average end-systolic and end-diastolic displacement estimates. As ARFI-induced displacements are inversely related to stiffness, a systolic to diastolic stiffness ratio was estimated by
taking a ratio of the inverse ARFI-induced displacements at these points.

### 6.3.4 Non-invasive ARFI imaging of myocardial stiffness

A closed chest *canine* subject was anesthetized and placed on a surgical table in a prone position. The table had an opening at the bottom that allowed transthoracic imaging of the heart from below the animal. With the transducer held in place by hand, passive and active single-line M-mode ARFI images of the left ventricular free wall were acquired at a transmit focus of 2.0 cm. The global ECG was also recorded and temporally registered with the ARFI images. Respiration was controlled and temporarily halted during each ARFI imaging acquisition. Passive and active M-mode ARFI images were compared and inspected for indications of changing myocardial stiffnesses. Due to increased physiological motion and jitter within the ARFI images associated with transthoracic imaging, displacement estimates were masked at pixels whose variance in displacement estimates measured after the end-time threshold exceeded $1\mu m^2$.

### 6.4 Results

#### 6.4.1 ARFI imaging of the cardiac cycle

An assessment of the amount of motion artifact within the ARFI images is shown in Figure 6.1. Using a passive ARFI imaging sequence, the performance of the motion filter was reflected by the levels of residual displacement within the M-mode displacement plot. The absolute residual displacement plot in Figure 6.1b indicates that physiological motion artifacts were reduced to below $0.2\mu m$ at all points of the cardiac cycle. As all ARFI images presented in this chapter were acquired and
Figure 6.1: Absolute residual displacements from a passive, single-line extended M-mode ARFI image of an ovine left ventricular free wall. (a) The B-mode image, formed along the long axis of the left ventricle, shows the lateral position and region of interest of the single M-mode line. With the global ECG shown below, (b) the absolute residual displacements plot indicates motion artifacts within the ARFI imaging acquisitions were small and below 0.2 µm through all points of the cardiac cycle.

processed using a single protocol, residual displacements presented in Figure 6.1 are likely to reflect the levels of motion artifact in all subsequent ARFI images.

Also, the matched global ECG in Figure 6.1b contains a pacing artifact at times when the external pacing stimulus was applied. As the pacing wire was positioned atrially, this artifact coincided with atrial systole and supplanted the P-wave normally present within the standard ECG. Instead, a waveform that more resembled a QRS complex was recorded. This pacing artifact was observed in all global ECG measurements made within these experiments.

The average left ventricular pressure, left ventricular volume, ARFI-induced displacements within the left ventricular free wall, and global electrocardiogram through a single cardiac cycle are shown in Figure 6.2. The lateral position and regions
Figure 6.2: (b) LV pressure, (c) LV volume, (d) ARFI-induced displacement within left ventricular myocardium, and (e) global ECG plots through a single cardiac cycle. The lateral position and regions of interest of the M-mode line are marked within (a) the matched B-mode image taken at t=0 and from the first recorded heartbeat. The four phases of the cardiac cycle, isovolumic contraction (red diamonds), ejection (pink squares), isovolumic relaxation (blue triangles), filling (cyan circles), and their transition points (black xs) were identified from PV analysis and labeled accordingly in each plot.

of interest for the ARFI-induced displacement plot are shown in the B-mode image in Figure 6.2a. Left ventricular pressure and volume curves, shown in Figure 6.2b-c, can be seen to exhibit normal pressure-volume behavior, as the maximum changes in pressure correlated with periods of nominal changes in LV volume and vice versa. Meanwhile, ARFI-induced displacements can be observed to be inversely related to LV pressures, as increases in pressure were accompanied by decreases in ARFI-induced displacements during ventricular systole while the opposite trend was apparent during diastole.
Figure 6.3: Parametric pressure, volume, and inverse ARFI-induced displacement plots of the cardiac cycle. (a) The traditional pressure-volume loop of normal left ventricular function, proceeding in a counterclockwise manner, provides insight into the segmentation of the cardiac cycle into its four phases: isovolumic contraction (red diamonds), ejection (pink squares), isovolumic relaxation (blue triangles), filling (cyan circles), and the transition points (black xs). (b) A three-dimensional parametric plot including inverse ARFI-induced displacements provides an indication of the changes in myocardial elasticity through the cardiac cycle.

