Published in final edited form as:

Ultrasound Med Biol. 2019 May ; 45(5): 1112–1130. doi:10.1016/j.ultrasmedbio.2018.12.011.

Noninvasive Measurement of Dynamic Myocardial Stiffness using Acoustic Radiation Force Impulse Imaging

Vaibhav Kakkad^{a,*}, Melissa LeFevre^b, Peter Hollender^a, Joseph Kisslo^b, and Gregg E. Trahey^{a,c}

^aDepartment of Biomedical Engineering, Duke University, Durham, North Carolina, USA

^bDepartment of Cardiology, Duke University Hospital, Durham, North Carolina, USA

^cDepartment of Radiology, Duke University Medical Center, Durham, North Carolina, USA

Abstract

Myocardial stiffness exhibits cyclic variations over the course of the cardiac cycle. These trends are closely tied to the electro-mechanical and hemodynamic changes in the heart. Characterization of dynamic myocardial stiffness can provide insights into the functional state of the myocardium as well as allow for differentiation between the underlying physiological mechanisms that lead to congestive heart failure.

Previous work has demonstrated the potential of acoustic radiation force impulse (ARFI) imaging to capture temporal trends of myocardial stiffness in experimental preparations such as the Langendorff heart as well as on animals in open-chest and intracardiac settings. This study aims to investigate the potential of ARFI to measure dynamic myocardial stiffness on human subjects, in a noninvasive manner through transthoracic imaging windows.

ARFI imaging was performed on twelve healthy volunteers to track stiffness changes within the interventricular septum (IVS) in the parasternal long-axis (PLAX) and short-axis (PSAX) views. Myocardial stiffness dynamics over the cardiac cycle were quantified using five indices: stiffness ratio, rates of relaxation and contraction, and time constants of relaxation and contraction. Yield of ARFI acquisitions was evaluated based on metrics of signal strength and tracking fidelity such as displacement signal-to-noise, signal-to-clutter level, temporal coherence of speckle, and spatial similarity within the region-of-excitation (ROE). These were quantified using the mean ARF-induced displacements over the cardiac cycle, the contrast between the myocardium and the cardiac chambers, the minimum correlation coefficients of RF signals, and the correlation between displacement traces across simultaneously-acquired azimuthal beams, respectively.

Forty-one percent of ARFI acquisitions were determined to be “successful” using a mean ARF-induced displacement threshold of 1.5 μ m. “Successful” acquisitions were found to have higher i) signal-to-clutter levels, ii) temporal coherence, and iii) spatial similarity compared to

*Corresponding Author: Vaibhav Kakkad, Department of Biomedical Engineering, 1427 FCIEMAS, Box 90281, Durham, NC 27708; v.kakkad@duke.edu; Phone, +1(919)660-5146.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

“unsuccessful” acquisitions. Median values of these three metrics, between the two groups, were measured to be 13.42 dB vs. 5.42 dB, 0.988 vs. 0.976, and 0.984 vs. 0.849, respectively. Signal-to-clutter level, temporal coherence, and spatial similarity were also found to correlate with each other. Across the cohort of healthy volunteers, stiffness ratio was measured to be 2.74 ± 0.86 ; rate of relaxation was 7.82 ± 4.69 /s and contraction was -7.31 ± 3.79 /s; time constant of relaxation was 35.90 ± 20.04 ms, and contraction was 37.24 ± 19.85 ms. ARFI-derived indices of myocardial stiffness were found to be similar in both views.

These results demonstrate the feasibility of using ARFI to measure dynamic myocardial stiffness trends in a noninvasive manner and also highlight the technical challenges of implementing this method in the transthoracic imaging environment.

Keywords

Myocardial stiffness; Transthoracic; Echocardiography; Acoustic Radiation Force; Noninvasive; ARFI; Clutter; Temporal Coherence

Introduction

Congestive heart failure (CHF) affects nearly 5.7 million people in the United States alone (Mozaffarian et al., 2016) and is projected to increase by 46%, impacting over 8 million over the next 15 years (Heidenreich et al., 2013). CHF can arise from a variety of root causes such as hypertension (Levy et al., 1996), coronary artery disease (Gheorghiade and Bonow, 1998), several forms of cardiomyopathy (McCrohon et al., 2003; Harris et al., 2006; Ng et al., 2005; Maron et al., 2006), as well as chemotherapy-induced cardiotoxicity (Kremer et al., 2001; Swain et al., 2003). In most cases, the structural and functional changes in the heart due to CHF are accompanied by alterations in the stiffness of the cardiac muscle (Watanabe et al., 2006; Borbély et al., 2005; Conrad et al., 1995; Zile et al., 2015; Westermann et al., 2008).

Myocardial Stiffness and Cardiac Function

Myocardium exhibits complex changes in its mechanical properties over the cardiac cycle. These dynamics are induced by a combination of electrical, chemical, and mechanical stimuli that all impact cardiac function. Myocardial stiffness is considered to be one such important mechanical property; and can be estimated through hemodynamic analysis of pressure-volume (PV) loops (Burkhoff et al., 2005). Slopes of the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (ED- PVR) are considered to be correlates of myocardial stiffness at the respective cardiac phases. These have been shown to be associated with the systolic and diastolic function of the heart, respectively (Sunagawa et al., 1983; Zile and Brutsaert, 2002). This methodology can also be extended to model dynamics of myocardial stiffness over the entire cardiac cycle using the concept of time-varying elastance (Suga and Sagawa, 1974). This model has been applied to study changes in the peak rates of ventricular pressure rise (during contraction) and fall (during relaxation) as a function of heart-rate, inotropic states, and loading conditions (Suga et al., 1973; Little, 1985).

PV loop analysis is widely considered to be the gold standard for the characterization of cardiac function. Myocardial stiffness measurements computed using PV loops are indirect in the sense that they are derived using hemodynamic theory. They provide a global estimate of chamber properties, but do not represent regional variations in the material that the chamber is composed of. While PV loop analysis provides a wealth of functional information to guide cardiovascular pathophysiological studies, their clinical utility is limited by their invasive nature. Tracking temporal changes in pressure and volume with high precision requires cardiac catheterization and thus renders this technique unsuitable as a diagnostic procedure.

Noninvasive Measurement of Myocardial Stiffness

Elastography methods, using ultrasound (Doherty et al., 2013b) or magnetic resonance imaging (MRI) (Mariappan et al., 2010), are capable of measuring the mechanical properties of soft tissues in a noninvasive manner and have been the topic of significant research over the last two decades.

Magnetic resonance elastography (MRE) uses MRI to track waves induced in soft tissues due to externally-coupled mechanical actuators. These vibrations are tracked and fit to mechanical models to estimate stiffness moduli. MRE has been shown to capture cyclic trends of myocardial stiffness (Kolipaka et al., 2010) as well as to quantify changes in end-diastolic and end-systolic stiffness with variations in loading conditions (Kolipaka et al., 2011) and contractility (Kolipaka et al., 2012), respectively. More recently, the diagnostic potential of MRE has been investigated in porcine models of amyloidosis (Arani et al., 2016), hypertension (Mazumder et al., 2017a), and myocardial infarction (Mazumder et al., 2017b; Arunachalam et al., 2018). Initial results have also been demonstrated on human volunteers (Sack et al., 2009; Wassenaar et al., 2016).

Ultrasound-based transient elastography methods such as acoustic radiation force impulse (ARFI) imaging and shear wave elasticity imaging (SWEI) have also been investigated in a variety of experimental settings. In open-chest experiments on canine and ovine subjects, both ARFI and SWEI have been demonstrated to be sensitive to temporal trends of myocardial stiffness through the cardiac cycle (Hsu et al., 2007; Couade et al., 2011). Similar results have also been presented using catheter-mounted intracardiac echocardiography probes (Hollender et al., 2012, 2013). ARFI has also been shown to be useful for near real-time monitoring of cardiac ablation procedures on human subjects (Bahnon et al., 2014). Short-term changes in ARFI- and SWEI-derived myocardial stiffness in response to inotropic agents and variations in coronary perfusion pressure have also been demonstrated using rodent hearts in Langendorff set-ups (Pernot et al., 2011; Vejdani-Jahromi et al., 2015). ARFI- and SWEI-derived indices of dynamic myocardial stiffness have also shown to be well correlated to each other (Vejdani-Jahromi et al., 2016).

Acoustic Radiation Force Impulse (ARFI) Imaging and Shear Wave Elasticity Imaging (SWEI)

ARFI and SWEI rely on the ability of ultrasound to remotely generate and track micron-level mechanical vibrations in soft tissue (Nightingale et al., 2003). This phenomenon is

explained by the concept of acoustic radiation force (ARF). The dynamic mechanical response of tissue can be used to discern its local mechanical properties. Steering the push and track beams across a spatial extent allows for the interrogation of spatial variations in tissue stiffness (i.e., 2D ARFI or SWEI). Similarly, temporal variations in tissue stiffness can be measured by repeating the push and track pulses over time at a fixed spatial location (i.e., M-mode ARFI or SWEI).

