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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 ± 27 ms and -28 ± 27 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 ± 6.8 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.[1] 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.[2] Currently, increased QRS width is the only dyssynchrony criterion that is recommended in clinical routine.[3] Because of significant limitations of QRS width as criterion, there is a need for alternative or supplementary methods that can improve patient selection.

Clinical Perspective on p 414

Dyssynchrony is defined as uncoordinated regional myocardial contractions[3] and may in principle have the following etiologies: (1) electrical conduction delay that causes nonuniform timing of myocyte depolarization, (2) abnormalities in excitation-contraction coupling, and (3) abnormal myocardial contractility or load that causes regional delay in fiber shortening. This implies that mechanical dyssynchrony may have electrical as well as nonelectrical etiologies, and these must be differentiated because CRT is primarily designed for correcting electrical conduction delay. In the present study, we will refer to the different etiologies as primary electrical dyssynchrony, excitation-contraction–related dyssynchrony, and primary mechanical dyssynchrony, respectively. The

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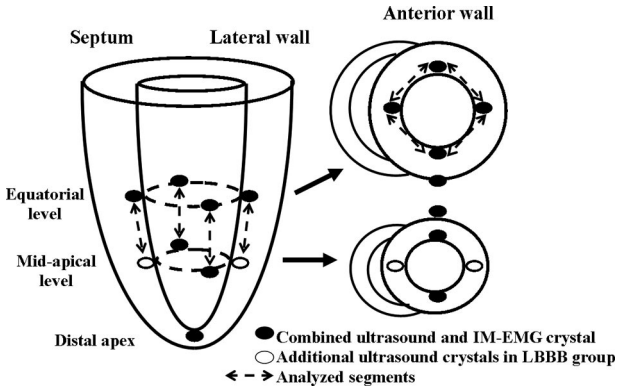

Figure 1. Schematic illustration of placement of myocardial crystals.

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 dyssynchrony. 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

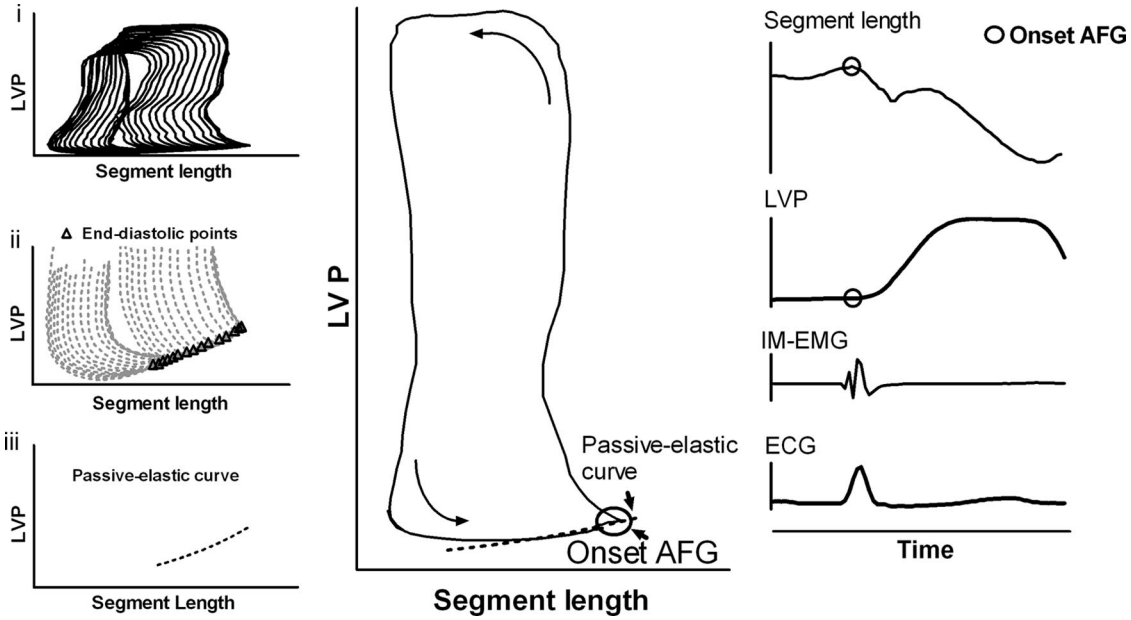

Figure 2. Measurement of onset AFG in a representative experiment. Left, Construction of passive elastic curve. i, Pressure-segment length loops during caval constriction; ii, high-gain LVP showing end-diastolic points; and iii, exponential fit to end-diastolic points. Middle, Onset AFG was defined as the first coordinate of the pressure segment length loop that leads to a deviation from the passive-elastic curve. Right, Timing of onset AFG was extracted from either LVP or segment length traces.

