Mechanism of prolonged electromechanical delay in late activated myocardium during left bundle branch block

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Russell K, Smiseth OA, Gjesdal O, Qvigstad E, Norseng PA, Sjaastad I, Opdahl A, Skulstad H, Edvardsen T, Remme EW. Mechanism of prolonged electromechanical delay in late activated myocardium during left bundle branch block. Am J Physiol Heart Circ Physiol 301: H2334–H2343, 2011. First published October 7, 2011; doi:10.1152/ajpheart.00644.2011.—During left bundle branch block (LBBB), electromechanical delay (EMD), defined as time from regional electrical activation (REA) to onset shortening, is prolonged in the late-activated left ventricular lateral wall compared with the septum. This leads to greater mechanical relative to electrical dysynchrony. The aim of this study was to determine the mechanism of the prolonged EMD. We investigated this phenomenon in an experimental LBBB dog model (n = 7), in patients (n = 9) with biventricular pacing devices, in an in vitro papillary muscle study (n = 6), and in a mathematical simulation model. Pressures, myocardial deformation, and REA were assessed. In the dogs, there was a greater mechanical than electrical delay (82 ± 12 vs. 54 ± 8 ms, P = 0.002) due to prolonged EMD in the lateral wall vs. septum (39 ± 8 vs. 11 ± 9 ms, P = 0.002). The prolonged EMD in late activated myocardium could not be explained by increased excitation-contraction coupling time or increased pressure at the time of REA but was strongly related to increased rate of rise in LV pressure (LVP). Results in humans were consistent with experimental findings. The papillary muscle study and mathematical model showed that EMD was prolonged at higher dP/dr because it took longer for the segment to generate active force at a rate superior to the load rise, which is a requirement for shortening. We conclude that, during LBBB, prolonged EMD in late-activated myocardium is caused by a higher dP/dr at the time of activation, resulting in aggravated mechanical relative to electrical dysynchrony. These findings suggest that LV contractility may modify mechanical dysynchrony.

left bundle branch block; electromechanical delay; heart failure; cardiac resynchronization therapy; echocardiography

PATIENTS WITH left bundle branch block (LBBB) commonly demonstrate left ventricular (LV) mechanical dys synchrony, and the most prominent features are early contraction of the interventricular septum and delayed contraction of the LV lateral wall (6) during the isovolumic contraction phase. This abnormal contraction pattern is due to slowing of intraventricular electrical conduction with early activation of the septum and late activation of the LV lateral wall. However, several studies have shown that there is a discrepancy between electrical and mechanical activation (7, 12) and Prinzen et al. (12) showed that the delay in onset shortening (OS) between early and late-activated segments exceeds the delay in electrical conduction during pacing-induced dys synchrony. Recently, Russell et al. (9) confirmed this finding in a canine model of LBBB. This means that the time interval from regional electrical activation (REA) to OS is prolonged in late-activated regions (Fig. 1) and hence that mechanical dysynchrony is aggravated relative to the electrical dys synchrony. This observation may have clinical relevance since it implies that timing of myocardial shortening by echocardiography or other imaging modalities may overestimate the degree of electrical dys synchrony. The mechanism explaining the difference between electrical and mechanical dysynchrony remains to be determined.

The aim of the present study was to determine the mechanism of increased mechanical delay relative to electrical delay in late-activated myocardium during LBBB. First we investigated if the prolonged mechanical delay was due to an increased excitation-contraction coupling time in late-activated segments by measuring the time from myocardial electrical activation to the first sign of mechanical activation. Second, we investigated if the delay was due to a load-dependent mechanism by assessing if load [LV pressure (LVP)] or rate of rise in load (LV dP/dt) affected electromechanical delay (EMD).

The mechanisms were first explored in an experimental LBBB dog model. The EMD was also studied in humans with LBBB. Furthermore, we performed an in vitro rabbit papillary muscle study where the relationship between load and delay in OS could be investigated in a highly controlled manner. Finally, we applied a mathematical model to explain the physics that govern the timing of OS.

METHODS

In Situ Dog Study

Seven mongrel dogs of either sex and body weight 35 ± 1 kg were anesthetized, ventilated, and surgically prepared, including a median sternotomy as previously described (11). 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. LBBB was induced by radiofrequency ablation as previously described (6). Inflatable cuffs were placed around the aorta, and inferior and superior vena cava, allowing for controlled vascular constriction. After instrumentation, the edges of the pericardium were incised. The National Animal Experimentation Board approved the study. The laboratory animals were supplied by Center for Comparative Medicine, Oslo University Hospital, Rikshospitalet, Norway.