For a fixed acoustic intensity and pulse duration, the magnitude of ARF-induced displacement is inversely proportional to tissue stiffness (Palmeri et al., 2006). ARFI imaging exploits this relationship to yield relative estimates of tissue stiffness by tracking the displacement-recovery trend along or near the axis of the push beam for a duration of 1–3 ms after the push. SWEI estimates absolute stiffness based on the shear wave speed and an assumed mechanical model (Sarvazyan et al., 1998). Estimation of the shear wave speed requires tracking the displacements across a field-of-view in azimuth or elevation for 5–10 ms following the push. In principle, SWEI could be used throughout the cardiac cycle. However, tracking shear wave propagation proves to be a challenging task in cases where the background tissue is also moving, such as the heart which exhibits rapid, multi-dimensional motion. Additionally, the amplitude of shear waves decays with distance away from the axis of the push beam, making them increasingly difficult to track in stiff and highly attenuating media. Lastly, the curved geometry of the heart walls and spatial (transmural or base-to-apex) changes in the fiber orientation make it difficult to track the polarization of propagating shear waves at large azimuthal angles. These effects can introduce noise and/or bias in shear wave speed estimates. Despite these challenges, implementations of SWEI for transthoracic imaging have shown promising preliminary results on human subjects for measuring myocardial stiffness in diastole. Song et al. demonstrated the feasibility of measuring the passive stiffness of myocardium at end-diastole using SWEI in pediatric volunteers (Song et al., 2016). Additionally, Villemain et al. showed changes of passive myocardial stiffness in adults as a function of age as well as differentiation between healthy volunteers and patients with hypertrophic cardiomyopathy (Villemain et al., 2018).

In contrast to SWEI, ARFI imaging uses higher amplitude on-axis displacements and requires a relatively short duration to compute a stiffness estimate. Thus, ARFI could be used to overcome some of the technical obstacles inherent to imaging the heart in the transthoracic environment. The primary goal of this study is to assess the feasibility of tracking dynamic myocardial stiffness using M-mode ARFI through the cardiac cycle via transthoracic imaging windows. We also present ARFI-derived indices to characterize the temporal trends of myocardial stiffness, and analyze beat- to-beat repeatability and consistency in a cohort of healthy volunteers.

Materials and Methods

Sequence Design

Custom beam sequences were developed to acquire M-mode ARFI data on a clinical ultrasound scanner, Siemens Acuson SC 2000™ (Siemens Medical Solutions Inc., Malvern, PA, USA), and implemented using an adult cardiac phased array, Siemens 4V1c. B-mode

imaging was used for live image guidance; upon achieving the desired view, the M-mode ARFI sequences were initiated.

M-mode ARFI data were acquired in three configurations differentiated by the parameters of the tracking transmit beams. The first configuration used focused beams in the fundamental mode; this will be referred to as “fundamental-focused” (FF). The second two configurations employed pulseinversion harmonic imaging using either a focused transmit beam, “harmonic-focused” (HF), or a plane wave transmission, “harmonic-plane” (HP). In all three cases, the ARF excitation (or push) was generated using a focused beam. In the focused configurations (FF and HF), the focal depth of the tracking transmit beam was set to be the same as that of the push beam, while in the plane wave configuration (HP) the focus of the tracking transmit was set to 1000 mm, so as to achieve a near-planar transmit wavefront. All other parameters of the three sequences were identical.

Parallel receive beamforming (Shattuck et al., 1984) was used to synthesize seven simultaneously-acquired and dynamically focused beams on receive. These were uniformly spaced over a 0.4° angular span using a virtual apex of 300 mm behind the probe face. This configuration resulted in 70% spatial overlap of the -6 dB beamwidth between adjacent receive beams at a 50 mm focus and limited their azimuthal extent to within 1.16 mm on either side of the axis of the push beam.

Each of the three M-mode ARFI sequences was comprised of 175 ARFI ensembles that were repeated along the center-line of the B-mode field-of-view (FOV). Individual ARFI ensembles were 28.5 ms long and included a $300\mu\text{s}$ push with 112 tracking pulses (56 before and after the push). The ensembles were temporally contiguous so as to achieve continuous tracking at a pulse repetition frequency (PRF) of 4 kHz and a push PRF of 35 Hz. Each M-mode ARFI sequence thus spanned 5 s.

Push beams were centered at a frequency of 2.8 MHz and focused between 45–65mm, yielding F-numbers between 2.38 to 3.44. In the fundamental- focused (FF) configuration, the tracking was performed at a center frequency of 3.2 MHz. The two harmonic configurations (HP and HF) used a 2 MHz transmission with a receive frequency of 4 MHz. In the pulse-inversion harmonic cases, echoes from alternate transmit pulses were combined using the fully-sampled approach (Doherty et al., 2013a) to maintain the temporal sampling rate of 4 kHz. The mechanical index (MI) and the spatial-peak pulse-average intensity (I_{sppa}) for the push beams were measured to be below 1.65 and 430 W/cm^2 , respectively. MI and I_{sppa} were computed using a fixed attenuation value of 0.3 dB/cm/MHz. The same voltage was used for push and track beams. The temperature rise at the face of the probe for individual M-mode ARFI sequences was measured to be under 3°C .

Table 1 provides a summary of the sequence parameters. A complete dataset was acquired over the span of 60 s and consisted of a B-mode cine clip and beamformed in-phase and quadrature (IQ) data (i.e. focused, summed, and demodulated signals) for the three tracking configurations. The B-mode cine clip was used for anatomical reference while the raw M-mode echo data were used for displacement estimation as well as computation of signal quality metrics.

Clinical Data Acquisition

The sequences described above were used to acquire data on twelve healthy volunteers with no history of cardiovascular disease at the out-patient Cardiology Clinic at Duke University Hospital. Imaging was performed by an experienced cardiac sonographer after receiving informed consent from study participants in accordance an IRB-approved protocol (Duke IRB Pro00032068). As part of recruitment into the study, participants were given an abbreviated cardiac ultrasound exam performed by the sonographer to screen for structural or functional abnormalities. All participants were found to be asymptomatic. No exclusions were made based on image quality. Study participants spanned an age range of 22–35 years and a body mass index (BMI) range of 20–24 kg/m². They showed heart-rates in the range of 48–98 bpm and left ventricular ejection fractions in the range of 55–68 %.

Data acquisition was performed in two standard transthoracic echocardiographic (TTE) views: parasternal long-axis (PLAX) and short-axis (PSAX). In both views, the myocardial wall of interest was the interventricular septum (IVS). Up to three repeated acquisitions were performed in each view. Study participants were not asked to hold their breath given the prolonged duration of the acquisitions. In addition to B-mode cine clips and raw M-mode echo data, trigger output signals from the ultrasound scanner (corresponding to each transmit event) and the electrocardiogram (ECG) were also acquired simultaneously. These signals were used to retrospectively align the M-mode ARFI acquisitions with the cardiac cycle. Imaging was performed in normal sinus rhythm and no arrhythmias were observed during or after ARFI acquisitions.

Data Processing

Beamformed IQ data for the M-mode ARFI sequences were acquired over axial range, time (spanning the 175 ensembles), and azimuthal angle (corresponding to the seven simultaneously-acquired receive beams). Data for the different azimuthal angles was processed independently. Figure 1(a,b) shows conventional B-mode and M-mode images in the PSAX view. The region-of-excitation (ROE) of the push beam is indicated by the green rectangle on the B-mode image. The M-mode image is presented for the central azimuthal angle over a 1200 ms segment and shows the IVS around a depth of 50 mm. The dotted green lines on the M-mode image indicate the temporal positions of ARF pushes. The ECG corresponding to the M-mode image is shown in Figure 1(c).

Axial displacements were computed using a phase-shift estimator (Loupas et al., 1995) and averaged over a 5λ axial kernel, corresponding to a 1.92 mm axial extent. Incremental displacement estimates were calculated by comparing the phase-shifts between successive tracking events (i.e., 1→2, 2→3, 3→4...). These were then cumulatively summed through time to yield the raw displacement traces over the duration of the acquisition. Data from the four tracking events immediately following each ARF push were not used for displacement estimation due to the presence of high amplitude echoes from the push pulse.

Background tissue motion was suppressed by applying a 3rd-order high-pass Butterworth filter with a cutoff frequency of 75 Hz through time (Kakkad et al., 2015). The filter was applied in the forward and reverse directions to minimize phase distortions. Motion-filtered

displacement traces in the IVS for two representative ensembles, in mid-diastole (gold) and mid-systole (purple), are shown in Figure 1(d). The time vectors of the displacement traces are aligned such that the push, indicated by the gray band, begins at 0 ms. Closed circles represent measured displacements while open circles represent quadratically-interpolated estimates for time steps that were excluded from the displacement estimation process.

M-mode ARFI images, as shown in Figure 1(e), were generated by taking the difference between the measured displacement at 1.5 ms (shown in the solid black line) and the last tracking event prior to the push pulse. The systematic decrease in amplitude of the push away from the center of the ROE was compensated for by scaling the displacement data across the azimuthal angles based on a parabolic fit about the central angle. M-mode ARFI images were computed for all seven angles within the ROE, however, images presented herein represent only the central angle. Spatio-temporal regions-of-interest (ROIs) in the IVS were manually outlined using the conventional M-mode images. These ROIs, indicated by the green dotted lines in Figure 1(e), were superimposed onto the M-mode ARFI images and used to extract displacement data constrained to the myocardium.