Table 1. Hemodynamic and Timing Variables

	Load Alteration and Ischemia				LBBB and BVP		
	Baseline (n=8)	Caval Constriction (n=7)	LAD Occlusion (n=8)	BVP During Ischemia (n=8)	Baseline (n=6)	LBBB (n=6)	BVP (n=4)
Hemodynamic variables and ECG							
Heart rate, bpm	129±21	133±19	132±22	139±17	121±17	122±13	120±28
QRS width, ms	67±3	66±5	63±3	60±6	68±5	116±7*	72±11
Systole, ms	268±41	254±29	263±49	256±25	277±16	331±10*	306±33*
LV dP/dt_{max}, mm Hg/s	1488±237	991±295*	1371±331	1353±312	1202±224	969±107*	1154±210
LV EDP, mm Hg	9±1	5±2*	11±3	10±2	10±3	10±3	9±4
Electromechanical delay							
Time from onset R in IM-EMG to onset AFG, ms	14±7	15±6	16±9	17±8	12±7	13±7	18±10
Dyssynchrony variables							
Time of onset R in IM-EMG, ms							
Peak intersegment difference	10±3	10±4	9±2	11±5	15±7	53±20*	19±7
SD of timing	4±1	4±1	4±1	4±2	6±3	22±2*	7±2
Time of onset AFG, ms							
Peak intersegment difference	9±5	8±5	13±8	16±8	13±6	55±8*	27±6*
SD of timing	4±2	3±2	5±3	6±2	5±2	22±4*	10±3
Time of onset S, ms							
Peak intersegment difference	36±11	43±12	50±13*	55±21*	41±15	103±19*	53±20
SD of timing	14±4	18±6	20±5*	22±10*	15±6	38±7*	19±7
Time of Peak S, ms							
Peak intersegment difference	41±18	76±23*	65±21*	70±37*	43±18	110±33*	38±8
SD of timing	17±7	28±9*	24±9*	27±15*	15±6	38±11*	14±4
Time of peak systolic strain, ms							
Peak intersegment difference	27±10	45±22*	53±27*	46±23*	41±20	69±38*	57±23
SD of timing	11±4	18±9	21±9*	19±12	14±1	23±11*	19±5

BVP indicates biventricular pacing; LAD, left anterior descending; LV dP/dtmax, 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.[5] 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[7] 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).

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

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

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

*$P<0.05$.

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 from15±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

