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Martin V. Andersen[a,*], Cooper Moore[b], Peter Søgaard[c], Daniel Friedman[d], Brett D. Atwater[d], Kristine Arges[d], Melissa LeFevre[d], Johannes J. Struijk[a], Joseph Kisslo[d], Samuel E. Schmidt[a], Olaf T. von Ramm[b]

[a]*Aalborg University, 9220 Aalborg, Denmark*
[b]*Duke University, Durham, NC 27708, USA*
[c]*Aalborg University Hospital, Department of Cardiology, 9000 Aalborg, Denmark*
[d]*Duke University Hospital, Durham, NC 27710, USA*

Abstract

Recently, we have developed a high frame rate echocardiographic imaging system capable of acquiring images at rates up to 2500 per second. High imaging rates were used to quantify longitudinal strain parameters in patients with echocardiographic normal function. This data can serve as a baseline for comparing strain parameters in diseased states. The derived timing data also shows the propagation of mechanical events in the left ventricle throughout the cardiac cycle. High frame rate echocardiographic images were acquired from 17 patients in the apical four chamber view using Duke University's phased array ultrasound system, T5. B-mode images were acquired at 500-1000 images per second by using 16:1 or 32:1 parallel processing in receive, using up to 14 cm scan depth, and an 80° field of view using a 3.5 MHz, 96 element linear array. The images were analyzed using a speckle-tracking algorithm tailored for high frame rate echocardiographic

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*Corresponding Author: Martin Vandborg Andersen, Fredrik Bajers Vej 7, 9000 Aalborg, Denmark; Email, mvan@hst.aau.dk

images developed at Aalborg and Duke University. Four specific mechanical events were defined using strain curves from six regions along the myocardial contour of the left ventricle. The strain curves measure the local deformation events of the myocardium and are independent of the overall cardiac motion. We found statistically significant differences in the temporal sequence among different myocardial segments for the first mechanical event described, the myocardial tissue shortening onset ($P < 0.01$). We found that the spatial origin of tissue shortening was located near the middle of the interventricular septum in patients with echocardiographic normal function. The quantitative parameters defined here, based on high speed strain measurements in patients with echocardiographic normal function, can serve as a means of assessing degree of contractile abnormality in the myocardium and enables the identification of contraction propagation. The relative timing pattern among specific events with respect to the Q wave may become an important new metric in assessing cardiac function and may, in turn, improve diagnosis and prognosis.

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Introduction

Echocardiography has become the method of choice for assessing ventricular systolic and diastolic function, and strain and strain rate echocardiographic measurements have emerged as important indicators of cardiac function (Risum et al., 2013; Ponikowski et al., 2016). These are parameters of local myocardial function which can be derived from both Tissue Doppler Imaging (TDI) and 2 dimentional (2D) B-mode echocardiographic images (Cikes et al., 2014; Brekke et al., 2014; Andersen et al., 2016a). Strain is defined as the fractional change in the length of local myocardial tissue with respect to a baseline length of that tissue, and is measured as a fractional deformation (Mada et al., 2014).

Typical conventional phased array ultrasound systems can acquire 2D B-mode images with an 80° field of view, 0.5° angular sampling, and a scan depth of 12 cm at around 60 images per second (Papadacci et al., 2014; Bunting et al., 2017b; Moore et al., 2015). Conventional frame rate (60 images per second) is adequate for assessment of morphology and global myocardial performance. However, the propagation of electrical excitation through the Purkinje fibers of the anterior and posterior fascicles travels at least 2 m/sec (Cikes et al., 2014). This means that conventional ultrasound lacks the temporal resolution to resolve the mechanical events associated with electrical activation. To describe the myocardial contraction wave fronts associated with depolarization, ultrasound images must be acquired at a high frame rate comparable to diagnostic electrocardiography (ECG), which is sampled at 500 Hz (i.e. comparable with 500 images per second) or higher for diagnostic purposes (Cikes et al., 2014).

Since the 1980s, efforts have been directed towards increasing the sampling rate of phased array ultrasound systems to gain myocardial contraction information. TDI is conventionally acquired at 150 samples per second for the left ventricle and 250 samples per second for singular wall evaluation. Despite TDI being limited by the inherent 1 dimentional (1D), the improvement of temporal resolution has been shown to increase the diagnostic value compared to convention 2D B-mode ultrasound images. However, even with TDI, the sample rate may be too slow to resolve some mechanical events like shear waves associated with mitral and aortic valve closure that propagate at up to 7 m/s (Brekke et al., 2014; Durrer et al., 1970; Hasegawa and Kanai, 2011; Tong et al., 2016). Shattuck et al. (1984) described a method for increasing 2D frame rates by receiving multiple lines in parallel from a widened transmit beam, Exploso scanning, one of the most commonly used methods for increasing frame rates in commercial systems (Cikes et al., 2014; Shattuck et al., 1984).

Clinical feasibility and application of several echocardiographic techniques for measuring mechanical properties such as myocardial stiffness are currently being investigated (Correia et al., 2016; Hollender et al., 2017; Melki et al., 2017; Strachinaru et al., 2017; Pislaru et al., 2014; Vos et al., 2017; Bunting et al., 2017b,a; Villemain et al., 2018). Offline post processing of the radio frequency (RF) data is commonly used for improving the image quality of the reconstructed ultrasound sequences and improve tracking accuracy of optical flow methods (Poree et al., 2016; Joos et al., 2018; Song et al., 2013; Grondin et al., 2017). It should be noted that while a high frame rate can be produced with compounding methods such as motion compensation com-

pounding, the reduction of temporal resolution is directly proportional to the number of compounded acquisitions and not the frame rate (Joos et al., 2018; Poree et al., 2016; Cikes et al., 2014). Konofagou et al. (2010) created a method they call Electromechanical Wave Imaging, which requires RF data to automatically segment and estimate deformation of the the myocardium. The segmented deformation images are normally presented superimposed on a low frame rate ultrasound detected B-mode images (Luo and Konofagou, 2010; Konofagou et al., 2010; Provost et al., 2010, 2015; Bunting et al., 2017a; Melki et al., 2017).

