Evaluation of Left Ventricular Dyssynchrony by Onset of Active Myocardial Force Generation

A Novel Method That Differentiates Between Electrical and Mechanical Etiologies

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Background—Better clinical tools for measuring left ventricular electrical dyssynchrony are needed. The present study investigates if onset of active myocardial force generation (AFG) may serve as a measure of electrical dyssynchrony.

Methods and Results—In anesthetized dogs, we evaluated left ventricular mechanical dyssynchrony by 2 different approaches. First, we measured timing of peak myocardial shortening velocity and strain. Second, we measured the first sign of tension development by onset AFG as defined by the myocardial pressure-segment length loop upward shift from its passive-elastic state. Electrical dyssynchrony was measured by intramyocardial electromyograms (IM-EMG). Dyssynchrony was quantified as peak intersegment time difference and as standard deviation of timing for 6 to 8 myocardial segments. During baseline, reduced preload and myocardial ischemia shortening velocity and strain indicated segmental mechanical heterogeneity, whereas onset AFG and onset R in IM-EMG indicated synchronous activation of all segments. After induction of left bundle-branch block, all methods indicated dyssynchrony. Peak intersegment time difference for shortening velocity and strain showed weak correlations ($r=0.17$ and 0.16) and weak agreements (mean differences, $-48\pm27$ ms and $-28\pm27$ ms, respectively) with IM-EMG. Onset AFG by pressure-segment length loops, however, correlated well with IM-EMG ($r=0.93$), and agreement was good (mean difference, $-0.6\pm6.8$ ms). Results were similar for standard deviation of timing. Onset AFG from pressure-strain analysis by echocardiography showed accuracy similar to sonomicrometry.

Conclusions—Onset AFG was an accurate marker of myocardial electrical activation and was superior to shortening velocity and strain. Identification of electrical dyssynchrony by onset AFG may be feasible clinically using left ventricular pressure-strain analysis. (Circ Cardiovasc Imaging. 2010;3:405-414.)

Key Words: heart failure • dyssynchrony • cardiac resynchronization therapy • echocardiography

Cardiac resynchronization therapy (CRT) has proved to be an effective treatment option in chronic heart failure but is limited by lack of response in about 30% of patients. A number of echocardiographic indices, including onset and peak myocardial ejection velocity by tissue Doppler imaging (TDI), have been proposed to improve patient selection for CRT. However, the conclusion after a large, multicenter trial was that the tested echocardiographic indices did not provide enough predictive value to be recommended as selection criteria. Currently, increased QRS width is the only dyssynchrony criterion that is recommended in clinical routine. Because of significant limitations of QRS width as criterion, there is a need for alternative or supplementary methods that can improve patient selection.
latter 2 we also refer to as nonelectrical etiologies of dyssynchrony. We believe that clear differentiation between etiologies is essential for the understanding and appropriate clinical interpretation of dyssynchrony indices.

The general objective of this study was to establish a method that can differentiate between electrical and nonelectrical etiologies of left ventricular (LV) dyssynchrony. As a reference method for timing of regional electrical activation, we used onset R in intramyocardial electromyograms (IM-EMG). As a reference method for mechanical activation, we introduce onset of active myocardial force generation (AFG) calculated from regional myocardial pressure-segment length and pressure-strain loops. Electromechanical activation time was measured as time from onset R in IM-EMG to onset AFG. Mechanical dyssynchrony was measured as regional differences in timing of myocardial shortening velocity and strain. By exclusion, dyssynchrony was categorized as primary mechanical when it could not be attributed to delay in electrical activation or prolongation of electromechanical activation time.

In the present study, electromechanical activation time remained constant during a wide range of interventions. This implies that onset AFG had a constant time delay relative to local electrical activation, and we therefore propose onset AFG as a surrogate for timing of electrical activation. The specific objectives of the study were to test the hypotheses that onset AFG represents a means to quantify primary electrical dyssynchrony and to differentiate between electrical and nonelectrical etiologies of LV intraventricular dysynchrony. In addition, we evaluated the ability of myocardial shortening velocity and strain to serve as markers of primary electrical dyssynchrony. The study was carried out in a dog model during different loading conditions, during myocardial ischemia, and after induction of left bundle-branch block (LBBB).