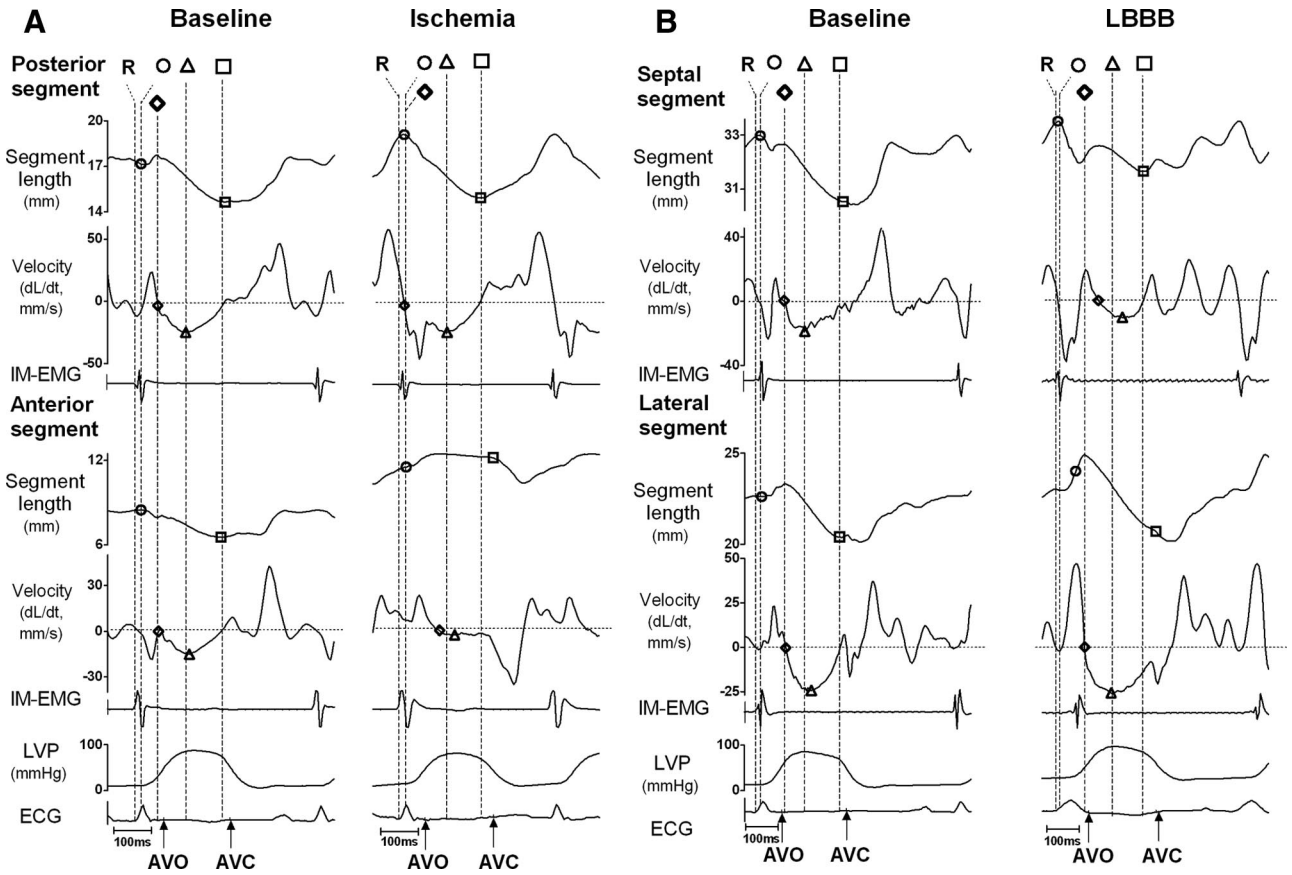

Figure 3. Representative traces. A, Posterior and anterior segments during baseline and ischemia; B, septal and lateral segments during baseline and LBBB. Vertical dotted lines indicate earliest occurrence of onset R in IM-EMG (R), onset of AFG (O), onset of peak ejection velocity (◇), peak ejection velocity (Δ), and peak systolic shortening (□). Aortic valve opening (AVO) and closing (AVC) indicated by arrow.

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 value was 0.93 and mean differences was −0.57, measured by sonomicrometry (Table 2). Similarly, there were strong correlations between time from onset R in ECG to onset AFG by sonomicrometry and echocardiography and time to onset R in IM-EMG (Figure 7).

Regional Mechanical Activation by Shortening Indices

Figure 3 shows representative examples of shortening indices measured by sonomicrometry and their relationship to regional electrical activation by onset R in IM-EMG and to mechanical activation by onset AFG. During baseline, reduced filling and myocardial ischemia, the variability in peak intersegment time difference for the shortening indices, was substantial and far exceeded the variability in onset R in IM-EMG and in onset AFG (Tables 1 and 2 and Figure 4). Similarly, the SD of timing for shortening indices exceeded the values for timing of onset R in IM-EMG and onset AFG. During LBBB, onset of shortening velocity showed less variability than peak shortening velocity and peak strain (Table 1). In the group with ischemia, we did not find significant electrical conduction delay and biventricular pacing in this group did not improve LV function or reduce mechanical dyssynchrony (Table 1).