From parametric PV analysis, shown in Figure 6.3a, the four phases of the cardiac cycle were determined and segmented by their respective shapes and colors in all subplots of both Figures 6.2 and 6.3. A three-dimensional parametric representation of the three temporally registered plots in Figure 6.2b-d is also provided in Figure 6.3b. Inverse ARFI-induced displacements are plotted to provide a more direct representation myocardial stiffness.

From these plots, LV pressures can be seen to have increased rapidly through isovolumic contraction (red diamonds) and reached its maximum steady-state pressure at the end of this phase. These increased pressures were maintained through the entire next phase of ejection (pink squares). Similarly, the ARFI-induced displacements fell during isovolumic contraction and varied little through ejection. However,
unlike LV pressure, the steady-state minimum ARFI-induced displacement was not achieved at the transition point between isovolumic contraction and ejection; rather, it occurred shortly before the end of isovolumic contraction. During diastole, a pressure decrease through isovolumic relaxation (blue triangles) was accompanied by an increase in the ARFI-induced displacements. LV pressures remained relatively constant through filling (cyan circles) and reached a minimum value at the middle of filling. In contrast, the ARFI-induced displacements continued to rise through filling and achieved a maximum value at the onset of isovolumic contraction.

### 6.4.2 ARFI imaging of left ventricular function

A complete summary of results of each factor of left ventricular function and their effects on the end-systolic and end-diastolic stiffnesses and the rate of systolic stiffening, as determined by ARFI imaging, is presented in Table 6.2.

<table>
<thead>
<tr>
<th>Parameter Change</th>
<th>Heart Rate</th>
<th>Preload</th>
<th>Afterload</th>
<th>Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-systolic stiffness</td>
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<td>⇓</td>
<td>⇑</td>
<td>⇑</td>
</tr>
<tr>
<td>End-diastolic stiffness</td>
<td>⇑</td>
<td>⇓</td>
<td>⇓</td>
<td>nc</td>
</tr>
<tr>
<td>Systolic stiffening rate</td>
<td>⇓</td>
<td>⇓</td>
<td>⇑</td>
<td>nc</td>
</tr>
</tbody>
</table>

Table 6.2: ARFI imaging of myocardial function summary. (nc = no change)

The ARFI-induced displacement plots within the left ventricular free wall at various heart rates are shown in Figure 6.4b. As the variable heart rates produced three global ECGs of three different durations, these plots were aligned via their QRS complexes so that end-diastole and ventricular systole were temporally registered. The global ECG at the bottom of Figure 6.4b corresponds to the acquisition made at a heart rate of 150 bpm.

The end-systolic ARFI-induced displacements for all three curves were similar,
Figure 6.4: Single-line M-mode ARFI imaging at increasing heart rates. The lateral location and region of interest are marked within (a) the B-mode image. (b) ARFI-induced displacement plots reflect left ventricular function at three different heart rates: 100 (blue plot), 120 (green plot), and 150 (red plot) beats per minute. The three displacement plots were temporally registered at the QRS complex and the matched ECG shown below the plots corresponds to the 150 bpm acquisition. The ARFI-induced displacement plots indicate that the end-systolic displacement was unaffected by heart rate, while the end-diastolic displacements decreased with increasing heart rates.

indicating that the end-systolic stiffness was independent of heart rate. Perhaps the most noticeable difference between the three curves was in the maximum ARFI-induced displacement at end-diastole. As the heart rate increased, this value decreased, suggesting an increase in the end-diastolic stiffness. The rates of systolic stiffening also appeared to decrease with increasing heart rate as the slopes of the displacements falling during ventricular systole decreased.

Single-line M-mode ARFI-induced displacement plots before and after decreasing preload are shown in Figure 6.5. Again, the end-systolic displacement estimates appeared similar in both ARFI-induced displacement curves, indicating that the
end-systolic stiffness was preload independent. End-diastolic displacements were slightly higher than the baseline measurements, suggesting that the end-diastolic stiffness decreased with smaller preloads. The rate of systolic stiffening appears also to be lower at decreased preloads as the end-systolic displacement was achieved later in time than the baseline.