Methods

Animal Preparation

Fourteen mongrel dogs of either sex and body weight of 32.5 ± 3.2 kg were anesthetized, ventilated, and surgically prepared as previously described.4 In addition, pacemaker leads were attached epicardially on the LV lateral wall and right atrium and endocardially in the right ventricular outflow tract close to the septum. The National Animal Experimentation Board approved the study. The laboratory animals were supplied by Center for Comparative Medicine, Rikshospitalet University Hospital, Oslo, Norway.

Hemodynamic Measurements

Aortic, left atrial, and LV pressures (LVP) were measured by micromanometers.4 A fluid-filled catheter in the left atrium served as an absolute pressure reference.

Sonomicrometry and Regional Electromyograms

In each dog, 2-mm sonomicrometry crystals (Sonometrics Corp, London, Ontario, Canada) with bipolar electrodes for measuring...
Table 1. Hemodynamic and Timing Variables

<table>
<thead>
<tr>
<th>Load Alteration and Ischemia</th>
<th>Baseline (n=8)</th>
<th>Cavil Constriction (n=7)</th>
<th>LAD Occlusion (n=8)</th>
<th>BVP During Ischemia (n=8)</th>
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<tr>
<td>Hemodynamic variables and ECG</td>
<td></td>
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<tr>
<td>Heart rate, bpm</td>
<td>129±21</td>
<td>133±19</td>
<td>132±22</td>
<td>139±17</td>
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<tr>
<td>QRS width, ms</td>
<td>67±3</td>
<td>66±5</td>
<td>63±3</td>
<td>60±6</td>
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<tr>
<td>Systole, ms</td>
<td>268±41</td>
<td>254±29</td>
<td>263±49</td>
<td>256±25</td>
</tr>
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<td>LV dp/dt(_{max}), mm Hg/s</td>
<td>1488±237</td>
<td>991±296*</td>
<td>1371±331</td>
<td>1353±312</td>
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<tr>
<td>LV EDP, mm Hg</td>
<td>9±1</td>
<td>5±2*</td>
<td>11±3</td>
<td>10±2</td>
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<tr>
<td>Time of onset R in IM-EMG to onset AFG, ms</td>
<td>14±7</td>
<td>15±6</td>
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<td>17±8</td>
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<tr>
<td>Time of onset S, ms</td>
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<tr>
<td>Time of peak systolic strain, ms</td>
<td>27±10</td>
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<td>53±27*</td>
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<tr>
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<tr>
<td>Time of onset R in IM-EMG, ms</td>
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<td>Peak intersegment difference</td>
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<td>Peak intersegment difference</td>
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<td>50±13*</td>
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<td>SD of timing</td>
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<td>Peak intersegment difference</td>
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<td>76±23*</td>
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<td>SD of timing</td>
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<tr>
<td>Peak intersegment difference</td>
<td>11±4</td>
<td>18±9</td>
<td>21±9*</td>
<td>19±12</td>
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<tr>
<td>Peak intersegment difference</td>
<td>27±10</td>
<td>45±22*</td>
<td>53±27*</td>
<td>46±23*</td>
</tr>
<tr>
<td>SD of timing</td>
<td>14±1</td>
<td>23±11*</td>
<td>19±5</td>
<td>14±4</td>
</tr>
</tbody>
</table>

SD of timing indicates biventricular pacing; LAD, left anterior descending; LV dp/dt\(_{max}\), maximal time derivative of LV pressure; and LV EDP, LV end-diastolic pressure; IM-EMG, intramyocardial electromyogram; AFG, active force generation; S, myocardial shortening velocity during ejection. Values are means±SD. Dimensions are measured by sonomicrometry. SD of timing was calculated as standard deviation for 6 to 8 segments of time from onset R in ECG to timing of each of the indices. \*P<0.05 versus baseline.