Metrics of Signal Strength and Tracking Fidelity

M-mode ARFI data within the spatio-temporal ROI representing the IVS were averaged through range, azimuth, and time over individual cardiac cycles to yield u_{cyc} . This metric quantifies the mean ARF-induced displacement in the myocardium (after filtering out background motion) and was used as an indicator of signal strength. Acquisitions with a mean u_{cyc} over all cardiac cycles $< 1.5 \mu\text{m}$ were considered to be “unsuccessful”. This threshold was determined using the Cramér-Rao Lower Bound (Walker and Trahey, 1995), which predicts the uncertainty in displacement estimation using partially-correlated signals. For the parameters defined in Table 1, the predicted standard deviation of individual displacements estimates (jitter) is approximately equal to $1.5 \mu\text{m}$.

Quantitative metrics to assess the level of acoustic clutter and out-of-plane motion were also derived using the raw M-mode echo data. Contrast in echo magnitude between the right ventricular (RV) cavity and the myocardium in the IVS was used to estimate the signal-to-clutter level (Kakkad et al., 2018). The RV cavity, which appears shallow to the IVS in the PLAX as well as PSAX views, was outlined manually. Contrast was defined as the ratio of the mean envelope-detected IQ data (prior to log compression) within the spatio-temporal ROIs representing the IVS divided by the same in the RV cavity and was measured for individual heart beats. Figure 2(a) and 2(b) illustrate a low- and high-clutter example, respectively.

The temporal coherence of speckle was used to determine the level of decorrelation from lateral, elevational, and rotational motion as well as temporal noise. IQ data for 2 ms temporal windows were remodulated to radio-frequency at a sampling frequency of 80 MHz and processed through a normalized cross-correlation operation anchored to the first time step in the window. A 5-A kernel (1.92mm) and $1/2\text{-}\lambda$ axial search range (0.19mm) were used. Large axial displacements ($> 1/2\text{-}\lambda$) were compensated for by adjusting the axial location of the search range using cumulative displacements. The minimum correlation achieved over each temporal window ($\rho_{\min}$) was used to quantify the level of speckle

decorrelation. The process was repeated for several uniformly-spaced 2 ms windows across the cardiac cycle and synthesized into M-mode maps of temporal coherence. The 2 ms window length was chosen to represent a reasonable duration over which an ARFI measurement can be acquired. Figure 3(a,b) shows M-mode maps for high and low temporal coherence cases, respectively. High ρ_{min} within the IVS over the entire cardiac cycle as well as a clear distinction between the myocardium and the cardiac chambers is observed in Figure 3(a). Comparatively, Figure 3(b) shows a more uneven spatio-temporal distribution within the IVS.

Signal quality was also measured based on spatial consistency or similarity of the displacement trends within the ROE i.e., across the simultaneously acquired beams in azimuth. Assuming structural uniformity of the myocardium across the ROE, this metric is indicative of the mechanical signal-to-noise ratio. This was quantified by correlating traces of mean displacement through range within the IVS across the seven azimuthal angles and reported using the mean Fisher-transformed Pearson correlation coefficients (ρ). This metric is referred to as the spatial similarity and was also computed on a beat-by-beat basis. Figure 4(a) and 4(b) depict examples with high and low spatial similarity, respectively.

The performance of each metric at distinguishing “successful” from “unsuccessful” acquisitions was analyzed using receiver-operator-characteristic (ROC) curves and quantified using the area under the curve (AUC).

Indices of Dynamic Myocardial Stiffness

Five indices characterizing the temporal dynamics of myocardial stiffness over the cardiac cycle were derived from the M-mode ARFI data. These indices are: stiffness ratio, rates of relaxation and contraction ($rate_R$ and $rate_C$), and time constants of relaxation and contraction (τ_r and τ_c). ARFI-derived indices of myocardial stiffness were computed for the IVS on a beat-by-beat basis between successive systolic intervals.

The stiffness ratio was calculated by dividing the mean displacements within the IVS over successive pairs of diastolic and systolic temporal windows. The positions of these windows were defined using ECG landmarks and chosen to capture the myocardium in mid-mechanical diastole and systole i.e., in its most relaxed and contracted states, respectively. The diastolic window, indicated by the gold bands in Figure 5(a,b), was centered at 85% of the T-P interval while the systolic window, indicated by the purple bands in Figure 5(a,b), was centered over the T-wave. The width of each window was set to 10% of the R-R interval. Mean displacement in diastole (u_D) and systole (u_S) are shown in Figure 5(b) as horizontal dotted lines. Stiffness ratios were computed independently for each azimuthal angle.

Mean displacements over axial range (within the IVS) for all measured time points over the cardiac cycle and for all azimuthal angles (seven around the ROE) are depicted in the shaded circles in Figure 5(b). A 5-point median filter through time (corresponding to 142 ms) was used to suppress outliers. Rates and time constants were derived by modeling segments of this curve using the four-parameter logistic model shown in equation 1.

$$\hat{u}(t) = u_S + \frac{u_D - u_S}{1 + e^{(t - t_0)/\tau}}, \quad (1)$$

where, u_S and u_D represent the displacement in systole and diastole, respectively, t_0 represents the temporal center of the logistic function, and τ represents its time constant.

The transition from systole to diastole indicates mechanical relaxation of the myocardium while diastole to systole indicates active contraction. The fitting operation was performed using MATLAB's fit function (The Math- Works Inc., Natick, MA) which implements a constrained, robust, nonlinear least squares Trust-Region algorithm. Representative fits for relaxation and contraction are shown in Figure 5(b) in solid red and blue lines, respectively. Rates of relaxation and contraction were computed by taking the peak of the derivative of the corresponding fit. The vertical dotted lines in Figure 5(b) indicate the positions at which the peak derivatives were extracted. Time constants of relaxation and contraction were defined as the time constant of the logistic equation for the respective transition.

Temporal consistency i.e., beat-to-beat variability of ARFI-derived indices of myocardial stiffness was assessed using the median average deviation (MAD) from the median and reported as a percentage.

Results

Signal Strength and Yield

A total of 204 M-mode ARFI acquisitions were collected in the study across twelve volunteers, in two TTE views (PLAX and PSAX), and using three tracking configurations (FF, HP, and HF). Acquisitions were considered to be “unsuccessful” if mean displacement within the IVS over all cardiac cycles in the acquisition (u_{cyc}) was $< 1.5 \mu\text{m}$, or if the conventional M-mode image showed significant artifacts due to breathing or gross motion. Acquisitions where the ARF push was unable to generate a measurable displacement or where extra-cardiac structures corrupted the echo data from the myocardium were rejected.

Examples of “successful” and “unsuccessful” acquisitions are presented in Figure 6. ARFI displacements in Figure 6(b) show a consistent and cyclic pattern over the cardiac cycle, as evidenced by the alignment to the ECG as well as the motion profile of the valve (in the lower third of the M-mode image). Measured displacements are relatively homogeneous across depth within the IVS. In comparison, Figure 6(d) shows consistently low displacements in all phases of the cardiac cycle with some spatio-temporal heterogeneity in the systolic phases. Mean displacement within the IVS over the full acquisition was $3.85 \mu\text{m}$ in Figure 6(b) and $0.83 \mu\text{m}$ in Figure 6(d). In Figure 6(f), breathing artifacts can be observed over substantial segments of the acquisition (0–1900ms and 2600–4500ms). These artifacts are not aligned with the cardiac cycle, manifest as transient high amplitude echoes on the conventional M-mode image, and obscure the IVS.

Figure 7 presents a bar graph of the number of M-mode ARFI acquisitions collected in the study across volunteers split by TTE view (in shades of gray). The number of acquisitions that were determined to be “successful” are indicated in green. Out of the twelve volunteers, at least one “successful” acquisition was acquired on eight volunteers in PLAX and six volunteers in PSAX. Six volunteers yielded “successful” acquisitions in both views while no “successful” acquisitions could be performed on four volunteers. Table 2 provides a summary of the acquisition yield as a function of tracking configuration and TTE view. Yield was slightly lower for PLAX (38%) compared to PSAX (44%). The two focused configurations (FF and HF) showed higher yield (45% each) compared to the HP case (32%). All combined, 84 out of 204 acquisitions (41%) were determined to be “successful”.

Metrics of signal strength, tracking fidelity, and ARFI-derived indices of dynamic myocardial stiffness were computed and analyzed on a beat-to-beat basis. These are presented here using the median and interquartile range (IQR). Statistical significance for select comparisons was determined using a Mann-Whitney U-test and reported using the p-value. The 84 “successful” acquisitions contained 343 cardiac cycles. Within “successful” acquisitions, by tracking configuration, there were 125 (36%) cardiac cycles in FF, 93 (28%) in HP, and 125 (36%) in HF. By view, there were 158 (46%) in PLAX and 185 (54%) in PSAX. The 120 “unsuccessful” acquisitions contained 491 cardiac cycles. These were distributed by beamforming configuration as 148 (30%) in FF, 191 (39%) in HP, and 152 (31%) in HF and by view as 275 (56%) in PLAX and 216 (44%) in PSAX.

Displacement Signal-to-Noise

Figure 8 illustrates a comparison between mean ARF-induced displacements within the IVS for “successful” acquisitions in diastolic and systolic temporal windows. These displacements are measured after the application of the motion filter and each data point represents an individual cardiac cycle. Mean displacements over the entire cardiac, prior to the ARF push (for matched cardiac cycles) is also shown for reference. The diastolic and systolic displacements are computed using the first track after the push (1.5 ms) while the “pre-push” displacement was extracted 10 ms prior to it. The “pre-push” displacements serve as an indication of the noise floor in this context. Figure 8(a) compares displacements across tracking configuration while (b) compares them based on TTE view.