The ARFI-induced displacement curves, before and after increasing afterload, are shown in Figure 6.6. The end-systolic stiffness appeared unaffected, as the minimum ARFI-induced displacements were similar between the two plots. Also, the end-diastolic displacements were higher after increasing afterload than measured in the baseline case. A sharper drop in ARFI-induced displacements was also observed.
Figure 6.6: Single-line M-mode ARFI imaging of increased afterload via an intravenous phenylephrine drip. The lateral location and region of interest of the M-mode ARFI line are shown in (a) the matched B-mode image. (b) ARFI induced displacement plots from the baseline (blue plot) to increased afterload (green plot) indicate that the end-diastolic stiffness has decreased while the rate of systolic stiffening has increased. Myocardial elasticity at end-systole appears unchanged after an increase in afterload.

during myocardial contraction, suggesting the rate of systolic stiffening increased.

The changes in myocardial left ventricular function due to an increase in contractility are reflected within the two ARFI-induced displacement plots in Figure 6.7. Both displacement plots had similar end-diastolic displacements, indicating that the diastolic stiffness was unaffected by the calcium chloride injection. The rates of systolic stiffening between the two curves also appeared to be similar. However, the baseline ARFI-induced displacement curve reached its minimum value and then slowly began to rise. The increase in contractility was reflected in the post-injection (green) plot by a continuing decline in displacements up to the T-wave and the onset of ventricular repolarization.
Figure 6.7: Single-line M-mode ARFI imaging of increased contractility due to an injection of calcium chloride. (a) The B-mode image indicates the lateral location and region of interest for (b) the ARFI-induced displacement plots. When comparing the baseline (blue plot) and increased contractility curves (green plot), diastolic ARFI-induced displacements and the systolic rates of stiffening appear unaffected. However, the end-systolic displacements are lower, indicating that the stiffness of the contracted myocardium has increased with increased contractility.

6.4.3 ARFI imaging comparison with PV analysis

A comparison between systolic and diastolic ratios of stiffness and elastance is shown in Figure 6.8. Multiple PV loops are shown with the ESPVR and EDPVR (red dashed lines) marked in Figure 6.8a. The end-systolic and end-diastolic elastances were then calculated from these relations to be 1.28 mmHg/mL and 0.65 mmHg/mL, thereby resulting in a systolic to diastolic elastance ratio of 1.96. The corresponding average ARFI-induced displacement plot is shown in Figure 6.8b. The average end-systolic and end-diastolic ARFI-induced displacements were measured to be 6.22 and 10.82 µm, respectively. From these data, a systolic to diastolic stiffness ratio
Figure 6.8: ARFI imaging comparison with PV analysis. With (a) pressure-volume analysis, the end-systolic and end-diastolic pressure-volume relations (red dashed lines) can be determined with an end-systolic to end-diastolic elastance (slope) ratio of 1.96. From (b) the ARFI-induced displacement curves, a similar end-diastolic to end-systolic ARFI-induced displacement ratio of 1.74 is measured.

was measured to be 1.74.

6.4.4 Non-invasive ARFI imaging of myocardial stiffness

Passive and active single-line M-mode ARFI images of a canine left ventricular free wall are shown in Figure 6.9. The lateral location and region of interest are marked within the matched B-mode image in Figure 6.9a. The traditional M-mode images in Figure 6.9b and f display similar changes in myocardial wall thicknesses through the cardiac cycle. By matching each M-mode image with their respective ECGs in Figure 6.9e and i, a single phase of left ventricular wall thickening can be seen to occur coincident with the onset of the QRS complex. Additionally, two phases of wall thinning can be observed: one shortly after the T-wave and the other coincident with the P-wave. These two phases can be used to demarcate early (passive) and late (atrial) filling, respectively.

