Transthoracic Cardiac Acoustic Radiation Force Impulse Imaging

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 2013
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Abstract

This dissertation investigates the feasibility of a real-time transthoracic Acoustic Radiation Force Impulse (ARFI) imaging system to measure myocardial function non-invasively in clinical setting. Heart failure is an important cardiovascular disease and contributes to the leading cause of death for developed countries. Patients exhibiting heart failure with a low left ventricular ejection fraction (LVEF) can often be identified by clinicians, but patients with preserved LVEF might be undetected if they do not exhibit other signs and symptoms of heart failure. These cases motivate development of transthoracic ARFI imaging to aid the early diagnosis of the structural and functional heart abnormalities leading to heart failure.

M-Mode ARFI imaging utilizes ultrasonic radiation force to displace tissue several micrometers in the direction of wave propagation. Conventional ultrasound tracks the displacement response of the tissue to the force. This measurement is indicative of tissue stiffness, and it is repeated rapidly at a location through the cardiac cycle, recording relative changes in myocardial stiffness through time. ARFI imaging was previously shown capable of measuring myocardial properties and function via invasive open-chest and intracardiac approaches and is applied here via standard transthoracic echocardiography transducers and views.

The prototype imaging system described in this dissertation is capable of rapid acquisition, processing, display of ARFI images and shear wave elasticity imaging (SWEI) movies, and calculation of output measurement metrics. Presented in this
work is a rigorous safety analysis, including finite element method (FEM) simulations of tissue heating, hydrophone intensity and mechanical index (MI) measurements, and thermocouple transducer face heating measurements. For the pulse sequences used in later animal and clinical studies, results from the safety analysis indicates that transthoracic ARFI imaging can be safely applied at rates and levels realizable on the prototype ARFI imaging system.

Preliminary data are presented from in vivo trials studying changes in myocardial stiffness occurring under normal and abnormal heart function. Presented is the first use of transthoracic ARFI imaging in a serial study of heart failure in a porcine model. Results demonstrate the ability of transthoracic ARFI to image cyclically-varying stiffness changes in healthy and infarcted myocardium under good B-mode imaging conditions at depths in the range of 3–5 cm. Challenging imaging scenarios such as deep regions of interest, vigorous lateral motion and stable, reverberant clutter are analyzed and discussed.

Results are then presented from the first study of clinical feasibility of transthoracic cardiac ARFI imaging. At the Duke University Medical Center, healthy volunteers and patients having magnetic resonance imaging-confirmed apical infarcts were enrolled for the study. The number of patients who met the inclusion criteria in this preliminary clinical trial was low, but results showed that the limitations seen in animal studies were not overcome by allowing transmit power levels to exceed the FDA mechanical index limit. The results suggested the primary source of image degradation was clutter rather than lack of radiation force. Additionally, the transthoracic method applied in its present form was not shown capable of tracking propagating ARFI-induced shear waves in the myocardium.

Under current instrumentation and processing methods, results of these studies support feasibility for transthoracic ARFI in high-quality B-Mode imaging conditions to depths of 5 cm. Transthoracic ARFI was not shown able to discriminate infarct
from artifacts, or able to tracking progressive heart failure in the presence of clutter. This work does provide evidence that transthoracic ARFI imaging is a safe, non-invasive method, but clinical efficacy as a diagnostic tool will need to be addressed by further development to overcome current challenges and increase robustness to sources of clutter in transthoracic imaging.
to Laura.
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Abbreviations

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<td>ARF</td>
<td>acoustic radiation force</td>
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<td>ARFI</td>
<td>acoustic radiation force impulse</td>
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<td>B-Mode</td>
<td>brightness mode</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CDU</td>
<td>Cardiac Diagnostic Unit</td>
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<tr>
<td>CMR</td>
<td>cardiac magnetic resonance imaging</td>
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<tr>
<td>CNR</td>
<td>contrast-to-noise ratio</td>
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<tr>
<td>DOF</td>
<td>depth of field</td>
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<td>DUMC</td>
<td>Duke University Medical Center</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FEM</td>
<td>finite element method</td>
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<td>FOV</td>
<td>field of view</td>
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<td>FPS</td>
<td>frames per second</td>
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<tr>
<td>GUI</td>
<td>graphical user interface</td>
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<td>IACUC</td>
<td>Institutional Animal Care and Use Committee</td>
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<td>ICE</td>
<td>intracardiac echocardiography</td>
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<td>IEC</td>
<td>International Electrotechnical Commission</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
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</table>
IQ: in-phase and quadrature

\( I_{SPPA} \): spatial peak-pulse average intensity of an ultrasound pulse

IVS: intraventricular septum

LV: left ventricle/ventricular

LVFW: left ventricular free wall

M-Mode: motion mode

MI: mechanical index

MRI: magnetic resonance imaging

PV: pressure-volume

PHI: protected health information

PRF: pulse repetition frequency

PRI: pulse repetition interval

PVC: premature ventricular contraction

RF: radiofrequency

ROI: region of interest

ROE: region of excitation

SNR: signal-to-noise ratio

SWEI: shear wave elasticity imaging

TGC: time-gain compensation

TI: thermal index

TTE: transthoracic echocardiography

Symbols

\( c_o \): speed of sound

\( \rho_o \): material density

\( Z \): acoustic impedance
\( F \) radiation force
\( I \) temporal average acoustic intensity
\( \alpha \) acoustic amplitude attenuation coefficient
\( \lambda_u \) ultrasound wavelength
\( f_c \) center frequency of ultrasound pulse
\( T \) kernel size
\( BW \) fractional bandwidth of ultrasound transducer
\( \rho \) correlation between reference and tracked RF-data
\( F \) F/# of focal configuration \((F = \frac{z}{D})\)
\( z \) focal depth
\( D \) aperture size
\( c \) acoustic or compressional wave speed
\( c_T \) shear (or transverse) wave speed
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Introduction

1.1 Clinical Motivation and Significance

Cardiovascular disease remains the most likely cause of death in developed countries, accounting for more than 811,000 deaths in 2008 in the United States [100]. Many forms of cardiac disease involve changes in myocardial stiffness, and one such disease is heart failure [65]. In 2008, 1 in 9 death certificates in the U. S. mentioned heart failure. This major public health problem shows increasing prevalence [88], currently accounting for 5–10% of all U. S. hospital admissions and for approximately 250,000 deaths per year [107].

In recent AHA/ACC Guidelines for the Diagnosis and Management of Heart Failure [61], current definitions and diagnostic paradigms are outlined. Heart failure is described as a clinical syndrome characterized from stages A-D. Cardiologists are quite proficient at identifying patients in stage B who lack other symptoms and signs of heart failure, but have a low ejection fraction (EF), as well as patients in stages C and D who present with signs and symptoms of heart failure. Detecting abnormalities of those patients in stage A, or those in stage B with preserved EF,
remains an elusive goal with clinical benefit [61]. If a method can be developed to identify those patients, early interventions might prevent the development of heart failure, increasing survival rate of patients, helping reducing hospitalizations, and lowering healthcare costs.

1.2 Measurement of Myocardial Structure and Function

Currently, assessment of cardiac function and anatomy is guided by both noninvasive and invasive modalities. Planar chest x-ray is typically the first imaging modality performed in a full cardiac workup, allowing for noninvasive assessment of heart size and shape, as well as the exclusion of non-cardiac etiologies such as fractured ribs or pneumonia. Chest x-ray is less useful for indication of dysfunction in which the cardiac silhouette appears normal, nor does it allow for direct assessment of myocardial function. Approximately half of all radiographic exams performed in the U. S. are chest x-rays [76].

Besides planar chest x-ray, echocardiography is the most commonly performed imaging modality, which is routinely used in the assessment of left and right ventricular function, wall motion, and chamber flow velocities [47]. Ultrasound has been used for decades to measure cardiac dynamics by A-Mode (1940’s), M-Mode (1950’s), and B-Mode (1970’s) in 1-D, 2-D and 3-D (1990’s) [80].

Arteriography and ventriculography are minimally-invasive procedures used to characterize coronary arterial disease and assess ventricular function. Arteriography characterizes lumen diameter of coronary arteries with excellent precision and reproducibility and is required prior to angioplasty, bypass grafting, and stenting [107]. Arteriography is less useful for characterizing diffuse disease within cardiac tissue, or for evaluation of function. Ventriculography is used to assess both left and right ventricular function, and allows visualization of the size and shape of the ventricles, measurement of wall thickness, and identification of filling defects. Both
arteriography and ventriculography carry a small complication risk.

For directly measuring cardiac compliance and elasticity, the gold standard is the Pressure-Volume (PV) loop plotted across several cardiac cycles [10]. This method has been used since the 1950’s and is used extensively in the laboratory setting for basic mechanics studies. It has not achieved routine clinical use due to the placement of an invasive pressure catheter, though non-invasive methods of making PV loops have been explored [17].

Contrast-enhanced Cardiac MRI provides high resolution images of anatomy, assessment of function, and the fine visualization of cardiac viability. Cost and availability have somewhat limited the widespread clinical use of MRI for cardiac applications [107]. Both MRI and echocardiography are used extensively to observe cardiac anatomy, to image dynamics, and to provide information on regional wall motion abnormalities indicative of local infarct and ischemia. Cardiac MRI has become the gold standard for measuring ventricular mass, volumes, EF, and cardiac viability. Further, it can be used to distinguish between myocardial infarct-related and non-infarct-related causes of systolic dysfunction, such as amyloidosis, sarcoidosis, hemachromatosis, and hypertrophic cardiomyopathy [119].

A more efficacious imaging system for diagnosing and visualizing normal and abnormal function could potentially benefit millions of patients suffering from heart failure, especially for the diagnosis of heart failure with preserved EF. An inexpensive, noninvasive method to measure myocardial stiffness and LV relaxation would provide a useful tool to cardiologists. Current clinically-viable measurement techniques to assess myocardial stiffness are either invasive or involve image-derived metrics combined with mechanical models, or both. Cardiac imaging of myocardial motion, strain and strain rates, blood flow, and tissue perfusion all provide indirect measurements of mechanical parameters. We are aware of only one other example of in vivo cardiac elasticity imaging by radiation force-induced methods presented at a conference [93].
In that work, one example of a shear wave propagating during diastole in a healthy volunteer was shown for a single acquisition. No other currently-utilized methods allow direct measurement of cardiac stiffness, contractility, or rates of myocardial stiffening/softening that are central to the diagnosis of cardiac disease.

1.3 Development and Feasibility of a Non-Invasive, Real-Time System to Measure Myocardial Stiffness and Function

Recent work has shown ARFI imaging capable of measuring stiffness and monitoring function in rapidly moving heart tissue [52]. Intracardiac echocardiography has utilized ARFI imaging to identify areas of radiofrequency ablation in the myocardium [36, 34]. Furthermore, Shear Wave Elasticity Imaging (SWEI) is a novel modality demonstrated to effectively characterize tissue elasticity [105] by analyzing the propagation of shear waves through a localized tissue region. Differences in variation in shear propagation velocity through the cardiac cycle may be able to differentiate normal from abnormal myocardium.

This thesis presents preliminary research on applying Acoustic Radiation Force Impulse (ARFI) imaging methods via transthoracic echocardiography to interrogate myocardial stiffness through the cardiac cycle. This work examines whether transthoracic ARFI imaging can, repeatably and noninvasively, measure cardiac stiffness to advance the aim of early diagnosis of structural heart abnormalities. The methods explored here could lay the foundation for a clinical screening and monitoring tool to noninvasively measure myocardial stiffness and monitor cardiac dysfunction that could lead to heart failure.

This thesis is organized as follows: Chapter 2 provides a brief background to the fundamentals of ultrasound imaging, acoustic radiation force, ARFI imaging, SWEI, and ultrasound biosafety. Chapter 3 describes the development of a real-time display system for transthoracic ARFI imaging. Chapter 4 presents a thorough
safety analysis of the methods used in transthoracic cardiac ARFI imaging. Chapter 5 presents an *in vivo* feasibility study of using transthoracic cardiac ARFI imaging to detect myocardial dysfunction in a *porcine* model. Chapter 6 contains results of clinical trials of a transthoracic cardiac ARFI imaging study of healthy volunteers and patients with known apical infarcts. Finally, Chapter 7 discusses the implications of these investigations and presents the ongoing and future work derived from this research.
2

Background

2.1 Diagnostic Ultrasound Imaging

Medical ultrasonic imaging operates by transmitting high-frequency acoustic pulses into soft tissue. To generate this ultrasonic acoustic wave, computer-controlled electric voltage waveforms are applied across piezoelectric elements in a transducer array. The elements bulge in thickness at megahertz (MHz) frequency, and these vibrations generate pressure waveforms which emanate from the transducer surface, through matching layers and a focusing lens, and into the body. Timing delays across the width (lateral or azimuthal dimension) of the array are applied to the electric signals sent to the piezoelectric elements, causing the acoustic waves to be focused at a given axial depth and steered off axis. These delays are reset to steer in another direction or continuously updated to accomplish dynamic depth focusing while receiving returned echoes.

The acoustic waves which propagate from the transducer are scattered and reflected in the medium due to acoustic impedance mismatches. Acoustic impedance, $Z \text{(rayl)}$, is a physical property defined by the Equation (2.1), where $\rho_o$ is the mate-
rial density \( (kg/m^3) \), \( c_o \) is the speed of sound \( (m/s) \) through the material, and \( \beta \) is its bulk modulus \( (N/m^2) \).

\[
Z = \rho_o c_o = \sqrt{\rho_o \beta}
\]  

(2.1)

The acoustic backscatter pressure waves are converted into electrical waveforms by the same piezoelectric transducer elements, and dynamic delay times are applied to each channel. These electrical signals are summed across individual elements into beamformed voltage traces, with time basis measured relative to start of transmission of the outgoing acoustic pulse. The envelope of the backscattered wave is known as amplitude mode (A-Mode) ultrasound. When that envelope signal is squared, it represents the intensity from impedance mismatches encountered by the 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. In most applications, the speed of sound in the body is assumed to be a constant value of 1540 m/s. The sound speed in tissues and structures in the body varies considerably leading to image artifacts and defocussing of the ultrasound beam due to phase aberration.

The transmit/receive location is then electronically or mechanically translated or steered across the transducer aperture in order to interrogate the entire field of view (FOV) and create a two or three-dimensional brightness mode (B-Mode) image. If the location is instead kept constant and repeated through time, a motion mode (M-Mode) image can be formed at that position.

Attenuation of ultrasound in a material occurs due the effects of scattering and absorption. For the case of tissue composed of ideal Rayleigh scatterers, the scattering will depend on the frequency of excitation, radius, density and compressibility of the scatterer within its surroundings \([22]\).
2.2 Acoustic Radiation Force

Acoustic radiation force is a body force, which is applied by an acoustic wave to absorbing or reflecting targets in the propagation path, through a transfer of momentum [111]. The spatial distribution of the radiation force field is determined by the transmit beam’s acoustic parameters, focus, and the tissue properties.

The contribution of absorption is in the direction of wave propagation, whereas that of scattering is dependent upon the angular scattering properties of the target. When the target has an axis of symmetry perpendicular to the direction of wave propagation (i.e. the target is spherical), the radiation force due to scattering is also entirely in the direction of wave propagation. In this situation, the radiation force \( F \) is given by [118]:

\[
F = \Pi_a + \Pi_s - \int \gamma \cos \theta rd\theta \langle E \rangle, \tag{2.2}
\]

where \( \Pi_a \) is the total power absorbed by the target, \( \Pi_s \) is the total power scattered by the target, \( \gamma \) is the magnitude of the scattered intensity, \( \theta \) is the scattering angle, \( rd\theta \) is an area element of the projection of the target onto the axial/lateral plane, and \( \langle E \rangle \) is the temporal-average energy density of the propagating acoustic wave.

In tissue, the majority of the attenuation of an acoustic wave is due to absorption [94, 20], and the contribution by scattering to the radiation force can be neglected. When it is assumed that tissue behaves as an incompressible, linearly viscous fluid at ultrasonic frequencies and that the ultrasound wave propagates as a plane wave, the radiation force applied to tissue becomes [111, 87]:

\[
|\vec{F}| = \frac{2\alpha\vec{I}}{c}, \tag{2.3}
\]

where \( \vec{F} \) is a body force (force per unit volume) and is the acoustic radiation force \([\text{kg/}(s^2\text{cm}^2)], \text{or dynes}/(1000 \text{ cm}^3)]\), \( c \) [m/s] is the speed of sound in the medium, \( \alpha \)
$\alpha$ [m$^{-1}$] is the absorption coefficient of the tissue, and $\bar{I}$ [Watts/cm$^2$] is the temporal average intensity of the acoustic beam at a given spatial location in the tissue. For a focused acoustic beam propagating through soft tissue, the force is effectively applied from the probe surface to just beyond the focal region of the acoustic beam.

Although acoustic radiation force is a phenomenon associated with the propagation of all acoustic waves, it is not negligible at levels of diagnostic B-Mode ultrasound. Displacements due to radiation force are concentrated in magnitude in the depth of field where the ultrasound energy is focused. For measurable displacements of several microns to be achieved in tissue, either the instantaneous intensity or the acoustic pulse length must be increased roughly two orders of magnitude beyond what is commonly used for B-Mode imaging.

2.3 Acoustic Radiation Force Impulse (ARFI) imaging

Acoustic Radiation Force Impulse (ARFI) imaging is a method developed and refined over the past fourteen years [83, 85]. ARFI imaging relies on the use of radiation force from pulses with lengths typically between 30 $\mu$s and 1 ms to induce focused displacements in soft tissue. These localized displacements are tracked with conventional ultrasonic pulses and displacement estimation methods such as normalized cross correlation or phase-shift autocorrelation [73, 64]. The tissue response to the radiation force is monitored both spatially and temporally.