Combining the sub-groups, the median and IQR of the displacements were measured to be 3.04 (1.59) μm in diastole, 1.19 (0.33) μm in systole, and 0.03 (0.12) μm prior to the push. These were statistically distinct from each other ($p < 0.0001$). Diastolic displacements were slightly lower in the HP configuration, 2.50 (1.23) μm , compared to FF, 3.37 (1.66) μm ($p < 0.0001$), and HF, 3.18 (1.39) μm ($p < 0.001$). Diastolic displacements were also found to be slightly higher in PLAX, 3.34 (1.88) μm compared to PSAX, 2.85 (1.24) μm ($p < 0.01$). Systolic displacements across the tracking configurations and between the two views were found to be roughly identical.

Metrics of Tracking Fidelity

“Successful” and “unsuccessful” acquisitions were compared on the basis of the proposed metrics of tracking fidelity: contrast, temporal coherence, and spatial similarity. Figure 9

presents a comparison of these metrics between the two groups. Each group is further subdivided based on the tracking configuration used. Tracking fidelity is not expected to vary preferentially with TTE view, thus the two views were combined in this analysis for brevity. Each data point represents an individual cardiac cycle.

Contrast across all “successful” acquisitions was measured to be 13.17 (7.11) dB. For “unsuccessful” acquisitions contrast was substantially lower, 5.42 (7.31) dB. This difference was statistically significant with a $p < 0.0001$. For each group, contrast was found to be higher for the two configurations that employed harmonic imaging (HP and HF). Within the “successful” group, contrast using FF, HP, and HF was measured at 11.07 (5.14) dB, 14.12 (8.48) dB, and 16.62 (7.05) dB, respectively.

Temporal coherence, quantified using ρ_{min} , was measured at 0.988 (0.007) for “successful” acquisitions. The same for “unsuccessful” acquisitions was 0.976(0.018). However, unlike in the case of contrast where both groups displayed a large degree of variability, temporal coherence for “successful” acquisitions exhibited a relatively low variance. Across the tracking configurations, ρ_{min} for “successful” acquisitions had IQRs of 0.008, 0.006, and 0.004 in FF, HP, and HF, respectively. For “unsuccessful” cases the same were 0.014, 0.021, and 0.015. Temporal coherence achieved the highest values and lowest variability in “successful” acquisitions in the HF configuration; ρ_{min} in this case was 0.991 (0.004).

Spatial similarity (ρ) was found to follow trends similar to temporal coherence. In the case of “successful” acquisitions, across the three tracking configurations, ρ was calculated to be 0.989(0.021), 0.958(0.043), and 0.988 (0.021) for FF, HP, and HF, respectively. “Unsuccessful” acquisitions exhibited lower ρ values of 0.890 (0.115), 0.806 (0.171), and 0.856 (0.147) for FF, HP, and HF, respectively. Spatial similarity exhibited a larger range of values as compared to temporal coherence.

The three metrics of tracking fidelity were found to be partially correlated. Figure 10(a,b,c) depicts the relationships between each pair of metrics for both “successful” and “unsuccessful” acquisitions. Temporal coherence and spatial similarity values were Fisher-transformed (Silver and Dunlap, 1987) for this analysis to represent them as continuous unbounded variables. All pairs show a moderate positive trend with linear correlation coefficients of 0.675 for contrast vs. temporal coherence, 0.474 for contrast vs. spatial similarity, and 0.591 for temporal coherence vs. spatial similarity. ROC curves for individual metrics are shown in Figure 10(d). AUC was 0.81 when using only contrast, 0.85 when using only temporal coherence, and 0.91 when using spatial similarity. The optimal cut-offs for each metric, i.e., where efficiency of classification is maximized were found to be 9.48 dB for contrast, 0.985 for temporal coherence, and 0.953 for spatial similarity. These cut-offs are indicated in the horizontal and vertical lines in Figure 10(a,b,c). As observed previously, “successful” acquisitions showed high values for all three metrics and thus were clustered in the upper right quadrant of these graphs.

Indices of Dynamic Myocardial Stiffness

ARFI-derived indices of dynamic myocardial stiffness were computed on a beat-by-beat basis for all cardiac cycles in “successful” acquisitions. Figure 11 and 12 illustrate examples of “successful” acquisitions in PLAX and PSAX, respectively.

In both cases, the B-mode and M-mode images exhibit good border delineation of the IVS and a clear distinction between the myocardium and the cardiac chambers. Contrast, temporal coherence, and spatial similarity in both case are substantially greater than the optimal cut-offs determined using the ROC curves. M-mode ARFI data, displayed in the semi-transparent color overlay, shows a cyclic pattern with high displacements during diastole and low displacements in systole. These trends are further exemplified by the alignment of the ECG signal with the trace of mean displacements through range within the IVS. Diastolic temporal windows, indicated by gold bands, and systolic temporal windows, indicated by purple bands, generally capture the peak and trough of the M-mode displacement traces through the cardiac cycle. The five ARFI-derived indices of dynamic myocardial stiffness are displayed in the table below the B-mode image.

Table 3 presents a statistical summary of the five ARFI-derived indices of dynamic myocardial stiffness divided by TTE view. These were computed using all cardiac cycles in “successful” acquisitions. Statistically significant differences between the two views were not observed for any of the indices computed in this study.

Figure 13 depicts the level of temporal consistency or beat-to-beat variability for the ARFI-derived indices. For this analysis, tracking configurations acquired sequentially, i.e., as part of a single dataset, were combined provided the individual acquisitions were considered to be “successful”. Median absolute deviations (MAD) as a percentage of the median are presented for datasets with 10 or more cardiac cycles. Stiffness ratios were found to be the most consistent from beat-to-beat with average MAD of 12.26%. Rates and time constants, however, exhibited a significantly higher level of temporal variability, with average MADs in the range of 30.62–33.28%.

Discussion

This study had three main objectives: i) to assess the feasibility of tracking the temporal dynamics of myocardial stiffness using ARFI imaging in a noninvasive manner, ii) to extract quantitative indices from M-mode ARFI data that characterize changes in myocardial stiffness over the cardiac cycle, and iii) to evaluate the temporal consistency of these indices under *in vivo* conditions and establish reference values in a cohort of healthy volunteers.

Challenges for Transthoracic ARFI and Potential Solutions

The transthoracic imaging environment presents several obstacles for ARF-based techniques such as ARFI and SWEI. The main challenges are: i) generating strong ARF pushes in the myocardium, ii) tracking micron-level displacements in an accurate and precise manner in the presence of acoustic clutter and out-of-plane motion, and iii) separating ARF-induced displacements from the background cardiac motion.

M-mode ARFI acquisitions were categorized as “successful” or “unsuccessful” based on the mean ARF-induced displacement over the duration of the acquisition, i.e., across multiple cardiac cycles. ARF-induced displacements above the threshold of $1.5\ \mu\text{m}$ were only observed in 41% of the 204 acquisitions. This low yield can be attributed to a variety of factors that are discussed here. ARF-induced displacements are directly proportional to the acoustic intensity generated in the target tissue of interest (Nightingale et al., 2002); thus conditions that allow for the use of tightly focused beams through a low attenuation acoustic path are favorable for ARFI imaging. The ability to focus ultrasound beams is governed by aperture size and target depth. In TTE, the azimuthal and elevational aperture sizes are limited by the intercostal spaces to 18–20 mm. However, the targets of clinical interest such as the IVS and LV free wall appear at depths of 50–70 mm and 110–130 mm, respectively. This combination results in weakly focused beams with F-numbers on the orders of 2.5–3.5 at the IVS and 5.5–6.5 at the LV free wall. While a substantial portion of the propagation path, in TTE, consists of weakly attenuating blood, the chest wall, which appears in the near-field, is composed of highly attenuating structures such as muscle and connective tissue (Mast, 2000). Thus, a large fraction of the acoustic energy in the push pulses is absorbed in the near field and does not contribute to the mechanical excitation. These factors limit the ability to generate large ARF-induced displacements at the targets of interest.

Displacement signal strength could be improved by using longer push pulses and/or higher voltages i.e., acoustic pressures. The push pulses used in this study were $300\ \mu\text{s}$ long with an MI of 1.65. These were limited due to the scanner power supply hardware and probe heating considerations. For most soft tissues, ARF excitations of up to 1 ms are still considered to be impulsive (Palmeri et al., 2006). Thus, for a fixed MI, utilizing a 1ms push pulse would lead to an increase in the push strength by three times compared to the sequences used in this study. Likewise, stronger push pulses could also be generated by increasing the pressures up to the FDA-enforced MI limit of 1.9 (Barnett et al., 2000). The use of longer pulse durations and elevated pressures will have to be calibrated against the increased power output and potential for tissue and transducer face heating (Bouchard et al., 2009) as well as the risk of inducing cavitation (Apfel and Holland, 1991).