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-

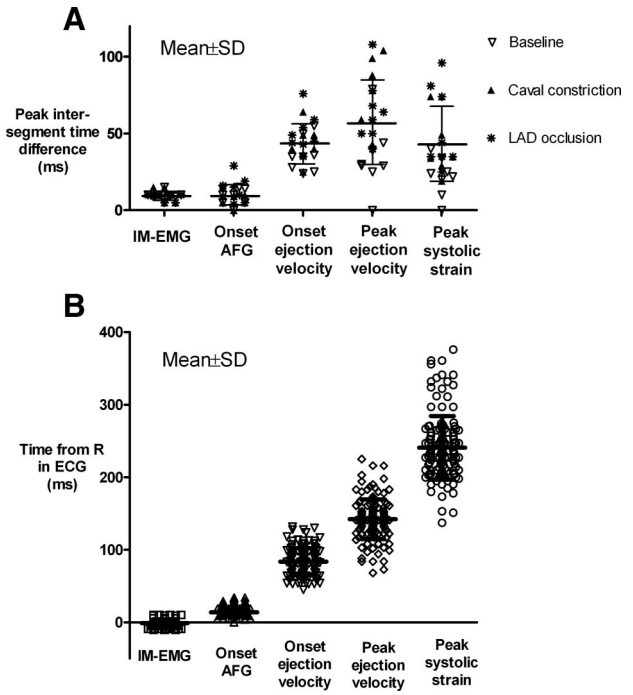

Figure 4. A, Peak intersegment time difference during baseline, load alteration, and ischemia. B, Pooled data during baseline, load alteration, and ischemia illustrating the variability in time from onset R in ECG to timing of different dyssynchrony indices by sonomicrometry. Lines show means±SD for pooled data.

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 constant; hence, onset AFG tracked changes in timing of electrical 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.

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 reduction in regional contractility or changes in load. By exclusion, delay was attributed to mechanical factors when onset AFG was synchronous throughout the ventricle.

During load alterations and ischemia, there were marked regional differences in timing of myocardial shortening velocity and strain, whereas IM-EMG and onset AFG indicated synchronous electrical and mechanical activation. Furthermore, electromechanical activation time remained unchanged. Therefore, the segmental differences in timing of onset S, peak S, and peak strain during load alterations and ischemia could not be attributed to delay in electrical conduction or delay in electromechanical activation. These findings imply that the observed dyssynchrony during changes in load and ischemia represents primary mechanical dyssynchrony, probably caused by nonuniformities in regional contractility during ischemia or wall stress during changes in load.[8]

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 observation that electromechanical activation time remained unchanged 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 al[9] showed increased electromechanical delay in the latest activated 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 al[9] 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 during 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.