When physiologic motion is present in the tissue or region of interest, such as the case of cardiac imaging, additional processing methods are sometimes used to separate the motion induced by the radiation force pulse from the underlying tissue motion due to the cardiac cycle or respiration [38]. One such method for motion filtering uses a quadratic curve fit to several displacement estimates of the physiologic motion before the application of the radiation force excitation and at a time after the excitation, once the tissue is assumed to have recovered to its natural motion [53].
The quadratic function fit is subtracted from the sequence of measured displacements, having the effect removing the slower physiological motion while preserving the relatively faster ARFI-induced motion [46].

A transducer array on a diagnostic scanner is used to alternately generate the radiation force and track the resulting displacements. Because the technique is implemented with software modifications of a diagnostic ultrasound scanner, the method can provide co-registered and near-simultaneous ARFI, B-Mode, M-Mode, and color Doppler images.

Insight can be gained into the local viscoelastic properties of soft tissue in vivo and in vitro in many tissues and organs [83, 51, 102]. Additionally, ARFI imaging has been shown to be clinically useful in a variety of applications including: breast [108], cardiovascular [34], hepatic [35], prostate [120], and peripheral vascular imaging [31].

ARFI imaging has been shown capable of characterizing the elastic properties of the myocardium, with initial studies performed in animals with an open-chest preparation [54, 57, 6] or via catheters using intracardiac echocardiography (ICE) [59, 51, 34]. The use of ARFI imaging to study the heart using a transthoracic approach has been limited to this point to a few initial animal studies [56, 9, 55] and human cases presented in conferences [93, 8]. In this dissertation, development of cardiac ARFI imaging from a transthoracic approach are presented. ARFI imaging applied in this way could markedly improve clinicians’ ability to noninvasively characterize cardiac stiffness, significantly enhancing cardiologists ability to advise patients and alter the course of treatment.

2.4 Shear Wave Velocimetry

Along with localized displacement within the region of ultrasonic beam propagation, an ARFI excitation produces shear waves that propagate transverse to the direction of longitudinal wave propagation. The phase velocity of generated shear waves has
been shown to be reflective of tissue’s shear modulus [4, 39, 90]. Sarvazyan [105] named this method Shear Wave Elasticity Imaging (SWEI), first envisioned using impulsive radiation force to remotely generate shear waves and to quantify tissue stiffness based upon their propagation speed. Groups at Duke [84, 89, 103], and others [4, 18, 79], have developed methods to estimate the resulting shear wave speed and, in some cases, to reconstruct shear modulus distributions from radiation force-induced shear waves in soft tissue.

In a linear, isotropic, elastic medium, the speed of these shear waves ($c_T$) can be expressed as follows:

$$c_T = \sqrt{\frac{\mu}{\rho}} = \sqrt{\frac{E}{2(1+\nu)\rho}},$$  \hspace{1cm} (2.4)

where $\mu$ is the shear modulus, $E$ is the Young’s modulus, $\nu$ is the Poisson’s ratio, and $\rho$ is the density of the tissue. When the medium maintains transverse isotropy, as is the case with skeletal muscle, conventional isotropic models can still be applied to calculate $\mu$ or $E$ from $c_T$ if they are properly adapted [72]. As the degree of anisotropy becomes more complicated, as in myocardial tissue, the relationship between shear wave velocity and shear modulus grows increasingly complex and is not clearly known. Yet, it is reasonable to expect that shear wave velocimetry will continue to reflect underlying stiffness properties.

Preliminary data suggest that fiber orientation does not significantly impact peak displacement [7]. Additionally, since on-axis ARFI imaging typically relies on relative measurements, only changes in fiber orientation during a single acquisition have the potential of artifactually influencing this relative measurement.

To measure shear wave velocity, several methods have been used by researchers including the Lateral Time-to-Peak (TTP) algorithm [89], Time-to-Peak-Slope (TTPS) [104], the RANSANC method [117], and the LatSum method [103]. For example,
lateral TTP is a time-of-flight method that tracks the peak shear-wave-induced displacement as a function of the lateral distance of a point from the excitation focus. Linear regression is performed on the TTP displacement versus lateral position data. The slope of this regression yields the estimated shear wave velocity. This technique has been used to quantify shear moduli in tissue-mimicking phantoms and in vivo human liver studies [89]. A typical range for shear wave velocities in soft tissue is 1 to 5 m/s [5].

Many tissues are structurally anisotropic, resulting in a directionally-dependent shear wave propagation [72, 44]. Gennisson [44] investigated the anisotropy in shear wave propagation parallel and perpendicular to the direction of skeletal muscle fiber. Parallel-to-perpendicular shear wave velocity ratios of 2.8 and 4.0 were measured for excised bovine muscle and in vivo human bicep muscle, respectively. There similarly exists a high degree of structural anisotropy in cardiac muscle [71]. Shear wave velocimetry has been shown to be capable of measuring the mechanical properties of tissue, not just their relative spatial and temporal variations as provided by ARFI methods [7, 51]. Results have supported the viability of cardiac shear wave velocimetry and the characterization of shear wave anisotropy in vivo [6].

2.5 Sources of Image and Signal Degradation in Echocardiography and ARFI Imaging

There are many factors which affect quality of cardiac B-Mode imaging and the displacement estimates in ARFI imaging, including SNR, jitter, bias, decorrelation from physiologic motions of displacement, rotation, and shearing, reverberation and phase aberration from near-field layers, clutter and write-in from off-axis structures, and shearing under the point spread function. These factors will be reviewed and quantified where possible for their expected impact on results to follow. Much of the simulation and experimental work which examined these factors in the context
of liver ARFI [38, 97] can be applied to cardiac ARFI imaging.

**Cardiac Velocity, Acceleration, and Motion**

ARFI imaging utilizes small displacements relative to the physiologic strains seen in the heart, and thus high correlation between tracking lines is necessary to maintain low jitter magnitude and adequate image SNR. There is significant potential for decorrelation in the ARFI tracking signal from the effects of the heart twisting, shearing, and moving in the lateral or elevation dimension. Research groups have utilized some of these physiologic cardiac motions as the primary stimuli for other elasticity imaging modes such as cardiac strain, strain rate imaging [29], and aortic-valve closure lamb wave imaging [63]. In ARFI imaging, however, cardiac motion profiles are a noise source which may significantly decorrelate tracking lines, increase the magnitude of jitter errors, and lower the measurement SNR.

The peak expected velocity and acceleration in the heart are $> 16$ cm/s and 190 cm/s$^2$ respectively as reported in the literature [19, 99]. Over a 1 ms duration, this maximum velocity leads to a displacement of 160 μm, an order of magnitude larger than the displacement induced by an ARFI push in our application. These maximum magnitudes will likely only be encountered during peak contraction and relaxation in the cardiac cycle, and velocity and acceleration will be significantly lower during the rest of the cardiac cycle. The magnitude of tracking error after motion filtering will vary with these magnitudes. This motion tracking error in cardiac ARFI has been shown to approach 1.5 μm after the onset of ventricular systole [54], when physiological tissue velocity and acceleration is largest.

**Clutter from Near-Field Reverberation and Off-Axis Scatterers**

In simulations for abdominal imaging, Pinton et. al [98] reported the primary source of degradation in B-Mode fundamental imaging was reverberation from near-field
structures. Improvements of 26 dB in the reverberation clutter was reported for harmonic imaging compared with fundamental. The largest factor of degradation in the harmonic signal was found to be phase aberration before clutter. These results can applied to echocardiography, but other factors of motion and decorrelation will also have an impact.

Clutter is one of the most problematic imaging artifacts in echocardiography, obscuring ventricular borders, introducing noise into blood flow measurements, and impacting the performance of displacement estimation algorithms in elasticity imaging [113, 95, 70]. The clutter noise can be stronger than the myocardium itself, obscuring visualization of myocardial borders [112]. Clutter in transthoracic cardiac images can originate from reverberations and write-in from off-axis echoes. A 3-D speckle tracking study by Lediju [69] was able to differentiate clutter from stationary structures, such as the ribcage and chest wall, from clutter in the ventricle associated with moving structures. When clutter was adjacent to the myocardial wall, the two segments tracked coherently with similar displacements. Clutter farther from the myocardial wall did not correlate well with any segment of tissue, and displacements were temporally and spatially complex.

Bias and Jitter in Displacement Estimation

Bias is the mean of the displacement error, while jitter is error for the bias, or the standard deviation of the displacement error. Time delay estimation is commonly used in ARFI for tissue displacement measurements. When performed on partially-decorrelated speckle signals, estimation will be subject to large false peaks and jitter errors [116, 14].

Jitter, the magnitude of displacement tracking error, places a fundamental limit on the performance of displacement estimation techniques. It is described by the
Cramér-Rao lower bound (CRLB) [116]:

$$\sigma \geq \sqrt{\frac{3}{2f_c^2 \pi^2 T (BW^3 + 12BW)}} \left[ \frac{1}{\rho^2} \left( 1 + \frac{1}{SNR^2} \right)^2 - 1 \right]$$  \hspace{1cm} (2.5)

where jitter, \( \sigma \), depends on signal-to-noise ratio (SNR), fractional bandwidth of the transducer \((BW)\), kernel length \((T)\), correlation coefficient between reference and tracked RF-data \((\rho)\), and center frequency of the tracking \((f_c)\).

The minimum displacement estimate variance predicted by the CRLB may be small (0.2 \( \mu m \)), but in low SNR and the presence of increased physiological motion and speckle pattern decorrelation, the magnitude of displacement estimate errors (jitter) will rise. Jitter reduction can be achieved with higher tracking frequency, higher transducer bandwidth, increased kernel size, and better correlation between tracked lines.

**Shearing Under the Lateral Width of the Tracking Beam**

In M-Mode ARFI imaging, the precise stress that is applied to the tissue for a given radiation force excitation is not known due to a number of factors including unknown material properties in the tissue such as absorption, defocussing effects of phase aberration from body wall fat, and unknown boundary conditions. Consequently, the absolute magnitude of a single detected displacement is not a quantitative measurement of tissue properties such as Young’s modulus. But when compared with ARFI-induced displacements at the same depth at a different lateral location or at another time in the cardiac cycle, these displacements can be used to infer relative stiffness differences, when the assumption is made that a similar (still unknown) stress is applied at that place or time.

ARFI imaging induces relatively small displacements in tissue using a highly-localized forcing function and a similarly sized beam for tracking. This scenario
poses problems for estimating peak displacement magnitudes due to the presence of shearing under the tracking point spread function [77]. The displaced region has dimensions on the same scale as beam used to track the motion, and there exists a range of induced displacements within this tracking beam, causing shearing leading to decorrelation of the echo signal and an underestimation of the peak displacement [77]. The amount of decorrelation seen from this effect is a function of the relative pushing and tracking beam dimensions and the level of peak displacement relative to the wavelength of the ultrasound tracking beam.

In the setup used for transthoracic ARFI imaging, the pushing and tracking beam have the same lateral and elevation dimensions, and the reduction in the expected peak displacement is underestimated by a factor of 2 [77]. The displacements induced are less than 4% of the wavelength, so the decorrelation predicted from this effect is less than 1% [77]. However, this reduction in peak displacement does not pose a significant problem to M-Mode ARFI imaging due to its relative nature, as the peak will be affected in the same way through time. However, the decrease in echo correlation from the nonuniform displacement of scatterers within the tracking point spread function will contribute to increased jitter and may be more problematic.

Quadratic Motion Filter

In this dissertation, a quadratic axial motion filter was used which had been previously developed [54, 46], and it was applied to a single axis, the dimension of beam propagation. A quadratic function-fit motion filter assumes that any estimated motion not associated with the applied radiation force will be of constant acceleration. The filter used five reference estimates before the radiation force excitation and one or more estimates after the push, when the tissue has been assumed to have recovered. The time chosen for this recovery will influence the amount of ARFI displacement that is removed along with the physiologic motion. An earlier
time step in compliant tissue will only allow partial recovery from the radiation force excitation, and the peak displacement that remains after filtering will underestimate the true displacement of the tissue. A late time step will allow the tissue to more fully recover from the radiation force excitation, but the physiologic motion may be more problematic through this longer tracking interval, due to decorrelation and changes in acceleration of the tissue that violate the assumptions of the quadratic motion filter. Experiments [53] and simulations [46] previously validated that when the criterion of constant acceleration holds true, the motion filter performs well in removing axial transducer/physiological motion from displacement estimates in a cardiac application.

Components of physiological motion in the lateral or elevation dimensions are neither detected by axial displacement estimation nor removed by the filter, and will decorrelate the lines used for tracking, as will rotation and shearing motions. Across the cardiac cycle, these combined effects move different tissue through the M-Mode focus and region of interest. Within a single ARFI acquisition that lasts a few milliseconds, the uni-axial motion filter performs sufficiently [54, 46] well. For tracking the a moving segment of tissue over longer durations as in M-Mode or SWEI through the cardiac cycle, 2-D or 3-D methods would offer some improved performance for tracking bulk motions and strain at the cost of computational complexity and processing time [16, 43, 67].

2.6 Safety Limits and Regulations

In the United States, the acoustic output levels utilized by diagnostic ultrasonic imaging systems are subject to limits and guidelines published by the Food and Drug Administration (FDA). These guidelines were established in response to the Medical Device Amendments of 1976 and were based on the measured existing output levels at that time, which had no reported bioeffects. These limits were not based
on scientific studies of maximum thresholds for damage, but nevertheless persisted until new metrics were introduced in 1992 [40]. The Output Display Standard [2] outlined methods to report acoustic output levels with on-screen indicators of thermal index (TI) and mechanical index (MI), which were metrics implemented as new higher limits, created to address concerns of insufficient image quality. These metrics attempted to relate acoustic output guidelines to potential bioeffects, but the MI and spatial-peak, time-averaged intensity ($I_{SPTA}$) thresholds were still tied to the pre-existing limits [40].

Newer ultrasound methods that have been developed, such as harmonic imaging, contrast agent imaging, and ARFI imaging, use beam sequences which are often near the upper end of the intensity boundaries [66, 37]. In ARFI imaging, MI values can exceed 1.9 when the excitation frequency is low and the transmit level is high, such as the case of deep abdominal or transthoracic imaging. Pulse durations can be up to 1 millisecond in some cases, and so concerns may exist for these methods regarding both mechanical and thermal safety.

2.6.1 Ultrasonic Mechanical Effects

The U. S. FDA regulations currently designate most diagnostic ultrasound imaging and Doppler devices as Class 2, and as such, they must be demonstrated to be substantially equivalent in terms of safety and effectiveness to a device legally marketed before the 1976 FDA Medical Device Amendments or to another device which had already achieved Class 2 status. In order to evaluate equivalent safety, the FDA defines acoustic output metrics to quantitatively compare different devices.

The Mechanical Index (MI) and Cavitation Risk

The MI was developed in the late 1980’s from calculations and experiments on the approximate acoustic pressure amplitude to cause optimally-sized bubbles to burst,
or undergo inertial cavitation [3]. Cavitation is bubble expansion followed by rapid collapse, potentially causing damaging shock waves, highly localized tissue damage, rapid temperature increase, and production of highly-reactive free radicals. The phenomenon of cavitation is generally observed when there are air bubbles already present in fluid which is subsequently exposed to large negative pressures. This is a frequency dependent phenomenon, with lower frequencies requiring lower peak negative pressures to induce cavitation. The definition of the Mechanical Index (MI) used by the FDA is shown below:

\[
MI = \frac{p_{r,\alpha}(z_{MI}) f_{awf}^{-1/2}}{C_{MI}}
\]

(2.6)

where, \(C_{MI} = 1 \text{ MPa} \cdot \text{MHz}^{-1/2}\); \(p_{r,\alpha}(z_{MI})\) is the attenuated peak-rarefractional acoustic pressure at depth \(z_{MI}\); \(z_{MI}\) is depth on the beam axis from the external transducer aperture to the plane of maximum attenuated (derated) pulse-intensity integral \((\text{pii})\); \(f_{awf}\) is the acoustic-working frequency; and \(\alpha\) is the acoustic attenuation coefficient, which for the MI calculation is taken to be 0.3 dB/cm/MHz.

The original theoretical framework assumed the presence of a bubble at the optimal diameter to produce the cavitation effect, that the bubble was surrounded by fluid, and the applied pulse was a single cycle [3]. The results within that framework found a cavitation threshold for MI of only 0.7, well below the known safe levels of 1.9 level used by the FDA. The method did not include models of viscoelastic tissue or extended pulse durations used in Doppler or elasticity imaging modalities such as ARFI imaging. Thus the FDA MI threshold (1.9) to avoid cavitation in soft tissue is very conservative, since it is based upon the assumptions of the presence of an optimal air bubble and of modeling soft tissue as water.

When no contrast agents such as saline micro-bubbles or commercial microspheres are used, the potential for acoustic cavitation has been shown to be low.
In the absence of bubbles, the risk for cavitation induced bioeffects has been reported to be exceedingly low for $MI < 4.0$.

While specific safety guidelines do not exist for ARFI-like duration and intensity pulses, a proposed acoustic output threshold equation has been reported in the literature for empirically observed tissue damage in mammalian brain $in vivo$ [32]. It included both thermal and cavitation damage mechanisms, and it will be applied here to ARFI pulses. In the study, a threshold for tissue damage, with either a mechanical cavitation or thermal mechanism, was found to be related to the product of Intensity (linearly extrapolated, derated, $in situ$, $I_{SPPA}$, W/cm$^2$) times the square root of time. Their data indicated values for tissue damage ranging from 250-500 W/cm$^2$ sec$^{1/2}$, depending upon the ultrasonic frequency. This threshold will be used along with other methods to calibrate the relative safety of the ARFI pulse sequences.