Tracking of micron-level displacements using ultrasound is generally performed using normalized cross-correlation, on radio-frequency (RF) signals or using phase-shift algorithms in the case of in-phase and quadrature (IQ) data. Acoustic clutter and multi-dimensional background motion of the targets of interest can severely impact the precision as well as accuracy of tracked displacements. In simulations, clutter in the form of stationary echoes has been shown to introduce bias into displacement estimates (Pinton et al., 2006). The superposition of stationary echoes with a strength of $-5\ \text{dB}$ resulted in a 24% bias in tracked displacement. In the context of TTE, reverberation between tissue layers in the near-field can generate a substantial level of high amplitude stationary echoes and consequently corrupt M-mode ARFI data. Moreover, non-stationary clutter can also arise from structures that move with the cardiac or respiratory cycles, such as off-axis myocardium, pericardium, and lung tissue.

Tracked axial displacements represent a combination of background myocardial motion as well as ARF-induced displacements. Suppression of background motion in ARFI

applications has traditionally been accomplished using quadratic motion filters. However, the performance of these filters can be sensitive to the specific combination of parameters used (Giannantonio et al., 2011). Frequency-based filters have been shown to be equally effective at suppressing background myocardial motion for transthoracic applications (Kakkad et al., 2015) and were utilized here. As shown in Figure 8, “Pre-push” displacements over the full cardiac cycle showed minimal bias and low variance after application of a 3rd-order high-pass Butterworth filter with a cutoff frequency of 75 Hz. For “successful” acquisitions, measured displacements in all phases of the cardiac cycle were found to be distinct from the noise floor. In diastole, displacements were always higher than systole (for “successful” acquisitions). The subtle decrease in diastolic displacements in the harmonic-plane wave configuration could be attributed to a spatial averaging effect as a result of the broader point-spread function of the tracking transmit beam (Czernusiewicz et al., 2013).

Measurement uncertainty for unbiased displacement estimators is defined by the Cramer-Rao Lower Bound (Walker and Trahey, 1995) which relates the standard deviation of displacement estimates, or jitter, to ultrasonic tracking parameters such as frequency, bandwidth, kernel length, SNR, and speckle correlation. While axial displacements can be tracked using the techniques mentioned above, translational motion in other dimensions (azimuth and elevation) or rotational motion lead to speckle decorrelation and a consequent amplification of jitter. For typical parameters used in TTE, 3.5 MHz center frequency, 80% bandwidth, 5- λ kernel, and 60 dB channel SNR, and a correlation coefficient of 0.992, jitter is predicted to be 1.52 μm . However, jitter is sensitive to speckle decorrelation and rises quickly to 3.1 μm at a correlation coefficient of 0.97; these values represent the uncertainty associated with a single displacement estimate. In practice, however, displacements are averaged across partially overlapping spatio-temporal kernels to suppress variance at the cost of reduced resolution.

The results presented herein focus on measuring the stiffness of the IVS through the PLAX and PSAX views. M-mode ARFI, in principle, could also be used to interrogate other segments of the heart through different views; the apex and the IVS could be accessed in the apical 4-chamber or 2-chamber views. In our previous experience, attempts to use apical views to target the apex but were hampered by reverberant acoustic clutter due to the proximity of the apex to the chest wall and pericardium. In the case of the IVS through apical views, the myocardium appears in a vertical orientation and exhibits substantial lateral motion which causes it to move in-and-out of the region-of-excitation (ROE). While this was a challenge for this implementation of M-mode ARFI where the ROE was fixed in azimuth, it could be overcome in the future by following the gross lateral motion of the myocardial walls using (2D speckle tracking techniques) and adaptively adjusting the angle of the ARF ensembles accordingly.

Acoustic clutter and speckle decorrelation due to multi-dimensional tissue motion are, to some degree, inherent to the physics of cardiac ultrasound imaging. However, their detrimental impact on M-mode ARFI is dependent on the specific magnitude of each source of signal degradation. As shown here, coarse estimates of the signal-to-clutter level can be generated using contrast between the myocardium and the cardiac chambers, while motion-

induced speckle decorrelation can be quantified using temporal coherence. These metrics are extracted from the same echo data used for ARFI processing and thus have potential to serve as adaptive indicators of signal quality. Similarly, spatial similarity of displacement traces across simultaneously-acquired beams within the ROE captured the effect of acoustic SNR as well as jitter using the tracked displacement signals. Not only were all three metrics found to be significantly higher for “successful” acquisitions vs. “unsuccessful” acquisitions, they were also found to be correlated with each other. As illustrated in Figure 10(a,b), decreasing contrast was associated with a general decrease in temporal coherence as well as spatial similarity. This suggests that “low contrast” could be attributed to either poor acoustic SNR (i.e., poor penetration) or a high level of non-stationary clutter from moving sources. In comparison, reduced contrast due to stationary clutter from static sources would maintain high temporal coherence and spatial similarity.

The three metrics can individually be used to categorize acquisitions into “successful” or “unsuccessful”. Their ability to do so was quantified using AUC of the ROC curves. All three metrics performed did a good job of separating the two groups with spatial similarity doing the best (AUC = 91). While these metrics are highly correlated, they do inherently represent different “failure modes” and could be combined to form an adaptive, displacement-magnitude independent method to assess the reliability of M- mode ARFI acquisitions.

For instance, the combination of contrast and temporal coherence can serve as an indicator to distinguish between acquisitions that are corrupted due to an inability to accurately track displacements from those where a viable ARF excitation could not be generated. 49 of the 491 (9.98%) cardiac cycles in “unsuccessful” acquisitions were found to be above the optimal cutoffs for contrast and temporal coherence determined using the ROC analysis, i.e., 9.48 dB for contrast and 0.985 for temporal coherence. In these cases, while tracking conditions were favorable, the mean tracked displacements were measured to be below the 1.5 μm cutoff. Thus, stronger ARF-excitation could yield viable M-mode ARFI data for such acquisitions. Using the theoretical estimates, a contrast threshold of 10 dB and a temporal coherence threshold of 0.985 would limit the bias due to stationary echoes to < 10% and jitter to < 2 μm . Spatial similarity was found to be the most efficient differentiator. It inherently combines the effects of acoustic SNR, jitter, as well as low ARF-induced displacement while making the assumption of uniformity over the ROE. Lastly, as employed here, the mean displacement over the cardiac cycle could also be used as an indicator of “success”.

Temporal Dynamics of Myocardial Stiffness

In acquisitions where a measurable ARF-displacement was able to be generated and the tracking conditions were favorable, M-mode ARFI, implemented on a clinical ultrasound system and an adult cardiac phased array, was successful at tracking changes in stiffness of the interventricular septum (IVS) over the cardiac cycle. These trends were captured in both transthoracic echocardiographic (TTE) views studied here.

Figure 8(a) shows a decrease in the magnitude of the ARF-induced diastolic displacement for the harmonic plane wave case, compared to the two focused cases. This could be

attributed to a spatial averaging effect of the (laterally) broader point spread function of the tracking beam when using plane waves (McAleavey et al., 2003). This result was also observed when using the same sequences to measure elasticity phantoms. Mean ARF-induced diastolic displacements were also found to be lower in PSAX versus PLAX, as shown in Figure 8(b). Diastolic shear wave speeds have been found to be faster in PSAX compared to PLAX (Song et al., 2016). Similarly, ARF-induced displacements have also been shown to be impacted by material anisotropy (Hossain et al., 2017). Thus, this result could be a manifestation of the change in fiber orientation between the two views. Systolic displacements did not show such subtle trends, potentially due to lower displacement magnitude and thus lower SNR. These hypotheses were not explicitly addressed in this *in vivo* study and could be better characterized through controlled experiments on *ex vivo* myocardium.

Temporal trends in the M-mode ARFI data exhibited excellent alignment with the expected physiological changes over cardiac cycle as indicated by the ECG. ARF-induced displacements, which are inversely proportional to tissue stiffness, were highest during the latter half of the T-P segment which is marked by low electrical as well as mechanical activity. During this phase of the cardiac cycle, also referred to as diastasis, pressure in the left ventricle is at its lowest and the myocardium is in a relaxed state (Stouffer, 2017). In contrast, low displacements, indicating high stiffness, were measured in the S-T segment i.e., during ejection; pressure is expected to hit its peak in this phase following active contraction of the myocardium. Smooth transitions were observed between these two extremes. Active contraction manifests in the M-mode ARFI data as a steady decrease in displacement immediately following the R-wave; while relaxation is seen as a gradual increase in displacement after the T-wave. These findings are consistent with previous implementations of ARFI and SWEI in animals using open-chest preparations (Hsu et al., 2007), intracardiac echocardiography (ICE) (Hollender et al., 2013), as well as in Langendorff experiments (Pernot et al., 2011; Vejdani-Jahromi et al., 2015).

Heart-rate dependent changes in the relative duration of systole and diastole are also reflected in the M-mode ARFI data. The diastolic duration has been shown to have an inverse relationship with heart-rate (Chung et al., 2004) while the systolic duration has been found to be less sensitive (Cui et al., 2008). In the example portrayed in Figure 12(b), the heart-rate is 70bpm and the fraction of the cardiac cycle with high displacements (diastole) and low displacements (systole) are roughly equal. In contrast, Figure 6(b) and Figure 11(b) show longer segments where the displacement is consistently high; heart-rate in these cases was 53 and 55 bpm, respectively. The temporal trends of myocardial stiffness and their correlation with the ECG signal were found to be highly repeatable from beat-to-beat as well as across different volunteers. These trends could be used to augment current diagnostic methods for detection of regional conduction abnormalities that may not be captured on the global ECG.