At Duke University we have developed an experimental clinical high frame rate B-mode ultrasound system which acquires images at up to 2500 images per second while maintaining the live high frame rate 2D echocardiographic image presentation necessary during clinical scanning using the Exploso scan approach (Moore et al., 2015; Shattuck et al., 1984). Through a collaboration between Aalborg and Duke University, we developed the Continuous Speckle-Feature Tracking (CFT) Algorithm validated for computing strain from high frame rate detected B-mode echocardiographic images (Andersen et al., 2016a,b; Moore et al., 2015).

The objective of this clinical study was to develop a set of quantitative descriptors for strain in patients with echocardiographic normal function, using the high frame rate ultrasound system and this software. These descriptors can be used as a basis for comparison to those derived from patients with abnormal function.

Here, we present apical four chamber longitudinal strain measurements derived from high frame rate ultrasound images (500 per second or above)

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using the CFT Algorithm from 17 patients with echocardiographic normal function.

Materials and Methods

T5 System

To acquire high frame rate detected 2D B-Mode echocardiographic images, Duke University's experimental ultrasound system, T5 (Duke University, Durham, NC, USA), was used. Echocardiographic images were acquired using a 3.5 MHz, 96-element, 1D phased array (Volumetrics, Durham, NC, USA), where the theoretical diffraction-limited azimuth resolution was 1.2° and axial resolution was 0.44 mm. To maintain adequate spatial sampling, echocardiographic images contained 160 unique receive directions with an angular sampling of 0.5° for a total field of view of 80°. The axial sampling was 0.25 mm and scan depth was either 120 mm or 140 mm depending on the patient. To increase frame rate, the ultrasound system used a single defocused transmit beam focused at -30 cm (i.e. 30 cm behind the transducer) and 16 or 32 parallel receive processing channels per receive element, also known as 16:1 or 32:1 exploso scanning. For 16:1, 10 transmit-receive operations were required to create an image. The resulting images for 16:1 exploso scanning were acquired at 500 images per second (I_{500}). For 32:1, 5 transmit-receive operations were required to create an image. The resulting images for 32:1 exploso scanning were acquired at 1000 images per second (I_{1000}). Data was exported from the system as detected B-mode 2D echocardiographic images in the native ballistic coordinate system. A single lead ECG was recorded synchronously with the echocardiographic images and was used to identify

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individual cardiac cycles. The ECG was used to manually identify the onset of the Q wave, which we defined as the zero time of each cardiac cycle. For an in depth description on data acquisition using the T5 system we refer to Moore et al. (2015).

Patient Data

The study was approved by the Duke Institutional Review Board and written consent was obtained from each individual patient using an independent recruiter before any study procedure was performed. Each patient was identified, approached and subsequently recruited during routinely ordered echocardiographic examination at the Duke University Hospital Clinic. 20 patients with normal echocardiographic function volunteered to participate in this study. All patients with echocardiographic normal function had a QRS duration shorter than 100 ms, diagnosed with normal cardiac anatomy and function based on clinical functional assessment using a conventional ultrasound system. Patients with any of the following conditions were excluded from the echocardiographically normal group in the study:

- Poor image quality (2 or more myocardial segments not visualized)

- Previously diagnosed heart disease

- QRS duration > 100 ms

- Abnormal cardiac anatomy

- Impaired cardiac function (left ventricular ejection fraction < 50%)

- Atrial fibrillation

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- Diagnosed valvular stenosis

- Diagnosed valvular regurgitation

T5 images from 3 patients had to be excluded from this study due to poor image quality. Therefore, the results in this study are from 17 patients with echocardiographic normal function (6 male, 11 female) with an average age of 42 ± 17 years.

A trained sonographer acquired 5 seconds of echocardiographic images of the patients' apical four chamber view with a simultaneously recorded single lead ECG for both I_{1000} and I_{500}. The best image sequence was selected with respect to image quality and where shadows from ribs and lungs were avoided. If the entire left ventricle was visible in both sequences I_{1000} was selected (I_*). In 11 of the 17 patients the I_{1000} sequence was chosen. Because the CFT Algorithm assumes that the heart ends in the initial location, a cardiac cycle was selected in I_* with similar end diastolic translation for the analysis.

Data Analysis

The CFT Algorithm was used for offline analysis of the detected high frame rate B-mode echocardiographic images to estimate motion and deformation; the algorithm was developed at Aalborg and Duke University using MATLAB (MathWorks, Natrick, MA, USA) (Andersen et al., 2016a,b). The CFT Algorithm is based on the idea of dividing the myocardial tissue into segments, and then detecting motion of each region independently. By isolating segments, local tissue deformation could be identified since global myocardial

motion caused by tissue deformation outside the individual segment did not affect the measured shortening inside each individual segment.

One common method of expressing tissue changes is to measure how much individual segments have contracted or stretched with respect to an initial tissue size at the onset of the Q wave. The fractional change in tissue length with respect to an initial size is strain (Cikes et al., 2014; Brekke et al., 2014).