Another study of rats found it possible to spontaneously nucleate gas bubbles out of tissue or fluid and then cause cavitation using a two-stage sequence [49]. A first stage of a 3 MPa peak negative pressure waveform with 1 ms duration was used to promote micro-bubble generation. A second stage, or cavitation stage, consisted of 5.1 MPa peak pressure and was applied for between 5 and 50 ms. A high intensity focused ultrasound (HIFU) system and transducers with frequency of 350 kHz, 700 kHz or 1.05 MHz, were used to generate these desired waveforms. Pressures below 2 MPa did not induce cavitation, and results further indicated that exposure to just the second stage (radiation effect), without the first stage (micro-bubble generation), does not cause premature ventricular contractions (PVCs). Furthermore, the effect was reduced at higher frequencies and lower pulse duration, such as those comparable to ARFI parameters.
Premature Ventricular Contraction

Cavitation most often occurs along with the induction of PVCs and highly localized myocardial cell death, in the setting of externally applied intravenous contrast [82, 101, 26, 81]. One of these studies showed that with contrast micro-bubbles, peak rarefactional pressures of as low as 0.1 MPa caused PVCs from cavitation in mice, but the effect was not seen when saline was injected instead [101].

Studies by Dalecki and MacRobbie using frogs and mice found the pressure threshold for producing a PVC with a single 5 ms duration pulse of ultrasound at center frequency 1.2 MHz was between 2 and 5 MPa [27, 74]. This threshold increased with decreasing pulse duration and increasing frequency. In ARFI imaging, shorter pulses (0.3–1 ms) and higher frequencies are used (2–7 MHz) than was used here, making the respective threshold likely much higher than 5 MPa. Regardless, the arrhythmogenic effect was temporary, with the heart returning to normal sinus rhythm after each PVC and showing no permanent damage to cardiomyocytes [27].

A study involving rats reported a small incidence (0.74 %) of PVCs, cavitation, and microscopic cell death arising from ultrasound excitation in the absence of contrast but utilizing very high mechanical indices (MI=5.7) and a long pulse duration of 2 ms [82]. A water path to an in situ rat heart was used with derated in situ peak negative pressures of approximately 7 MPa and a frequency of 1.5 MHz. Sequences applying lower peak pressures were not reported to induce PVCs without intravenous contrast. This study did not explore pressure levels in the region between MI=5.7 and 1.9.

Finally, the only applicable study in humans showed evidence of ultrasonically induced cavitation or PVCs in the presence of intravenous contrast [15]. They tested both a therapeutic transthoracic transducer operating at 1 MHz, with MI of 1.3 and 20% duty cycle and a diagnostic transducer at 1.7 MHz operating at a MI of 1.7.
acquiring 1 B-Mode frame every 4 cardiac cycles. The therapeutic transducer frequently induced PVC’s (in 33 of 34 patients) when intravenous contrast was injected, but isolated PVCs were rarely induced when using the diagnostic transducer. These results as a whole will help guide the MI and peak negative pressure measurements presented in Chapter 4.

2.6.2 Ultrasonic Thermal Effects and the Thermal Index (TI)

Aside from concerns over the intensity of the applied pulse, there is potential risk in applying ultrasound at intermediate intensity levels for an extended time period, as tissue damage could be caused due to excessive heating. The FDA considers thermal increases less than 6°C in soft tissue to be safe [48]. The beam sequences and timing of data acquisition used for later experiments will be designed to ensure that the cumulative temperature increase does not exceed 4°C [91]. For comparison, therapeutic ultrasound procedures expose tissues to ultrasonic radiation force for sometimes several minutes to aggressively heat tissue; in contrast, ARFI pulses last tenths of milliseconds.

ARFI imaging uses acoustic radiation force to excite and displace tissues of interest. The energy that is transferred from the traveling wave into the target medium due to absorption results in both the application of radiation force and the heating of intervening tissue. The rise in temperature in the tissue can be modeled with the linear bio-heat transfer equation [86, 96]:

\[
\dot{T} = k\delta T - \frac{T}{\tau} + \frac{q_v}{c_v}
\]  

(2.7)

where \(q_v\) is the rate of heat production per unit volume, \(T\) is the temperature, \(\dot{T}\) is the rate of temperature rise, \(k\) is the thermal diffusivity, \(\tau\) is the time constant for perfusion and \(c_v\) is the specific heat per unit volume for tissue. Equation (2.7) can
be derived using the principle of conservation of energy in a small material element and the Fourier law of heat conduction.

For the case of a continuous, linear traveling plane wave, the heat-source function for an ultrasound beam can be characterized by [86, 110]:

\[ q_v = 2\alpha I \]  \hspace{1cm} (2.8)

This Equation (2.8) originates from the depth-dependent intensity loss of a traveling plane wave. A linear relationship exists between the intensity, application time, and temperature increase associated with the high intensity beam sequences.

In single-excitation ARFI imaging, the overall insonification times are very short. Tissue motion and the cooling effects of blood perfusion are neglected when simulations are undertaken to calibrate ARFI heating [91]. In extended, multiple-excitation sequences such as M-Mode ARFI and SWEI across one or more heartbeats, the combined effects of these factors would serve to reduce the thermal impact \textit{in vivo}. By completing focal heating simulations and transducer face temperature measurements, the thermal safety of ARFI sequences will be calibrated in Chapter 4.
Development and Safety Analysis of a Real-Time Transthoracic Cardiac ARFI Imaging System

This chapter will describe the pulse sequencing, system integration, and programming methods used in the development of a real-time transthoracic ARFI imaging scanner.

3.1 Pulse Sequencing for Imaging Modes

Two imaging beam sequence modes were developed for the Verasonics Research Platform (Verasonics, Inc. Redmond, WA) in support of transthoracic ARFI imaging. Both methods used the Philips / ATL P4-2 (Philips Healthcare, Andover, MA), a phased-array transducer with a center frequency of 2.5 MHz. The ultrasound parameters used in M-Mode ARFI imaging and SWEI through the cardiac cycle are listed in Table 3.1. In the first imaging mode, on-axis M-Mode ARFI imaging, the tissue region of interest (ROI) is the same as the region of excitation (ROE) along the line of initial radiation force excitation or “push” pulse. By repeating the ARFI “push” and track acquisition sequence through the cardiac cycle at the same location, the
measured displacements indicate the relative stiffness and timing of changes during the heartbeat. As shown in the middle column of Table 3.1, the M-Mode ARFI sequences collected 50 ARFI displacement responses at a rate of either 25 Hz or 50 Hz, and they used excitation pulses of 480 µm in duration. For the prototype system, the total amount of data that could be transferred in a single dataset was limited by the hardware. For M-Mode ARFI, the beamformed in-phase and quadrature (IQ) data was saved at a sampling rate of 1 pixel per wavelength.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>M-Mode ARFI</th>
<th>Value</th>
<th>SWEI</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound Scanner</td>
<td>Verasonics</td>
<td>Verasonics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probe</td>
<td>ATL P4-2</td>
<td>ATL P4-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquisitions</td>
<td>50</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquisition rate</td>
<td>25 or 50 Hz</td>
<td>3 Hz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push Frequency</td>
<td>2.0 MHz</td>
<td>2.0 MHz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Track Frequency</td>
<td>2.5 MHz</td>
<td>2.5 MHz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracking PRF (pulse repetition freq)</td>
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<td>6.4 kHz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracking Pulses</td>
<td>25</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demodulated IQ sampling</td>
<td>1 pixel/λ</td>
<td>2 pixels/λ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-channel RF sampling</td>
<td>N/A</td>
<td>4 samples/λ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push Cycles</td>
<td>960</td>
<td>1920</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push Duration</td>
<td>480 µs</td>
<td>960 µs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push F#</td>
<td>1.5-3.5</td>
<td>1.5-3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Push Focal Depth (lateral)</td>
<td>3-7 cm</td>
<td>3-7 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevation Focus</td>
<td>6.5 cm</td>
<td>6.5 cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The second transthoracic mode developed was cardiac shear wave elasticity imaging (SWEI). This mode also used radiation force impulses for excitation down the central line of the B-Mode field of view, but the ROI was offset laterally to either side of the central region of excitation at the focal depth. The propagation of the transverse displacement wave was tracked as it propagated across this ROI. The speed of wave propagation quantitatively indicated the stiffness of the tissue at that location and during that time point in the cardiac cycle. By repeating that sequence
at several times across one or more cardiac cycles, the quantitative stiffness and timing changes of the heart could be tracked. The parameters for the SWEI sequence are seen in the right column of Table 3.1. This SWEI sequence contained 11 “push” and track repetitions at a rate of 3 Hz, which was limited in rate and data set size by hardware. Each acquisition data set was transferred from the ultrasound system to computer memory and saved to disk. Fewer temporal samples were possible in this mode, due to the necessity of using finer spatial resolution of four samples per wavelength and saving the raw single-channel radiofrequency (RF) data from the scanner.

3.2 Real-time acquisition, processing and display

In order to quickly judge the success of the ARFI acquisitions in real-time during animal experiments and human clinical trials and to allow for mid-course corrections and adjustments, a real-time acquisition and display software tool was developed utilizing the Verasonics Research Platform. This ultrasound data acquisition system was connected to a Precision T7500 workstation (Dell Inc., Round Rock, Texas) with two hex-core 3.46 GHz Xeon processors (Intel Corp., Santa Clara, CA) and 24 GB of random access memory (RAM) for beamforming and processing of the collected data.

The pulse sequences discussed above were combined with a scanning mode which allowed live B-Mode imaging of a wide, deep field of view for aiming and adjusting imaging parameters. Several controls, including time-gain compensation (TGC) sliders, ARFI excitation focal depth, and transmit power levels for B-Mode and ARFI were made available for control via an on-screen graphical user interface (GUI). The pulse sequence, GUI controls, processing and display interface were all written using the MATLAB software package (The MathWorks, Inc., Natick, MA).

When the sonographer/cardiologist was satisfied with the field of view, focus,
and imaging parameter controls, the researcher/operator could then click the mouse button within the B-Mode window to start the preloaded ARFI or SWEI acquisition mode. During this time the live B-Mode image would pause temporarily while the ARFI imaging sequence was fired. For on-axis M-Mode ARFI imaging, this delay was only 2-4 seconds. For the cardiac SWEI sequence mode, the delay was 20 seconds due to the extended time required to transfer and save the larger raw dataset.

During this imaging delay, the data were transferred from the Verasonics Research Platform’s acquisition memory buffers to the attached computer’s RAM or hard disk drive. Processing algorithms included displacement estimation by a phase-based autocorrelation method [64] and motion filtering using a quadratic function fit [53, 46]. An M-Mode ARFI image was displayed for the on-axis case, whereas a displacement movie showing transverse wave propagation was displayed for the SWEI sequence mode.

This research platform provided a flexible sequence prototyping interface, and the robust power supply allowed for an ARFI excitation pulse with less temporal decay than previous implementations on the SONOLINE Antares™ and ACUSON S2000™ scanners (Siemens Healthcare USA, Issaquah, WA), allowing larger displacements than were available previously.

In addition to the simultaneous B-Mode, M-Mode and ARFI/SWEI acquisition, the patient’s electrocardiogram (ECG) was acquired in order to register and compare the imaging mode signals to the cardiac cycle. A portable ECG monitor was used to filter and amplify the patient’s ECG signal. A laptop, custom Labview software (National Instruments, Austin, TX) and data acquisition card were used to digitize and record the ECG signal and timing trigger pulses from the ultrasound scanner. Figure 3.1 includes a photograph and block diagram of the real-time system setup.
Figure 3.1: In (a), the Verasonics Research Platform, Dell Precision T7500 personal computer, transducer, ECG monitor, LCD display, keyboard and mouse are pictured. In (b), the block diagram also includes the imaging subject, the data acquisition interface board and the laptop which together record ECG and trigger signals for timing.

3.3 Assessment of Power Supply of Verasonics Research Platform

One motivation for the exploration of the Verasonics scanner as a platform for this work was the insufficiency of previous clinical scanners’ power supplies. The Verasonics has a power supply which was specifically designed to maintain full power output through an extended-duration pulse as necessary for applications such as high intensity focused ultrasound (HIFU) or ARFI imaging. In unpublished experiments by Fahey and Hsu, the Siemens SONOLINE Antares™ and Acuson S2000™ scanners had previously been shown to exhibit a temporal decay or “droop” when tasked with transmitting pulses of several hundred cycles. This became more problematic for projects such as deep abdominal ARFI imaging and transthoracic ARFI imaging compared to breast, vascular and thyroid imaging.
(a) Single “push”  
(b) Single “push”, normalized  
(c) Double “push”  
(d) Double “push”, normalized

Figure 3.2: Measured pressure amplitude curves. In the M-Mode ARFI sequence with a 0.48 ms excitation (a) and (b), the amplitude oscillates at the highest voltage level. In the SWEI sequence was a double “push” (c) and (d), pressure curves at 30 and 40 V oscillate significantly during the second “push”.

To assess and measure the temporal characteristics of the Verasonics power supply, the P4-2 phased-array transducer was mounted in a water tank. A wide-bandwidth membrane hydrophone (Onda Corporation, Sunnyvale, CA) was placed in the near field, or pre-focal region, of the acoustic field to protect the hydrophone from high pressures at the focus, but still record the shape of the transmit waveform when a high input voltage was used. The waveforms were recorded on a digital oscilloscope (Tektronix, Inc., Beaverton, OR) and the envelope of the signal was plotted in MATLAB. Pressure profiles from M-Mode ARFI (0.48 ms) and SWEI (0.96 ms) configurations are shown for various inputs voltage levels with two types of normalization in Figure 3.2.
In contrast to the behavior as seen previously on the Siemens scanners, this power supply did not exhibit temporal decay or “droop”. Rather, as the input voltage was increased from 10 to 40 Volts, the envelope of the signal tended to oscillate or become unstable toward the end of the extended pulse length. This was especially evident during the second part of the “double-push” excitation used in the SWEI sequences. There were no discernible consequences of this apparent oscillation as measured in phantom or \textit{in vivo} results. The capabilities of the power supply of the Verasonics Research Platform were an important enabling technology over the Siemens scanners used in earlier exploratory studies.

3.4 Validation by Simulation and Phantom

3.4.1 Methods

ARFI responses simulated were created in a manner described in detail previously [92, 90] and outlined below.

\textit{FEM Pre-Processing Mesh Generation}

A three-dimensional, rectangular, solid mesh was assembled using eight-noded, linear, elastic, brick elements (HyperMesh, Altair Computing Inc., Troy, MI).

\textit{Simulating Intensity Fields}

The FIELD II ultrasound simulation package [62] was used to generate an acoustic intensity field from a Philips / ATL P4-2 phased array transducer with various transmit configurations at different push frequencies and focal depths. Three-dimensional intensity fields were computed, normalized, and thresholded at 1% of the maximum, computed intensity to reduce computational overhead of the model. These normalized intensities were scaled to a peak \textit{in situ}, pulse-average intensity value of 900 W/cm$^2$, as in intensity measurements in Chapter 4. This intensity field was used
to find the body force values of the radiation force applied by the ARFI excitation, which were then converted to nodal point loads by concentrating the body force contributions each an element volume. For locations within ±10% of the focal depth, point loads were directed purely in the axial direction. For shallower locations closer to the transducer, point loads were directed toward the focal point; and for deeper locations, point loads were directed away from the focal point, consistent with the wave-propagation Poynting vector.

**FEM Implementation and Postprocessing**

The balance of linear momentum was solved numerically with the commercially available FEM package, LS-DYNA3D (Livermore Software Technology Corporation, Livermore, CA), using an explicit, time-domain, integration method. Postprocessing of dynamic displacement and stress fields was performed using LS-PREPOST (Livermore Software Technology Corporation, Livermore, CA) and custom-written MATLAB (The MathWorks Inc., Natick, MA) code.

The Young’s modulus and attenuation of the medium were varied over a range. Focal and material properties that were varied included focal depth of the radiation force excitation (3–7 cm), F# (1.5–3.5), transmit frequency (1.75–2.5 MHz), efficient α (0.3–0.6 dB/cm/MHz), and Young’s modulus (4.5 and 36.0 kPa). These parameters approximate the limits of the ranges appropriate for our transducer and cardiac imaging setup.

### 3.4.2 FEM Results of On-Axis M-Mode Tissue Response

Results of FEM simulations of tissue mechanical responses to radiation force induced by simulated excitation fields are presented in the figures to follow. Results shown here and through the rest of the studies correspond to displacements tracked 1.33 ms following the removal of radiation force, the earliest time for which a valid tracking
estimate is recorded on the Verasonics platform after a long transmit was fired. When
the heart is in systole, this time is during tissue recovery after the peak displacement,
and near the peak during diastole, providing good displacement contrast between the
two states in M-Mode ARFI imaging.

![Graph](image)

(a) Varying push transmit focus  (b) Varying push frequency

Figure 3.3: Simulation of influence of focus and frequency on relative displacement
at focus in media $\alpha=0.5$ and Young’s modulus 4.5 or 36 kPa. The displacements at
1.33 ms after the radiation force excitation are plotted. The largest displacements
of these configurations are generated in a compliant medium with a shallow push
focus and a low push frequency (longest push when number of transmit cycles is
held constant) for our transducer. With a deep focus, in a less compliant medium,
or at a higher push frequency, the displacement at the focus is reduced considerably.

Figure 3.3 can help guide expectations for pushing at depth and in contracting
muscle, such as cardiac tissue. At a focus below 5 cm, the displacement induced in
a medium with 4.5 kPa is less than 80% of that at a focus of 3 cm. In a medium
with a modulus of 36 kPa, the displacement is reduced by at least 50% as seen in
Figure 3.3a. The relative displacement magnitudes agree well with those published
by intracardiac [51] and epicardial methods [54]. Because there were a fixed number
of cycles used in the push transmit for these simulations, the longest push duration
possible would be obtained using the lowest frequency within the bandwidth of the
transducer. Figure 3.3b shows lower frequency yields larger induced displacement.
It quantifies one side of the trade-off between using a low frequency to generate
larger displacements and keeping the MI in a safe range as it is inversely related to
frequency$^{1/2}$. In practice, a transducer’s actual bandwidth may be narrower than what was assumed in simulation, and phantom tests showed a push transmit of 2.0 MHz was capable of the largest displacements when all other variables were held constant.