IM-EMG were implanted endocardially and epicardially as illustrated in Figure 1. In each of the dogs, 4 circumferential and 2 longitudinal (anterior and posterior) segments were measured (Figure 1). In the LBBB group, we additionally measured longitudinal dimension in the midsegments in septum and lateral wall. Because of technical difficulty with the crystal pair in the midsegment of the lateral wall, the basal segment was used instead in 3 dogs. Data were digitized at 200 Hz.

Echocardiography

A Vivid 7 ultrasound scanner (GE) was used to record color-coded TDI images in the apical 4- and 2-chamber views. Conventional 2-D grayscale images (frame rate, 63±13 s\(^{-1}\)) of the LV equatorial short-axis and 2-chamber views were acquired for speckle-tracking echocardiography (STE).

Data Analysis

Electrical Events and Electromechanical Activation Time

Timing of regional electrical activation was measured at onset R in IM-EMG, defined as the onset of the first spike that led to a deflection of more than 20% of total QRS amplitude. Electrical conduction time was calculated as time from onset R in ECG to onset R in IM-EMG. Electromechanical activation time was calculated as time from onset R in IM-EMG to onset AFG.

Regional Strain and Shortening Velocity

Myocardial strain by sonomicrometry was obtained using segment length as an analog for strain, and strain by echocardiography using STE. Myocardial shortening velocity by sonomicrometry was calculated as the time derivative of segment length and shortening velocity by echocardiography using TDI. The following time markers were measured for myocardial shortening velocity and strain: timing of onset of systolic shortening velocity; timing of peak shortening velocity during ejection (S); and timing of peak systolic strain.

Aortic valve opening, defined as start of upstroke of aortic pressure, was used to define time of onset ejection. Aortic valve closing, defined as peak negative dp/dt, was used to define end of systole.

Onset AFG by Sonomicrometry and LVP

The time of onset AFG was determined by analyzing myocardial pressure-segment length loops and was defined as the time when the pressure-segment length coordinate was shifted upward relative to the passive elastic curve for the same segment. The calculation of onset AFG is illustrated in Figure 2. The passive-elastic curve was constructed by an exponential fit to a series of end-diastolic pressure–segment lengths coordinates obtained during caval constriction. End-diastolic measurements were used to ensure that the myocardium was completely relaxed. Because the pressure–segment length relationship provides no timing information, onset AFG was
extracted from a corresponding time point in either the pressure or the segment length curve (Figure 2, right panel).

In segments with no sharp deflection from the passive elastic curve after onset of R in ECG (12 of 266 segments), we used 2 confidence intervals of the fitted passive elastic curve as cutoff to define a shift from a passive to an active state.

**Onset AFG by STE and LVP**

Onset AFG was also assessed by combining LVP with circumferential strain by STE. Because strain represents a relative value, this analysis does not provide a range of end-diastolic pressure–dimension relations, and the late diastolic portion of each loop was used to define the passive elastic state. Identification of onset AFG was based on subjective, visual assessment, defined as the first marked upward deviation of the pressure–strain loop that resulted in a continued upward shift after onset of R in ECG.

**Quantification of LV Dyssynchrony**

LV dyssynchrony was quantified by 2 different approaches: (1) as peak intersegment time difference, measured as time difference between the earliest and the latest activated segments, and (2) as standard deviation for 6 to 8 segments of time from onset R in ECG to timing of each of the indices, and will be referred to as SD of timing. In addition, we measured times from onset R in ECG to timing of each of the indices. The latter approach allows presentation of individual timing data from all segments and all animals in a single graph.

**Experimental Protocol**

The experimental protocol included measurements during baseline (n=8), reduced preload by transient caval constrictions (n=7), and myocardial ischemia by left anterior descending coronary artery occlusion for 15 minutes (n=8).

In the remaining 6 animals, LBBB was induced by radiofrequency ablation as previously described.6 Recordings were done during baseline, LBBB, and in 4 animals during biventricular pacing.