Sonomicroscopy and Regional Electromyograms

In each dog, 2-mm sonomicroscopy crystals (Sonometrics, London, Ontario, Canada) with bipolar electrodes for measuring intramyocardial electromyograms (IM-EMG) were implanted endocardially. Lon-
Vertical segment lengths were measured in the septum and in the lateral wall as illustrated in Fig. 2. Data were sampled at 200 Hz.

**Hemodynamic Measurements**

Aortic, left atrial, and LV pressures (LVP) were measured by micromanometers. A fluid-filled catheter in the left atrium served as absolute pressure reference, and the micromanometers were zero-adjusted using a long diastole after an extra systole induced at the end of each intervention. Aortic valve opening defined as the start of upstroke of aortic pressure, was used to define the time of onset ejection. Aortic valve closure and end of systole were defined as the time of peak negative LV dP/dt. End diastolic pressure was measured at the time of onset R in the electrocardiogram (ECG). LVP and dP/dt were measured at the time of REA (onset R in IM-EMG) for both the septal wall and the lateral wall, respectively.

**Experimental Protocol**

The experimental protocol included measurements during baseline, LBBB and LBBB with aortic constriction, LBBB with lateral LV pacing, and LBBB with biventricular pacing (BVP). Both pacing interventions were performed with an atrioventricular time of 80 ms, which ensured continuous ventricular pacing.

**Data Analysis**

**Electrical events.** Electrical conduction time was calculated as the time from onset R in the ECG to onset R in the IM-EMG. Timing of REA was measured at onset R in the IM-EMG, defined as the first deflection of \( \frac{1}{2} \) of total QRS amplitude (3). This definition was used, since the direction of current (i.e., polarity) across the EMG electrodes was unknown.

**Quantification of EMD.** EMD for LV septal and lateral wall segments was quantified by two different approaches: 1) as the time from REA to the onset of shortening (EMD_{OS}) and 2) as the time from REA to the onset of active force generation [AFG (EMD_{AFG})]. When a myocardial segment generates active force, the segment becomes stiffer than when it is purely passive. Hence, a higher pressure is needed to stretch the segment to the same degree, i.e., the pressure-segment length relation is shifted upward from its passive-pressure-length curve. We therefore assessed the time of onset of AFG as the instance the segment deviated upward from its passive-elastic pressure-length curve as shown in Fig. 3 and described in detail by Russell et al. (9). Timing of the onset AFG reflects the earliest mechanical sign of active force, and we therefore used EMD_{AFG} as the reference method for electromechanical coupling time.

**Clinical Study**

Nine patients (3 female) with heart failure (NYHA II-IV) and implanted BVP devices were included (mean age 70 ± 7 yr, 3 patients with ischemic cardiomyopathy and 6 patients with nonischemic dilated cardiomyopathy). All patients had LBBB with QRS >130 ms before implantation of the BVP device. Seven of the patients were considered as responders to BVP based on a reduction of end-systolic volume by >10%. The study was approved by the Regional Com-
mittee for Medical Research Ethics. All subjects gave written informed consent.

A Vivid 7 ultrasound scanner (GE Vingmed, Horten, Norway) was used to record conventional two-dimensional gray-scale images and color-coded tissue Doppler imaging (TDI) in apical four- and two-chamber and long-axis views (frame rate 108/1000/6/s). Recordings were performed with the BVP device on and off.

REA for septum and lateral wall was assessed using the pacemaker electrodes as regional EMGs. Onset of REA was defined as onset R in EMG as described above. Onset of shortening was assessed in septum and lateral wall segments using strain by TDI. Electrode position was verified by thoracic X-ray in two planes. Onset of shortening was assessed in midseptum and midlateral wall segments corresponding to the lead position using longitudinal strain by TDI in the four-chamber view. In two patients, the lateral wall electrode was placed posterolaterally, and mean timing of the posterior and lateral wall delay of OS was used. EMDOS for the septum and lateral wall was then calculated for each patient with pacing on and off.

In four patients scheduled for LV catheterization, LVP was measured by micromanometry (Mikro-Tip SPC-454F; Millar, Houston, TX), and simultaneous echocardiographic recordings were performed. A fluid-filled catheter in the LV served as absolute pressure reference.