3.4.3 Simulated Shear Wave Elasticity Responses

In the same FEM models, displacements outside of the region of excitation were simulated, allowing comparison of shear wave displacements and velocities with different media and focal configurations. Four combinations will be shown: focal depths of 3 and 7 cm and Young’s moduli of 4.5 kPa and 36.0 kPa. The average displacement in a 5 mm region just shallow to the focus was calculated for the lateral locations which were outside the initial region of displacement. The peak slope, or change in displacement through time, was found for these lateral locations. The shear wave speed was calculated using a linear fit to these points in the space-time plane.

Figure 3.4a shows an example of the displacements at the focal depth across the lateral dimension through time, while 3.4b shows the time derivative of the displacement data, or the slope of the curve.

Table 3.2 shows that the two foci have shear wave speed estimates within 6% of each other. The stiffer 36.0 kPa medium shows a shear wave speed roughly 3 times higher than the 4.5 kPa medium, in agreement with theory (as the shear wave speed is proportional to the square root of the shear modulus, which is proportional to the Young’s modulus). These shear wave speeds are comparable to those seen in diastole and systole in the heart as measured with intracardiac methods by Hollender [51].

3.4.4 Phantom Validation

In addition to the FEM simulations, M-Mode responses were measured experimentally using two uniform elasticity phantoms (CIRS Inc., Norfolk, VA), having Young’s
Table 3.2: Shear wave speed estimates from simulation of a P4-2 transducer with a 2.0 MHz Push in uniform media with $\alpha = 0.5$

<table>
<thead>
<tr>
<th>F#</th>
<th>Focus (cm)</th>
<th>Young’s modulus (kPa)</th>
<th>Shear wave speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>3.0</td>
<td>36.0</td>
<td>3.50</td>
</tr>
<tr>
<td>3.5</td>
<td>7.0</td>
<td>36.0</td>
<td>3.33</td>
</tr>
<tr>
<td>1.5</td>
<td>3.0</td>
<td>4.5</td>
<td>1.20</td>
</tr>
<tr>
<td>3.5</td>
<td>7.0</td>
<td>4.5</td>
<td>1.13</td>
</tr>
</tbody>
</table>

moduli 4.5 and 24 kPa respectively. Displacement measurements were made at 3 and 5 cm focal depths, at mechanical indices (MIs) 1.9 and 3.0. “No-push” ARFI sequences, in which the length of the excitation was shortened to that of a B-Mode tracking pulse, were also acquired. These no-push sequences illustrate the bias and jitter introduced into measurements by the displacement estimation and motion filtering operations.

Table 3.3 contains the means and standard deviations for the scans in the phantoms. The stiffness of the phantoms are similar to myocardial tissue in systole and diastole. We expect displacements in vivo to be lower than these measurements due to absorption from the body wall and to be corrupted by motion and decorrelation.
Table 3.3: Results of phantom validation of M-Mode ARFI sequences

<table>
<thead>
<tr>
<th>Focus (cm)</th>
<th>MI</th>
<th>Young’s modulus (kPa)</th>
<th>Push/No-push</th>
<th>Displacement (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.9</td>
<td>4.5</td>
<td>No-push</td>
<td>-0.02±0.03</td>
</tr>
<tr>
<td>5</td>
<td>1.9</td>
<td>4.5</td>
<td>No-push</td>
<td>-0.24±0.29</td>
</tr>
<tr>
<td>3</td>
<td>1.9</td>
<td>24.0</td>
<td>No-push</td>
<td>-0.03±0.03</td>
</tr>
<tr>
<td>5</td>
<td>1.9</td>
<td>24.0</td>
<td>No-push</td>
<td>-0.04±0.04</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>4.5</td>
<td>No-push</td>
<td>-0.03±0.03</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>4.5</td>
<td>No-push</td>
<td>-0.52±0.63</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>24.0</td>
<td>No-push</td>
<td>-0.04±0.02</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>24.0</td>
<td>No-push</td>
<td>-0.05±0.04</td>
</tr>
<tr>
<td>3</td>
<td>1.9</td>
<td>4.5</td>
<td>Push</td>
<td>5.83±0.97</td>
</tr>
<tr>
<td>5</td>
<td>1.9</td>
<td>4.5</td>
<td>Push</td>
<td>10.20±0.95</td>
</tr>
<tr>
<td>3</td>
<td>1.9</td>
<td>24.0</td>
<td>Push</td>
<td>3.18±0.15</td>
</tr>
<tr>
<td>5</td>
<td>1.9</td>
<td>24.0</td>
<td>Push</td>
<td>2.45±0.14</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>4.5</td>
<td>Push</td>
<td>17.59±5.52</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>4.5</td>
<td>Push</td>
<td>40.93±5.95</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>24.0</td>
<td>Push</td>
<td>7.54±0.41</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>24.0</td>
<td>Push</td>
<td>8.41±1.12</td>
</tr>
</tbody>
</table>

In the 24 kPa phantom, at a focal depth of 5 cm, we see the displacement is only 2.45 µm when an MI of 1.9 is used. This level can be detected in phantoms, but in the presence of physiologic motion, it may be challenging during parts of the cardiac cycle. Using an MI of 3.0 in that phantom boosted the displacement measured to 8.41 µm. It may be necessary to use higher MIs to induce large enough displacements to measure in the presence of motion and clutter in vivo. The no-push case showed a maximum bias of 0.5 µm, and a jitter of 0.6 µm.

3.4.5 Effect of Kernel Length

In displacement estimation, the kernel length, $T$, as described in the Cramér-Rao lower bound, Equation 2.5, is the length of time over which the each displacement estimate is computed. To show the effect of changing the kernel length used in displacement estimation in our signal processing, an example dataset (3 cm focus, MI=3.0, 24 kPa) from the above phantom study were processed with a 1-D autocor-
Table 3.4: Mean and standard deviation of displacements in the focal region (2.0–3.0 cm) in a uniform 24 kPa phantom with different kernel lengths used for displacement estimation by 1-D autocorrelation

<table>
<thead>
<tr>
<th>Kernel length</th>
<th>Displacement around focus (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 λ</td>
<td>6.64 ± 3.81</td>
</tr>
<tr>
<td>3 λ</td>
<td>6.47 ± 1.40</td>
</tr>
<tr>
<td>5 λ</td>
<td>6.42 ± 0.86</td>
</tr>
<tr>
<td>7 λ</td>
<td>6.39 ± 0.78</td>
</tr>
</tbody>
</table>

relator [64], using kernel lengths of 1, 3, 5, and 7 λ. Figure 3.5 shows example ARFI images from a single on-axis displacement which have been masked by the intensity of the tracking beam. With a kernel length of 1 the displacements (a) exhibit large variance spatially. As the kernel is increased from left to right, the variance in the estimates decrease, as shown in Table 3.4. The spatial variance of the displacement estimates decreases by a factor of 5 as the kernel length increases from 1 λ to 7. The axial resolution decreases as the kernel length is increased. A kernel length of 7 λ has been used to process the data in the rest of this dissertation due to the improvement in jitter reduction at the expense of possible axial resolution.
3.5 Discussion and Conclusions

In this chapter, we described the development of a real-time transthoracic ARFI imaging system capable of acquisition, processing, and display of ARFI images and SWEI movies for use in animal or clinical studies. We found the power supply of the Verasonics to be capable of extended-duration transmit waveforms, enabling deeper excitations compared to previous clinical scanners. We showed results from FEM simulations which calibrated our expectations for phantom and in vivo scanning. Specifically, we found that displacements at focal depths beyond 5 cm and a stiff medium would reduce the expected focal displacement by a factor of two each. We found the expected shear wave speeds for myocardial tissue in systole and diastole were 3.5 and 1.2 m/s respectively, within the range expected to be seen in soft tissue [5]. Phantom studies were presented which compared Young’s moduli, focal configurations, and two power levels: the FDA MI limit of 1.9 and exceeding that limit at 3.0. The effect of varying the kernel length was examined with example images from a phantom and a quantitative analysis.

These results demonstrate the expected performance of the prototype transthoracic ARFI imaging system. The thermal and mechanical safety of this system will be tested and calibrated in the following chapter.

3.6 Acknowledgments

For their contributions to this work, I acknowledge Dr. Mark Palmeri, Dr. Bisi Bell, V Kakkad, and Doug Giannantonio.
4.1 Introduction

Diagnostic ultrasound imaging has a long-standing record of safety and efficacy dating back to the 1950’s [80]. Currently, the U.S. Food and Drug Administration (FDA) regulates the acoustic output levels of diagnostic ultrasound imaging devices, as discussed in Chapter 2.

Before bringing the prototype system to the clinic, a thermal and mechanical safety analysis was performed to calibrate the output of the ARFI imaging and SWEI modes. The transthoracic sequences were calibrated using the methods below to limit heating of the tissue or transducer face to rises of less than 4 °C, to remain below Dunn and Fry’s intensity-time threshold [32], and to measure the MI and peak rarefactional pressure used at each input voltage.
4.2 Methods

4.2.1 Acoustic Intensity Measurement

The MI was developed as an indicator of potential for the mechanical bioeffects of cavitation and cell damage. The MI is defined as the derated, in situ peak rarefactive pressure (PRP) in MPa, divided by the center frequency in MHz [2]. Current FDA guidelines limit maximum output levels of diagnostic devices to an MI of 1.9 and a spatial peak, temporal average intensity ($I_{SPTA}$) of 720 mW/cm$^2$. The guidelines specify that acoustic output measurements be derated by an acoustic attenuation factor ($\alpha$) of 0.3 dB/cm/MHz to provide a better estimate of losses that would occur in tissue rather than the water in which they are measured [2]. However, the actual attenuation of myocardium and skeletal muscle is closer to 0.5 dB/cm/MHz and the propagation of ultrasound through water is subject to nonlinear effects, so in order to better estimate the in situ exposure, several measurement methods were used as discussed below.

Measuring the spatial peak, pulse average intensity $I_{SPPA}$, peak rarefactive pressure (PRP), and MI necessitates finding the peak location within the acoustic field emanated from the transducer. To that end, the transducer was mounted to a computer-controlled 3-D translation stage (Newport Corp., Irvine, CA). The Verasonics was programmed to transmit ten-cycle pulses, focused at depths ranging from 30 to 70 mm, with center frequency matching the ARFI excitation pulse (2 MHz) and pulse repetition frequency (PRF) of 10 Hz. The position of the transducer was first manually adjusted to place the hydrophone near the focus of the ultrasound field. Then the translation stage and oscilloscope were controlled using a custom Labview program in which an automated, iterative, peaking-finding algorithm compared the pressure measurements in a grid of points around the current location and moved to the position of maximum pressure amplitude. Once the global peak of the field
was found, pressure measurements were made in a small grid of points at a series of transmit power levels.

Due to the nonlinear propagation of ultrasound through water, the PRP reaches saturation levels at higher input power levels [109]. After the measurements were made in water, they were repeated with an attenuating condensed milk medium replacing the water path between the transducer face and the hydrophone surface.

A mixture of 80% condensed milk to 20% water was used to achieve an attenuation coefficient in the range of in vivo tissue. To calculate the achieved attenuation coefficient of the milk-water mixture, pressure measurements from the milk medium and those from water were compared at low input power (in the small-signal linear range). The slopes of two pressure-versus-voltage plots were used to determine the amount of attenuation and calculate the coefficient, $\alpha$ (per cm per MHz). After the measurements were made in the milk medium (at the position of peak intensity from water), the peaking algorithm was rerun to find the new peak location in the milk solution, which shifted due to attenuation.

The PRP measurements made in water were derated by $\alpha = 0.3$ and compared to the non-derated measurements made in the milk solution to better estimate in situ exposures. MI values were calculated for derated measurements made in water and non-derated pressures made in condensed milk solution.

4.2.2 Finite Element Method Tissue Heating Simulation

In addition to the mechanical impact of ultrasound, measurements were made to assure that the sequences were within applicable tissue heating limits. In order to evaluate the thermal safety of transthoracic ARFI imaging, finite element methods (FEM) were used to model the expected temperature rises within the tissue due to the acquisition sequences. To simulate the heating induced in tissue, the first step was to calculate the spatial distribution of acoustic intensity for a model of the
P4-2 transducer focused at 4.0 cm with an F/\# 2.0. This was done using FIELD II, a linear acoustic field simulation software program \([62]\). Intensity field data were normalized, and values less than 5% of the maximum intensity were neglected to reduce computation time. Normalized values were then scaled such that the peak matched the results of acoustic intensity measurements from above.

The resulting intensity field was subsequently converted to a field of initial temperatures using the solution to Equation (4.1), which is a simplification of the linear bio-heat transfer equation 2.7 and neglects conduction and perfusion:

\[
T_i = \frac{q_v t}{c_v}
\]  

where \(T_i\) is the approximate initial temperature at a point in space at the end of the insonification time, \(t\). This method is valid for our relatively short (< 1 ms) insonification time compared with the thermal diffusivity of the tissue being modeled \([91]\).

The model treated tissue as a thermally homogeneous, isotropic solid having a density of 1060 \(kg/m^3\), a specific heat of 4.2 \(Ws/cm^3/C\), and exhibiting quarter symmetry to reduce computation time. In order to simulate a continuum of tissue, the boundaries of the model were treated as insulating boundaries.

An implicit, time-domain finite element analysis package (LS-DYNA, Livermore Software Technology Corporation, Livermore, CA) was used to characterize the thermal response of the modeled tissue to the ARFI excitation or “pushing” beam. Tracking that was used during ARFI imaging employed standard B-Mode pulses which generally have a pulse length and energy less than 1% of the excitation. The temperature rises associated with these pulses are considered negligible and are ignored in this model.

With the spatial and temporal results of a single excitation, MATLAB was then used to determine tissue heating for an entire sequence of excitations, using the
convolution property of linear systems. The maximum temperature profile through time from a single “push” was extracted from the dataset of temperatures. Since these temperatures are the result a linear model and solver, the results from several temporally-delayed excitations can be superimposed with the appropriate delays to find a cumulative heating effect.

The effects of blood perfusion cooling and tissue motion would both tend to spread and reduce the applied heat. Both factors were neglected in this model, and thus, the results represent a conservative “worst-case” scenario. In this scenario the transmit beams all perfectly overlapped in the same segment of stationary tissue and no blood perfusion cooled the affected myocardial tissue. In reality, these effects are non-negligible (perhaps quite significant) in the vigorously moving, perfused heart.

4.2.3 Transducer-Face Heating Measurement

In addition to heat buildup in the target tissue near the focus or in the intervening path, there is a potential for significant heat to be deposited in the matching layer and lens of the transducer, in direct contact with the patient’s skin. To ensure the safety of the transthoracic ARFI imaging sequences, temperature rises were measured at the surface of the P4-2 transducer using a 36-gauge Type-T thermocouple placed on the center of the transducer face. An OMB-DAQ-3000, 16-bit/1-MHz USB data acquisition system (Omega Engineering, Stamford, CT) was used to digitize the signal which was captured using custom Labview software.

The Verasonics was programmed to operate the transducer with an ARFI excitation frequency of 2.0 MHz and tracking pulses at 2.5 MHz, with the same intensities and durations which would be used for the animal and clinical trials, as seen in Table 3.1. Heating profiles from M-Mode ARFI imaging data sets focused at a depth of 4.0 cm were acquired using a tissue-mimicking phantom (CIRS Corporation, Norfolk, VA). Ultrasonic transmission gel was used to ensure proper acoustic coupling from
the transducer to the phantom. The transducer face was allowed time to return to its steady-state diagnostic B-Mode imaging baseline temperature before each ARFI acquisition sequence was initiated. High frequency noise in the thermocouple data was removed with a running-average time domain filter.

4.3 Results

4.3.1 Acoustic Intensity Measurement

Nonlinear propagation of ultrasound through water threatens the simplifying assumptions required for using derated water-derived measurements [30, 21]. To address this issue, methods were developed for extrapolating measurements from the “quasi-linear”, small-signal region in water to the non-linear region, so that linear tissue attenuation models can be more accurately applied. The extrapolation approach can lead to overestimation of actual in situ values, because it ignores nonlinear losses that can occur in lossy media. This is a small effect in Figures 4.1 and 4.2, as seen when comparing the red line and blue curve. Figures 4.1 and 4.2 indicate that extrapolation can provide a reasonable estimate of PRP at the frequency used here. It is more problematic with higher frequency transducers, in which the extrapolated red lines would have much steeper slopes.

To make measurements in a way that is more comparable to in situ conditions, PRP’s are made in lossy media and shown as green dots in Figures 4.1 and 4.2. The PRP’s measured in water, derated assuming 0.3 dB/cm/MHz (blue curve) provides, in this case, a reasonable approximation to the PRP’s measured in the condensed milk solution (green dots), which had an attenuation coefficient similar to tissue.

Using the measured peak rarefractional pressures, MIs were calculated from the derated water, seen in Figure 4.3a. The ‘MI’ equivalent measurement made in attenuating condensed milk solution is seen in Figure 4.3b. For shallow focal depths, it was possible to achieve MIs that were above 3.0 by using voltage amplitude larger
than 30 V. For deeper focal depths of 50-70 mm, it was not possible to exceed MI of 3.0 even with a 45 V input voltage amplitude.

As described in Chapter 2, Fry and Dunn reported results of studies to quantify the dosages of ultrasound which caused permanent damage in feline brain tissue [42, 32]. In that work they suggested a safety metric using the product of the spatial-peak intensity (in W/cm$^2$) and the square root of the time (in sec$^{1/2}$) of the pulse was applied. To calculate this metric for the ARFI and SWEI sequences, the linearly-extrapolated derated intensities were measured in water at the input voltages used in the animal and clinical trials.

Using the P4-2 transducer with a 2 MHz excitation, 4.0 cm focus, and a derated water MI of 3.0, a spatial-peak, pulse-average intensity ($I_{SPPA}$) was measured to be 3000 W/cm$^2$. To examine the threshold metric for a single excitation, this pulse-average intensity could be used over just the time of a single ARFI excitation pulse. With durations of 0.48 ms in the case of M-Mode, or 0.96 ms in the case of SWEI, the threshold metrics are 66 or 93 respectively.