The absolute residual displacement image and plot in Figure 6.9c-d, respectively,
Figure 6.9: Passive and active transthoracic M-mode ARFI images of a canine left ventricular free wall. (a) The corresponding B-mode image displays a near long-axis cross section of the left ventricle with the left ventricular free wall spanning approximate axial depths between 1.2-2.0 cm. The lateral location and region of interest of the ARFI-induced displacement plots are also marked. (b and f) Traditional M-mode images show motion of the left ventricular free wall with two horizontal lines within the image marking the ARFI imaging region of interest. From the passive ARFI imaging sequence, (c) The absolute residual displacement image shows motion artifacts were small, and (d) the absolute residual displacement plot suggests that motion artifacts within the region of interest were below 0.5 $\mu$m at all points of the cardiac cycle. The active ARFI-induced displacement (g) image and (h) plot reflect cyclic activity inside the left ventricular free wall with larger displacements at diastole and smaller displacements at systole. (e and i) The matched ECGs for each acquisition are shown below.

indicated that motion artifacts were generally small, but increased at the onset of ventricular systole and during early filling. Nevertheless, motion artifacts were filtered to below 0.5 $\mu$m at all points of the cardiac cycle. Therefore, the nearly 2 $\mu$m systolic to diastolic variation in ARFI-induced displacements observed within the
active ARFI image in Figure 6.9g were likely the result of variations in myocardial stiffnesses through the cardiac cycle. As observed in all of the M-mode images presented in this thesis, ARFI-induced displacements were measured to be larger at diastole and smaller at systole, indicating that the myocardium was stiffer during systole and more compliant during diastole. The same trend can be observed within the matched ARFI-induced displacement plot in Figure 6.9h. Average diastolic and systolic ARFI-induced displacements were measured to be $2.44 \pm 0.09 \mu m$ and $0.44 \pm 0.04 \mu m$, respectively. These values produced a non-invasively acquired systolic to diastolic stiffness ratio of 5.5.

6.5 Discussion and Conclusions

A parametric analysis between temporally registered LV pressure, LV volume, and ARFI-induced displacement curves related myocardial stiffness to the four phases of the cardiac cycle. The parametric plots of these data indicated that the changes in myocardial stiffness generally followed the changes in LV pressures, as ARFI-induced displacements fell during isovolumic contraction and rose during isovolumic relaxation. However, the plots also showed that the steady-state ARFI-induced displacement through ejection was reached before the end of isovolumic contraction, while LV pressures continued to climb. Further, ARFI-induced displacements continued to rise through all of filling, while LV pressures remained relatively constant. These results suggest that myocardial stiffness and LV pressure, although related, are not exact analogues to each other.

Changes within the ARFI-induced displacement curves reflected changes in LV function as observed when altering four factors of myocardial function in these experiments. More encouragingly, the results presented in this chapter can generally
be corroborated by previous investigations and theories of myocardial elastance and LV function [29,70,78]. For end-systolic stiffnesses, the only change apparent within the ARFI images was a decrease in ARFI-induced displacements at end-systole with increased contractility. This result is consistent with previous research that used PV analysis to demonstrate that the end-systolic elastance was independent of load and heart rate and increased with an increase in contractility [35,96].

The Frank-Starling law of the heart states that the stroke volume is proportional to the load encountered by the heart at end-diastole [1,14,56]. As the end-systolic elastances and stiffnesses appear to be load independent, variations in stroke volume are unlikely to be a result of varying degrees of myocardial stiffening. However, an alternative method that could result in changes in stroke volume is from a change in the rates of systolic stiffening. Accordingly, studies have shown that slower heart rates had decreased ejection velocities and smaller stroke volumes [113]. The authors hypothesize that this relation can be observed within the rates of systolic stiffening within the ARFI-induced displacement curves. These rates decreased with smaller preloads and increased with larger afterloads. Likewise, as the load remained unchanged with increased contractility, the rate of systolic stiffening was also unchanged. As myocardial elastances are typically calculated only at end-systole and end-diastole, these rates of myocardial stiffening were previously unavailable. As a result, the ARFI imaging-determined changes in the rates of systolic stiffening cannot be corroborated by any previous PV analysis-based experiments.