ARFI-derived indices, especially rates and time constants showed a substantial degree of beat-to-beat variability. This could be attributed to a broad set of factors related to technical limitations of the ultrasound-based elastography methods as well as physiological changes in cardiac function due to autonomic reflexes. Even under tightly controlled experimental

conditions, hemodynamic parameters extracted from interventricular pressure changes have been found to show inherent variability (Freeman et al., 1993).

Limitations and Future Work

This study outlines some of the fundamental challenges of performing M- mode ARFI acquisitions through transthoracic windows. However, it does not explicitly address a number of factors associated with cardiac anatomy, physiology as well as higher-order technical limitations that could contribute to bias and variability in ARFI-derived indices of myocardial stiffness.

Given the reliance of ARFI on accurate tracking of micron-level displacements, even subtle movements of volunteers due to breathing or probe motion can lead to substantial artifacts. 41 out of 204 (20.1%) of acquisitions collected in this study had to be excluded on account of artifacts due to breathing and/or gross motion. Multidimensional motion (contraction and torsion) of the heart could also lead to some degree of spatial uncertainty in M-mode measurements of myocardial stiffness. Limiting ARFI acquisitions to shorter durations, performing them under breath-holds, and using 2D or 3D speckle tracking techniques to adaptively adjust the direction of the ARF ensembles could help improve yield and maintain spatial registration in future implementations.

Sampling rate is a critical factor when estimating a time-varying signal. In this study, temporal dynamics of myocardial stiffness were sampled at a push PRF of 35 Hz; this provided 28 stiffness estimates over the cardiac cycle at a heart-rate of 75 bpm. While this sampling rate allows for visualization of smooth transitions in myocardial stiffness between the various cardiac phases at the heart-rates tested here (48 – 98 bpm), it may not be sufficient at higher heart-rates. Undersampling the temporal trends of myocardial stiffness could mask critical features and lead to errors in the estimation of rates and time constants. Future work will look to address the accuracy of these indices as a function of sampling rate. Thermal safety considerations and hardware limitations could place a cap on the maximum achievable push PRF. However, multi-beat synthesis or gated-acquisitions could be used to boost the effective sampling rate over the cardiac cycle at the expense of assuming uniformity across multiple heart beats. Violation of this assumption could lead to increased standard deviation of computed indices.

While metrics of signal quality presented herein provide good differentiation between “successful” and “unsuccessful” acquisitions, they exhibit substantial variability within acquisitions that were identified as being “successful”. Changes in these metrics over successive cardiac cycles could, in part, contribute to the beat-to-beat variability in ARFI-derived indices of myocardial stiffness. A thorough analysis addressing the various noise sources in TTE and determining their relationship to the metrics of signal quality as well as the precision and accuracy of ARFI-derived indices will be the focus of future work.

Lastly, anatomical and physiological considerations such as body habitus, myocardial fiber orientation, higher-order material characteristics such as viscoelasticity, hemodynamic parameters (loading conditions), and spatial uniformity of myocardial mechanical properties (between the epicardial to endocardial segments and from apical to basal segments within

the IVS) are likely to contribute to variability in the measurement of ARFI-derived indices of myocardial stiffness and warrant further investigation.

Future work will not only focus on quantifying the impact of the factors listed above but also investigate the diagnostic potential of transthoracic ARFI-derived indices on cohorts of patients with confirmed cardiac disease. An investigation of correlations between clinically established metrics of cardiac function such as ejection fraction, Doppler-derived indices, and myocardial strain against ARFI-derived indices of dynamic myocardial stiffness would be extremely informative.

Conclusions

The results presented herein demonstrate the feasibility of using M-mode ARFI to measure temporal trends of myocardial stiffness through the cardiac cycle via transthoracic imaging windows. Dynamic myocardial stiffness of the IVS was captured in both TTE views tested in this study and quantified using the stiffness ratio as well as rates, time constants of contraction and relaxation. The yield of “successful” acquisitions, however, was limited; this was attributed to the inability to generate a measurable mechanical excitation in the myocardium as well as unfavorable conditions for tracking micron-level displacements. Metrics of tracking fidelity such as signal-to-clutter level, temporal coherence of speckle, and spatial similarity of displacement traces within the ROE were found to differentiate “successful” from “unsuccessful” acquisitions. ARF-derived indices of dynamic myocardial stiffness were found to be similar across the two views. Stiffness ratios exhibited good beat-to-beat repeatability while rates and time constants were less consistent. The values presented here were measured on healthy volunteers and serve as a reference for future studies aimed at noninvasive characterization of myocardial stiffness using ARFI in patients with clinical symptoms of cardiomyopathy.

Acknowledgements

The authors would like to thank Harrison Ferlauto, Kris Arges, Matt Baum, and Jennifer Tomfohr for assistance with data acquisition, Will Long, Matt Morgan, and Nick Bottenus for insightful comments on data processing and presentation methods, and Siemens Medical Solutions, USA for their inkind and technical support. This research is funded by the National Institutes of Health grants R01EB017711 and R37HL096023.

References

- Apfel RE, Holland CK. Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound. *Ultrasound in medicine & biology*. 1991;17:179–185. [PubMed: 2053214]
- Arani A, Arunachalam SP, Chang IC, Baffour F, Rossman PJ, Glaser K, Trzasko JD, Manduca A, McGee KP, Grogan M, et al. Cardiac magnetic resonance elastography as a quantitative non-invasive metric for myocardial stiffness: Initial pilot study in patients with cardiac amyloidosis, 2016.
- Arunachalam SP, Arani A, Baffour F, Rysavy JA, Rossman PJ, Glaser KJ, Lake DS, Trzasko JD, Manduca A, McGee KP, et al. Regional assessment of in vivo myocardial stiffness using 3d magnetic resonance elastography in a porcine model of myocardial infarction. *Magnetic resonance in medicine*. 2018;79:361–369. [PubMed: 28382658]
- Bahnsen TD, Eyerly SA, Hollender PJ, Doherty JR, KIM YJ, Trahey GE, Wolf PD. Feasibility of near real-time lesion assessment during radiofrequency catheter ablation in humans using acoustic

radiation force impulse imaging. *Journal of cardiovascular electrophysiology*, 2014;25:1275–1283. [PubMed: 25132292]

- Barnett SB, Ter Haar GR, Ziskin MC, Rott HD, Duck FA, Maeda K. International recommendations and guidelines for the safe use of diagnostic ultrasound in medicine. *Ultrasound in medicine and biology*, 2000;26:355–366. [PubMed: 10773365]
- Borbély A, van der Velden J, Papp Z, Bronzwaer JG, Edes I, Stienen GJ, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. *Circulation*, 2005;111:774–781. [PubMed: 15699264]
- Bouchard RR, Dahl JJ, Hsu SJ, Palmeri ML, Trahey GE. Image quality, tissue heating, and frame rate trade-offs in acoustic radiation force impulse imaging. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2009;56:63–76.
- Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *American Journal of Physiology-Heart and Circulatory Physiology*, 2005;289:H501–H512. [PubMed: 16014610]
- Chung CS, Karamanoglu M, Kovács SJ. Duration of diastole and its phases as a function of heart rate during supine bicycle exercise. *American Journal of Physiology-Heart and Circulatory Physiology*, 2004;287:H2003–H2008. [PubMed: 15217800]
- Conrad CH, Brooks WW, Hayes JA, Sen S, Robinson KG, Bing OH. Myocardial fibrosis and stiffness with hypertrophy and heart failure in the spontaneously hypertensive rat. *Circulation*, 1995;91:161–170. [PubMed: 7805198]
- Couade M, Pernot M, Messas E, Bel A, Ba M, Hagege A, Fink M, Tanter M. In vivo quantitative mapping of myocardial stiffening and transmural anisotropy during the cardiac cycle. *IEEE transactions on medical imaging*, 2011;30:295–305. [PubMed: 20851788]
- Cui W, Roberson DA, Chen Z, Madronero LF, Cuneo BF. Systolic and diastolic time intervals measured from doppler tissue imaging: normal values and z-score tables, and effects of age, heart rate, and body surface area. *Journal of the American Society of Echocardiography*, 2008;21:361–370. [PubMed: 17628402]
- Czernuszewicz TJ, Streeter JE, Dayton PA, Gallippi CM. Experimental validation of displacement underestimation in arfi ultrasound. *Ultrasonic imaging*, 2013;35:196–213. [PubMed: 23858054]
- Doherty JR, Dahl JJ, Trahey GE. Harmonic tracking of acoustic radiation force-induced displacements. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2013a;60:2347–2358.
- Doherty JR, Trahey GE, Nightingale KR, Palmeri ML. Acoustic radiation force elasticity imaging in diagnostic ultrasound. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2013b;60:685–701.
- Freeman GL, Prabhu SD, Widman LE, Colston JT. An analysis of variability of left ventricular pressure decay. *American Journal of Physiology-Heart and Circulatory Physiology*, 1993;264:H262–H268.
- Gheorghiade M, Bonow RO. Chronic heart failure in the united states: a manifestation of coronary artery disease. *Circulation*, 1998;97:282–289. [PubMed: 9462531]
- Giannantonio DM, Dumont DM, Trahey GE, Byram BC. Comparison of physiological motion filters for in vivo cardiac arfi. *Ultrasonic imaging*, 2011;33:89–108. [PubMed: 21710825]
- Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation*, 2006;114:216–225. [PubMed: 16831987]
- Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonidis JS, Khavjou O, Konstam MA, Maddox TM, et al. Forecasting the impact of heart failure in the united states: a policy statement from the american heart association. *Circulation: Heart Failure*, 2013;6:606–619. [PubMed: 23616602]
- Hollender P, Bradway D, Wolf P, Goswami R, Trahey G. Intracardiac acoustic radiation force impulse (arfi) and shear wave imaging in pigs with focal infarctions. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2013;60:1669–1682.
- Hollender PJ, Wolf PD, Goswami R, Trahey GE. Intracardiac echocardiography measurement of dynamic myocardial stiffness with shear wave velocity locimetry. *Ultrasound in Medicine and Biology*, 2012;38:1271–1283. [PubMed: 22579544]