When applying the algorithm, an operator with several years of experience with high frame rate echocardiographic images first marked the middle myocardial wall contour and the width of the myocardial wall (l_{myo}) in the frame corresponding to the onset of the Q wave ($t_0 = 0$ ms) on the ECG. Individual speckle were defined by local maxima in each frame. Features derived from a small neighborhood (5x5 pixel neighborhood) around individual speckle maxima were extracted to detect individual speckle motion from frame to frame recursively. A collection of coordinate points $\mathbf{p}(t)$, which were evenly distributed along the middle myocardial contour at t_0 as shown in Figure 1, were updated recursively using Equation (1):

$$\mathbf{p}_i(t) = \mathbf{p}_i(t-1) + \mathbf{d}_i(t) \tag{1}$$

, where $\mathbf{d}_i$ is a Gaussian weighted average of all Z_i speckle displacements ($\bar{\mathbf{x}}(t)$) between frame $t-1$ and t within a small radius ($l_{myo}/2$) around a coordinate $\mathbf{p}_i(t-1)$ at frame t as defined by Equation (2).

$$\mathbf{d}_i(t) = \sum_{z=1}^{Z_i} \bar{x}_z(t) \cdot \frac{G(|\mathbf{x}_z(t) - \mathbf{p}_i(t-1)| \, , \, l_{myo}/2)}{\sum_{z=1}^{Z_i} G(|\mathbf{x}_z(t) - \mathbf{p}_i(t-1)| \, , \, l_{myo}/2)} \tag{2}$$

, where $G(x, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\frac{x}{\sigma}^2}$, and $|\mathbf{x}|$ is the length of vector $\mathbf{x}$. The final value of $\mathbf{p}_i(t)$ is calculated using a Kalman filter. Longitudinal strain (ε) was

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estimated using the length of the myocardial contour as defined in Equation (3).

$$\varepsilon(t) = \frac{\sum L_j(t) - L_j(t_0)}{\sum L_j(t_0)} \tag{3}$$

, where $L_j(t) = |\mathbf{p}_i(t) - \mathbf{p}_{i+1}(t)|$. Six strain curves were calculated corresponding to different segments of the myocardial wall, see Figure 1.

- Basal septal wall.

- Mid septal wall.

- Apical septal wall.

- Apical lateral wall.

- Mid lateral wall.

- Basal lateral wall.

For comparison of contractile timing in patients with echocardiographic normal function, four mechanical events were defined by high frame rate strain curves (e.g. Figure 2), and the timing of these events with respect to the onset of the Q wave was recorded for all six segments of the myocardium. The four mechanical events to be quantified from high frame rate strain were the tissue shortening onset, tissue shortening cessation, tissue lengthening onset, and tissue lengthening cessation. To define these events in an automated, reproducible manner, three values were quantified from the high speed strain curves: maximum strain, or the peak positive strain for the myocardial segment; minimum strain, or the peak negative strain for

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the myocardial segment; and isometric diastolic strain, or the median value during the late diastolic period where the myocardium was nearly stationary in patients with echocardiographic normal function. These thresholds are indicated the by horizontal dashed lines in Figure 2. Next a linear line was fitted to the downstroke of the strain curve corresponding to active systolic ventricular contraction, and this line was labeled as the myocardial shortening line in Figure 2. In the same fashion, a second line, the myocardial lengthening line was fitted to the upstroke of the strain curve in early diastole corresponding to the rapid relaxation and rapid ventricular filling. The four timing events were then defined by the intersection of these lines with the relevant thresholds which allowed for a robust automated detection of these mechanical events.

The first event, tissue shortening onset, was defined by the intersection of maximum strain and the myocardial shortening lines that corresponded to the time at which the myocardial segment began active contraction. The detected value of the onset of tissue shortening is indicated in Figure 2, as are all other detected events to be described. The second event, tissue shortening cessation, was defined as the intersection of the myocardial shortening line and minimum strain value and corresponded to the end of myocardial deformation during that contractile period in that segment. The third event, the tissue lengthening onset, was defined by the intersection of the myocardial lengthening line and minimum strain value, corresponding to the beginning of rapid relaxation of the myocardium. The final event, tissue lengthening cessation, was defined by the intersection of the myocardial lengthening line and the isometric diastolic value.

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As four mechanical events were defined with respect to a common event, i.e. the onset of the Q wave, the intervals between these events could be readily quantized and hold further significance. The first interval was tissue shortening interval as defined by the interval between the tissue shortening onset and cessation corresponding to the amount of time during which each myocardial segment was actively contracting with associated deformation. The second interval was tissue isometric refractory interval as defined by the interval between tissue shortening cessation and tissue lengthening onset corresponding to the transition between systole and diastole when the myocardium was undergoing minimum to no regional deformation. The final interval was defined as the interval between tissue lengthening onset and cessation, or tissue relaxation interval corresponding to the rapid expansion of the myocardium in early diastole. A definition summary of the four mechanical events and the three intervals between is available in Table 1 for reference.

Statistical Analysis

For the statistical autoregressive mixed linear model analysis of event timings and intervals across myocardial segments, the SPSS software package (IBM Corporation, New York, USA) was used. The autoregressive mixed-effects linear model was used to compare the timing of events across myocardial segments to determine if one or more segments had statistically different timing difference compared to the other segments. Myocardial locations were used as repeated measurements and fixed-effects for this analysis, and F-test and P values were recorded from this analysis. The null-hypothesis was rejected when the within-subject location measurement differed. A P value <

0.05 was considered statistical significance. Post-hoc tests were performed and adjusted for multiple comparisons using Bonferroni correction where P value < 0.05 was considered statistically significant.

