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Quantitative parameters of high frame rate strain in patients with echocardiographic normal function

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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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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.

Keywords: Deformation Imaging, Strain, Algorithm, Speckle Tracking, Ultrasound, Echocardiography, High Frame Rate, Feature Tracking

1 **Introduction**

2 Echocardiography has become the method of choice for assessing ven-
3 tricular systolic and diastolic function, and strain and strain rate echocar-
4 diographic measurements have emerged as important indicators of cardiac
5 function (Risum et al., 2013; Ponikowski et al., 2016). These are param-
6 eters of local myocardial function which can be derived from both Tissue
7 Doppler Imaging (TDI) and 2 dimensional (2D) B-mode echocardiographic
8 images (Cikes et al., 2014; Brekke et al., 2014; Andersen et al., 2016a). Strain
9 is defined as the fractional change in the length of local myocardial tissue with
10 respect to a baseline length of that tissue, and is measured as a fractional
11 deformation (Mada et al., 2014).

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

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

41 Clinical feasibility and application of several echocardiographic techniques
42 for measuring mechanical properties such as myocardial stiffness are currently
43 being investigated (Correia et al., 2016; Hollender et al., 2017; Melki et al.,
44 2017; Strachinaru et al., 2017; Pislaru et al., 2014; Vos et al., 2017; Bunting
45 et al., 2017b,a; Villemain et al., 2018). Offline post processing of the radio
46 frequency (RF) data is commonly used for improving the image quality of
47 the reconstructed ultrasound sequences and improve tracking accuracy of op-
48 tical flow methods (Poree et al., 2016; Joos et al., 2018; Song et al., 2013;
49 Grondin et al., 2017). It should be noted that while a high frame rate can
50 be produced with compounding methods such as motion compensation com-

51 pounding, the reduction of temporal resolution is directly proportional to
52 the number of compounded acquisitions and not the frame rate (Joos et al.,
53 2018; Poree et al., 2016; Cikes et al., 2014). Konofagou et al. (2010) created a
54 method they call Electromechanical Wave Imaging, which requires RF data
55 to automatically segment and estimate deformation of the the myocardium.
56 The segmented deformation images are normally presented superimposed on
57 a low frame rate ultrasound detected B-mode images (Luo and Konofagou,
58 2010; Konofagou et al., 2010; Provost et al., 2010, 2015; Bunting et al., 2017a;
59 Melki et al., 2017).

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

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

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

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

78 **Materials and Methods**

79 *T5 System*

80 To acquire high frame rate detected 2D B-Mode echocardiographic im-
81 ages, Duke University’s experimental ultrasound system, T5 (Duke Univer-
82 sity, Durham, NC, USA), was used. Echocardiographic images were acquired
83 using a 3.5 MHz, 96-element, 1D phased array (Volumetrics, Durham, NC,
84 USA), where the theoretical diffraction-limited azimuth resolution was 1.2°
85 and axial resolution was 0.44 mm. To maintain adequate spatial sampling,
86 echocardiographic images contained 160 unique receive directions with an an-
87 gular sampling of 0.5° for a total field of view of 80° . The axial sampling was
88 0.25 mm and scan depth was either 120 mm or 140 mm depending on the pa-
89 tient. To increase frame rate, the ultrasound system used a single defocused
90 transmit beam focused at -30 cm (i.e. 30 cm behind the transducer) and 16
91 or 32 parallel receive processing channels per receive element, also known as
92 16:1 or 32:1 exploso scanning. For 16:1, 10 transmit-receive operations were
93 required to create an image. The resulting images for 16:1 exploso scanning
94 were acquired at 500 images per second (I_{500}). For 32:1, 5 transmit-receive
95 operations were required to create an image. The resulting images for 32:1
96 exploso scanning were acquired at 1000 images per second (I_{1000}). Data was
97 exported from the system as detected B-mode 2D echocardiographic images
98 in the native ballistic coordinate system. A single lead ECG was recorded
99 synchronously with the echocardiographic images and was used to identify

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

104 *Patient Data*

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

- 116 • Poor image quality (2 or more myocardial segments not visualized)
- 117 • Previously diagnosed heart disease
- 118 • QRS duration > 100 ms
- 119 • Abnormal cardiac anatomy
- 120 • Impaired cardiac function (left ventricular ejection fraction $< 50\%$)
- 121 • Atrial fibrillation

- 122 • Diagnosed valvular stenosis
- 123 • Diagnosed valvular regurgitation

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

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

137 *Data Analysis*

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

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

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

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

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

, 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).