### Papillary Muscle Study

Four New Zealand White rabbits (3.0 ± 0.2 kg body wt) were sedated (0.01 ml/kg hypnorm) and subsequently euthanized (50 mg/kg pentobarbital sodium). After cardioectomy, the hearts were perfused retrogradely, and right ventricular papillary muscles (n = 6) were excised as previously described (1). The papillary muscles were prepared, mounted, and equilibrated in organ baths (31°C) with a protective physiological salt solution (2.5 mM Ca^{2+}) containing 2,3-butanedione monoxime (BDM, 30 mM). During contraction studies, BDM was omitted, and the muscles were field stimulated at 1 Hz with impulses of 5 ms duration and voltage at ~20% above individual threshold in a similar oxygenated solution. The National Animal Experimentation Board approved the study.

Onset of electrical activation was defined as the start of the stimulation spike. Onset of shortening was defined as the first data point after peak length of the papillary muscle that led to continued shortening. Data were sampled at 2,000 Hz.

To assess if the load at the time of activation affected the delay from electrical activation to OS, we activated the papillary muscle at different isotonic loads [F = 40, 50, 60, and 70% of F_{max} (Table 1 and Fig. 4A)], where F_{max} was peak isometric force developed by the

### Table 1. Papillary muscle study

<table>
<thead>
<tr>
<th>Isotonic Load</th>
<th>Ramp Load</th>
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<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Time from electrical activation to onset of shortening, ms</td>
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<tr>
<td>dF/dt at time of electrical activation, mN/s</td>
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Values are means ± SD. dF/dt, time derivative of rise in applied load. *P < 0.05 vs. isotonic load.
muscle]. We subsequently measured the time from electrical activation to OS.

To assess if rate of load rise (dF/dt) at the time of activation (equivalent to dP/dt in the in vivo heart) affected the delay from electrical activation to OS, we activated the papillary muscle and applied linearly increasing load (dF/dt) at different slopes from the time of electrical activation (Fig. 4B), i.e., ramp loading. Different slopes were applied by linearly increasing F from preload to 40, 50, 60, and 70% of Fmax in a constant time interval (Table 1 and Fig. 4B).

Mathematical Model Study

We investigated the relationship between load and EMD in a mathematical model of the LV wall that included both active and passive myocardial forces (8). The total myocardial force is the sum of both the active contractile force and the passive elastic force. The active force is generated by the actin-myosin cross bridges, and the passive elastic force is generated by deformation of myocardial tissue. According to Newton’s third law, the internal myocardial force must be equal to the externally applied load. We therefore modeled the myocardial tissue as an elastic spring in parallel with an active force-generating element so the two myocardial force components added up to match the applied load, as shown in Fig. 5. We used measured data from one of the papillary muscles to prescribe the properties of the active and passive elements. The measured isometric force trace (Fig. 6) starting from the time of electrical activation was prescribed as the force (Fa) generated by the active element (Fig. 5). The passive properties were approximated as linear-elastic, and Hooke’s law was used to calculate the passive force: Fp = K × e.

Fig. 4. Papillary muscle experiment. A: delay in onset shortening as a function of isotonic load. B: delay as a function of dF/dt.

Fig. 5. Simulation model (left) and results for applied isotonic (middle) and ramp (right) load. The strain traces are shown in the top middle and top right where onset shortening is marked with a circle on each trace. The applied loads are shown in the bottom middle and bottom right. Onset of shortening occurred simultaneously for all levels of isotonic loads, whereas there was increased delay in onset shortening when the applied load increased at higher rates. Zero strain corresponds to the length of the muscle at rest (i.e., in a situation with zero load and no active force).
In the period of an additional 23 ms before the lateral segment generated active force more rapidly than the applied load (emphasized by a thicker dashed $dF/dt$), the rate of load rise was close to 0 mN/s at the time of septal activation (0 ms), and the force traces. In the simulation case with 100% septal contractility ($F_{max}$), the segment maintained 100% contractility and was activated 30 ms after the applied load was calculated as one-half of the time average of the active force in the two segments and starting at a preload of 4 mN. They were both exposed to the same applied load. The lateral segment was stretched when applied load rose at a higher speed than lateral active force, whereas the segment shortened following the time of crossover of the rates. The panel on the right shows lateral segment electromechanical delay (EMD) from regional activation to onset shortening for different simulation cases with varying septal contractility.