Results

Initial observations of strain curves derived from high frame rate ultrasound images revealed complex motions of myocardial tissue that cannot be appreciated from strain curves derived at lower frame rate, i.e. below 100 images per second, such as are typical in current clinical practice, see Figure 3. Of primary interest was the timing of the four deformation events previously defined: tissue shortening onset, shortening cessation, lengthening onset, and lengthening cessation. General trends in high frame rate strain curves that are not typically observed at lower frame rates include various morphologies of the precontractile peak in strain that occurs subsequent to atrial contraction. An example has been illustrated in Figure 2, occurring between 0 and 125 ms. Six distinct morphological strain patterns were identified in normal individuals from the high speed strain curves during the isometric contraction. Examples of the strain curves for each pattern is illustrated in Figure 4 and described in Table 2. When echocardiographic images are recorded at lower frame rate, patients demonstrated patterns resembling Pattern I, most likely due to insufficient temporal sampling or a smoothing filter employed during processing. While no analysis of the isometric patterns were done, it is worth noting that a between the 6 strain rate curves from single cardiac cycle 2 or more of these isometric patterns may be present in different segments.

The cohort of 17 patients with echocardiographic normal function included in this study had an average R-R interval of 864 ± 200 ms, and all timing events were referenced to the onset of the Q wave as t_0. The temporal distribution of mechanical events in each of the myocardial segments can be seen in Figure 5. The solid lines represent the average delay from the Q wave for each event in patients with echocardiographic normal function with the 95% confidence intervals indicated by the horizontal error bars centered on each data point. Full results of the statistical segmental analysis of each event are presented in Table 3.

Using the autoregressive mixed effects linear model, tissue shortening onset was found to occur at statistically different time points in different myocardial segments (F = 6.12, P < 0.001). The mid septal wall had the earliest tissue shortening onset of all segments with an average of 94.1 ± 4.8 ms across all 17 patients. The duration of tissue shortening onset across all segments was found to be 13.2 ms, see Table 4. Compared to the other five segments individually, it was found that the mid septal wall was not significantly earlier than the basal lateral wall (P = 0.103) yet was significantly earlier than the basal septal (P = 0.012), apical septal (P < 0.001), apical lateral (P = 0.003), and mid lateral walls (P = 0.037), see Table 5.

For tissue shortening cessation in patients with echocardiographic normal function, there was found to be a clear progression from basal septal wall through the apex to the basal lateral wall, as can be seen in Figure 5. The duration of tissue shortening cessation across all segments was found to be 23.9 ms. However, there was not a statistically significant difference in the timing of the tissue shortening cessation between the six segments (F = 0.893,

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P = 0.491).

For tissue lengthening onset, mid septal wall was found to be the location of first lengthening with other segments beginning to lengthen in sequence around the ventricle, with the basal lateral wall beginning to lengthen last. The duration of tissue lengthening onset across all segments was found to be 15.7 ms. Of note, lengthening onset in the basal septal wall occurred closer in time to the basal lateral wall (2.5 ms prior) than to the anatomically adjacent mid septal wall (13.2 ms later). Tissue lengthening onset was not found to differ significantly across the six segments (F = 2.382, P = 0.052).

Tissue lengthening cessation was measured to occur first in the mid septal wall and last in the basal lateral wall, with no clear propagation pattern between segments. The duration of tissue lengthening cessation across all segments was found to be 11.4 ms. There was not a significant difference in the timing of tissue lengthening cessation between the six myocardial segments (F = 1.121, P = 0.358). Detailed statistical breakdown of all timing events can be seen in Table 4.

The intervals between the four mechanical events are shown graphically in Figure 6, and the statistical breakdown is shown in Table 6. As seen in Figure 6, the tissue shortening interval, or interval between the tissue shortening onset and cessation, was the longest of the three intervals with an average of 267.7 ms across all patients and myocardial segments. Tissue isometric refractory interval, or the interval between of tissue shortening cessation and lengthening onset, was the shortest interval, 89.7 ms, on average. Tissue relaxation interval, or the interval between onset and cessation of tissue lengthening, was 138.4 ms on average. For the tissue shortening interval,

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the basal septal wall had the shortest interval (262.6 ± 1.8 ms) while basal lateral wall had the longest interval (271.0 ± 13.0 ms). Statistical analysis of the tissue shortening interval across all six myocardial segments did not yield a significant difference between segments (F = 2.123, P = 0.074), despite trends seen in Figure 6. For the tissue isometric relaxation interval, the basal lateral wall had the shortest interval (81.6 ± 12.2 ms) while the basal septal wall had the longest interval (106.5 ± 10.7 ms). Statistical analysis of the six segments yielded significant difference in the isometric relaxation interval between the six myocardial segments (F = 2.710, P = 0.029). Post hoc tests using Bonferroni correction found a significant difference in the isometric relaxation interval between the basal and mid septal walls (P = 0.013), see Table 5. For myocardial tissue relaxation interval, the basal lateral wall had the shortest interval (133.0 ± 10.5 ms), and the apical septal wall had the longest interval (148.9 ± 9.0 ms). Analysis of all six segments showed no significant difference for tissue relaxation intervals between segments (F = 1.110, P = 0.364).

Discussion

With the advanced high frame rate real time system, T5, we were able to analyze patients with echocardiographic normal function at a sampling speed comparable to that of ECG .