- Hossain M, Moore CJ, Gallippi CM. Acoustic radiation force impulse-induced peak displacements reflect degree of anisotropy in transversely isotropic elastic materials. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2017;64:989–1001.
- Hsu SJ, Bouchard RR, Dumont DM, Wolf PD, Trahey GE. In vivo assessment of myocardial stiffness with acoustic radiation force impulse imaging. *Ultrasound in Medicine and Biology*, 2007;33:1706–1719. [PubMed: 17698282]
- Kakkad V, Kuo L, Bradway D, Trahey G, Sivak J, Kisslo J. In vivo transthoracic measurements of acoustic radiation force induced displacements in the heart over the cardiac cycle. In: *Ultrasonics Symposium (IUS)*, 2015 IEEE International IEEE, 2015 pp. 1–5.
- Kakkad V, LeFevre M, Roy Choudhury K, Kisslo J, Trahey GE. Effect of transmit beamforming on clutter levels in transthoracic echocardiography. *Ultrasonic imaging*, 2018;0161734618770359.
- Kolipaka A, Aggarwal SR, McGee KP, Anavekar N, Manduca A, Ehman RL, Araoz PA. Magnetic resonance elastography as a method to estimate myocardial contractility. *Journal of Magnetic Resonance Imaging*, 2012;36:120–127. [PubMed: 22334349]
- Kolipaka A, Araoz PA, McGee KP, Manduca A, Ehman RL. Magnetic resonance elastography as a method for the assessment of effective myocardial stiffness throughout the cardiac cycle. *Magnetic resonance in medicine*, 2010;64:862–870. [PubMed: 20578052]
- Kolipaka A, McGee KP, Manduca A, Anavekar N, Ehman RL, Araoz PA. In vivo assessment of mr elastography-derived effective end-diastolic myocardial stiffness under different loading conditions. *Journal of Magnetic Resonance Imaging*, 2011;33:1224–1228. [PubMed: 21509882]
- Kremer L, Van Dalen E, Offringa M, Ottenkamp J, Voute P. Anthracycline- induced clinical heart failure in a cohort of 607 children: long-term followup study. *Journal of Clinical Oncology*, 2001;19:191–196. [PubMed: 11134212]
- Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *Jama*, 1996;275:1557–1562. [PubMed: 8622246]
- Little WC. The left ventricular dp/dtmax-end-diastolic volume relation in closed-chest dogs. *Circulation research*, 1985;56:808–815. [PubMed: 4006092]
- Loupas T, Powers J, Gill RW. An axial velocity estimator for ultrasound blood flow imaging, based on a full evaluation of the doppler equation by means of a two-dimensional autocorrelation approach. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, 1995;42:672–688.
- Mariappan YK, Glaser KJ, Ehman RL. Magnetic resonance elastography: a review. *Clinical anatomy*, 2010;23:497–511. [PubMed: 20544947]
- Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an american heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation*, 2006;113:1807–1816. [PubMed: 16567565]
- Mast TD. Empirical relationships between acoustic parameters in human soft tissues. *Acoustics Research Letters Online*, 2000;1:37–42.
- Mazumder R, Schroeder S, Mo X, Clymer BD, White RD, Kolipaka A. In vivo quantification of myocardial stiffness in hypertensive porcine hearts using mr elastography. *Journal of Magnetic Resonance Imaging*, 2017a;45:813–820. [PubMed: 27564862]
- Mazumder R, Schroeder S, Mo X, Litsky AS, Clymer BD, White RD, Kolipaka A. In vivo magnetic resonance elastography to estimate left ventricular stiffness in a myocardial infarction induced porcine model. *Journal of Magnetic Resonance Imaging*, 2017b;45:1024–1033. [PubMed: 27533317]
- McAleavey SA, Nightingale KR, Trahey GE. Estimates of echo correlation and measurement bias in acoustic radiation force impulse imaging. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2003;50:631–641.
- McCrohon J, Moon J, Prasad S, McKenna W, Lorenz C, Coats A, Pennell D. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation*, 2003;108:54–59. [PubMed: 12821550]

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, et al. Heart disease and stroke statistics 2016 update: a report from the American Heart Association. *Circulation*, 2016;133:e38–e360. [PubMed: 26673558]
- Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. *Archives of internal medicine*, 2005;165:1425–1429. [PubMed: 15983293]
- Nightingale K, McAleavey S, Trahey G. Shear-wave generation using acoustic radiation force: in vivo and ex vivo results. *Ultrasound in Medicine and Biology*, 2003;29:1715–1723. [PubMed: 14698339]
- Nightingale K, Soo MS, Nightingale R, Trahey G. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. *Ultrasound in Medicine and Biology*, 2002;28:227–235. [PubMed: 11937286]
- Palmeri ML, McAleavey SA, Fong KL, Trahey GE, Nightingale KR. Dynamic mechanical response of elastic spherical inclusions to impulsive acoustic radiation force excitation. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2006;53.
- Pernot M, Couade M, Mateo P, Crozatier B, Fischmeister R, Tanter M. Real-time assessment of myocardial contractility using shear wave imaging. *Journal of the American College of Cardiology*, 2011;58:65–72. [PubMed: 21700091]
- Pinton GF, Dahl JJ, Trahey GE. Rapid tracking of small displacements with ultrasound. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, 2006;53:1103–1117.
- Sack I, Rump J, Elgeti T, Samani A, Braun J. Mr elastography of the human heart: noninvasive assessment of myocardial elasticity changes by shear wave amplitude variations. *Magnetic resonance in medicine*, 2009;61:668–677. [PubMed: 19097236]
- Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound in Medicine and Biology*, 1998;24:1419–1435. [PubMed: 10385964]
- Shattuck DP, Weinshenker MD, Smith SW, von Ramm OT. Explososcan: A parallel processing technique for high speed ultrasound imaging with linear phased arrays. *The Journal of the Acoustical Society of America*, 1984;75:1273–1282. [PubMed: 6725779]
- Silver NC, Dunlap WP. Averaging correlation coefficients: Should Fisher's z transformation be used? *Journal of Applied Psychology*, 1987;72:146.
- Song P, Bi X, Mellema DC, Manduca A, Urban MW, Pelliikka PA, Chen S, Greenleaf JF. Pediatric cardiac shear wave elastography for quantitative assessment of myocardial stiffness: a pilot study in healthy controls. *Ultrasound in Medicine and Biology*, 2016;42:1719–1729. [PubMed: 27140522]
- Stouffer G. *Cardiovascular hemodynamics for the clinician*. John Wiley & Sons, 2017.
- Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circulation research*, 1974;35:117–126. [PubMed: 4841253]
- Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circulation research*, 1973;32:314–322. [PubMed: 4691336]
- Sunagawa K, Maughan WL, Sagawa K. Effect of regional ischemia on the left ventricular end-systolic pressure-volume relationship of isolated canine hearts. *Circulation research*, 1983;52:170–178. [PubMed: 6825214]
- Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. *Cancer*, 2003;97:2869–2879. [PubMed: 12767102]
- Vejdani-Jahromi M, Nagle M, Jiang Y, Trahey GE, Wolf PD. A comparison of acoustic radiation force-derived indices of cardiac function in the Langendorff perfused rabbit heart. *IEEE transactions on ultrasonics, ferro-electrics, and frequency control*, 2016;63:1288–1295.
- Vejdani-Jahromi M, Nagle M, Trahey GE, Wolf PD. Ultrasound shear wave elasticity imaging quantifies coronary perfusion pressure effect on cardiac compliance. *IEEE transactions on medical imaging*, 2015;34:465–473. [PubMed: 25291788]

- Villemain O, Correia M, Mousseaux E, Baranger J, Zarka S, Podetti I, Soulat G, Damy T, Hagege A, Tanter M, et al. Myocardial stiffness evaluation using noninvasive shear wave imaging in healthy and hypertrophic cardiomyopathic adults. *JACC: Cardiovascular Imaging*, 2018.
- Walker WF, Trahey GE. A fundamental limit on delay estimation using partially correlated speckle signals. *IEEE Transactions on Ultrasonics, Ferro-electrics, and Frequency Control*, 1995;42:301–308.
- Wassenaar PA, Eleswarpu CN, Schroeder SA, Mo X, Raterman BD, White RD, Kolipaka A. Measuring age-dependent myocardial stiffness across the cardiac cycle using mr elastography: A reproducibility study. *Magnetic resonance in medicine*, 2016;75:1586–1593. [PubMed: 26010456]
- Watanabe S, Shite J, Takaoka H, Shinke T, Imuro Y, Ozawa T, Otake H, Matsumoto D, Ogasawara D, Paredes OL, et al. Myocardial stiffness is an important determinant of the plasma brain natriuretic peptide concentration in patients with both diastolic and systolic heart failure. *European heart journal*, 2006;27:832–838. [PubMed: 16464912]
- Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation*, 2008;117:2051–2060. [PubMed: 18413502]
- Zile MR, Baicu CF, Ikonomidis J, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation*, 2015:CIRCULATIONAHA-114.
- Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part i: diagnosis, prognosis, and measurements of diastolic function. *Circulation*, 2002;105:1387–1393. [PubMed: 11901053]