Since the M-Mode and SWEI sequences used for cardiac applications are composed of several excitations over the course of 1–4 seconds, examining an entire ARFI sequence requires using the temporal-average intensity (rather than pulse-average) and taking into account the duty cycle of the pulse sequence. To calculate this duty cycle, only the time during ARFI excitation is considered ‘on-time’ and the short B-Mode tracking pulses are neglected as ‘off-time’. In this scenario, the peak intensity is reduced by this duty cycle, but the time duration used is that of the entire acquisition sequence, rather than just the pulse duration. By taking into account the whole sequence and the duty cycle, the results are shown in Table 4.1 and are far below the levels (250-500) of reported damage.
Table 4.1: Fry and Dunn Threshold

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Pulse Dur. (ms)</th>
<th>PRI (ms)</th>
<th>Duty Cycle (%)</th>
<th>$I_{SPTA}$ (W/cm²)</th>
<th>$\sqrt{t}$</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Hz SWEI</td>
<td>0.96</td>
<td>333.3</td>
<td>0.29</td>
<td>8.7</td>
<td>$\sqrt{3.67}$</td>
<td>16.7</td>
</tr>
<tr>
<td>50 Hz M-Mode</td>
<td>0.48</td>
<td>19.52</td>
<td>2.46</td>
<td>74</td>
<td>$\sqrt{1}$</td>
<td>73.8</td>
</tr>
<tr>
<td>25 Hz M-Mode</td>
<td>0.48</td>
<td>40</td>
<td>1.21</td>
<td>36.3</td>
<td>$\sqrt{2}$</td>
<td>51.3</td>
</tr>
</tbody>
</table>

4.3.2 Finite element method (FEM) model results

Example temperature plots from the FEM simulation study are shown in Figure 4.4, with the SWEI sequence in (a) and the M-Mode ARFI imaging in (b). The peak temperature occurred just shallow to the ARFI “push” focus, just after the last transmit event in either case.

The full FEM tissue heating simulation results are shown in Table 4.2. The $I_{SPTA}$’s used in this simulation correspond to MIs of 1.9, 2.5, and 3.5 at this focal depth of 4.0 cm. They include sequences used in the animal and clinical studies as well as even more aggressive configurations to explore the safe domain of possible sequences for future applications. As seen in the table, three of the simulated configurations exceed a temperature increase of 4°C, while one exceeds 7°C. None of these four were configurations that would be used in the studies, but it is interesting to note that the problematic configurations all had an $I_{SPPA}$ which corresponded to an MI over 3.5 for this 4.0 cm focal depth.

Here, a worst-case scenario is assumed in which all of the pushing beams overlap spatially, and any effects of blood flow or tissue motion are neglected. These factors could presumably have quite a large cooling effect in cardiac tissue near the ventricles. Also, these results are for single acquisitions (of multiple “pushes”), but if several acquisitions were to be taken in a short time, the cumulative heating effect may become problematic. In that case, a more complex model which includes the effects of tissue motion or conduction from blood flow may be more useful in determining
Table 4.2: Tissue Heating Simulation Results

<table>
<thead>
<tr>
<th>Acq. Rate (Hz)</th>
<th>Pulse Dur. (ms)</th>
<th>$I_{SPPA}$ (W/cm²)</th>
<th>Peak Temp. Rise (°C)</th>
<th>at Depth (cm)</th>
<th>at Time (s)</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>3.0</td>
<td>0.96</td>
<td>800</td>
<td>0.15</td>
<td>3.81</td>
</tr>
<tr>
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<td>1500</td>
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</tr>
<tr>
<td>5</td>
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<td>0.96</td>
<td>3000</td>
<td>0.58</td>
<td>3.78</td>
</tr>
<tr>
<td>11</td>
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<td>0.96</td>
<td>800</td>
<td>0.24</td>
<td>3.75</td>
</tr>
<tr>
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<td>0.96</td>
<td>1500</td>
<td>0.45</td>
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<tr>
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<td>3000</td>
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<td>0.96</td>
<td>800</td>
<td>0.62</td>
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</tr>
<tr>
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<td>1500</td>
<td>1.17</td>
<td>3.78</td>
</tr>
<tr>
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<td>1.21</td>
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<tr>
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<td>800</td>
<td>1.92</td>
<td>3.79</td>
</tr>
<tr>
<td>200</td>
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<td>1500</td>
<td>3.60</td>
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<td>0.48</td>
<td>3000</td>
<td>7.20</td>
<td>3.76</td>
</tr>
</tbody>
</table>

more accurate in situ heating exposures.

4.3.3 Transducer Face Heating During ARFI Imaging

In addition to simulating the heat that could build up at the focus or in the inter-
vening tissue layers, the temperature at the transducer-skin interface is another site
of concern for heat buildup.

Figure 4.5 shows example heating curves from thermocouple measurements on
the face of the transducer. Four different configurations are plotted here: the first
two groups (Figure 4.5a and 4.5b) are from 0.96 ms excitation length SWEI pulses,
<table>
<thead>
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<th>Acq. Rate (Hz)</th>
<th>Voltage (V)</th>
<th>Peak Temp. Rise (°C)</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
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</tbody>
</table>

while the third and fourth (d,d) use 0.48 ms ARFI imaging “push” pulses. The voltages in the figure correspond to the levels used in the laboratory and clinic.

Table 4.3 shows the complete results from thermocouple measurements of sequences which would be used in the animal and clinical studies to come. The face heating measurements are all below 1.3 °C, a level that is safe to apply in single-shot acquisitions. However, as with the FEM simulation results, if several acquisitions were fired in a short time, relative to heat dissipation, then the overall temperature increase at the skin might exceed 4–6 °C, and thus case should be taken to limit the acquisition rate.
4.4 Discussion and Conclusions

In this chapter, we presented a safety analysis, using FEM models, thermocouple, and hydrophone measurements to assess and calibrate the thermal and mechanical impact of transthoracic ARFI and SWEI sequences. Results from the FEM simulations show that with appropriate choice of acquisition rate, the tissue temperature increases induced by M-Mode ARFI imaging or SWEI measurements can be kept under $4^\circ$C, well within the thermal limits imposed by the FDA for short duration diagnostic imaging in soft tissue. The face heating measurements showed temperature rises from single acquisitions of ARFI imaging or SWEI sequences, even at MIs up to 4.0, were less than $1.3^\circ$C. With appropriate decisions of input voltage and acquisition rate, transthoracic ARFI imaging and SWEI can be applied in a safe manner for animal studies or clinical trials.

4.5 Acknowledgments

For their contributions to this chapter, I want to acknowledge Dr. Kathy Nightingale, Dr. Mark Palmeri, Ned Rouze, Stephen Rosenzweig, V Kakkad, Doug Giannantonio, and Ocean Lou.
Figure 4.1: Peak Rarefractional Pressure (PRP) values measured in water (black), PRP water measurements derated by 0.3 dB/cm/MHz (blue), PRP derated-water measurements linearly extrapolated from small-signal values (red lines), and PRP measurements made in an condensed milk solution with $\alpha = 0.36$ dB/cm/MHz; (green points). Derating water by 0.3 dB/cm/MHz (blue line) provides reasonable agreement with the milk measurements (green dots). Linear extrapolation (solid red lines) overestimates the milk measurements, due to nonlinear losses that occur at higher pressures in the milk. The transducer was focused from 30 mm (a) to 60 mm (d) with F# varying linearly from 1.5 to 3.0
Figure 4.2: Peak Rarefractional Pressure (PRP) values measured in the same manner as in Figure 4.1, but with a 70 mm focus, F# 3.5, and condensed milk solution with $\alpha=0.54$ dB/cm/MHz. As in Figure 4.1, derating water by 0.3 dB/cm/MHz (blue line) provides reasonable agreement with the milk measurements (green dots).

Figure 4.3: Mechanical Index values, measured in water (a), derated by 0.3 dB/cm/MHz, and ‘MI’ measurements made in a condensed milk solution (b) with $\alpha=0.36$ dB/cm/MHz for 30–60 mm and $\alpha=0.54$ dB/cm/MHz for 70 mm. MIs are at 1.9 for input voltages 20–34 V for various foci, and below 3.0 for voltages below 30 V for all foci.
Figure 4.4: Example FEM tissue heating simulation results of shear wave elasticity imaging (SWEI) (a) and M-Mode ARFI sequences (b). In the SWEI case, 11 acquisitions were simulated at 3 Hz with 0.96 ms “pushes”. For the M-Mode ARFI example shown here, 50 acquisitions were simulated at 25 Hz with 0.48 ms “pushes”. The peak heating for these two examples are 0.91 °C and 2.28 °C respectively, and the peak occurs just shallow to the focus at the end of the sequence. Both configurations used an MI of 3.5, exceeding that used in the animal and clinical studies, but even so, for single acquisitions, temperature rises remain well within limits.
Figure 4.5: Thermocouple transducer face heating temperature traces for SWEI (a,b) and M-Mode ARFI sequences (c,d). All configurations show face heating less than 1.3 °C, indicating a safe level for single acquisitions.
5.1 Introduction

Heart failure with preserved EF is a difficult condition to diagnose and monitor [121]. Most direct measures of the condition of the cardiac muscle are either expensive, slow, difficult to perform, require interventional procedures, or unreliable in their diagnostic performance. Using a non-invasive method such as transthoracic echocardiography to implement ARFI imaging could help to diagnose the condition of the myocardium and enable monitoring of the physical properties of the heart. The goal of this study is to refine experimental methods and test the feasibility of transthoracic ARFI imaging to measure properties of the myocardium before and after inducing heart failure.

5.2 Methods

5.2.1 Study Protocol

Eight porcine subjects were studied in an experimental model intended to progressively induce worsening heart failure. All study protocols were approved by the
Institutional Animal Care and Use Committees (IACUC) of Duke University and the third-party surgical laboratory (Synecor, LLC, Durham, NC) used in the first phase of the study. One of the pigs was used as a control, and the other were given focal infarctions through a series of foam embolizations directed through the left anterior descending (LAD) coronary artery. The occlusion method was initially designed to induce progressive global heart failure, but actually led to the animals having a pathology of an acute infarction. Additionally, subsequent imaging revealed that the embolization was not specific to the LAD but also affected other epicardial coronary artery distributions.

![Figure 5.1](image)

**Figure 5.1:** One of the surgical suites at Synecor, LLC., with our heart rate monitor and Verasonics Research Platform with live B-Mode display and real-time ARFI displacement image.

The embolizations caused focal infarctions in the intraventricular septum (IVS), apex and left ventricular free wall (LVFW). The animals were imaged using ultrasound several times over the course of the study: once prior to the embolization, and several times following, over a time period 150 days. The first series of experiments was performed at Synecor, while the final imaging study for each animal was completed at Duke.

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5.2.2 Animal Preparation

Twenty-four hours prior to each scanning session or surgery, the back of the animals neck were shaved and a narcotic analgesic fentanyl patch was applied. On the day of the study, cefazolin and iron dextran were administered, the animal was sedated with ketamine hydrochloride, and isoflurane anesthetic gas was administered via a mask. The animal was then shaved, ECG patches were applied, and an IV line was established in a leg vein. An endotracheal tube was inserted, and the animal was placed on a ventilator. An orogastric tube was passed into the stomach to prevent rumen aspiration. ECG leads were attached so that heart rate and rhythm could be monitored and recorded alongside the ARFI imaging trigger signal. An intravenous infusion of NaCl was maintained throughout the study. A femoral artery was accessed via the Seldinger technique \[106\]; arterial blood-gas and electrolyte measurements were made hourly, and corrections were made as needed.

5.2.3 Ultrasound Scanning Protocol

Images were acquired using the Verasonics scanner and the P4-2 phased-array transducer operating at 2.5 MHz. The scanner was programmed with custom beam sequences to excite the myocardium with focused acoustic radiation force (ARF) impulses and to detect the subsequent tissue response. Raw RF or demodulated IQ data were obtained for later analysis. Images were acquired from both parasternal long-axis and apical 4-chamber views in the left ventricles, in and out of infarcted regions. The excitation and tracking sequence was repeated rapidly in the same location to generating either 25 Hz ARFI M-Mode images or 3 Hz SWEI movies at a single “push” steering angle. The beam sequences and signal processing methods used in this study are the same as those described in Chapter 4. A summary of the relevant imaging parameters can be found in Table 3.1.

With the animal in a prone position, the images were acquired through a window
removed from the bottom of the surgical table. The animals were imaged from the following positions to examine several regions and targets of interest. From the left lateral decubitus position, a 4-chamber view allowed imaging of the lateral wall, septal wall, and anterior wall. With the subject in a supine position and the transducer in a mid-sternal location, a parasternal long-axis view allowed imaging of the antero-septal wall, short-axis anterior, and septal walls. Finally, a subcostal view was obtained with the transducer at the inferior part of the sternum to image the LV apex.

5.2.4 Terminal Imaging Session

Electroanatomical Mapping

After the transthoracic scanning was complete, electroanatomical substrate mapping (EAM) was used to delineate post-infarct scar [23, 34]. EAM systems, such as the CARTO XP EP Navigation System (Biosense Webster; Diamond Bar, CA) use magnetic or electrical field-based tracking to locate catheter electrode tips in the heart. The location data are used to construct heart chamber geometries and chamber surface voltage maps [45]. Myocardial infarct scar is identifiable by bipolar voltage (BPV) less than 1.50-mV [23]. A point-by-point BPV map was made of the porcine LV using a CARTO XP EP System.

Tissue Preparation and ex vivo Imaging

At the end of the heart failure protocol, each animal was transported to Duke for the final imaging session. Following transthoracic imaging, intracardiac and open-chest epicardial imaging was completed for unrelated studies. At the end of the study, 20 mg of Gadolinium was injected 10 minutes prior to euthanasia. Pigs were euthanized with a potassium infusion. The whole heart was excised and placed in a secure container. The heart was thoroughly washed and filled with Fomblin® (Solvay...
The heart was suspended within a jar and placed in a 3T MRI scanner. Delayed-contrast enhanced imaging was performed serially through the whole heart. Image slices were exported for further analysis and verification of infarct location.

The heart was stored in a freezer overnight, cut into 0.5 cm thickness cross-sectional slices, and photographed for visualization of infarct locations.

5.2.5 Multi-beat Synthesis

To compile the M-Mode ARFI displacement data acquired across multiple heartbeats, a technique called multi-beat synthesis [58, 51] was used to register estimates from several acquisition frames onto a single heartbeat. The standard deviation of each individual displacement estimate within the tracked axial region of interest and the correlation of the tracking pulse to the reference pulse were used to exclude the bad estimates by setting thresholds of $\rho = 0.9$ and standard deviation twice larger than the mean in the region. These masks excluded low quality estimates from further processing. Using matched ECG data as in Figure 5.2, the remaining displacement estimates were registered to each preceding R-wave complex. The data points were grouped into time bins and resampled so all estimates could be registered on a single beat.

For the M-Mode sequences, the 50 temporal samples cover all phases of the cardiac cycle for the central steering angle. Twenty evenly spaced time bins were used to subdivide one heart cycle, with each of the 50 estimates placed into the nearest bin. The mean and standard deviation were found for all the estimates within each bin. This method allowed the assessment of temporal repeatability of ARFI displacements. It did rely, however, on acquisitions being made in a stable region of interest, and it was sensitive to shifts in position or changes in motion. Multibeat synthesis also performs poorly in combining data in cases of arrhythmia.
Figure 5.2: Multibeat synthesis combines samples taken over multiple acquisitions onto a single beat. (a) shows the peaks detected in the ECG wave from a single acquisition and displacement estimates across the two second interval. A timing remapping is found for each R-wave to R-wave segment, which is applied to the displacement data as seen in (b). Once combined with other acquisitions in the same ROI, means and standard deviations are found for data in each vertical band.

5.2.6 Model Fitting

In order to get quantitative values for comparison out of the synthesized displacement data curves, a piecewise-linear model was fit to the experimental data. The model fit two flat displacement levels and two sloped lines connecting the levels. The time periods of each segment were allowed to vary in MATLAB’s robust curve fit [33], in which the bi-square weight method was used to reduce the influence of outliers in the data. Figure 5.3 shows an example multibeat synthesis curve and the points from the fit of the model overlayed. The metrics that were accessible from the model include the displacement during systole and diastole, the time durations of the segments for systole, diastole, and the transitions between them (isovolumic contraction and relaxation). From these primary values the additional following parameters were calculated: displacement difference and rate of change in displacement between the phases.
5.3 Results

5.3.1 Pre-injection Scanning At Synecor

The intended progressive dysfunction model of the study was not properly achieved, as the embolizations of foam into the coronary arteries caused an acute focal infarct rather than a progressive reduction in function. After prematurely losing four of the initial cohort of pigs, the protocol was altered to a smaller embolization procedure performed just once, rather than multiple times over several weeks.

The farm pigs used in the study, one of which is pictured in Figure 5.1, were relatively small at the onset, with average mass $30.1 \pm 2.0$ kg. They grew rapidly, however, and the infarcts became quite deep relative to the skin surface. This did not pose a problem for the intracardiac echocardiography segment of the study which is not presented here, but it profoundly impacted the scientific conclusions that could be drawn from the transthoracic segment presented in this dissertation. For most of the animals’ fields of view, the infarcts were at depths that were beyond the capabilities of the designed Verasonics ARFI sequences. The field of view of the ARFI data acquisition reached only to 7.0 cm, and the infarcts were often at or beyond that depth. Also, for focal configurations past 6 cm, there was inadequate “push” from radiation force that reached the depth of interest to produce measurable
displacements.

Three infarcted animals survived the embolization process. Together with the one control animal, the four were scanned up to five times at Synecor over the course of the study and were scanned a final time at the Duke Center for Emerging Cardiovascular Technologies surgical suite, shown in Figure 5.4.