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

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

163 estimated using the length of the myocardial contour as defined in Equation
164 (3).

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

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

- 167 • Basal septal wall.
- 168 • Mid septal wall.
- 169 • Apical septal wall.
- 170 • Apical lateral wall.
- 171 • Mid lateral wall.
- 172 • Basal lateral wall.

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

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

195 The first event, tissue shortening onset, was defined by the intersection
196 of maximum strain and the myocardial shortening lines that corresponded
197 to the time at which the myocardial segment began active contraction. The
198 detected value of the onset of tissue shortening is indicated in Figure 2, as are
199 all other detected events to be described. The second event, tissue shortening
200 cessation, was defined as the intersection of the myocardial shortening line
201 and minimum strain value and corresponded to the end of myocardial defor-
202 mation during that contractile period in that segment. The third event, the
203 tissue lengthening onset, was defined by the intersection of the myocardial
204 lengthening line and minimum strain value, corresponding to the beginning
205 of rapid relaxation of the myocardium. The final event, tissue lengthening
206 cessation, was defined by the intersection of the myocardial lengthening line
207 and the isometric diastolic value.

208 As four mechanical events were defined with respect to a common event,
209 i.e. the onset of the Q wave, the intervals between these events could be
210 readily quantized and hold further significance. The first interval was tissue
211 shortening interval as defined by the interval between the tissue shortening
212 onset and cessation corresponding to the amount of time during which each
213 myocardial segment was actively contracting with associated deformation.
214 The second interval was tissue isometric refractory interval as defined by
215 the interval between tissue shortening cessation and tissue lengthening on-
216 set corresponding to the transition between systole and diastole when the
217 myocardium was undergoing minimum to no regional deformation. The fi-
218 nal interval was defined as the interval between tissue lengthening onset and
219 cessation, or tissue relaxation interval corresponding to the rapid expansion
220 of the myocardium in early diastole. A definition summary of the four me-
221 chanical events and the three intervals between is available in Table 1 for
222 reference.

223 *Statistical Analysis*

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

233 0.05 was considered statistical significance. Post-hoc tests were performed
234 and adjusted for multiple comparisons using Bonferroni correction where P
235 value < 0.05 was considered statistically significant.

236 **Results**

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

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

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

276 For tissue shortening cessation in patients with echocardiographic normal
277 function, there was found to be a clear progression from basal septal wall
278 through the apex to the basal lateral wall, as can be seen in Figure 5. The
279 duration of tissue shortening cessation across all segments was found to be
280 23.9 ms. However, there was not a statistically significant difference in the
281 timing of the tissue shortening cessation between the six segments ($F = 0.893$,

282 $P = 0.491$).

283 For tissue lengthening onset, mid septal wall was found to be the location
284 of first lengthening with other segments beginning to lengthen in sequence
285 around the ventricle, with the basal lateral wall beginning to lengthen last.
286 The duration of tissue lengthening onset across all segments was found to be
287 15.7 ms. Of note, lengthening onset in the basal septal wall occurred closer in
288 time to the basal lateral wall (2.5 ms prior) than to the anatomically adjacent
289 mid septal wall (13.2 ms later). Tissue lengthening onset was not found to
290 differ significantly across the six segments ($F = 2.382$, $P = 0.052$).

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

298 The intervals between the four mechanical events are shown graphically
299 in Figure 6, and the statistical breakdown is shown in Table 6. As seen
300 in Figure 6, the tissue shortening interval, or interval between the tissue
301 shortening onset and cessation, was the longest of the three intervals with
302 an average of 267.7 ms across all patients and myocardial segments. Tissue
303 isometric refractory interval, or the interval between of tissue shortening ces-
304 sation and lengthening onset, was the shortest interval, 89.7 ms, on average.
305 Tissue relaxation interval, or the interval between onset and cessation of tis-
306 sue lengthening, was 138.4 ms on average. For the tissue shortening interval,

307 the basal septal wall had the shortest interval (262.6 ± 1.8 ms) while basal
308 lateral wall had the longest interval (271.0 ± 13.0 ms). Statistical analysis
309 of the tissue shortening interval across all six myocardial segments did not
310 yield a significant difference between segments ($F = 2.123$, $P = 0.074$), de-
311 spite trends seen in Figure 6. For the tissue isometric relaxation interval, the
312 basal lateral wall had the shortest interval (81.6 ± 12.2 ms) while the basal
313 septal wall had the longest interval (106.5 ± 10.7 ms). Statistical analysis of
314 the six segments yielded significant difference in the isometric relaxation in-
315 terval between the six myocardial segments ($F = 2.710$, $P = 0.029$). Post hoc
316 tests using Bonferroni correction found a significant difference in the isomet-
317 ric relaxation interval between the basal and mid septal walls ($P = 0.013$),
318 see Table 5. For myocardial tissue relaxation interval, the basal lateral wall
319 had the shortest interval (133.0 ± 10.5 ms), and the apical septal wall had
320 the longest interval (148.9 ± 9.0 ms). Analysis of all six segments showed
321 no significant difference for tissue relaxation intervals between segments (F
322 $= 1.110$, $P = 0.364$).