For tissue shortening onset, the mid septal wall was measured to initially start to shorten first in the healthy human heart, where the timing differences were significant as compared to the basal septal, apical septal, apical lateral, and mid lateral walls. There was no significant difference in tissue shortening

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onset between any of the other walls. Similar results of the mid septal wall shortening first have been reported before using velocity curves derived from high frame rate TDI and M-mode imaging (Brekke et al., 2014; Hasegawa and Kanai, 2011; Kanai, 2009). The mid lateral wall was the last segment where tissue shortening onset was identified which is in accordance with electrical propagation through the left ventricle. The average tissue shortening onset propagating velocity between the first and all other wall segments was calculated using an average myocardial contour of 190 mm was calculated to 5.6 m/s for patients with echocardiographic normal function. This velocity for patients with echocardiographic normal function seems high when compared, for example, to the conduction velocities in the Purkinje fibers of 2-4 m/s (Brekke et al., 2014; Kanai, 2009; Durrer et al., 1970). However, as demonstrated by Durrer et al. (1970) the high velocity may be reasonable considering that there are multiple locations of excitation in the human heart (Durrer et al., 1970). In our strain model, we divide the myocardium into approximately equal sized myocardial regions and assumed a single excitation location. If more than one region is activated within a short delay from the first region, then the apparent contraction propagation may appear much higher than often quoted 1-2 m/s propagation velocity in the myocardium (Durrer et al., 1970).

No significant difference was measured in the tissue shortening interval across patients with echocardiographic normal function. However, a significant difference in tissue shortening onset was found between the mid septal wall and the mid lateral wall. The largest average difference in onset time was 13.2 ms. It was only possible to detect a significant difference in the

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temporal measurements here because the high temporal resolution of 4 ms or better. At 60 images per second, the minimum temporal resolution would have been 33.3 ms. Also, no significant differences were observed during isometric relaxation. For the rapid relaxation of myocardial tissue at the beginning of the diastolic period of the cardiac cycle, no significant difference was found. The length of tissue relaxation was longest at the apical septal wall, and monotonically decreased with increased distance from this location as seen in Table 6 and Figure 6.

Future studies involve identifying the patterns in known conduction disorder patients such as Left Bundle Branch Block (LBBB) to find statistical differences between them and patients with echocardiographic normal function. It is anticipated that major divergence from the timing data patients with echocardiographic normal function derived in this study will be associated with various pathologic conditions such as conduction abnormalities.

The iso-volumetric contraction often becomes the focus of high frame rate electromechanical studies. We identified 6 distinct isometric contraction patterns for the strain curves, see Table 2 and Figure 4. These early stretches have been mentioned in prior literature (Joos et al., 2018; Andersen et al., 2016a; Brekke et al., 2014; Tong et al., 2016). As alluded to in the result section these isometric contraction patterns have a low spatial resolution, which for this study was limited to 6 strain curves. The low spatial resolution may obfuscate the origin of the differing patterns. Because multiple patterns can appear in the same patient, these waves may potentially be propagating mechanical wave fronts that propagates through the myocardium with different onset times and locations. The patterns could potentially have atrial origin

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and describe the atrial-ventricular coordination. However, this was outside the scope of this study. Further studies of the iso-volumetric contraction is needed, as our group expect that electromechanical mapping of these early stretches and contractions prior to the tissue shortening period may hold information of clinical significance.

Limitations

Data was only recorded with a single lead ECG. To accurately describe electro-mechanical coupling, a 12-Lead ECG would be better suited. Furthermore, the reduced image quality inherent in high frame rate ultrasound made patient selection more difficult and limited the number of walls that could be imaged in this study. Apical two and three chamber views generally had poor image quality. Here a 6-segment model based on the apical four chamber views is used. Using apical two and three chamber views could provide a 16- or 18-segment model, which would provide more information for describing contraction. Additionally, the 2D nature of B-mode echocardiographic images may confound the identification of the propagating waves within the 3 dimentional (3D) structure of the heart. This may compromise the accuracy of velocity determinations, which would make high frame rate 3D echocardiography increasingly important as a diagnostic tool.

Conclusions

Using high speed images, our algorithm allowed us to identify the origin of initial myocardial tissue shortening in echocardiographically normal patients. Here, the middle of the interventricular septum was the myocardial segment where the initial myocardial tissue shortening onset occurred in the

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normal patient population. We found the timing of this event significant as compared to that of the other myocardial segments except the basal interventricular septum in the normal heart. We believe that temporal sequences of mechanical tissue shortening propagation through the left ventricle is of clinical significance. When identifying physiological mechanical events during the cardiac cycle, an acquisition rate of 500 images per second or higher should be used to adequately resolve the events for diagnostic purposes. The high temporal resolution data derived from the longitudinal strain measurements in a normal cohort developed here can serve as a more precise means of assessing cardiac function. The technique used in this study may become an important tool for investigating electromechanical coupling and describing cardiac function in both patients with echocardiographic normal function and abnormal function.

Acknowledgements

References

Andersen MV, Moore C, Arges K, Søgaard P, Østergaard LR, Schmidt SE, Kisslo J, Von Ramm OT. High-Frame-Rate Deformation Imaging in Two Dimensions Using Continuous Speckle-Feature Tracking. Ultrasound in Medicine and Biology, 2016a;42:2606–2615.

Andersen MV, Moore C, Schmidt SE, Søgaard P, Struijk JJ, Kisslo J, Ramm OTV. Feature Tracking Algorithm for Circumferential Strain using High Frame Rate Echocardiography. In: Computing in Cardiology Conference (CinC), 2016. Vol. 43, 2016b. pp. 885–888.

Brekke B, Nilsen LCL, Lund J, Torp H, Bjastad T, Amundsen BH, Stoylen A, Aase Sa. Ultra-high frame rate tissue Doppler imaging. Ultrasound in medicine & biology, 2014;40:222–31.

Bunting E, Lambrakos L, Kemper P, Whang W, Garan H, Konofagou E. Imaging the Propagation of the Electromechanical Wave in Heart Failure Patients with Cardiac Resynchronization Therapy. Pacing and Clinical Electrophysiology, 2017a;40:35–45.