Due to a lack of infarct samples to compare the three pigs with the control over the course of the study, the analysis presented herein will follow the repeatability of M-Mode ARFI measurements in a single animal over time. The animal studied here was scanned during five transthoracic imaging sessions at Synecor, and a final experiment at Duke. Ejection fraction measurements for this animal were $52.5 \pm 7.5\%$ pre-embolization and $38.0 \pm 5.7\%$ 8 days post-embolization. Its mass increased from 29 kg to over 57 kg during the course of four months. Over time, the imaging became more challenging, as seen in the complete set of multibeat synthesis data curves are presented in Appendix A.
In the first study, five of the six views (all but the apical short-axis septum) in the analysis show trends of displacements consistent with expected physiologic contraction during systole and relaxation in ventricular diastole. An example ARFI image acquisition from the first scan of the lateral wall of the LV is shown in Figure 5.5. The displacements in the myocardium (d) rise and fall with the relaxation and contraction of the heart with good synchronization to the ECG (b). During the rapid change in acceleration at the onset of contraction and relaxation, the quadratic motion filter performs poorly with large variance estimates seen during transitions between low-displacement and high-displacement states in the displacement curve (d).

Throughout the pre-injection scans at Synecor, six regions of interest were acquired: (a) apical four-chamber lateral wall, (b) apical four-chamber long-axis septum, (c) short-axis septum, (d) parasternal long-axis septum, (e) parasternal short-axis septum, and (f) short-axis inferior wall. The multibeat synthesis for these views are shown in Appendix A.

In the second imaging session, there were only two views that displayed displacement trends relatively free of high variance corruption (Figures A.2a and A.2f).

The third study showed much better beat-to-beat repeatability and trends across six of the eight views (Figures A.3c, A.3d, A.3e, A.3f, A.3g, and A.3h).

In the fourth imaging study, results in that the apex (Figure A.4a), lateral wall (A.4b and A.4d), and long-axis septum (A.4e) showed good estimates in diastole and systole. In a ROI that was a possible a lateral infarct (Figure A.4c), results displayed large variance estimates, with relatively low mean displacement through the cardiac cycle.

In the final imaging session, only the apical long-axis septum displayed substantial differences between systole and diastole with narrow variance.

The results in Table 5.1 show good beat-to-beat repeatability for the shallow api-
Figure 5.5: Images from healthy lateral wall of the LV from the initial scan of a porcine subject. B-mode was unavailable in the early studies. (d) displays highly repeatable cyclic variation of ARFI displacement in the region of interest, which is marked in white in (c). The ECG signal in (b) shows excellent synchronization to the ARFI results.

cal 4-chamber lateral wall in most of the imaging sessions, as displayed in multibeat synthesis Figures A.1a, A.2a, A.3d, A.4b, A.5d, and A.6d.

For most of the views, particularly the apical short-axis septum (shown in Figures A.1e, A.2c, A.3f, A.5e, and A.6c), the variance across the multiple beats and acquisitions became progressively worse over the course of the study as the animal grew.

In the fifth serial study of the animal at Synecor, only the apical LV (Figure
A.5a) showed low variance estimates in systole.

In order to compare these multibeat synthesis curves more quantitatively, the mean displacements were fit to a piece-wise linear model across the heartbeat segment. Some of these curves contained some poor estimates and produced fits that did not reflect the actual underlying stiffness changes of the myocardium.

The views scanned more than twice are shown for comparison in Table 5.1. The results indicate that the diastolic displacements were consistently higher than those of systole. Most of the fits exhibited ratios of systolic-to-diastolic displacements in a range between 1.2:1 and 3.5:1, similar to numbers found by epicardial and transthoracic (5.5:1 with n=1) methods published by Hsu [55]. The stiffening rates appear to be consistently faster than the corresponding relaxation rates. The variability in the rate metrics across multiple scans is quite high, since it relies on a derivative of noisy data.

5.3.2 Terminal Study

By the time the animal was scanned the final time, it had grown to be quite large, with mass 62 kg. This fact was problematic for transthoracic scanning through thick layers of skin and fat. The size of the animal limited available views of the infarcts that were in some cases at depths that exceeded the maximum ARFI acquisition field of view (7 cm).

In the case studies are shown, there was only one field of view that contained apical infarct in the range possible for ARFI imaging. The other infarct location was in the interventricular septum which could be visualized in B-Mode echo, but at the depth of 7.5 cm, it was too deep for transthoracic ARFI methods (as they are currently implemented), to displace or to track. Results from this final study will be shown, analyzed and discussed for the spared myocardium, presumed infarct, as well as suspected imaging artifacts

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Table 5.1: Model fit parameter results from serial animal studies. $D_{dia}$ is displacement ($\mu m$) in diastole; $D_{sys}$, ($\mu m$) systole; ratio is $D_{dia}/D_{sys}$; $-dD/dt$ is stiffening rate ($\mu m/s$); $+dD/dt$ is softening rate ($\mu m/s$).

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</table>
**Healthy Myocardial Region**

The parasternal short-axis position allowed the anterior septum to be viewed at a depth of 4 cm. The myocardium appeared to be contracting vigorously with each heartbeat, and later MRI images confirmed a lack of infarct at this first ROI.

![Figure 5.6](image)

**Figure 5.6**: Images from a segment of healthy myocardium from the anterior septum in a *porcine* subject. The B-mode (a) shows a wide field of view and the vertical line indicates the M-Mode location. (b) displays highly repeatable cyclic variation of ARFI displacement in the region of interest, which is marked in white in (e). The ECG signal in (c) shows excellent synchronization to the ARFI results.
An example acquisition from this ROI is shown in Figure 5.6. The displacement plot shown in 5.6b) shows a large variation in displacement through the cardiac cycle, with relatively low variation through depth, indicated by the error bars. The displacement through time was very consistent over the three heartbeats in the ECG signal (5.6c). The B-mode image (5.6a) showed a minimal amount of clutter. The cine loop movie exhibited physiologic motion that was primarily in the axial direction, which can be compensated by the 1-D motion filter used in processing the data. The M-Mode (5.6d) and M-Mode ARFI images (5.6e) display the manually-traced axial ROI which was used for the displacement analysis.

There were five acquisitions at this site, all acquired with an MI of 3.0 for this 4 cm focal depth. The multibeat synthesis process which was previously described was then used to co-register all of the R-waves from the five acquisitions. The overlayed data was used in further analysis.

![Figure 5.7: Multibeat synthesis result from viable myocardium in terminal study](image)

Five acquisitions from this region of interest were combined with multibeat synthesis with the combined mean and standard deviation plotted in Figure 5.7. The synthesized displacement data had a range of 3.6–13.6 µm with a diastolic-to-systolic displacement ratio of 3.78, which was in the same range as reported from epicardial methods [52].
**Infarcted Tissue at Apex**

![B-Mode Image](image1)

![ARFI Displacement](image2)

![ECG Signal](image3)

![M-Mode Image](image4)

![M-Mode ARFI Image](image5)

**Figure 5.8**: Images from a segment of suspected infarct in the apex in a *porcine* subject. The mean displacements in the ROI (b) remain low (< 2 µm) through the cardiac cycle, suggesting a stiff, non-contracting target. The M-Mode image in (d) shows very little motion of the cardiac tissue.

In Figure 5.8, an example dataset from a suspected infarct in the apex is shown. Low ARFI displacement through the cardiac cycle as seen in Figure 5.8b and 5.8e. The M-Mode shows little motion of the ROI 5.8d. This suspected infarct region was captured in two subsequent acquisitions which appeared stiff and non-contractile.
When the results from each heartbeat in these two acquisitions are overlayed via multibeat synthesis, the resulting plot can be seen in Figure 5.9, which shows low displacements through the cardiac cycle and poor temporal repeatability.

![Graph showing ARFI displacements](image)

**Figure 5.9**: Multibeat synthesis results from two acquisitions in infarcted tissue at the apex. ARFI displacements are less than 2 µm in the infarct. The large variance in many of the estimates indicates low temporal repeatability across the two acquisitions and heartbeats. The displacements in systole and diastole do not show clear trends of contraction and relaxation through the cardiac cycle.

*Shallow, Compliant Structure*

Near the same suspected infarct location, the two subsequent acquisitions displayed a shallow, compliant structure that appeared to obscure the region of interest with high displacements in the tracking line. An example image set from these two is shown in Figure 5.10. Suspected reverberation from this proximal structure may have caused the ROI to track coherently with the layer above. The region of interest appears to stiffen and soften similar to healthy myocardium. This phenomenon was observed in several of the animal studies. In the B-Mode cine loop for this case, there did not appear to be large physiologic motion in the lateral or elevation directions. A possible explanation of this phenomenon is that the layer of fat proximal to the myocardium was being passively stretched by the contraction of healthy cardiac tissue out of plane from the infarct and imaging plane. This observed pattern of displacement through the cardiac cycle appeared similar to that seen in healthy myocardium, and
Figure 5.10: Images from a segment of infarcted myocardium with a compliant structure proximal to the ROI. The highly-displacing target in (e) confounds the analysis of the myocardial region below it marked by the white horizontal lines. This evidence does not support our hypothesis that infarct and healthy myocardium can be discriminated definitively with transthoracic ARFI methods.

Clutter

In addition to stable clutter than appeared from near field reverberation and write-in from stationary layers and structures, in some fields of view, clutter patterns were
observed to be moving out of phase with myocardial motion. This signal was often as bright as that from the myocardium, and since the displacement estimator tracks the dominant signal, this clutter caused high variance spatial and temporal estimate results.

In a short axis septal view from this same experiment, an example image set is shown in Figure 5.11. There is a pattern of moving clutter visible in the cine clip and was just right of center in the B-Mode image (Figure 5.11a). The pattern of displacements through the cardiac cycle exhibited a large variance through time and across the axial extent of the ROI in Figure 5.11e.

**Infarct Location Verification**

During the final animal study, the electrical and anatomical properties of the LV were mapped, and these electroanatomical substrate mapping (EAM) results shown in Figure 5.12. They images clearly delineate post-infarct scar with bipolar voltages less than 1.50 mV, from unaffected myocardium. The location of the myocardial infarct scar in the apical-septal LV apex.

Prior to the completion of the experiment, a Gadolinium contrast agent was injected while the animal was still alive. After euthanasia, the heart was excised and scanned using a 3T MR scanner before being prepared for histology sectioning and photography. The MRI volume renderings (Figure 5.13) show areas of infarct and healthy tissue. Infarcted tissue appears in the MR image as bright white, and healthy myocardium appears darker. Areas of apparent infarct include tissue at the apex and along the territories of the LAD coronary artery, and in the left ventricular free wall. Results agree well with the electrical map of the LV.

Finally, photographs of the sliced heart tissue are seen in Figure 5.14a, where the white areas of the photographs indicate infarcts near the apex, septum, and free wall of the LV. The healthy myocardium appeared red. White regions near the base of
Figure 5.11: Parasternal short axis view of inferoseptum with clutter field overlaying myocardial ROI. B-mode (a) shows clutter near the M-Mode location. The ARFI displacement image (e) shows high displacements with large variance through depth in the ROI.

the heart were supporting cartilage, rather than infarct.

5.4 Discussion and Conclusions

In this chapter, it was shown that transthoracic ARFI imaging could be used to measure relative stiffness through the cardiac cycle in porcine hearts in vivo. When
Figure 5.12: Electroanatomical bipolar voltage (BPV) map of apical-septal myocardial infarct in the left ventricle. Bipolar voltage below 1.50-mV indicates the presence of scar.

Figure 5.13: Gadolinium-enhanced MRI volume renderings of one of the porcine hearts, showing infarct in the left ventricular free wall (a), at the apex (b), and left anterior descending (LAD) coronary artery (c).

The B-Mode quality was good and clutter was limited, ARFI focal depths between 3 and 5 cm were possible.

In a companion intracardiac echocardiography (ICE) imaging study performed alongside the transthoracic approach presented here, Hollender, et al., published results of M-Mode ARFI and SWEI in views of the LVFW (two infarcts and three healthy) and IVS (three of each) [50]. The infarcts in both views showed on-axis ARFI displacements ratios between 1.5:1 and 2:1. The healthy subjects displayed ratios between 2:1 and 3:1. He also did an analysis of shear wave velocities in 6
Figure 5.14: View of the excised heart specimen from the anterior (a), and several slices from base to apex (b–e). Infarct and connective tissue appears white, while healthy myocardium is red. Infarct is seen in the apex, anterior wall, lateral wall, and interventricular septum in the sections.

healthy pigs before embolization from the same study [51]. The results of these two papers demonstrate that underlying stiffness contrast did exist in the animals which were scanned by ICE and TTE methods. If the region of excitation can be increased to the 5–7 cm range, transthoracic ARFI may be able to be shown feasible at making similar measurements non-invasively.

As the animals grew larger throughout the study, challenges were encountered in tracking through reverberant clutter and inadequate excitation at depth due to absorption from thicker proximal tissue layers. The size of the hearts also presented challenges in reaching the infarcts within the field of view. Only one infarct location was in a relatively accessible apical position and imaged in the study.

One view of the suspected infarct displayed the tissue motion as non-contractile and ARFI displacement as stiff through the cardiac cycle. Two others views in the same region displayed larger displacements, possibly attributable to clutter from structures appearing proximal to the suspected infarct in the pericardium or chest wall fat and muscle. Neither the MRI volumes nor the gross pathology slices displayed evidence supporting a compliant region at the site of the infarct.
Image artifacts discussed here have limited the ability of transthoracic ARFI to discern infarct from healthy myocardium in the cases examined. Results of this study support the need for continued development of the methods and testing clinical viability of transthoracic cardiac ARFI imaging.

The observations from this animal study influenced the plans for the subsequent clinical trial, and the focus was narrowed to the relatively more accessible apical view and targets in the range of 3–5 cm. We also planned to study the effects of carefully varying the MI level of the applied radiation force, from the FDA MI limit of 1.9 up to 3.0.

5.5 Acknowledgments

The study in this chapter was made possible by members of the Trahey lab, Wolf lab, and the staff at Synecor, LLC. Thanks to Peter Hollender for writing code for multibeat synthesis and parametric fit. Other thanks is necessary for Dr. Robi Goswami for scanning, Dr. Han Kim and Dr. Lowie Van Assche for MR scanning, Dr. Doug Dumont, Dr. Brett Byram, Dr. Bisi Bell, Ellen Dixon-Tulloch, Peter Hollender, Stephanie Eyerly for help with the terminal study and histology, Dongwoon Hyun, and Brittany Potter. This study was funded by NIH grant 5 R37 HL096023-04 and R01EB01248.
Clinical Transthoracic Cardiac ARFI Imaging

6.1 Introduction

ARFI imaging was previously shown able to differentiate malignant from normal tissue in stationary structures such as human breast [108], prostate [120], and liver [35]. ARFI has also been used to image the heart from intracardiac [58] and open-chest methods [52]. However, application of ARFI methods in human transthoracic echocardiography has not been reliably demonstrated. For this pilot clinical study, the feasibility of using transthoracic cardiac ARFI imaging in a clinical setting was tested by enrolling patients with known infarcts and volunteers with healthy hearts.

Accurate non-invasive assessment of the heart is critical to optimal care in cardiology. The current non-invasive gold-standard for identification of myocardial infarction and infiltrative disease is cardiac magnetic resonance imaging (CMR) [41, 1, 60, 13, 75, 114, 115]. However, CMR is not portable, has limited availability, and can be prohibitively expensive. In addition, CMR precludes many patients with indwelling cardiac devices and those with significant claustrophobia. In contrast, transthoracic echocardiography (TTE) is portable, cheap, and ubiquitous in medical
centers. In addition, TTE has an excellent safety profile due to its lack of ionizing radiation. Although TTE effectively characterizes myocardial function, it is limited in its ability to specifically assess myocardial segments for abnormalities in stiffness or elasticity that may be caused by damaged tissue, with such findings suggesting infarction or other myocardial disease [41]. It is hypothesized that metrics of myocardial function may be obtainable using Acoustic Radiation Force Impulse (ARFI) imaging, and this may lead to effective characterization of damaged myocardium using TTE.

Some patients produce poor quality B-Mode ultrasound images under the current FDA regulations. The causes of this image degradation can include clutter from off-axis scatterers or reverberation from body wall layers, poor focus due to phase aberration from sound speed inhomogeneities or aberrating layers, or increased attenuation through a longer signal path in patients with larger body habitus. Guided by previous results in animal models, we tested the effect of changing mechanical index (MI) utilized for the ARFI “push” excitation on ARFI measurement quality. As a part of this clinical protocol, the Duke University Medical Center (DUMC) institutional review board (IRB) granted permission for the use of intensities exceeding the FDA MI limit of 1.9, up to a level of less than 4.0, based on the safety analyses performed.

We had originally hypothesized that at the higher MI level, the ARFI displacement signal would improve relative to the background noise due to motion, clutter, and other sources, and this improvement would be reflected in a higher diastolic-to-systolic displacement ratio when using MI = 3.0. However, through our experience in the animal studies, we got a better insight into the factors which complicate the analysis in transthoracic cardiac imaging. The first of these factors is motion. We have shown the ability model and compensate for tissue motion and strain in the axial dimension of our setup quite well over the time scale (1-3 µs) of our acquisition.
Motion in lateral and elevation dimensions are not tracked by our filters and would instead contribute to decorrelation of our tracking estimates, but over this short time scale we often saw the signals remain well correlated, indicating that these motions, as well as shearing and rotation, were not a significant contributor to error in the displacement estimates. The main difficulty with these motion profiles is they challenge our assumption of a spatially homogeneous ROI, moving targets with varied physical properties through the tracking beam through the cardiac cycle. Rather than monitoring the stiffness changes of a particular ROI through time, motion often caused us to measure responses from different tissue targets at points in the cardiac cycle. These tissues may increase or decrease the observed displacements depending on their stiffness, contraction, and motion pattern, further complicating our analysis.