At increased heart rates, a decreased rate of systolic stiffening was accompanied with an increase in the end-diastolic stiffness. We hypothesize that these are complementary phenomena, both reflecting the Frank-Starling law of the heart. An increase in heart rate resulted in a shortening in the periods of isovolumic relaxation and filling, thereby restricting the amount the myocardium could relax within that
time interval. As a result, the myocardium was unable to fully relax and appeared stiffer at end-diastole. The shortened relaxation times and stiffer myocardium resulted in a smaller end-diastolic volume and reduced load on the heart. Accordingly, the Frank-Starling law predicts a reduction of stroke volume, which may be reflected by the observed decrease in systolic stiffening rates.

As exponential functions are typically used to approximate the EDVPR, the end-diastolic elastances are believed to be proportional to load [13]. This relationship can be seen within the results presented in this chapter as the end-diastolic ARFI-displacements after decreasing preload were measured to be slightly higher than the baseline acquisition. As an increase in contractility should not affect the load, the end-diastolic ARFI-induced displacements were similar between the plots before and after injection of calcium chloride. However, an increase in the end-diastolic ARFI-induced displacement was also observed in Figure 6.6 with an increase in afterload. This result implies that the myocardium was more compliant with increased afterload and therefore is contradictory to the preload results and previous diastolic PV investigations. Additional studies are necessary to investigate this discrepancy.

The systolic to diastolic elastance and stiffness ratios were shown to be comparable, further suggesting that the two may be similar metrics. However, neither method produces a ratio that exactly reflects the actual myocardial stiffness ratio between systolic and diastolic elastic moduli. PV analysis measures chamber pressures and volumes without any interrogation of the myocardial tissue itself. Consequently, elastances are indirect measures of myocardial properties and stiffness. Although ARFI imaging measures displacements within myocardial tissue, an exact correlation between ARFI-induced displacement and stiffness is unknown. Previous studies have demonstrated that the displacement estimates within the ARFI images are affected by both ARFI imaging sequence parameters and tissue properties, and therefore any
displacement ratio using these data is an approximate stiffness ratio [85,86].

The transducer was not removed from the heart for each before and after acquisition and the two were acquired shortly after one another. Therefore, the authors hypothesize that the repeatability of the ARFI imaging acquisitions was sufficient to allow the comparisons made within this chapter. However, as the transducer was removed between acquisitions and an appreciable amount of time elapsed between experiments, a degree of variability between the ARFI-induced displacement plots makes inter-experimental comparisons problematic. This can be seen in the variations between the four baseline ARFI-induced displacement plots. These variations can be attributed to many factors including transducer position and orientation as well as the progression of myocardial performance through each experiment. Therefore, inter-experimental comparison of ARFI-induced displacement data was not performed.

Similarly, PV comparisons between acquisitions also produced inconsistent results as the long axis was difficult to maintain through the experiments and therefore were not presented. It is likely that improved and repeatable registration of the transducer onto the surface of the heart and the maintenance of a single orientation would ensure a single alignment of the imaging plane and produce better results. Expansion of these imaging methods to three-dimensional imaging would be better suited for estimating left ventricular volumes and would therefore provide a more accurate comparison between PV analysis and ARFI imaging.

The transthoracic M-mode ARFI images in Figure 6.9 demonstrate the feasibility of non-invasively measuring these potential myocardial performance metrics. These non-invasive M-mode ARFI images demonstrated the same cyclic variations in ARFI-induced displacements with sufficient filtering of motion artifacts. The active M-mode ARFI images estimated a 5.5:1 stiffness ratio that was comparable to
the 5.3:1 myocardial stiffness ratio, calculated epicardially in another canine heart in Chapter 3. However, the transthoracic ARFI-induced displacement plots did not entirely match those acquired epicardially, as the drop in ARFI-induced displacements and indication of myocardial stiffening appeared to occur after the P-wave and not with the onset of the QRS complex. This observation may be an artifact of cardiac motion or the reorientation of the myocardial fibers with respect to the transducer. Another explanation is that the myocardium could be stiffening passively due to an increase in left ventricular pressure during atrial contraction. Studies modeling myocardial elasticity with active and passive components predict a degree of diastolic stiffening as a result of an increase in left ventricular pressure at the end of filling [68, 102, 120, 121]. However, additional ARFI imaging research and sequence developments are necessary to better characterize this phenomenon.