Bunting E, Papadacci C, Wan E, Sayseng V, Grondin J, Konofagou E. Cardiac Lesion Mapping in vivo using Intracardiac Myocardial Elastography. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2017b;3010:1–1.

Cikes M, Tong L, Sutherland GR, D'Hooge J. Ultrafast cardiac ultrasound imaging: Technical principles, applications, and clinical benefits. JACC: Cardiovascular Imaging, 2014;7:812–823.

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Correia M, Provost J, Chatelin S, Villemain O, Tanter M, Pernot M. Ultrafast Harmonic Coherent Compound (UHCC) Imaging for High Frame Rate Echocardiography and Shear-Wave Elastography. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2016;63:420–431.

Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation, 1970;41:899–912.

Grondin J, Sayseng V, Konofagou EE. Cardiac Strain Imaging with Coherent Compounding of Diverging Waves. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2017;3010:1–1.

Hasegawa H, Kanai H. High-frame-rate echocardiography using diverging transmit beams and parallel receive beamforming. Journal of Medical Ultrasonics, 2011;38:129–140.

Hollender P, Kuo L, Chen V, Eyerly S, Wolf P, Trahey G. Scanned 3-D Intracardiac ARFI and SWEI for Imaging Radio-Frequency Ablation Lesions. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2017;64:1034–1044.

Joos P, Porée J, Liebgott H, Vray D, Baudet M, Faurie J, Tournoux F, Cloutier G, Nicolas B, Garcia D. High-Frame-Rate Speckle-Tracking Echocardiography. IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL, 2018;65:720–728.

Kanai H. Propagation of Vibration Caused by Electrical Excitation in the Normal Human Heart. Ultrasound in Medicine and Biology, 2009;35:936–948.

469 Konofagou EE, Luo J, Saluja D, Cervantes DO, Coromilas J, Fujikura K.
470 Noninvasive electromechanical wave imaging and conduction-relevant ve-
471 locity estimation in vivo. Ultrasonics, 2010;50:208–215.

472 Luo J, Konofagou E. A fast normalized cross-correlation calculation method
473 for motion estimation. IEEE transactions on ultrasonics, ferroelectrics, and
474 frequency control, 2010;57:1347–57.

475 Mada RO, Duchenne J, Voigt JU. Tissue Doppler, Strain and Strain Rate
476 in ischemic heart disease "How I do it". Cardiovascular Ultrasound,
477 2014;12:38.

478 Melki L, Costet A, Konofagou EE. Reproducibility and Angle Independence
479 of Electromechanical Wave Imaging for the Measurement of Electrome-
480 chanical Activation during Sinus Rhythm in Healthy Humans. Ultrasound
481 in Medicine and Biology, 2017;43:2256–2268.

482 Moore C, Castellucci J, Andersen MV, Lefevre M, Arges K, Kisslo J, Von
483 Ramm OT. Live high-frame-rate echocardiography. IEEE Transactions on
484 Ultrasonics, Ferroelectrics, and Frequency Control, 2015;62:1779–1787.

485 Papadacci C, Pernot M, Couade M, Fink M, Tanter M. High-contrast ultra-
486 fast imaging of the heart. IEEE Transactions on Ultrasonics, Ferroelectrics,
487 and Frequency Control, 2014;61:288–301.

488 Pislaru C, Pellikka PA, Pislaru SV. Wave propagation of myocardial stretch:
489 Correlation with myocardial stiffness. Basic Research in Cardiology,
490 2014;109:1–12.

23

Ponikowski P, Voors A, Anker S, Bueno H, Cleland JGF, Coats A, Falk V, Jose Ramon Gonzale rissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands) PvdMTN, Document. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Society of Cardiology, 2016;18:891–975.

Poree J, Posada D, Hodzic A, Tournoux F, Cloutier G, Garcia D. High-Frame-Rate Echocardiography Using Coherent Compounding with Doppler-Based Motion-Compensation. IEEE Transactions on Medical Imaging, 2016;35:1647–1657.

Provost J, Costet A, Wan E, Gambhir A, Whang W, Garan H, Konofagou EE. Assessing the atrial electromechanical coupling during atrial focal tachycardia, flutter, and fibrillation using electromechanical wave imaging in humans. Computers in Biology and Medicine, 2015;65:161–167.

Provost J, Lee WNLWN, Fujikura K, Konofagou E. Electromechanical Wave Imaging of Normal and Ischemic Hearts In Vivo. IEEE Transactions on Medical Imaging, 2010;29:625–635.

Risum N, Strauss D, Sogaard P, Loring Z, Hansen TF, Bruun NE, Wagner G, Kisslo J. Left bundle-branch block: The relationship between electrocardiogram electrical activation and echocardiography mechanical contraction. American Heart Journal, 2013;166:340–348.

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.

Song P, Zhao H, Urban M, Manduca A, Pislaru S, Kinnick R, Pislaru C, Greenleaf J, Chen S. Improved Shear Wave Motion Detection Using Pulse-Inversion Harmonic Imaging with a Phased Array Transducer. IEEE transactions on medical imaging, 2013;32:2299–2310.

Strachinaru M, Bosch JG, van Dalen BM, van Gils L, van der Steen AF, de Jong N, Geleijnse ML, Vos HJ. Cardiac Shear Wave Elastography Using a Clinical Ultrasound System. Ultrasound in Medicine and Biology, 2017;43:1596–1606.

Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. American Journal of Cardiology, 2011;107:927–934.
URL http://dx.doi.org/10.1016/j.amjcard.2010.11.010

Tong L, Ramalli A, Tortoli P, Fradella G, Caciolli S, Luo J, D'hooge J. Wide-angle tissue doppler imaging at high frame rate using multi-line transmit beamforming: An experimental validation In Vivo. IEEE Transactions on Medical Imaging, 2016;35:521–528.

Villemain O, Correia M, Mousseaux E, Baranger J, Zarka S, Podetti I, Soulat G, Damy T, Hagège A, Tanter M, Pernot M, Messas E. Myocardial Stiffness Evaluation Using Noninvasive Shear Wave Imaging in Healthy and

536   Hypertrophic Cardiomyopathic Adults. JACC: Cardiovascular Imaging,
537   2018;C:1–11.

538 Vos HJ, van Dalen BM, Heinonen I, Bosch JG, Sorop O, Duncker DJ, van der
539   Steen AF, de Jong N. Cardiac Shear Wave Velocity Detection in the
540   Porcine Heart. Ultrasound in Medicine and Biology, 2017;43:753–764.

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Figure Captions

Figure 1: shows the myocardial segmentation of an apical four chamber view of a left ventricle at the onset of the Q wave (t_0). The ventricle was segmented into six different segments. (1) Blue: basal septal wall (BSW), (2) Light blue: mid septal wall (MSW), (3) Cyan: apical septal wall (ASW), (4) Green: apical lateral wall (ALW), (5) Yellow: mid lateral wall (MLW), (6) Orange: basal lateral wall (BLW).

Figure 2: shows four different mechanical events occurring during the cardiac cycle. The figure contains, (strain) strain curve from the basal septal wall (ECG) 1-lead electrocardiograph. Three horizontal lines are displayed, (maxSL) maximal strain line, (minSL) minimum strain line, and (medianSL) median of isometric diastolic strain. The two sloped red lines, (MSL) follow the myocardial shortening line, and (MLL) myocardial lengthening line. The crossing between maxSL and MSL is defined as tissue shortening onset (TSO). The crossing between MSL and minSL is defined as tissue shortening cessation (TSC). The crossing between MLL and minSL is defined as tissue lengthening onset (TLO). The crossing between medianSL and MLL is defined as tissue lengthening cessation (TLC).

Figure 3: shows the strain curves from a 27-year-old male with no diagnosed cardiac abnormalities. The left image is an apical four chamber view at t_0 with the color of the contour representing strain for each myocardial strain wall segment. The right image shows the corresponding strain curves for each wall segment and an ECG.

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565 **Figure 4:** shows 6 different stain curve patterns seen during the isometric

566 contraction after Q wave onset. Each subplot shows strain as a function

567 of time normalized to the isometric contraction.

568 **Figure 5:** shows the temporal delay between the onset of the Q wave (t_0)

569 and the myocardial tissue shortening onset (TSO), shortening cessation

570 (TSC), lengthening onset (TLO) and lengthening cessation (TLC) for

571 each myocardial wall segment. The x-axis shows time for the basal

572 septal wall (BSW), mid septal wall (MSW), apical septal wall (ASW),

573 apical lateral wall (ALW), mid lateral wall (MLW) and basal lateral wall

574 (BLW) respectively. The solid lines and error bars represent the average

575 and the 95% confidence interval of the measurements, respectively. The

576 dotted lines represent results from a LBBB patient.

577 **Figure 6:** shows the (a) tissue shortening interval, (b) tissue isometric re-

578 fractory interval, and (c) tissue relaxation interval. The x-axis shows

579 the results for the basal septal wall (BSW), mid septal wall (MSW),

580 apical septal wall (ASW), apical lateral wall (ALW), mid lateral wall

581 (MLW) and basal lateral wall (BLW) respectively. The solid lines and

582 error bars represent the average and the 95% confidence interval of the

583 measurements, respectively. The dotted lines represent results from a

584 LBBB patient.

Tables

Table 1: describes the definitions of the four mechanical events and three intervals between the events.

Event and interval definitions

Event	Definition
Tissue shortening onset	The time where the tissue shortening line crosses the total maximum measured strain value, see Figure 2.
Tissue shortening cessation	The time where the tissue shortening line crosses the total minimum measured strain value, see Figure 2.
Tissue lengthening onset	The time where the tissue lengthening line crosses the total minimum strain, see Figure 2.
Tissue lengthening cessation	The time where the tissue lengthening line crosses the median strain value of the isometric diastolic strain phase, see Figure 2.
Tissue shortening interval	Interval between tissue shortening onset and tissue shortening cessation.
Tissue isometric refractory interval	Interval between tissue shortening cessation and tissue lengthening onset.
Tissue relaxation interval	Interval between tissue lengthening onset and tissue lengthening cessation.

Table 2: Description of 6 strain patterns during the isometric tissue shortening interval immediately following the atrial kick, see Figure 4.

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Isometric strain contraction patterns

Pattern	Description
Pattern I	Parabolic with one clear peak of prestretching with monotonically increasing stretch before the peak and monotonically decreasing stretch following the peak.
Pattern II	Two distinct camel-like prestretching peaks of equal amplitude with a clear decrease in prestretching between the peaks.
Pattern III	Two distinct peaks of differing prestretching, with the second peak being the stronger.
Pattern IV	Two distinct peaks of differing prestretching, with the first peak being the stronger.
Pattern V	Single late peak with slow or no stretching before the peak and rapid shortening post peak.
Pattern VI	Single early peak characterized by rapid prestretching and a period of slow or no shortening before rapid shortening.

Table 3: shows the statistical results (F and P values) for the linear fixed-effects model for the mechanical events and intervals.