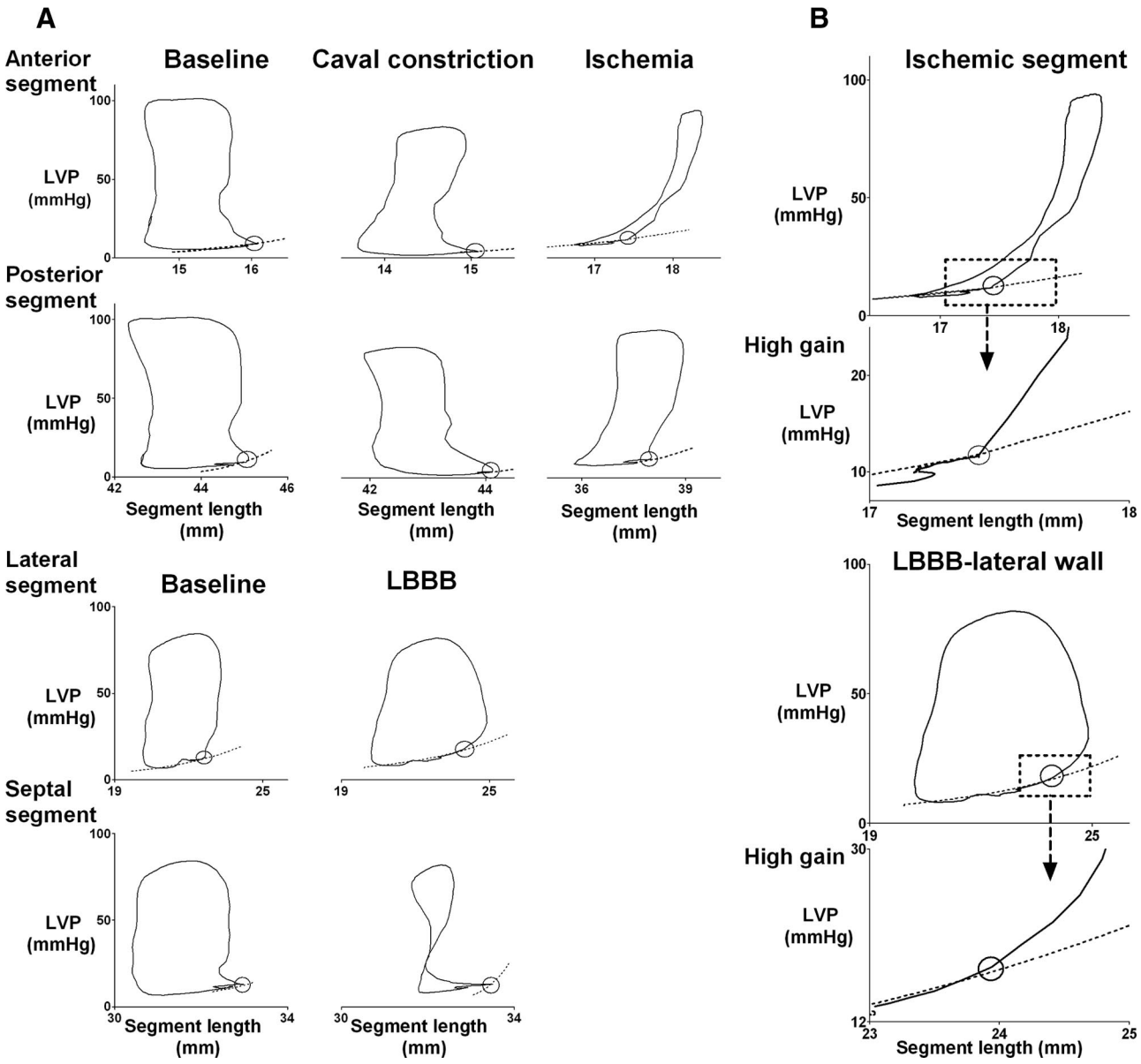

Figure 5. Representative pressure–segment length loops. A, Representative pressure-segment length loops and passive elastic curves (dotted lines) with identification of onset AFG. B, LV pressure with high gain and illustrates how onset AFG was defined in segments with early systolic lengthening. In these cases, onset AFG corresponded to onset of an upward-shift of the pressure–segment length loop relative to the passive elastic curve.

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

Table 3. Dyssynchrony by Echocardiography

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

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.

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 dyssynchrony. 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.[11] 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[12,13] despite findings in the RETHINQ trial,[14] 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,[12,15] the main intended purpose for CRT is to synchronize LV electrical dispersion. To improve patient selection, it