323 Discussion

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

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

331 onset between any of the other walls. Similar results of the mid septal wall
332 shortening first have been reported before using velocity curves derived from
333 high frame rate TDI and M-mode imaging (Brekke et al., 2014; Hasegawa
334 and Kanai, 2011; Kanai, 2009). The mid lateral wall was the last segment
335 where tissue shortening onset was identified which is in accordance with elec-
336 trical propagation through the left ventricle. The average tissue shortening
337 onset propagating velocity between the first and all other wall segments was
338 calculated using an average myocardial contour of 190 mm was calculated
339 to 5.6 m/s for patients with echocardiographic normal function. This ve-
340 locity for patients with echocardiographic normal function seems high when
341 compared, for example, to the conduction velocities in the Purkinje fibers of
342 2-4 m/s (Brekke et al., 2014; Kanai, 2009; Durrer et al., 1970). However, as
343 demonstrated by Durrer et al. (1970) the high velocity may be reasonable
344 considering that there are multiple locations of excitation in the human heart
345 (Durrer et al., 1970). In our strain model, we divide the myocardium into
346 approximately equal sized myocardial regions and assumed a single excita-
347 tion location. If more than one region is activated within a short delay from
348 the first region, then the apparent contraction propagation may appear much
349 higher than often quoted 1-2 m/s propagation velocity in the myocardium
350 (Durrer et al., 1970).

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

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

364 Future studies involve identifying the patterns in known conduction dis-
365 order patients such as Left Bundle Branch Block (LBBB) to find statistical
366 differences between them and patients with echocardiographic normal func-
367 tion. It is anticipated that major divergence from the timing data patients
368 with echocardiographic normal function derived in this study will be associ-
369 ated with various pathologic conditions such as conduction abnormalities.

370 The iso-volumetric contraction often becomes the focus of high frame rate
371 electromechanical studies. We identified 6 distinct isometric contraction pat-
372 terns for the strain curves, see Table 2 and Figure 4. These early stretches
373 have been mentioned in prior literature (Joos et al., 2018; Andersen et al.,
374 2016a; Brekke et al., 2014; Tong et al., 2016). As alluded to in the result sec-
375 tion these isometric contraction patterns have a low spatial resolution, which
376 for this study was limited to 6 strain curves. The low spatial resolution may
377 obfuscate the origin of the differing patterns. Because multiple patterns can
378 appear in the same patient, these waves may potentially be propagating me-
379 chanical wave fronts that propagates through the myocardium with different
380 onset times and locations. The patterns could potentially have atrial origin

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

386 *Limitations*

387 Data was only recorded with a single lead ECG. To accurately describe
388 electro-mechanical coupling, a 12-Lead ECG would be better suited. Fur-
389 thermore, the reduced image quality inherent in high frame rate ultrasound
390 made patient selection more difficult and limited the number of walls that
391 could be imaged in this study. Apical two and three chamber views gener-
392 ally had poor image quality. Here a 6-segment model based on the apical
393 four chamber views is used. Using apical two and three chamber views could
394 provide a 16- or 18-segment model, which would provide more information
395 for describing contraction. Additionally, the 2D nature of B-mode echocar-
396 diographic images may confound the identification of the propagating waves
397 within the 3 dimensional (3D) structure of the heart. This may compromise
398 the accuracy of velocity determinations, which would make high frame rate
399 3D echocardiography increasingly important as a diagnostic tool.