Mixed linear model statistics

Event	F	P
Tissue shortening onset	6.116	**.000**
Tissue shortening cessation	.893	.491
Tissue lengthening onset	2.328	.052
Tissue lengthening cessation	1.121	.358
Tissue shortening interval	2.123	.074
Tissue isometric refractory interval	2.710	**.028**
Tissue relaxation interval	1.110	.364

Table 4: shows the mean and standard deviation ($\mu \pm \sigma$) and 95% confidence interval for the mechanical events tissue shortening onset, tissue shortening cessation, tissue lengthening onset, and tissue lengthening cessation with respect to the locations basal septal wall (BSW), mid septal wall (MSW), apical septal wall (ASW), apical lateral wall (ALW), mid lateral wall (MLW), and basal lateral wall (BLW).

Events

		[ms]	95% Confidence Interval [ms]	
Event	Location	$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue shortening onset	BSW	103.1 ± 4.8	93.3	113.0
	MSW	94.1 ± 4.8	84.2	103.9
	ASW	105.7 ± 4.8	95.9	115.4
	ALW	107.3 ± 4.8	97.5	117.1
	MLW	107.3 ± 5.0	97.2	117.4
	BLW	106.9 ± 4.9	96.8	117.0

		[ms]	95% Confidence Interval [ms]	
Event	Location	$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue shortening cessation	BSW	360.9 ± 10.0	340.5	381.3
	MSW	370.6 ± 10.0	350.2	391.1
	ASW	370.1 ± 10.0	349.7	390.6
	ALW	374.7 ± 10.2	354.0	395.3
	MLW	377.5 ± 11.6	354.2	400.9
	BLW	384.8 ± 11.5	361.6	408.0

		[ms]	95% Confidence Interval [ms]	
Event	Location	$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue lengthening onset	BSW	467.4 ± 13.5	439.4	495.4
	MSW	454.2 ± 13.5	426.3	482.2
	ASW	456.9 ± 13.5	429.0	484.9
	ALW	464.2 ± 13.6	436.1	492.4
	MLW	466.2 ± 14.1	437.2	495.1
	BLW	469.9 ± 14.0	441.1	498.8

		[ms]	95% Confidence Interval [ms]	
Event	Location	$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue lengthening cessation	BSW	601.7 ± 15.1	570.4	633.0
	MSW	594.4 ± 15.1	563.2	625.7
	ASW	605.8 ± 15.1	574.6	637.0
	ALW	601.5 ± 15.2	570.0	633.0
	MLW	603.6 ± 15.8	571.2	636.1
	BLW	604.7 ± 16.0	571.9	637.5

Table 5: shows the post-hoc tests for statistical significance (P) for the locations basal septal wall (BSW), mid septal wall (MSW), apical septal wall (ASW), apical lateral wall (ALW), mid lateral wall (MLW), and basal lateral wall (BLW), respectfully. Values were adjusted for multiple comparison using Bonferroni correction.

Post Hoc T-tests

| | | | | 95% Confidence Interval [ms] | |
Event	(I) Location	(J) Location	P	Lower Bound	Upper Bound
Tissue onset shortening	MSW	BSW	**.012**	-16.9	-1.2
		ASW	**.000**	-19.2	-4.0
		ALW	**.003**	-23.4	-3.0
		MLW	**.037**	-26.0	-.4
		BLW	.103	-26.8	1.2

| | | | | 95% Confidence Interval [ms] | |
Event	(I) Location	(J) Location	P	Lower Bound	Upper Bound
Tissue isometric refractory interval	BSW	MSW	**.013**	3.0	42.9
		ASW	.426	-7.0	46.4
		ALW	1.000	-16.2	48.3
		MLW	1.000	-22.8	56.8
		BLW	1.000	-16.0	65.6

Table 6: shows the mean and standard deviation ($\mu \pm \sigma$) and 95% confidence interval for the mechanical intervals with respect to the locations basal septal wall (BSW), mid septal wall (MSW), apical septal wall (ASW), apical lateral wall (ALW), mid lateral wall (MLW), and basal lateral wall (BLW).

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Intervals

Event	Location	[ms] $\mu \pm \sigma$	95% Confidence Interval [ms] Lower Bound	Upper Bound
Tissue shortening interval	BSW	262.6 ± 10.8	240.9	284.3
	MSW	287.5 ± 10.8	265.8	309.2
	ASW	264.5 ± 10.8	242.8	286.2
	ALW	266.9 ± 11.0	244.8	289.0
	MLW	265.8 ± 13.7	238.6	293.0
	BLW	271.0 ± 13.0	245.0	296.9

Event	Location	[ms] $\mu \pm \sigma$	95% Confidence Interval [ms] Lower Bound	Upper Bound
Tissue isometric refractory interval	BSW	106.5 ± 10.7	84.7	128.3
	MSW	83.6 ± 10.7	61.8	105.4
	ASW	86.8 ± 10.7	65.0	108.6
	ALW	90.4 ± 11.1	68.0	112.9
	MLW	89.5 ± 12.6	64.2	114.8
	BLW	81.7 ± 12.2	57.1	106.3

Event	Location	[ms] $\mu \pm \sigma$	95% Confidence Interval [ms] Lower Bound	Upper Bound
Tissue relaxation interval	BSW	133.7 ± 9.1	115.2	152.2
	MSW	140.2 ± 9.0	121.9	158.5
	ASW	148.9 ± 9.0	130.6	167.2
	ALW	138.0 ± 9.3	119.1	156.9
	MLW	136.7 ± 10.7	115.4	158.1
	BLW	133.0 ± 10.5	111.9	154.0

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622 **Video Captions**

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