where $K$ is the spring constant and $e$ is the strain measured relative to resting length. $K$ was found from linear regression of the force-strain relationship from passive stretching of the papillary muscle. The active and passive myocardial forces were set to equal the applied load ($F_L$): $F_L = F_a + F_p = F_a + K \times e$. This equation may be rewritten as: $e = (F_L - F_a)/K$. Furthermore, the time derivative of this equation is:

$$\frac{de}{dt} = \left(\frac{dF_L}{dt} - \frac{dF_a}{dt}\right)/K$$

We first simulated isotonic loading and ramp loading, similar to the situation in the papillary muscle study, and assessed the time from activation to OS. We used the same levels of applied loads (40, 50, 60, and 70% of $F_{max}$) and loading rates ($dF/L/dt$) as in the papillary muscle study for isotonic loading and ramp loading, respectively. We subsequently simulated an LBBB situation with two segments coupled in series, representing a septal and lateral wall segment. The active force in the two segments was set equal to the measured isometric force trace, but the active force was delayed by 30 ms in the lateral wall segment. They were both exposed to the same applied load. The applied load was calculated as one-half of the time average of the active force in the two segments and starting at a preload of 4 mN (Fig. 6). Timing of the onset of shortening was assessed in the two segments and investigated in relation to load, rate of load rise, and rate of active force rise.

We finally applied the model to investigate how septal contractility affected lateral wall EMD via the applied load. Several simulations were run where active force in the septal segment was scaled by a factor from 0.5 to 1.5 (i.e., a change from 50 to 150% septal contractility). Applied load was calculated as above. The lateral segment maintained 100% contractility and was activated 30 ms after the septal segment. Changes in EMD in the lateral wall were related to changes in septal contractility.

Statistical Analysis

Values are expressed as means ± SD. Variables are compared using least-squares linear regression and Pearson correlation coefficients. Regression analysis was used to identify significance for load-dependent predictors of EMD$_{OS}$. For multiple comparisons (Table 2), we used repeated-measurements ANOVA with Bonferroni post hoc test (SPSS 15.0; SPSS, Chicago, IL). All post hoc tests were compared with baseline. $P < 0.05$ was considered significant.

RESULTS

**In Situ Dog Study**

**EMD during LBBB.** In each animal, we induced LBBB, which led to increased electrical delay and QRS width (Table 2). Compared with baseline, electrical delay between the two walls increased from 8 ± 9 to 54 ± 8 ms ($P = 0.009$), indicating a dysynchronous electrical activation sequence. The delay between OS in the lateral and septal wall was also prolonged (82 ± 12 ms, $P < 0.001$), confirming the presence of mechanical dyssynchrony and indicating that timing of OS exceeds underlying electrical dyssynchrony. During LBBB, EMD$_{AFG}$ remained constant compared with baseline in both walls, indicating a constant excitation-contraction coupling time. Although EMD$_{OS}$ was practically unaltered in the septum (11 ± 9 ms), it was prolonged markedly in the late-activated lateral wall (39 ± 8 ms, $P = 0.002$). LV dP/dt at the time of electrical activation also increased significantly for the lateral wall compared with septum: 191 ± 83 vs. 30 ± 39 mmHg/s (Table 2 and Fig. 7). However, there were only minor changes in LVP at the time of REA between the two walls: 9 ± 3 vs. 11 ± 3 mmHg for septum and lateral wall, respectively (Fig. 8). The minor increment in pressure was a result of the nonlinear dP/dt rise, i.e., dP/dt did not increase until the last phase of the interval between activation of the two regions, as shown in the dP/dt trace between the two dashed vertical lines in Fig. 7.
EMD during lateral wall pacing and BVP. Electrical delay between the two walls decreased to $-7 \pm 9$ and $-10 \pm 13$ ms for BVP and lateral wall pacing, respectively, compared with LBBB ($54 \pm 8$ ms), indicating resynchronization of the electrical activation sequence with slightly earlier lateral wall activation compared with the septum. The improvement in electrical resynchronization was mirrored by better mechanical resynchronization of the delay between OS in the septum and lateral wall (Table 2).

The prolonged EMD_{OS} seen in the lateral wall during LBBB was reversed acutely and returned to baseline values of $11 \pm 7$ ms for BVP and $14 \pm 6$ ms for lateral wall pacing (Table 2).