Another factor influencing the successful measurement of myocardial tissue properties is the clutter which is seen in many images. If that clutter is caused from reverberation ring-down of near-field tissue layers, it can contribute significantly to the signal backscatter from the myocardium. This clutter can appear stationary or moving, and may have a flat or varying displacement response through the cardiac cycle. Clutter can also appear in an image due to write in from out-of-plane targets within the elevation beam width or off-axis structures from the lateral side lobes of the beam pattern. These clutter sources are often observed to have a motion profile uncorrelated to that of the myocardial ROI, and they may decrease the displacement ratio and increase the spatial and temporal variance of the estimates in the ROI. Finally, due to the cyclic nature of motion around the heart, except for cases of transducer or respiratory motion, all of these sources of corruption could exhibit good beat-to-beat repeatability, making that a poor metric for judging the success of acquisitions. Table 6.1 summarizes the expected effects of these confounding factors on measurements in transthoracic ARFI imaging.
Table 6.1: Expected effects of various confounding factors on the displacement ratio, jitter, beat-to-beat repeatability, and correlation in transthoracic ARFI measurements

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<tr>
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So, in this study it was thought that the myocardial displacement ratio may not be increased just by raising the MI if the sources of error were primarily near-field reverberation, off-axis clutter-generating targets, and motion of heterogeneous tissue. In these cases, the displacements tracked may just scale with the input power if the source of signals, but not reflect the properties of the ROI. However, in cases without these clutter and motion artifacts, but where sufficient radiation force does not reach the ROI due to prohibitively high attenuation or a long propagation path, the SNR may be improved by increasing the MI. The results of this study would suggest the primary source of degradation encountered in the imaging method.

6.2 Methods

6.2.1 Patient Population and Recruitment

Two subject populations were included in the study: 1) Healthy volunteers to serve as a control group, without coronary artery disease (CAD), CAD equivalents, or other systemic infiltrative disease and 2) Patients with known myocardial infarction, ideally localized by prior cardiac magnetic resonance (CMR) imaging. The study excluded minors as they were unlikely to have myocardial infarction, and healthy minors were not an appropriate reference group for adult patients with prior myocardial damage.
Due to risks associated with high mechanical index, patients receiving intravenous contrast agents were also excluded.

Subjects who met the inclusion criteria and none of the exclusion criteria were identified by key study personnel at the Duke University Medical Center’s (DUMC) Cardiac Diagnostic Unit (CDU). Patients were identified in the CDU itself, as expected if the patient had a previously scheduled echocardiogram. Otherwise, patients on the inpatient wards who met inclusion criteria were also approached. For patients to be screened for participation, access to Protected Health Information (PHI) was required by key personnel prior to consent.

All patients scheduled for an echocardiogram in the Cardiac Diagnostic Unit were screened prior to their scheduled appointment. This screen included an assessment of their medical history for evidence of prior myocardial infarction or CAD equivalents such as Diabetes Mellitus. Additionally, the screen determined if the patients had prior CMR imaging demonstrating the presence or lack of myocardial disease. Additionally, because only left ventricle was studied, patients were not screened for implantable pacemaker or defibrillator leads, since these would be located in the right ventricle. No PHI was recorded prior to written consent, which was obtained from all subjects prior to their inclusion in the study.

6.2.2 Data Acquisition and Imaging Protocol

We received IRB approval to use the Verasonics Research Platform to collect ARFI image measurements at up to six regions of interest in the heart at two or more intensity levels. The following myocardial segments of the left ventricle were targeted for imaging from the two-chamber or four-chamber views in the apical window: apex, septum, lateral wall, anterior wall, and inferior wall. For each segment, several ARFI sequences were recorded to evaluate reproducibility of the data. In each region of interest, M-Mode ARFI acquisitions were made using a “push” with Mechanical
Index (MI) at the current FDA diagnostic limit of 1.9 as well as power levels of MI = 2.5 and/or MI = 3.0. The power level of the ARFI excitation pulses and short tracking pulses are not controlled independently in the methods programmed on the Verasonics Research Platform, and thus the power level of the tracking pulses was increased in tandem. For each patient or volunteer, in addition to the acquisitions of M-Mode ARFI, two cardiac SWEI datasets were taken at the apex at MI’s of 1.9 and 3.0.

During imaging, patients were positioned in the supine or oblique positions on the examination table. ECG electrodes were attached in order to synchronize image analysis with the QRS complex, and to allow continuous monitoring throughout the study by the physician present. The ECG recordings acquired with the ARFI pulses were saved for later analysis. Patients were asked to hold their breath for approximately 2–4 seconds for each image while data was acquired and transferred.

ARFI sequences with parameters from Table 3.1 were acquired with the electrocardiogram. Real-time feedback was displayed during the imaging session, and the raw single-channel radiofrequency or in-phase and quadrature (IQ) ultrasound data were stored during the procedure and were further processed off-line. Final analysis was performed off-line utilizing the MATLAB software package with methods as in Chapter 5.

In addition to the multibeat synthesis and model fit described previously, two other analyses were performed in this study. The first was examining the acquired SWEI data for signs of propagating shear waves \textit{in vivo}. This was done using a version of the autocorrelation displacement estimator which compared each tracking pulse to the one before it, finding not cumulative displacement, but incremental motion or velocity of tissue at each point [54]. This velocity was monitored at an axial depths within ROI’s in the myocardium and chest wall. If waves were seen traveling laterally from the on-axis region of excitation, the speed of propagation
could be calculated and would indicate the shear modulus of the tissue at that time in the cardiac cycle.

The final analysis examined the sources of noise in transthoracic ARFI images. In three datasets with and without radiation force excitations ("push" and "no-push" sequences), four axial depth regions of interest were selected for analysis including the chest wall, pericardium, myocardium and ventricle or far wall. Through the fifty acquisitions, four metrics were calculated from within each ROI and plotted with the ECG. The tissue motion, ARFI displacement after motion filtering, and correlation coefficient were computed for the tracking pulse 1.3 ms after the radiation force excitation compared to the reference pulse occurring before the push. Finally, the M-Mode signal level was plotted for the four ROI through the cardiac cycle. For the ROI’s that were in the ventricle, the signal level measurement indicated the level of clutter present. These metrics enabled comparisons between some of the factors affecting image quality and ARFI measurements.

6.3 Results

In this preliminary study, 11 subjects were enrolled. There were 7 males and 4 females, with a mean age of 48.6 (range 20-89) years. Seven were in the healthy volunteer subset, and four were patients with infarct. Two of the infarct patients’ data were excluded from analysis due to failure of the ECG data acquisition system during scanning.

In previous cardiac ARFI imaging animal studies acquired using epicardial and ICE methods in vivo, published results demonstrated excellent repeatability and spatial and temporal stability of measurements in the heart [57, 34]. Using a linear array on the surface of the heart, Hsu, et. al., showed diastolic-to-systolic displacement ratios of 3:1 in healthy myocardium and a noise floor below 1.5 µm through the cardiac cycle [54]. Using a linear array in an open chest preparation, Bouchard,
et al. demonstrated the ability to track shear waves in the myocardium and detect
differences in shear wave speed with various fiber orientations, indicating sensitivity
to tissue anisotropy [7]. Hollender, et al. showed both M-Mode ARFI and SWEI
results from the same animals in the last chapter, with elevated shear wave speeds
and reduced displacements in infarct [51]. Both the epicardial and ICE methods
exhibited excellent B-Mode image quality and a low level of clutter in the ventricles.

In contrast, using a transthoracic echocardiography method, results from animal
and clinical trials illustrate a large influence of clutter and motion on the measured
displacements. The backscattered ultrasound received by the transducer is made
up of contributions from scatterers in the myocardial region of interest as well as
reverberation from near-field tissue layers and contributions from structures out of
the region of interest but within the elevation beam thickness or lateral side lobes.
Clutter can be generated from structures which are stationary or moving in directions
sometimes different than the myocardium. The patterns of motion and the stiffness
of the clutter-generating structures complicated the analysis of displacement results
in the heart.

6.3.1 General Observations

In many views observed in these studies, the correlation of the tracking signal re-
mained high (> 0.9) and estimates of axial motion were well modeled by the quadratic
filter. But the measured ARFI displacements were severely affected by the magnitude
and motion of the clutter component relative to the signal from the myocardium.
When the signal strength of the backscatter from the clutter approached the level
of the myocardium, the resulting measured displacements depended on the charac-
teristics of the motion and properties of the clutter source as much as, or even more
than, that of the myocardium. Due to the cyclic nature of motion around the heart,
these detected displacements could also exhibit good beat-to-beat repeatability, con-
founding our ability to separate “good” estimates of the function the myocardium from those representing the clutter instead.

Where the clutter field was observed in B-Mode to be stable and stationary, “flat” displacement responses were observed through the cardiac cycle, regardless of the underlying stiffness changes of the myocardium in the region of interest. In views where moving clutter patterns were observed in B-Mode, they were sometimes out of phase with the myocardium, and the variance of the displacement estimates was high both spatially and temporally, as will be demonstrated in examples to follow.

Tables 6.2 and 6.3 contain the displacement results from the model fits of all the healthy volunteers. For all the subjects at either MI 1.9 or MI 3.0, the average diastolic-to-systolic displacement ratios are in the range seen in epicardial [54] and ICE ARFI imaging [51]. There is considerable variation in the displacements between different views within each volunteer and across the 7 subjects. The displacements for diastole are higher than those in systole for all the views and patients. When the MI was increased from 1.9 to 3.0, the diastolic and systolic displacements increased in all the views and subjects. But these displacements are detected from backscatter originating from both the myocardium as well as a clutter component. Either of these components could be affected by the increase in transmit power of the radiation force excitation and tracking pulses. In our current experimental and signal processing methods, we do not have an effective way of separating the contributions from clutter and the myocardium in the overall tracked displacement signal. So, even though larger displacements were detected in systole and diastole, the measured displacement ratio did not reliably increase, likely due to the contribution of clutter in the tracked signal.
Table 6.2: Model fit parameter results from clinical trials of the first 5 healthy volunteers across all available views. $D_{\text{dia}}$ is displacement (µm) in diastole; $D_{\text{sys}}$, (µm) systole; ratio is $D_{\text{dia}}/D_{\text{sys}}$:

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Table 6.3: Continuation of model fit parameter results from clinical trials of healthy volunteers 6 and 7 across all available views. $D_{\text{dia}}$ is displacement (µm) in diastole; $D_{\text{sys}}$, (µm) systole; ratio is $D_{\text{dia}}/D_{\text{sys}}$.

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6.3.2 Healthy Volunteers

M-Mode ARFI Results

Even in the healthy volunteers, quality of acquisitions varied greatly between views and across subjects. In most volunteers, the views at a focus of 3.0–3.5 cm, namely the apical 4-chamber and 2-chamber views of the apex, were successful. The following example (Figure 6.1) is an acquisition from the apex of volunteer 5. It shows a decreased displacement during systole, and a short period of motion in early diastole. The diastolic-to-systolic displacement ratio for this acquisition is about 2:1.

In many of the volunteers, the apex exhibited the highest beat-to-beat repeatability. The multibeat synthesis curves for the apex are included in Figure 6.2 for comparison for the two power levels. The results from the first (a and b), second (c and d), third (e and f), and sixth (k and l) volunteers exhibited lower variance in displacement in the multibeat synthesis curves than the other cases.

The entire set of multibeat synthesis curves on which the fits and metrics were
Figure 6.1: An example M-Mode ARFI acquisition from healthy volunteer 5 with an input MI of 3.0 had a systolic displacement around 2.5 µm and diastolic displacement between 4 and 5. There were two samples in early diastole in which had large variance in displacement through depth due to the effect of cardiac motion.

SWEI Acquisition Results

In addition to the M-Mode ARFI, SWEI acquisitions were taken for each participant in the study for the apical 4-chamber view of the apex. Two SWEI acquisitions were taken at the end of each study, one at an MI of 1.9 and another at 3.0. This ROI was thought to be the best chance for successful measurements due to the relatively accessible focal depth between 3.0–3.5 cm and limited lateral cardiac motion. At this shallow depth, there was less clutter, and the larger F# of 1.5–1.75 yielded a larger displacement SNR and a narrower tracking beam.

In the SWEI movies displayed as real-time feedback, and in shear sequence results analyzed off-line, it appeared that there was visible wave propagation in the stationary tissue. These propagating waves appeared shallow to the myocardium, in
Figure 6.2: Multibeat synthesis curves for apical 4-chamber view in healthy volunteers. In volunteers 1, 2, 3, and 6 the variance of the estimates decreases at MI of 3 compared to 1.9, and Changing the MI increases the level of displacements, but does not improve variance or ratios in the other patients for this view.
(a) Comparison of SWEI data in fat and myocardium

(b) Example shear wave from outside heart

Figure 6.3: SWEI results are shown for the first healthy volunteer. Shear waves were detected in the fat and muscle outside the heart. Inside the myocardium, the effects of decorrelation and clutter prevented the successful detection of wave propagation for all of the subjects.

The pericardium or fat and muscle layers in the body wall, as seen in Figure 6.3. The acquisitions of shear wave sequences from all subjects in the study were reviewed and did not yield any successful detections of wave propagation within the myocardium for either an MI of 1.9 or 3.0. Further development with regard to displacement estimation, motion filtering, and wave speed estimation may be necessary in future progress in transthoracic cardiac SWEI.
Table 6.4: Model fit parameter results from clinical trials of infarct patients across all views. $D_{\text{dia}}$ is displacement ($\mu$m) in diastole; $D_{\text{sys}}$, ($\mu$m) systole; ratio is $D_{\text{dia}}/D_{\text{sys}}$;

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6.3.3 Patients with Known Apical Infarct

There were 4 patients enrolled in the study with contrast-enhanced MR-confirmed apical infarct. Of the four patients, two were excluded from data analysis due to a failure in ECG acquisition.

Table 6.4 contains the displacement results from the model fits from the two included infarct patients. The first patient exhibited large displacements in many of the views analyzed, and the displacement ratios vary quite a bit between views and MI levels. Examples from this patient will be examined in detail later in this section. The second infarct patient showed displacements that were lower and ratios that were closer between views and MI levels, more in line with our hypothesis of lower ratios in areas of infarct.
Figure 6.4: Images from a segment of myocardium from the apex in the apical 4-chamber view show ringdown into the ventricle from a proximal clutter-generating target (a). The ARFI displacement plot (b) shows large, repeating diastolic displacements in the myocardial region of interest. These high displacements (e) were not expected in infarct. It is possible that clutter from a compliant structure proximal to the ROI was causing large displacements to be detected through the myocardium and into the ventricle, as supported by the detection of correlated displacements in the blood signal.

Infarct Patient 1

The acquisition shown in Figure 6.4 is from the first infarct patient. The displacement plot shown in 6.4b) shows a very high diastolic displacement pattern in the
myocardium, despite MR-confirmed infarct. It was hypothesized that low displacements would be observed through the cardiac cycle in the regions of interest containing infarct. The bright structure in the B-Mode and M-Mode images (6.4a, 6.4d) is thought to be within the pericardium, shallow to a thin layer of suspected infarct in the myocardium. The acoustic ringdown from this echogenic structure is thought to be obscuring the tracking in the ROI below. This phenomenon of an echogenic, shallow target reverberating into the region of interest was encountered in several animal and human studies. This phenomenon will be examined further in an analysis to follow.

**Premature Ventricular Contractions**  The ECG signal for this acquisition (Figure 6.4c) shows normal sinus rhythm. In other acquisitions from this patient, premature ventricular contractions (PVC’s) were detected before, during and after ARFI scanning, such as the example in Figure 6.5. There were a total of 11 PVC’s observed in the 230 seconds of ECG data recorded before or after ARFI acquisitions at a frequency of 1 PVC per 20.9 sec. There were 4 PVC’s in the 92 seconds of ECG data recorded during ARFI acquisitions at a lower frequency of 1 PVC per 23 sec. These results show there was not an increased rate of PVC’s during ARFI acquisitions over the baseline rate of occurrence. There were a total of 46 ARFI acquisitions for this patient, and in the 4 when PVC’s were observed, 1 was at a transmit MI of 1.9 and 3 were at a transmit MI of 3.0. These isolated ectopic beats were likely related to the underlying cardiomyopathy and infarct. The ECG signal was monitored continuously during the study, but only short segments of data were recorded around each ARFI acquisition. During the study, it was observed that PVC’s occurred more often during breath hold around each acquisition compared with normal breathing. In the other eight subjects, there were no PVC’s observed in over 3000 seconds of recorded ECG. These results suggest the PVC’s were attributable to the poor state of health
of the infarct patient rather than due to the ARFI excitations via a mechanical or thermal mechanism.

![Figure 6.5: Example PVC arrhythmia during ARFI acquisition](image)

**Apical View** In this infarct patient, several regions of interest from the apical view all showed trends similar to that expected for healthy tissue. The curves in Figure 6.6 were all acquired from similar apical windows, and it is possible that each was affected by the bright structure mentioned above in Figure 6.4. The results show large ratios of diastolic-to-systolic displacements and fairly narrow variance indicating good beat-to-beat repeatability.

![Figure 6.6](image)

**Figure 6.6:** These curves are from an apical window and show apparent stiffening and relaxation through the cardiac cycle, possibly due to ringdown from a proximal clutter-generating target.
Infarct Patient 2

The second infarct patient dataset which was included in this analysis contained three ROI (2-chamber apex, 4-chamber apex, and apical inferior wall) which exhibited a cyclic trend through the cardiac cycle. The other three targets, however, displayed either a flat response through time, or large variance indicating poor repeatability.

It will take a larger sample study to determine if the result in infarct which demonstrated an echogenic, compliant pericardial target are repeatable across more patients. The two infarct patients that were excluded due to lack of ECG signal also exhibited large displacements in the pericardium, but it is premature to call this a repeatable trend without the accompanying ECG data and repeated results in further studies.

6.3.4 Analysis of Sources of Degradation for ARFI and M-Mode Images

In the following section, three sample views will be examined the clinical trials with conventional M-Mode ARFI imaging sequences and “no-push” sequences where the ARFI excitation pulse is replaced with a M-Mode tracking pulse. The “no-push” sequences allow examination of motion, clutter, and performance of the motion filter in the absence of a radiation force excitation.