**Statistical Analysis**

Values are expressed as means±SD. Variables were compared using least-squares linear regression, Pearson correlation coefficients, intraclass correlation coefficients, and Bland-Altman methods. For multiple comparisons (Table 1) we used repeated-measurements ANOVA with least-squares differences post test (SPSS 15.0, SPSS Inc; Chicago, Ill). All post hoc tests are compared with baseline. P<0.05 was considered significant.

Because correlation analysis does not take into account multiple measurements within an individual agreement, the Bland-Altman method with reference intervals based on agreement between methods of measurement with multiple observations per individual was used to account for this (Table 2).

To assess interobserver variability, 20 segments from 6 experiments including all interventions were randomly selected and analyzed by 2 independent observers, using the interclass correlation coefficient (α value) and Bland-Altman method.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

**Results**

**Regional Electrical Activation by IM-EMG**

Figure 3 shows representative IM-EMG traces with distinct R waves and illustrates that electrical activation was essentially simultaneous in all segments during baseline and ischemia. This was reflected in the dyssynchrony indices peak intersegment time difference and SD of timing for onset R in IM-EMG, which indicated synchronous electrical activation (Table 1). Figure 4, lower panel, presents times from onset R in ECG to onset R in IM-EMG from all segments in all animals and confirms a remarkable uniformity in timing of electrical activation during baseline, reduced preload, and ischemia (1±5 ms).

Induction of LBBB caused an increase in QRS duration from 68±5 ms to 116±7 ms (P<0.05), and there was marked delay in onset R in IM-EMG in the lateral wall relative to septum (Figure 3). Peak intersegment time difference increased from 15±7 ms to 53±20 ms (P<0.05) and SD of timing from 6±3 ms to 22±2 ms (P<0.05), indicating electrical dyssynchrony. Biventricular pacing caused reversal of QRS duration and electrical dyssynchrony indices to baseline values, indicating electrical resynchronization. When timing of onset R in IM-EMG in subepicardium and subendocardium was compared, we found no significant change with any of the interventions. Induction of ischemia was associated with a slight increase in endocardial-to-epicardial delay from 4±5 ms to 6±5 ms (P=0.72).

**Regional Mechanical Activation by Onset AFG**

Representative LV pressure-segment length loops are displayed in Figure 5. In most cases, AFG was represented by a sharp deflection in the lower right corner of the LV pressure-segment length loop and coincided with onset of shortening. In ischemic segments and in the LV lateral wall during LBBB, however, there was early systolic lengthening, and AFG did not coincide with onset of shortening. This is illustrated in Figure 5B, which shows that onset AFG was represented by a bend in the pressure-segment length loop near end-diastole at a time when there was continuing lengthening. At this point, the pressure-segment length loop was shifted upward relative to the passive elastic curve, which implies that the myocardium was stiffer. In contrast, an entirely passive segment would have followed the passive elastic curve. Therefore, the upward-shift served as confirmation of active tension development in the segment and

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**Table 2. Correlation and Agreement Between IM-EMG and Dyssynchrony Indices**

<table>
<thead>
<tr>
<th></th>
<th>Intraclass Correlation Coefficient</th>
<th>Mean Difference ± SD, ms</th>
<th>Reference Interval, ms</th>
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</thead>
<tbody>
<tr>
<td>Peak intersegment time difference, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset R in IM-EMG to onset AFG</td>
<td>0.93</td>
<td>0.6±6.8</td>
<td>11.1–10.0</td>
</tr>
<tr>
<td>Onset R in IM-EMG to peak S velocity</td>
<td>0.17</td>
<td>47.7±26.9</td>
<td>3.4–91.9</td>
</tr>
<tr>
<td>Onset R in IM-EMG to peak systolic strain</td>
<td>0.16</td>
<td>28.4±26.5</td>
<td>72.6–15.8</td>
</tr>
<tr>
<td>SD of timing, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset R in IM-EMG to onset AFG</td>
<td>0.93</td>
<td>0.2±2.6</td>
<td>4.2–4.5</td>
</tr>
<tr>
<td>Onset R in IM-EMG to peak S velocity</td>
<td>0.18</td>
<td>16.4±9.8</td>
<td>38.2–5.4</td>
</tr>
<tr>
<td>Onset R in IM-EMG to peak systolic strain</td>
<td>0.13</td>
<td>9.8±9.8</td>
<td>36.8–17.1</td>
</tr>
</tbody>
</table>

AFG indicates active force generation; S, myocardial shortening velocity during ejection.