Relationship Between LVP and Rate of Pressure Rise at Time of REA

For all interventions, there was a strong correlation between the rate of pressure rise (LV $dP/dt$) and increased EMD_{OS} ($r = 0.88$), which remained significant also after adjusting for LVP at the time of activation ($p < 0.001$) (Fig. 9A). There was a weak correlation between EMD_{OS} and LVP at the time of activation ($r = 0.38$). When adjusting for the increase in $dP/dt$ at the time of activation, however, this was not significant ($P = 0.61$), indicating that LVP at the time of activation does not affect the timing of OS.

Clinical Study

In patients with implanted BVP devices, electrical delay between the LV lateral wall and septum increased from $15 \pm 7$ to $94 \pm 19$ ms ($P < 0.001$) when pacing was switched off, indicating a dysynchronous electrical activation sequence. The ECG showed a typical LBBB pattern with QRS width of $162 \pm 20$ ms. When pacing was off, the delay between OS in the lateral and septal wall was also prolonged ($156 \pm 25$ ms), confirming the presence of mechanical dyssynchrony. There was also an increased delay from REA to OS in the late-activated lateral wall ($64 \pm 11$ ms) compared with the septum ($2 \pm 5$ ms) ($P < 0.001$) (Fig. 1). This increased delay was subsequently reversed when pacing was switched on (Table 3).

In the four patients with simultaneous LVP measurements, $dP/dt$ was increased markedly at the time of activation in the late-activated segments when pacing was off (Table 3 and Fig. 9A).

Papillary Muscle Study

There was no prolongation of EMD_{OS} when applied load was held constant (isotonic) at the different isotonic levels at the time of activation, suggesting that timing of OS is not affected by the magnitude of load per se (Table 1 and Fig. 4A).
When the rate of applied force \( \frac{dF}{dt} \) on the papillary muscle was increased, we observed a progressive delay in EMDOS from 16 ± 2 to 40 ± 12 ms \( (P < 0.001) \) when the rate was increased from zero at isotonic load to maximum applied \( \frac{dF}{dt} \) \((110 ± 47 \text{ mN/s}) \) with a plateau at 70% \( F_{\text{max}} \) (Table 1 and Fig. 4B). There was a strong correlation between the increase in \( \frac{dF}{dt} \) at the time of activation and delay in OS with a median \( r \) value of 0.97 (0.85–0.99 minimum-maximum, \( P < 0.02 \) in the different muscles). Correlation in a representative muscle is shown in Fig. 9B.

This indicates that timing of OS is highly dependent on the rate of rise in force \( \frac{dF}{dt} \) at the time of activation, confirming findings in the lateral wall seen in the dog model and in the patients.

**Mathematical Model Study**

When simulating isotonic load, the muscle was increasingly prestretched at increasing levels of isotonic load. The onset of shortening, however, occurred simultaneously (after 6 ms) in all cases, independent of isotonic load levels (Fig. 5, middle).
In contrast, there was a gradual increase in time to OS (6, 22, 30, 39, and 56 ms) for the five different rates of increasing load (Fig. 5, right).

In the LBBB simulation case, the onset of septal shortening occurred shortly (6 ms) after it was activated, at a time when the rate of load rise was close to 0 mN/s (Fig. 6). Furthermore, the simulation showed that the onset of shortening occurred as soon as the rate of rise of active force in the segment exceeded the rate of rise in load, as shown in Fig. 6, left. Because load rise was increased substantially when the lateral segment was activated, the lateral segment required a longer time before it generated active force at a higher rate than the applied load (Fig. 6, bottom). Thus, the interval from activation to OS was prolonged and resulted in a larger delay in the OS compared with electrical activation (53 vs. 30 ms).

Changes in septal contractility substantially affected EMD in the lateral segment. This is indicated by the approximately doubling of EMD in the lateral segment when septal contractility was changed from 50 to 150% (Fig. 6, middle). Figure 6, right, shows the simulation case with 50% septal contractility. The reduced septal contractility reduced the rate of load rise at the time of activation of the lateral segment. Hence, the time interval until the rise of active force in the lateral segment overcame the rate of load rise was shorter compared with the case with higher septal contractility. Since OS occurred the moment when active force was generated at a rate superior to load rise, the time from activation to OS was also reduced.