Acquisitions of “Push” ARFI Sequences

To analyze the possible sources of degradation of the M-Mode and ARFI images, four regions in each of three cases were examined: chest wall, pericardium, myocardium, and ventricle/far wall. For each of these axial depths outlined in the M-Mode image, the total motion, ARFI displacement, correlation and M-Mode brightness were plotted for the time step 1.3 ms after the radiation force excitation. The motion and correlation results were computed relative to the track pulse 156 µs before the “push”. Figures 6.7, 6.8, 6.9 show analyses of three cases.
The first (Figure 6.7) is from an apical 4-chamber view of the lateral wall of the first infarct patient (see Appendix B, Figure B.8). The region of interest in the chest wall (marked in blue in the M-Mode b), shows a stationary pattern with correlation near 1. The pericardial region shows the brightest M-Mode signal level of the four regions (g), the most motion, and the largest ARFI displacement remaining after quadratic motion filtering. The correlation for all of the regions remains above 0.9 for most of the acquisition (f). The regions deep to the pericardium show trends that appear similar, suggesting that reverberation from this bright structure may be causing the tissue below it to track in tandem with it. The ventricle signal level remains quite high, only 10-15 dB below the level in the chest wall, and within 5 dB of the myocardium. The signal in the ventricle tracks with the tissue, providing clear evidence that it is clutter that is tracked in the ventricle rather than blood. This displacement pattern in the ventricle is repeatable beat-to-beat, showing a cyclic pattern indicating its source is contracting tissue, likely in the pericardium above.

The second analysis is from an apical 2-chamber view of the anterior wall of the 5th healthy volunteer (see Appendix B, Figure B.5). This location exhibited a large degree of lateral motion and it is likely that the bright target just to the right of the center line in the B-Mode image (Figure 6.8a) came into view at time 0.8 seconds, just after the QRS complex on the ECG plot (h). The motion and ARFI displacement (d and e) before and after this disruption were small, and correlation was above 0.95 (f). However, during the period between 0.8 and 1.4 seconds, the correlation drops precipitously for the three regions other than the chest wall.

A third set of images shows an apical 2-chamber view of inferior wall in the same healthy volunteer (Figure 6.8a). The motion that is seen in the deep myocardial wall (cyan line of d) is well removed by the motion filter. The ARFI displacements are small shallow and deep of the focus, but the ratio of diastolic to systolic displacement through the mid-myocardium is very high as seen in cand e. The correlation values
(f) remained high throughout the acquisition, dipping below 0.975 only during rapid motions of contractions and relaxation indicated in the ECG (h). These analyses demonstrate that when the B-Mode image is relatively free of clutter and lateral or elevation motion does not bring different structures through the ROI, M-Mode ARFI can measure myocardial stiffness at depths of 5 cm.

**Acquisitions of “No-Push” ARFI Sequences**

In the following figures, “no-push” sequences were acquired in similar views as the three ROI’s above. These acquisitions measure the physiologic motion, decorrelation, and performance of the motion filter in the absence of a radiation force excitation pulse. This analysis will demonstrate the bias and jitter in our estimates in these views and may point to the likely source of image degradation. The three “no-push” acquisitions will be compared to the measured displacements and correlation in the “push” cases discussed above.

In the first example (Figure 6.10), we see an apical 4-chamber lateral view comparable to Figure 6.7. Similar levels of physiologic motion occur in the myocardium (red line) in both the “push” and “no-push” cases of about ± 30 µm. The motion filter in the “no-push” case performs well, with residual motion error less than ± 1.5 µm in the myocardium (red line) through the cardiac cycle (e). The correlation level in the both cases remains above 0.9 for nearly all samples (f and f).

In the second “no-push” analysis, Figure 6.11, there exists a small influence of moving clutter seen in the B-Mode to the left of the center line (a) and that appears in the M-Mode line (b) after the T wave in both heart beats, but the large effect of motion and decorrelation seen in the “push” case (Figure 6.8) is not observed. There is some evidence of motion (d) and decorrelation (f) at isolated times in the cycle, but the results from this acquisition are not able to predict the pattern of motion and decorrelation in the “push” case, Figure 6.8.
The “no-push” acquisitions were recorded for all the views at the end of each imaging session, and it was challenging to repeat the precise views. In future studies, it would be beneficial to acquire the “push” and “no-push” data over a short time scale for better comparison. This example may be a slightly different view that does not have the same lateral motion and clutter targets.

The ROI in Figure 6.12 was also significantly different than Figure 6.9 due to the gap along the M-Mode line (b) and can be seen in the B-Mode image (6.12a). In the blood region, the motion filters fail and correlation falls, as expected as there is no tissue to track (e, f). The M-Mode brightness shows there is little clutter in the ventricle as the signal levels in the lower three ROI are 20 dB down from the chest wall region(g). These last two examples illustrate the difficulty in repeating an exact field of view later in the same imaging session.

6.4 Discussion and Conclusions

We report the first study that demonstrates a real-time system for making transthoracic ARFI imaging measurements in humans. Results support transthoracic ARFI as a safe, non-invasive, real-time method of examining the properties and function of the heart. Larger displacements were measured in diastole compared with systole for all ROI, views, and subjects, correlating with stiffer myocardium during systole. In views with good B-mode quality, displacement ratios were in the range published by others [54, 51].

6.4.1 Clutter

Increasing the transmit MI above the FDA limit of 1.9 increased measured displacements through the cardiac cycle and, for some views and subjects, improved the measurement variance and SNR. This increased displacement response measured in the presence of motion and clutter. Effects of reverberation clutter and motion of
heterogeneous tissue through the ROI confounded our ability to definitively attribute the measured displacements to the underlying myocardial tissue properties.

In healthy tissue, displacement ratios were stable across patients and did not vary significantly with input MI. Results of these studies support the observation that stationary and moving clutter have a large impact on variance and profile of measured displacements. For most views, clutter was shown to be the dominant source of image degradation. In this limited sample study it has not been shown feasible to quantitatively differentiate infarcted myocardium from healthy tissue in the presence of severe moving or stationary clutter.

6.4.2 Effect of Downsampling on Jitter and Bias

The Verasonics Research Platform acquires raw, single-channel RF data at a resolution of 4 samples per wavelength, not far above the Nyquist sampling rate. The resolution of the demodulated IQ data for these studies was only 1 pixel per wavelength in both the lateral and axial dimensions. In a study of tracking small displacements, Pinton, et. al., simulated the effect of downsampling and demodulating the RF data from 40 MHz (the sampling rate for the Siemens Antares ultrasound scanner) to many frequencies including 2 MHz, a downsampling factor of 20 [97]. His results showed that Loupas’ two-dimensional (2-D) autocorrelator [73] and Kasai’s 1-D autocorrelator [64] perform similarly in terms of bias and jitter above a downsampling factor of 10. He also showed that improvements in bias and jitter could be made by interpolating the IQ signal back up to the RF sampling rate. Jitter levels were cut by up to 5 dB when the data were re-interpolated and processed with Loupas’ algorithm. Similarly, bias levels also found to be lower for the upsampled data. In the Verasonics system, one can chose the lateral and axial pixel spacings for the IQ reconstruction. To make a large difference in terms of bias and jitter, the axial spacing of the IQ samples would need to halved to 0.5 λ or less. This would come
with trade-offs of decreased frame rates and narrowing of the lateral field of view. Besides interpolating and using Loupas’ estimator, another promising avenue to explore is using Bayesian estimators, which have been shown to improve performance compared with unbiased estimators such as those mentioned above [12]. Improved tracking methods may have significant impacts on the ability to show more general feasibility of these methods in the future.

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Figure 6.7: This group of plots shows factors affecting ARFI measurements in an apical 4-chamber lateral view with a compliant target in the pericardium. Four regions including chest wall (blue), pericardium (green), myocardium (red), and ventricle (cyan) are outlined in the M-Mode image (b). Motion, displacement, correlation and M-Mode brightness are plotted for these regions at the tracking time step (1.3 ms after the push) for 50 samples through the cardiac cycle (b-h).
Figure 6.8: An analysis of an apical 2-chamber anterior wall is shown. Lateral motion of a highly displacing clutter artifact are displayed. Chest wall (blue), pericardium (green), myocardium (red), and deeper wall (cyan) are outlined in the M-Mode image (b) were chosen for analysis. Motion, displacement, correlation, M-Mode brightness, and ECG are plotted in the right column (b-h).
Figure 6.9: Four regions in the apical 2-chamber inferior wall view are shown, including chest wall (blue), pericardium (green), myocardium (red), and deeper wall (cyan) outlined in the M-Mode image (b) were chosen for analysis. Motion, displacement, correlation and M-Mode brightness are plotted for these regions at our tracking time step (1.3 ms after the push) through the cardiac cycle in the right column (b-h).
Figure 6.10: No-push sequence in an apical 4-chamber lateral view similar to Figure 6.7. Correlation remains fairly high throughout the acquisition (f). The “no-push” M-Mode ARFI images in Figure c and the next two figures below show residual motion after filtering, and they are displayed on a color scale from -3 to +3 µm, with green representing zero displacement after filtering.
Figure 6.11: A “no-push” analysis of a view similar to Figure 6.8. There exists some clutter artifact in the ventricle in the B-Mode (a), and at the end of each T wave. Residual motion after filtering (e) shows good results at less than $\pm 3 \mu m$, even for periods of large motion (d) and decorrelation (f).
Figure 6.12: This ROI was significantly different than Figure 6.9 due to the gap along the M-Mode line (b). In the blood region, the motion filters fail and correlation falls, as there is no tissue to track (e, f). The M-Mode brightness shows little clutter in the ventricle as the signal levels in the lower three ROI are 20 dB down from the chest wall region (g).
7

Conclusions and Future Work

7.1 Conclusions

We have demonstrated feasibility of transthoracic cardiac Acoustic Radiation Force Impulse (ARFI) imaging. The non-invasive M-Mode ARFI images and displacement plots presented in this dissertation exhibit cyclic variations that reflect the local myocardial properties through time. Measurements were made in diagnostically relevant ROI and within FDA limits of MI and TI. Repeatability was tested for displacement levels in diastole and systole and the ratio between these levels. For repeated measurements in views with good B-Mode image quality, the ratios were comparable to methods previously published by intracardiac and epicardial approaches.

The dissertation described the development of a system capable of acquiring, processing and displaying transthoracic cardiac ARFI images in real-time. The system was built around a Verasonics Research Platform which contained a power supply capable of the extended transmit waveforms better able to displace tissues at depth. Custom MATLAB software was written to process the acquired data and display the ARFI images and SWEI movies in real-time to help guide scanning sessions and
provide feedback to cardiologists during studies.

An in-depth safety analysis was presented, demonstrating transthoracic ARFI imaging and SWEI methods can be used safely if appropriate choices are made to power levels and frame rates. FEM simulations showed heating above the acceptable range if power levels and acquisition rates were too aggressive. Thermocouple face heating measurements of the transducer surface for sequences used in clinical trials showed the heating was in a safe range, provided the sequences were not repeated at too fast a rate. The intensity measurements, MI calculations, and intensity-time thresholds calibrated the power levels of the scanner and allowed selection of \textit{in situ} magnitudes that were appropriate.

Results were presented from a \textit{porcine} model of healthy and infarcted hearts. An analysis was provided for available ROI segments in one subject before and after foam embolization. The animal was followed serially through repeated scans, showing good repeatability within ROI’s in high quality B-Mode environments. In a terminal study, analysis and cases were shown containing healthy myocardium, infarcted tissue, and observed artifacts. Electroanatomical measurements verified the presence of infarct \textit{in vivo}. The heart was then excised and imaged \textit{ex vivo} by MR imaging and histology, showing consistent localization of infarcts.

Finally, a clinical feasibility study was completed with healthy volunteers and patients with contrast-enhanced MRI-confirmed apical infarct. Transthoracic ARFI was shown able to measure displacements in the clinic, but was dependent on the depth of the ROI, the B-Mode image quality with regard to clutter, and the magnitude and direction of local cardiac motion of the clutter sources. Clutter was observed to be stationary in some patients and views, in those cases likely originating from reverberation from the chest wall and proximal tissue layers. In many of poor quality B-Mode images, clutter patterns were observed to move out of sync with the motion of the myocardial region of interest. Both stationary and moving
clutter contributed to the degradation of B-Mode and ARFI imaging. It was found that applying a larger MI excitation pulse did not improve the measurement SNR in the presence of this image degradation.

Through the preliminary investigations presented in simulation, phantom, animal and clinical trials here, a real-time prototype system was demonstrated for transthoracic cardiac ARFI imaging. Feasibility was shown with limits on the available transmit depths, B-Mode image quality, and motion profiles encountered.

7.2 Continuing Efforts and Future Work

The results in this dissertation warrant continued development, and before future animal and clinical studies are launched, steps must be taken to improve the performance of imaging in non-ideal B-Mode environments. The primary source of image degradation in the results presented was suspected to be clutter, and there are a number of techniques and improvements that can be made to mitigate the detrimental effects of this image artifact.

7.2.1 Hardware Improvements

*Multi-row 1.5-D Transducer*

A different transducer could make a significant improvement for transthoracic ARFI imaging. In a simulation and phantom study, 1.5-D transducer with multiple rows of piezoelectric elements yielded a 2.92 dB improvement in contrast-to-noise ratio relative to a conventional 1-D array. Analytical models of the expression for SNR and contrast were derived and validated with FEM simulations and simulated phantom images [28]. These results could be applied to transthoracic imaging. The ability to adaptively focus in the elevation plane during receive would decrease the effect of out-of-plane clutter via reduced elevational beam thickness. The lateral and elevation focal point could also be co-located, concentrating the “push” magnitude and
improving tracking. The improved focusing would allow for a reduction in underestimation bias and an increase in the correlation coefficient [78].

Clinical Platform

A migration should be made for the human transthoracic studies from the currently utilized Verasonics Research Platform to the Siemens Acuson SC2000\textsuperscript{TM} scanner. The SC2000 is a clinical scanner which has many parallel receive channels and a power supply able to sustain ARFI excitation pulses much like the Verasonics. But unlike the Verasonics, the SC2000 exhibits excellent B-mode image quality, harmonic imaging capabilities, lower noise floor, integrated ECG triggering and capture. All of this make it a suitable platform for clinical ARFI studies. This scanner also supports 3-D transthoracic and intracardiac probes, which could be developed into future ARFI tools and incorporated into studies.

7.2.2 Software Improvements

Adaptive Real-time Acquisition

In the real-time ARFI scanning scheme described in this thesis, a fixed acquisition rate was programmed for the sequence in advance. Only later in post-processing were corrupted displacement estimates detected and removed. An adaptive scheme to alter the ARFI sequence during the experiment could avoid acquiring data that would later be thrown out due to low correlation or large motion corruption.

In this acquisition scheme, a user would click at a specific point within the live B-Mode feedback window to select the steering angle and focal depth to analyze and program for the ARFI sequence. A high frame rate B-Mode sector around that steering angle would be acquired, triggered by the ECG signal. This data set would be processed and examined for magnitude of physiologic motion, decorrelation, and performance of the motion filters. From preliminary analyses in the clinical trials
in this dissertation, times to avoid include when residual motion error is above 1 μm or when correlation of the tracking pulse falls below a threshold of 0.9. In this manner, the times that are “good for ARFI” would be calculated at the selected ROI. Rather than using these quality threshold filters and multibeat synthesis in post-processing, the timing of the acquisition pulses would be set in real-time, using a variable repetition rate make estimates only in times detected as high quality. By acquiring at only the best times from the outset, this scheme would also eliminate any need for further manual intervention in post-processing and allow the diastolic and systole displacement and ratio metrics to be displayed just after acquisition.

This real-time feedback would be a large step forward in our ability to take the highest quality of measurements or to decide when ARFI and SWEI is not likely to be successful in a given ROI.

**Pulse Sequencing and Signal Processing**

Besides the hardware and acquisition scheme, improvements could be made as well to pulse sequencing and signal processing tools. Harmonic imaging has been shown to have significant positive impact on endocardial border definition and wall motion scoring, and it improves the visualization of both normal and abnormal cardiac structures [68]. Pinton et. al [98] reported improvements of 26 dB in the reverberation clutter for harmonic imaging compared with fundamental in an abdominal simulation study. Coherence-based clutter reduction methods [25], Bayesian speckle tracking and displacement estimation [11, 12] have all shown advantages in recent developments in laboratory or clinical settings. For the next generation transthoracic ARFI imaging system, these improvements may be able to expand the beyond the current scope of feasibility.
Appendix A

Multibeat Synthesis Results From Animal Study

The following pages contain the results of the multibeat synthesis analysis of the animal study presented in Chapter 5.
Figure A.1: Multibeat synthesis results for first imaging session.
Figure A.2: Multibeat synthesis results for second imaging session.
Figure A.3: Multibeat synthesis results for third imaging session.
Figure A.4: Multibeat synthesis results for fourth imaging session.
Figure A.5: Multibeat synthesis results for fifth imaging session.
Figure A.6: Multibeat synthesis results for final imaging session.
Appendix B

Multibeat Synthesis Results From Clinical Trial

The following pages contain the results of the multibeat synthesis analysis of the clinical study presented in Chapter 6.
Figure B.1: Multibeat synthesis results for healthy volunteer 1.
Figure B.2: Multibeam synthesis results for healthy volunteer 2.
Figure B.3: Multibeat synthesis results for healthy volunteer 3.
Figure B.4: Multibeat synthesis results for healthy volunteer 4.
Figure B.5: Multibeam synthesis results for healthy volunteer 5.
Figure B.6: Multibeat synthesis results for healthy volunteer 6.
Figure B.7: Multibeat synthesis results for healthy volunteer 7.
Figure B.8: Multibeat synthesis results for infarct patient 1.
Figure B.9: Multibeat synthesis results for infarct patient 2.
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