*P<0.05.
identified AFG. Results were similar when onset AFG was obtained from the LV pressure-strain loop assessment using STE (Table 3). This is illustrated by representative traces in Figure 6.

The electromechanical activation time, measured as time from onset R in IM-EMG to onset AFG, was essentially constant during all interventions, including ischemia and LBBB (Table 1). Therefore, changes in timing of onset AFG mirrored quite accurately changes in timing of onset IM-EMG (Table 1). This relationship was confirmed by strong correlations and good agreement between peak intersegment time difference for onset AFG and onset R in IM-EMG;

\[ r = 0.93 \]

mean difference was 1.1±3.4 ms. The intraclass correlation coefficient between the 2 observers was 0.99.

**Interobserver Variability**

Measurements of onset AFG by STE strain and LVP analyzed by 2 independent observers showed a mean difference between the 2 analyses of 1.1±3.4 ms. The intraclass correlation coefficient between the 2 observers was 0.99.

**Discussion**

The present study introduces assessment of onset AFG as a method to quantify LV electrical dyssynchrony and to differentiate between dyssynchrony with electrical and nonelectrical etiologies. In a clinical setting, this differentiation is essential, and unlike QRS duration, onset AFG gives regional information and allows for direct comparison between LV walls. The principle behind this novel method is that onset of active force generation is the first mechanical sign of actin-
activation, and delay due to mechanical factors such as

delay in electrical conduction, delay in electromechanical
components that may contribute to LV dyssynchrony, that is,
Mechanical Activation

Relationship Between Regional Electrical and
Mechanical Activation

In the present animal model, we measured each of the 3
components that may contribute to LV dyssynchrony, that is,
delay in electrical conduction, delay in electromechanical
activation, and delay due to mechanical factors such as

myosin interaction, and, in contrast to indices based only on
myocardial velocity and strain, it is independent of loading
conditions and contractility.

When using pressure-dimension curves, active forces are
verified by showing an upward shift of the LV pressure–
segment length relation relative to the passive elastic curve.
An upward shift means that a higher pressure (or force) is
needed to distend the segment to a given length, which
implies that stiffness is increased. With this approach, onset
AFG can identify mechanical activation even in segments
with systolic lengthening.

During changes in load, myocardial ischemia, and LBBB,
the electromechanical activation time was essentially con-
stant; hence, onset AFG tracked changes in timing of elec-
trical activation. Accordingly, onset AFG, which primarily
is a measure of mechanical activation, was an accurate measure
of electrical activation as well. The AFG method was feasible
not only with sonomicrometry but also when strain by STE
was used as an analog for segment length, suggesting a
potential for measuring onset AFG clinically during left heart
catheterization. Using onset R in IM-EMG as a reference
method for electrical dyssynchrony, we demonstrated that
onset AFG was superior to conventional timing indices based
on myocardial velocity and deformation.

As predicted, during LBBB there was LV dyssynchrony
by velocity and strain indices, and there was delay in
intraventricular conduction by IM-EMG, confirming the
presence of primary electrical dyssynchrony. The observa-
tion that electromechanical activation time remained un-
changed during all interventions implies that onset AFG
has potential to become a means to measure electrical
conduction delay and to identify mechanisms of LV
dyssynchrony as being either primary electrical or primary
mechanical, or a combination of the two.

The finding in the present study that electromechanical
delay remained unchanged after induction of LBBB is in
apparent contrast to previous studies that have used epicardial
sensors to measure electromechanical delay. Prinzen et al9
showed increased electromechanical delay in the latest acti-
vated segments during pacing in the right ventricular outflow
tract. However, the different findings in our study can be
explained by the different definition of mechanical activation,
that is, onset AFG versus onset of shortening. The latest
activated segment during LBBB must shorten against a
greater and more rapidly rising force than the early activated
segments since LVP has started to rise. Prinzen et al9
suggested that increased load at the time of activation could
explain the increased delay between electrical activation and
onset of shortening in late activated segments. However, the
mechanism for the increased delay has not been determined.
Therefore, we are currently performing a new study to
investigate potential mechanisms for this increased delay.