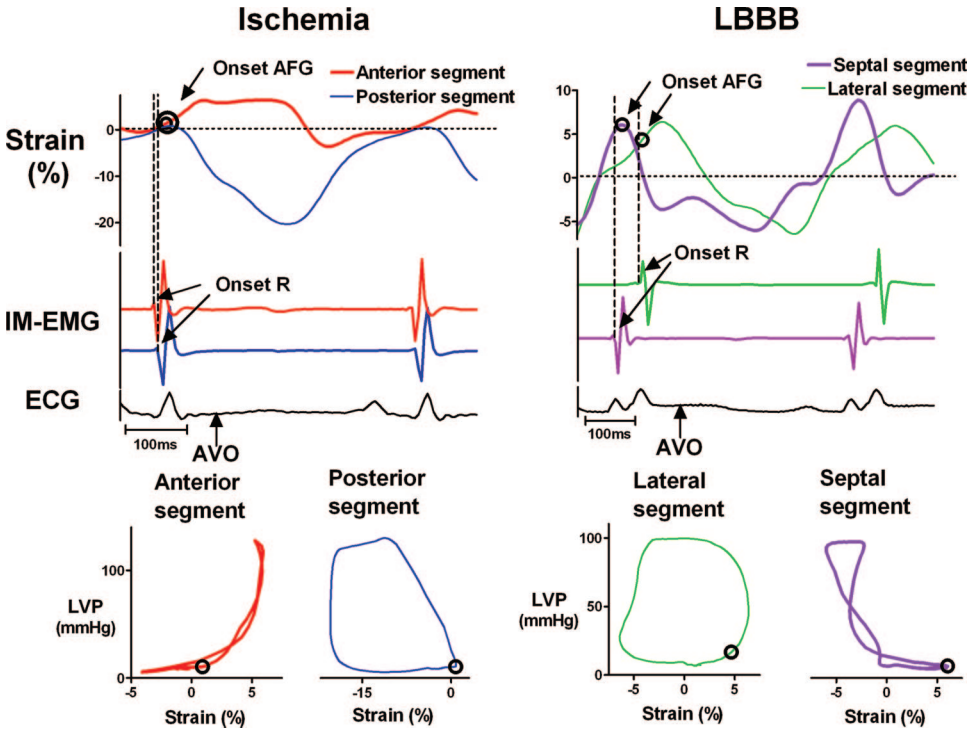

Figure 6. Assessment of onset AFG by LVP and strain by speckle-tracking echocardiography. Left, Representative traces for anterior (thick red trace) and posterior (thin blue trace) segments during ischemia. Right, Representative traces from septal (thick lilac trace) and lateral (thin green trace) segments during LBBB. Strain measurements are performed in short-axis view. Aortic valve opening (AVO) and closing (AVC) indicated by arrow.

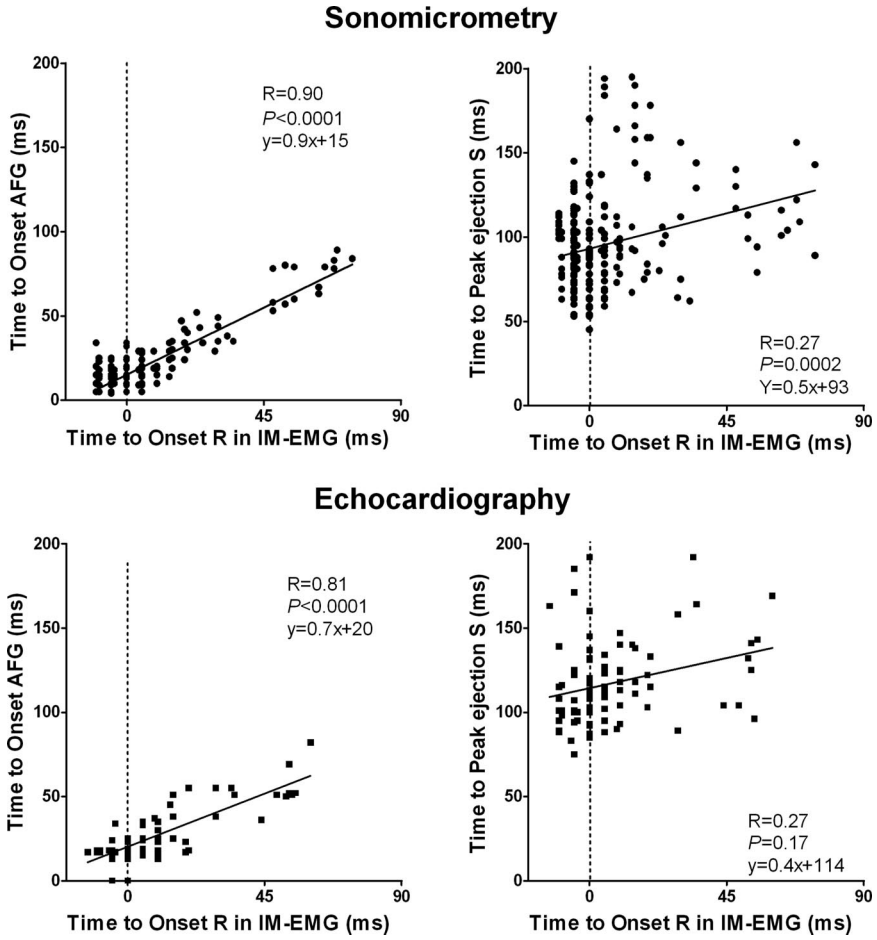

Figure 7. Relationships between time for onset R in IM-EMG to onset AFG and peak myocardial ejection velocity (S) by sonomicrometry and echocardiography, measured from onset R in ECG. Data from all interventions are included.

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.[16] 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.

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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.