400 **Conclusions**

401 Using high speed images, our algorithm allowed us to identify the origin
402 of initial myocardial tissue shortening in echocardiographically normal pa-
403 tients. Here, the middle of the interventricular septum was the myocardial
404 segment where the initial myocardial tissue shortening onset occurred in the

405 normal patient population. We found the timing of this event significant as
406 compared to that of the other myocardial segments except the basal inter-
407 ventricular septum in the normal heart. We believe that temporal sequences
408 of mechanical tissue shortening propagation through the left ventricle is of
409 clinical significance. When identifying physiological mechanical events dur-
410 ing the cardiac cycle, an acquisition rate of 500 images per second or higher
411 should be used to adequately resolve the events for diagnostic purposes. The
412 high temporal resolution data derived from the longitudinal strain measure-
413 ments in a normal cohort developed here can serve as a more precise means
414 of assessing cardiac function. The technique used in this study may become
415 an important tool for investigating electromechanical coupling and describ-
416 ing cardiac function in both patients with echocardiographic normal function
417 and abnormal function.

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541 **Figure Captions**

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

548 **Figure 2:** shows four different mechanical events occurring during the car-
549 diac cycle. The figure contains, (strain) strain curve from the basal
550 septal wall (ECG) 1-lead electrocardiograph. Three horizontal lines are
551 displayed, (maxSL) maximal strain line, (minSL) minimum strain line,
552 and (medianSL) median of isometric diastolic strain. The two sloped
553 red lines, (MSL) follow the myocardial shortening line, and (MLL) my-
554 ocardial lengthening line. The crossing between maxSL and MSL is
555 defined as tissue shortening onset (TSO). The crossing between MSL
556 and minSL is defined as tissue shortening cessation (TSC). The cross-
557 ing between MLL and minSL is defined as tissue lengthening onset
558 (TLO). The crossing between medianSL and MLL is defined as tissue
559 lengthening cessation (TLC).

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

565 **Figure 4:** shows 6 different strain 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.

585 **Tables**

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

588

Event and interval definitions

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

590

591 **Table 2:** Description of 6 strain patterns during the isometric tissue short-
 592 ening interval immediately following the atrial kick, see Figure 4.

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.
593 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.
594 Pattern VI	Single early peak characterized by rapid prestretching and a period of slow or no shortening before rapid shortening.

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

Mixed linear model statistics

Event	F	P
<i>Tissue shortening onset</i>	6.116	.000
<i>Tissue shortening cessation</i>	.893	.491
597 <i>Tissue lengthening onset</i>	2.328	.052
<i>Tissue lengthening cessation</i>	1.121	.358
<i>Tissue shortening interval</i>	2.123	.074
<i>Tissue isometric refractory interval</i>	2.710	.028
598 <i>Tissue relaxation interval</i>	1.110	.364

599 **Table 4:** shows the mean and standard deviation ($\mu \pm \sigma$) and 95% confidence
600 interval for the mechanical events tissue shortening onset, tissue short-
601 ening cessation, tissue lengthening onset, and tissue lengthening cessa-
602 tion with respect to the locations basal septal wall (BSW), mid septal
603 wall (MSW), apical septal wall (ASW), apical lateral wall (ALW), mid
604 lateral wall (MLW), and basal lateral wall (BLW).

Events

Event	Location	[ms]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue shortening	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
Tissue onset	MLW	107.3 ± 5.0	97.2	117.4
	BLW	106.9 ± 4.9	96.8	117.0

Event	Location	[ms]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue shortening	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
Tissue cessation	MLW	377.5 ± 11.6	354.2	400.9
	BLW	384.8 ± 11.5	361.6	408.0

Event	Location	[ms]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue lengthening	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
Tissue onset	MLW	466.2 ± 14.1	437.2	495.1
	BLW	469.9 ± 14.0	441.1	498.8

Event	Location	[ms]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	Lower Bound	Upper Bound
Tissue lengthening	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
Tissue cessation	MLW	603.6 ± 15.8	571.2	636.1
	BLW	604.7 ± 16.0	571.9	637.5

608 **Table 5:** shows the post-hoc tests for statistical significance (P) for the lo-
609 cations basal septal wall (BSW), mid septal wall (MSW), apical septal
610 wall (ASW), apical lateral wall (ALW), mid lateral wall (MLW), and
611 basal lateral wall (BLW), respectfully. Values were adjusted for multi-
612 ple comparison using Bonferroni correction.

Post Hoc T-tests

Event	(I) Location	(J) Location	P	95% Confidence Interval [ms]	
				Lower Bound	Upper Bound
Tissue 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
Tissue onset					

613

Event	(I) Location	(J) Location	P	95% Confidence Interval [ms]	
				Lower Bound	Upper Bound
Tissue isometric re-fractory 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

614

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

Intervals

Event	Location	[ms]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	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]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	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]	95% Confidence Interval [ms]	
		$\mu \pm \sigma$	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

620

621

622 **Video Captions**