Consistent with the study of Ruffy et al,10 we observed no
significant delay in subendocardial electrical activation dur-
ing short-term ischemia. Therefore, electrical delay could not
account for the observed dyssynchrony during ischemia.
Possibly, more severe and longer lasting ischemia could
induce conduction delays.10,11 The aim of the present study,
however, was to determine if onset AFG could identify
mechanical activation in segments with decreased regional
contraction, and we therefore used ischemia to depress
myocardial function. Furthermore, the principle of onset AFG
is such that it should identify delay in electrical activation
regardless of etiology.
Limitations

The present study used a heavily instrumented animal model, and this preparation may not always represent normal physiology. Although the open-chest condition and instrumentation may have induced some degree of LV dysfunction during baseline, this should not modify the main conclusions from this study.

The temporal resolution of measurements of timing of onset R in IM-EMG and onset AFG was 5 ms, and smaller regional differences in timing may not have been detected. However, the magnitude of electrical and mechanical dyssynchrony was in the order of 40 to 100 ms and therefore the temporal resolution was sufficient for the purpose of exploring mechanisms of dyssynchrony. The small sample size in this study may be viewed as a limitation; however, the consistency in our findings support our conclusions.

In the present study we investigated isolated mechanical and electrical dyssynchrony. In a clinical situation, however, one may encounter concomitant electrical conduction delay and regional impairment of contractility, and it remains to be determined if the proposed method will predict responses to CRT in these patients.

Potential for Clinical Application

CRT is designed to correct electrical intraventricular dyssynchrony, and QRS duration is currently the main criterion for selecting patients for CRT. However, based on previous studies, it is evident that QRS width has significant limitations as criterion for selecting patients for CRT. Unlike the QRS duration, onset AFG gives regional information and allows for direct comparison of electrical activation between LV walls. This would enable identification of electrical delay.
within the LV that might not be apparent or may be underestimated when assessing QRS duration.

The present experimental study suggests that onset AFG may represent a means to differentiate between primary mechanical and primary electrical etiologies of LV dysynchrony. If this method is feasible clinically, it could become a useful tool in the evaluation of candidates for CRT. Current echocardiographic indices provide quantitative information about the magnitude of dyssynchrony, but do not provide conclusive information regarding etiology and have limited ability to identify electrical conduction delay. This may help to explain why some patients who have dyssynchrony by echocardiography are nonresponders to CRT. The primary purpose of CRT is to synchronize patients with LV electrical conduction delay. Thus, a method that correctly identifies the cause of dyssynchrony may be important for better selection of CRT candidates. As demonstrated in this study, conventional echocardiographic indices have limited ability to differentiate between electrical and mechanical causes of dyssynchrony, whereas onset AFG represents a means to identify patients with primary electrical dyssynchrony. This may suggest that ejection phase indices, which have been widely used in clinical trials, may be suboptimal markers of electrical dyssynchrony. The importance of standardizing measurements was addressed in a recent review by Bax and Gorcsan. The findings in the present study, however, do not suggest that assessment of mechanical dyssynchrony is of little importance but rather that some dyssynchrony may not be amenable to CRT. Ultimately, the degree of mechanical synchrony is a key determinant of stroke volume and presumably of LV remodeling. A number of smaller studies have shown improved function in heart failure patients with narrow QRS despite findings in the RETHINQ trial, which showed no benefit. However, the mechanisms for improvement seen in these studies are thus far unknown and need to be investigated. Without understanding the underlying mechanism of improvement in this patient group, it is difficult to select patients that may benefit from CRT. Although there may be other beneficial effects of CRT such as improved left to right ventricular interaction, the main intended purpose for CRT is to synchronize LV electrical dispersion. To improve patient selection, it