**DISCUSSION**

In the present study, we investigated the mechanism of the apparently prolonged electromechanical activation time in late-activated LV lateral wall during LBBB. We did not observe any indication of prolonged excitation-contraction coupling time in the late-activated region. Furthermore, increased load (LVP) at the time of electrical activation in the late-activated lateral wall showed a weak relationship to the increased EMD and was not significant when adjusted for the increased dP/dt at the time of activation. However, there was a strong correlation between dP/dt at the time of activation and delay in OS.

The findings from the different substudies indicate that OS is delayed until the rate of rise of myocardial active force exceeds the rate of rise of applied load. Because the rate of rise of regional load in the intact heart is directly related to LV dP/dt, there will be a progressive increase in the time from electrical activation to OS at higher LV dP/dt.

Our results suggest that the prolonged delay from electrical activation to OS in late-activated segments increases the mechanical dyssynchrony by ~40–50% relative to the underlying electrical dyssynchrony, e.g., electrical dyssynchrony of 54 ms vs. mechanical dyssynchrony of 82 ms in the dog model (Table 2). In a clinical setting, understanding the mechanism of the prolonged delay is important for two main reasons: 1) the onset of shortening may potentially influence almost all dyssynchrony measurements performed by echocardiography. Because the time from electrical activation to OS differs substantially between early and late-activated segments, this means that OS may not serve as an accurate marker for electrical activation in assessment of dyssynchrony. 2) Mechanical dyssynchrony, measured as differences in OS, is dependent on both electrical propagation time in the LV and differences in regional EMDos. This means that prolongation of EMDos in late-activated segments may aggravate mechanical dyssynchrony, subsequently reducing LV function. Furthermore, because LV dP/dt reflects LV function and contractility,
ever, one may speculate that the same mechanisms that cause also explain the observation of increased EMDOS transmurally.

Normal electrical activation propagates from endocardium to the prolonged EMDOS in late-activated segments can be altered regardless of timing of LV activation. However, we showed that segment (constant timing of excitation-contraction coupling).

In the present study, we demonstrated that the time from electrical activation to the first sign of mechanical response for a all interventions, indicating a near-constant time from electrical activation (onset AFG) (Fig. 7). This means that, although the majority of segments. However, in late-activated segments become stiffer and hence develop active force before OS

Excitation-Contraction Coupling

We have previously shown that late-activated segments become stiffer and hence develop active force before OS occurs (9). Based on these findings, electromechanical activation sequence can be divided into three stages as follows: first electrical activation, then active force development for a segment (onset AFG), and finally OS. In a normal ventricle, active force development and OS occur almost simultaneously in the majority of segments. However, in late-activated segments during LBBB, the time from electrical activation to OS is prolonged, and OS occurs after the first sign of mechanical activation (onset AFG) (Fig. 7). This means that, although the segment is mechanically activated and becomes stiffer, it continues to stretch before OS occurs.

In the present study, we demonstrated that the time from electrical activation to onset AFG remained unchanged during all interventions, indicating a near-constant time from electrical activation to the first sign of mechanical response for a segment (constant timing of excitation-contraction coupling). Furthermore, EMD is considered to be an inherent property of the myocardium and should therefore remain unchanged regardless of timing of LV activation. However, we showed that the prolonged EMDOS in late-activated segments can be altered acutely by pacing interventions, indicating the absence of significant delay in excitation-contraction coupling time.

Previous studies have shown that EMDOS is prolonged transmurally from endocardium to epicardium (2, 10). In the present study, we did not look at EMDOS transmurally; however, one may speculate that the same mechanisms that cause prolonged EMDOS in late-activated segments in LBBB may also explain the observation of increased EMDOS transmurally. Normal electrical activation propagates from endocardium to epicardium. Increased rate of pressure rise at the time of epicardial activation, a higher radius of curvature that effectively increases epicardial loading, and possibly lower epicardial myofiber contractility (4) may all be factors that increase the time until the rate of active force development in the subepicardium overcomes the rate of rise of epicardial loading, so onset of shortening can occur.

Load and Rate of Rise in Load

Intuitively one may believe that it is the higher pressure at the time of activation of the lateral wall that is responsible for the increased delay from REA to OS. However, in the dog study, we found that it was not LVP at the time of regional activation but rate of pressure rise (LV dP/dt) that directly affected the delay from electrical activation to OS. To further investigate this, we performed a papillary muscle study where these two mechanisms could be isolated and tested in a controlled environment. When a constant force was applied, OS occurred without increased delay, even when applied force was substantially increased (70% of Pmax) (Table 1 and Fig. 4A). However, when we applied a rising force (simulating the continuous rise in LVP), the time to OS was delayed progressively with higher dF/dt (Table 1 and Fig. 4B).