A clear advantage of ARFI imaging over PV analysis is in its simpler method of interrogation. PV analysis requires an external modification of the operating conditions of the heart in order to incrementally vary the PV loops. Also, elastances are calculated across multiple heartbeats and only at end-systole or end-diastole. Fundamentally, ARFI imaging of a single heartbeat is capable of producing ARFI-induced displacement curves through the entire cardiac cycle. By continuously sampling through the cardiac cycle and across multiple heartbeats, ARFI imaging is capable of providing additional insight into myocardial performance not previously available with traditional PV analysis. Therefore, with the potential of non-invasive methods of acquisition and the presented advantages over PV analysis, ARFI imaging may provide a better and more clinically useful estimate of myocardial performance.
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Chapter 7

Conclusions and future work

7.1 Conclusion

We have demonstrated the feasibility of cardiac ARFI imaging. The ARFI-induced displacement plots and images presented in this thesis exhibited cyclic variations that reflected the changing elasticity of the heart through the cardiac cycle. The ARFI imaging-observed increases in myocardial stiffness was correlated with myocardial contraction and the systolic periods of the ECG. Also, ARFI imaging was able to distinguish an ablation lesion within myocardium by showing that the ARFI-induced displacements inside the lesion did not vary through the cardiac cycle as much as the surrounding, untreated myocardium.

Novel ARFI imaging sequences were developed in order to perform more quantitative ARFI imaging-based investigations of the heart. These sequences used parallel-receive, parallel-transmit excitation, parallel-transmit tracking, ECG-gating, multi-beat synthesis, and multiplexing to form high quality, high resolution ARFI images of the heart at all points of the cardiac cycle. The resultant ARFI-induced displacement curves provided new and previously unavailable information into the changing mechanical properties of myocardium. The accuracy of ARFI-induced displacement estimation was also increased. With these new sequences and improved ARFI imaging techniques, the application of ARFI imaging for the measurement of myocardial
performance was investigated.

ARFI imaging was able to determine a direction and velocity of propagation of mechanical stiffness through the myocardium. The measured velocities of myocardial stiffness propagation were comparable to typical values of measured electrical conductance velocities [9]. The measured epicardial electrophysiological wave propagation matched the direction of propagation of the stiffness waves, and the propagation velocities of the mechanical stiffness waves were observed to be comparable to, but slightly slower than, the electrical propagation velocities. From these results, we believe ARFI imaging is capable of measuring myocardial stiffness propagation through the heart and therefore a promising imaging modality to track an electromechanical wave that follows the electrical activation propagation within the heart.

Changes within the ARFI-induced displacement plots reflected changes in left ventricular function and myocardial performance. A parametric analysis of left ventricular pressure, volume and ARFI imaging-based stiffness revealed that myocardial stiffening occurred during isovolumic contraction while myocardial relaxation occurred during both isovolumic relaxation and filling. A comparison of ARFI imaging with pressure-volume analysis demonstrated that these two methods produced similar results. Also, the introduction of observing stiffening rates may provide previously unavailable insight into myocardial performance. Therefore, although additional investigations are necessary, we believe ARFI imaging to be a viable alternative to PV analysis in determining myocardial performance with the potential of becoming less invasive with greater accuracy.
7.2 Continuing Efforts

7.2.1 Continued Animal Studies

The results presented in this dissertation came from limited number of animals and only a single animal was imaged for the results presented in Chapter 6. Repeated \textit{in vivo} epicardial experiments with \textit{ovine} and \textit{canine} hearts are necessary to investigate the repeatability and widespread validity of these results. Further refinement of the acquisition methods to allow for better comparison with PV analysis is also necessary. Also, as a long-term goal of this research is the non-invasive acquisition of these ARFI images, continued transthoracic ARFI imaging studies will be performed, and the feasibility of intracardiac ARFI imaging of myocardial performance will be explored. The introduction of a catheter into the heart to acquire ARFI images would not increase the invasiveness of this procedure above PV analysis, as left ventricular pressures are also measured internally with the introduction of an intracardiac probe. Several studies have shown the utility of intracardiac echocardiography (ICE) for a variety of cardiac applications \cite{94, 101, 108, 116}, and initial investigations into intracardiac ARFI imaging have produced high-resolution ARFI images of the heart \cite{44}. Therefore, a comparison of transthoracic, intracardiac, and epicardial ARFI imaging methods will be performed in future animal studies.