Table 3. Dyssynchrony by Echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=8)</th>
<th>Ischemia (n=8)</th>
<th>LBBB (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak intersegment time</td>
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<td></td>
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<tr>
<td>difference, ms, by</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Onset R in IM-EMG</td>
<td>9±4</td>
<td>7±3</td>
<td>46±5*</td>
</tr>
<tr>
<td>Onset AFG by STE</td>
<td>8±10</td>
<td>9±7</td>
<td>42±15*</td>
</tr>
<tr>
<td>Onset S by TDI</td>
<td>26±13</td>
<td>54±23*</td>
<td>29±10</td>
</tr>
<tr>
<td>Peak S by TDI</td>
<td>29±13</td>
<td>62±35*</td>
<td>40±30</td>
</tr>
<tr>
<td>Peak systolic strain</td>
<td>48±30</td>
<td>71±32</td>
<td>62±26</td>
</tr>
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</table>

AFG indicates active force generation; S, myocardial shortening velocity during ejection; TDI, tissue Doppler imaging; STE, speckle-tracking echocardiography.

Values are means±SD. *P<0.05 versus baseline.

Figure 6. Assessment of onset AFG by LVP and strain by speckle-tracking echocardiography. Left, Representative traces for anterior (thick red trace) and posterior (thin blue trace) segments during ischemia. Right, Representative traces from septal (thick lilac trace) and lateral (thin green trace) segments during LBBB. Strain measurements are performed in short-axis view. Aortic valve opening (AVO) and closing (AVC) indicated by arrow.
would therefore seem logical to start by finding the patients with LV electrical disparity regardless of QRS width since we know this can be corrected by CRT.

One obvious disadvantage of the AFG method is that it requires invasive pressures. Many patients, however, undergo left heart catheterization as part of a workup before CRT, and this would give access to LV pressure and pressure-strain loops can be constructed. Furthermore, the use of LV pressure analogs should be assessed, for example, estimated from continuous wave Doppler in patients with mitral regurgitation. We therefore propose that onset AFG may be used to identify LV dyssynchrony caused by electrical conduction delay and may serve as a reference method for future testing of markers of electrical dyssynchrony. Clinical trials should be done to explore these possibilities.

Conclusions
The present study demonstrates that onset AFG is an accurate marker of timing of regional electrical activation, allowing for differentiation between primary electrical and primary mechanical dyssynchrony, independent of regional differences in load and contractility. Furthermore, it shows that current indices based on myocardial shortening velocity and strain have significant limitations, and although they measure dyssynchrony, they have limited ability to establish underlying etiology. Further studies should be performed to investigate if onset AFG can be used clinically to identify patients who may benefit from CRT.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Better methods for selection of patients for cardiac resynchronization therapy are required because 30% of patients do not have improved function based on the current QRS duration criterion. Echocardiographic ejection phase indices have previously been introduced without being able to aid patient selection. In this animal study, we introduce a novel method to evaluate dyssynchrony based on assessment of regional onset of active force generation (AFG), that is, the first mechanical sign of actin-myosin interaction. Our investigation showed a consistent correspondence between timing of AFG and regional electrical activation, indicating that AFG mirrors regional electrical activation. In contrast to QRS duration, which is a measure of the total right ventricular and left ventricular activation time, regional AFG may serve as a better measure of the direct electrical activation delay between the left ventricular segments. A patient with synchronous left ventricular activation would be less likely to respond to cardiac resynchronization therapy compared with a patient with long activation delay; hence, this information may complement QRS duration. In the present study, we showed that ejection phase echocardiographic dyssynchrony indices are dependent on regional contractile state (ischemia) and load as well as electrical activation delay. Thus, they failed to correctly identify the cause of dyssynchrony, which is important because cardiac resynchronization therapy is designed to correct electrical dyssynchrony. On the other hand, AFG correctly reflected electrical activation time and was not dependent on load or contractile state. The current limitations of the proposed AFG method are that it requires measurements of left ventricular pressure and segment length. In the present study, we showed that segment length may be substituted with segmental strain, which can be obtained by echocardiography. This is a method that should be further explored in patients undergoing left heart catheterization.
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