Figure 1:

(a) B-mode image in the parasternal short-axis (PSAX) view with the region-of-excitation of the ARF push (green rectangle) placed over the interventricular septum (IVS). (b,c) M-mode image in the same view and the corresponding ECG signal over a full cardiac cycle. Gross axial motion of the IVS as well as subtle variations in its speckle texture through time are observed. The temporal positions of ARF pushes are indicated by the dotted green lines. The gold and purple rectangles indicate ARFI ensembles in mid-mechanical diastole and systole, respectively. (d) Motion-filtered displacement profiles over the two ensembles. The gray band indicates the push; closed circles represent measured displacements while open circles represent interpolated estimates. Measured displacements at a fixed time (1.5 ms) are used to generate the M-mode ARFI image. (e) M-mode ARFI image (as a color overlay over the M-mode image) with outlines of the IVS indicated in the green dotted lines. Significantly higher displacements in mechanical diastole (compared to systole) are observed.

Figure 2:

M-mode images over one cardiac cycle for (a) high and (b) low signal-to-clutter cases in the parasternal short axis (PSAX) view. Contrast between the right ventricular (RV) cavity and the interventricular septum (IVS) is used as a surrogate for signal-to-clutter level and measured to be 20.67dB in (a) and 5.66 dB in (b).

Figure 3: M-mode images over a cardiac cycle for (a) high and (b) low temporal coherence case in the parasternal long axis (PLAX) view. High temporal coherence indicates minimal speckle decorrelation due to out-of-plane motion and temporal noise. Mean $\rho_{\min}$ within the IVS was measured to be 0.987 and 0.968 in (a) and (b), respectively.

Figure 4:

Mean displacements within the IVS over a cardiac cycle for all seven azimuthal angles across the ROE in cases with (a) high and (b) low spatial similarity. Under the assumption of uniform myocardium over the ROE, high spatial similarity indicates low jitter and viceversa. ρ within the IVS was measured to be 0.994 for (a) and 0.856 for (b).

Figure 5:

(a) ECG signal over a cardiac cycle with mid-mechanical diastolic and systolic windows marked using gold and purple bands, respectively. (b) Median displacements within the IVS for all azimuthal angles at multiple ARFI ensembles over the duration of the cardiac cycle (gray circles). Four-parameter logistic model to fit myocardial relaxation (red curve) and contraction (blue curve). Horizontal dotted lines indicate mean diastolic displacement (u_D) and mean systolic displacement (u_S). Vertical dotted lines indicate temporal position of the peak rate of relaxation (rate_R) (red) and the peak rate of contraction (rate_C) (blue). Time constant of relaxation (τ_R) and contraction (τ_C) are reflected by the curvature of the respective fits.

Figure 6:

B-mode and M-mode images for examples of “successful” (a,b) and “unsuccessful” (c,d,e,f) acquisitions. M-mode ARFI data are presented as a semi-transparent color overlay (between the dotted green lines) on the conventional M-mode image. The mean and standard deviation of diastolic and systolic displacements in (b) are $4.88 \pm 0.58 \mu\text{m}$ and $1.42 \pm 0.06 \mu\text{m}$, respectively. The same for (d) are $1.031 \pm 0.03 \mu\text{m}$ and $0.71 \pm 0.21 \mu\text{m}$. (f) illustrates an M-mode ARFI image that was corrupted by breathing/motion artifacts. These artifacts are not aligned with the cardiac cycle and present as high amplitude echoes on the conventional M-mode image and high displacements on the M-mode ARFI data.

Figure 7:
Bar graph depicting number of “successful” acquisitions across volunteers split by view. “successful” acquisitions were acquired in PLAX for eight volunteers, in PSAX for six volunteers, and in both views for six volunteers.

Figure 8:

Mean ARF-induced displacements within the IVS for “successful” acquisitions in diastolic and systolic temporal windows as well as prior to each ARF excitation over the entire cardiac cycle. The three groups are presented split by (a) track configuration and (b) TTE view. Box plots are as described in Figure 9. “Pre-push” displacements show minimal bias and a relatively narrow spread, 0.03 (0.12) μm . ARF-induced displacements in all cardiac phases exceed this noise floor. Displacements in diastole, 3.04 (1.59) μm are significantly higher than those in systole, 1.19 (0.33) μm .

Figure 9:

(a) Contrast (b) temporal coherence, and (c) spatial similarity for individual cardiac cycles in “successful” and “unsuccessful” acquisitions split by tracking configuration. For the box plots, the horizontal marker represents the median, the edges of the box represent the 25th and 75th percentile and the whiskers mark the furthest values not considered outliers. All three metrics were significantly higher for “successful” acquisitions compared to “unsuccessful” ones.

Figure 10:

(a,b,c) Pair-wise relationships between metrics of tracking fidelity across all acquisitions. A moderate positive trend was observed for all three pairs of metrics with good differentiation between “successful” and “unsuccessful” acquisitions. (d) ROC curves for individual metrics. All three metrics, used individually, do a good job of separating “successful” from “unsuccessful” acquisitions. The optimal cut-offs for the metrics were found to be 9.48dB for contrast, 0.985 for temporal coherence, and 0.953 for spatial similarity.

Figure 11: Example of a “successful” acquisition in PLAX. (a) B-mode image with the ROI (green box) placed over the IVS. (b) conventional M-mode image with ARFI data in the semi-transparent color overlay. (c) concurrent ECG signal and (d) mean displacement over depth within the IVS for all azimuthal angles. Diastolic and systolic temporal windows are indicated on (c) and (d) by gold and purple bands, respectively. The table below the B-mode image presents estimated indices of dynamic myocardial stiffness and metrics of signal quality. Displacement trends align well with the ECG and show good repeatability from beat-to-beat.

Figure 12: Example of a “successful” acquisition in PSAX. Description of the panels is as described in Figure 11. Estimates of stiffness ratio and rates of relaxation and contraction show good repeatability over the five cardiac cycles, however estimates of the time constants are found to be more variable.

Figure 13:

Beat-to-beat variability of ARFI-derived indices of dynamic myocardial stiffness. The temporal variability as quantified by the median absolute deviation (MAD) as a percentage of the median (of the particular index through time) is presented for “successful” acquisitions with ten or more cardiac cycles. The temporal consistency of stiffness ratios is substantially better than rates and time constants.

Table 1:

Parameters for M-mode ARFI Sequences.

Ultrasound Parameters		
	Push	Track
Frequency	2.8 MHz	Fundamental: 3.2 MHz Harmonic: 2 MHz (transmit) 4 MHz (receive)
Pulse Duration	300 μ s	Fundamental: 0.7 μ s Harmonic: 2.5 μ s
Transmit Focus	45–65 mm	Focused: 45–65 mm Plane Wave: 1000 mm
Receive Configuration		7:1 parallel Apex = –300 mm Angular Span = 0.4°
Pulse Repetition Frequency	35 Hz	4 kHz
MI	< 1.65	Fundamental: < 1.66 [*] Harmonic: < 1.08 [*]
I_{sppa}	< 430 W/cm ²	Fundamental: < 494 [*] W/cm ² Harmonic: < 132 [*] W/cm ²

MI = Mechanical index

 I_{sppa} = Spatial-peak pulse-average intensity^{*} Derived using transducer impulse response and measurements for the push beam.

Table 2:

Number of “successful” acquisitions across the two views for the three tracking configurations.

	PLAX	PSAX	Total	Yield
FF	15/35	16/33	31/68	45%
HP	10/35	12/33	22/68	32%
HF	15/35	16/33	31/68	45%
Total	40/105	44/99	84/204	
Yield	38%	44%		41%

PLAX = Parasternal Long Axis

PSAX = Parasternal Short Axis

FF = Fundamental-Focused

HP = Harmonic-Plane

HF = Harmonic-Focused

Table 3:

Summary of ARFI-derived indices of dynamic myocardial stiffness over all cardiac cycles acquired in “successful” acquisitions.

		Mean	Std.	95% CI
Stiffness Ratio	PLAX	2.81	0.81	[2.68 2.94]
	PSAX	2.67	0.91	[2.54 2.81]
Rate _R (1/s)	PLAX	8.07	5.16	[7.22 8.92]
	PSAX	7.61	4.25	[6.97 8.25]
Rate _C (1/s)	PLAX	-7.02	3.81	[-7.65 -6.40]
	PSAX	-7.58	3.76	[-8.16 -6.99]
τ_R (ms)	PLAX	35.26	20.97	[31.71 38.81]
	PSAX	36.42	19.29	[33.49 39.35]
τ_C (ms)	PLAX	40.65	21.94	[37.11 44.21]
	PSAX	34.34	17.43	[31.74 36.94]

PLAX = Parasternal Long-Axis

PSAX = Parasternal Short-Axis

Std. = Standard Deviation

CI = Confidence Interval