Segmental force is a sum of both active and passive elastic forces, which is equal to the external load according to Newton’s third law. Before activation, a higher pressure stretches and hence increases the passive force of a late-activated segment, thus maintaining the balance of external and internal forces. Subsequent activation and addition of active force should therefore result in instantaneous OS of the segment. However, a late-activated segment does not contract against a static pressure, but a pressure that has already started to rise. The pressure rise continues to stretch the segment until the generation of opposing contractile force is faster than the load rise. Active force development is nonlinear, i.e., it initially increases at a slow rate and gradually accelerates to a peak rate (5). Therefore, the higher the LV dP/dt, the longer it takes before active force is generated at a rate equal to and subsequently faster than the load rise, which delays OS and prolongs EMDOS.

These findings were confirmed in our mathematical model. By interpreting the equation derived from the model: de/dr = (dF/dr - dF_a/dr)/K, i.e., derivative of strain = (derivative of applied load - derivative of active force)/K, one can deduce that a segment will lengthen (de/dr > 0) when the load increases quicker than active force (dF_a/dr > dF/dr). Segment length is constant (de/dr = 0) when the load increases at the same rate as active force. Shortening (de/dr < 0) starts when dF_a/dr becomes greater than dF/dr, which means that OS occurs when active force increases more rapidly than load (dF_a/dr < dF/dr). In other words, if the applied load (LVP) increases more than the active contractile force in a segment during each time interval, the segment will be stretched. However, when active force increases more than applied load, the segment will shorten.

Clinical Implications

When selecting patients for cardiac resynchronization therapy, the clinician needs a marker that reflects electrical delay, which can be corrected by pacing. In the present paper, we
show that the observed mechanical dysynchrony during LBBB is not only due to electrical delay but that the rate of pressure rise (dP/dt) significantly contributes to mechanical dysynchrony. The difference in the time from electrical activation to OS in early vs. late-activated segments means that assessment of mechanical dysynchrony by echocardiography based on timing of OS may overestimate the underlying delay in electrical activation. Furthermore, since LV dP/dt reflects LV contractility, the magnitude of mechanical dysynchrony may vary with changes in LV function.

Because timing of OS may influence dyssynchrony measurements performed by echocardiography, understanding the determinants of OS is important. Furthermore, identifying the mechanisms of prolonged EMD (inherent changes in the myocardium vs. mechanical interactions) is essential for selecting appropriate treatment.

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. In the dog model, 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.

The small sample size in this study may be viewed as a limitation; however, the consistency in our findings supports our conclusions.

In the present study, we investigated isolated acute electrical dysynchrony. In a clinical situation, however, one may encounter more chronic changes in electrical conduction delay often associated with regional impairment of contractility. These patients may have prolonged excitation-contraction coupling; however, such changes would most likely exacerbate regional delays, making our findings relevant also in this patient group. Furthermore, previous studies have demonstrated transmural differences in excitation-contraction coupling time (4), but, to our knowledge, no study has shown regional differences, e.g., between the septum and lateral wall. If such differences also exist regionally, e.g., between the septum and lateral wall, this would have resulted in increased EMD_{AFG}, and the difference in excitation-contraction coupling time would not have been acutely altered by pacing interventions.

The mathematical model is a highly simplified representation of the heart and does not account for viscous or inertial properties among others. However, the results from the simulation were able to reproduce experimental findings, which indicate that the model included the main mechanics that determine the onset of shortening.

In conclusion, prolonged delay from REA to the onset of shortening in late-activated segments during LBBB is the result of an increased rate of pressure rise (LV dP/dt) at the time of activation. Therefore, a late-activated segment needs more time to generate active force at a higher rate than the rise of the applied load (LV dP/dt), which in turn leads to shortening of the segment. The prolonged delay substantially increased mechanical dysynchrony relative to the underlying electrical dysynchrony in LBBB patients, which implies that shortening indexes may overestimate the extent of electrical dysynchrony in these patients. These findings also suggest that changes in LV contractility may modify mechanical dysynchrony.

GRANTS

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DISCLOSURES

None.

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