7.2.2 Motion Filter Optimization

Current motion filtering techniques have been demonstrated to be capable of reducing physiological motion artifacts to a non-factor while imaging epicardially. However, the expansion of these techniques for non-invasively acquired ARFI images along with the progressing trend towards quantitative cardiac imaging dictate the
need for more robust and effective motion filters.

Little analysis has been performed for these interpolation-based motion filters in regards to the optimization of end-time thresholds as well as the pre- and post-excitation tracking intervals. Adaptive motion filters that take into account SNR, decorrelation, the global ECG, and the levels of physiological motion may prove to be critical to the success of non-invasive cardiac ARFI imaging. Additionally, current interpolation-based motion filters are pixel-by-pixel algorithms and therefore do not rely on any spatial information and other physiological motion estimates from surrounding pixels. Investigations into the characterization of cardiac motion and the potential of developing a spatially-interpolative motion filter are currently underway. Unlike the motion filters used in this thesis, these spatially-based motion filters may have the potential benefit of not having the temporal restriction of full tissue recovery within the tracking interval. Consequently, ARFI imaging acquisitions can be sequenced with shorter acquisition times and at increased frame rates.

7.3 Future Work

7.3.1 Shear Wave Velocimetry

Although the ARFI-induced displacement plots revealed insight into the performance and changing elasticities within the heart, the observed variations between the baseline plots underline a fundamental shortcoming of these analyses. Current methods of ARFI imaging cannot produce a quantitative measurement of stiffness, such as elastic modulus. Therefore, comparisons and interpretations of these displacement data are best performed relatively and without an absolute, quantitative metric of myocardial stiffness. A stiffness ratio was introduced in an attempt to
quantify a stiffening factor. However, as myocardial stiffness may change during systole, diastole, or both, variations within this ratio cannot be correlated directly to a stiffness change from a single event.

Alternative methods of radiation force imaging have measured shear wave propagation velocities to determine a material’s shear modulus, which can be converted to an elastic modulus, depending on tissue geometry and certain underlying assumptions [8, 81, 82, 98]. However, applying these methods for myocardial characterization is challenging due to the complex geometry and anisotropic elasticity of the heart. Nevertheless, an imaging plane containing myocardial fibers that run parallel to the transducer face could produce repeatable estimates of maximum shear wave velocities within the field of view. Future work will focus on the use of shear wave velocimetry as a potential method for the estimation of a stable and repeatable metric of myocardial stiffness.

7.3.2 Active and Passive Stiffness

A desired trait for any metric of myocardial performance is an independence from load. Accordingly, the end-systolic pressure-volume relation, which is widely considered to be load independent, is used to determine systolic function. However, load independence is not observed in the end-diastolic pressure-volume relation and therefore the assessment of diastolic function with elastance is more problematic. Recent studies have modeled myocardial elastance as having active and passive components, with the influence of load affecting mostly the passive component [120, 121]. As a result, the active elastance component may become a load independent measure of myocardial performance through both systole and diastole. These studies have modeled the heart as a pressurized structure and assigned analytic relations between left ventricular pressures, volumes, and elastances in order to iteratively determine
active and passive elastances through the cardiac cycle.

A similar analysis of active and passive stiffness is being considered with ARFI imaging. As there is a difference in pressures internal and external to the heart, a pressure gradient through the thickness of the myocardium is present, thereby resulting in a theoretical gradient in passive stiffnesses. Future investigations will attempt to visualize this elasticity gradient and model the measured ARFI-induced displacements with active and passive components. The relationships of these components with load will then be examined.
Bibliography


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Biography

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Refereed Publications:


