

Mechanisms of Abnormal Systolic Motion of the Interventricular Septum During Left Bundle-Branch Block

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Background—In a majority of patients with left bundle-branch block (LBBB), there is abnormal leftward motion of the interventricular septum during the preejection phase. This motion was considered to be passive, caused by early rise in right ventricular (RV) pressure, and has therefore been excluded from most indices of left ventricular (LV) dyssynchrony. If considered active, however, the leftward motion reflects onset of septal activation and should be included. We therefore investigated if the motion was a passive response to pressure changes or caused by active contraction.

Methods and Results—LBBB was induced in 8 anesthetized dogs with micromanometers. Cardiac dimensions were measured by sonomicrometry and echocardiography. Induction of LBBB resulted in preejection leftward motion of the septum, simultaneously with shortening of septal segments ($P<0.01$). In each experiment, preejection septal shortening occurred against rising LV pressure, consistent with active contraction. Furthermore, the LV pressure–segment length relationships were shifted upward ($P<0.01$) relative to the passive elastic curve, indicating stiffening of septal myocardium, confirming an active mechanism. Initially, RV pressure increased faster than LV pressure, suggesting that the leftward septal motion may have a passive pressure component. However, the passive component appeared to play a minor role. The magnitude of preejection septal shortening was modified by load alterations.

Conclusions—Leftward preejection motion of the septum during LBBB is mainly a result of active septal contraction, whereas alterations in diastolic ventricular pressures modulate the amplitude of this motion. The findings imply that the preejection phase should be included when assessing LV dyssynchrony. (*Circ Cardiovasc Imaging*. 2011;4:264-273.)

Key Words: dyssynchrony ■ CRT ■ septal beaking ■ septal flash ■ isovolumic contraction ■ LBBB

A majority of patients with left bundle-branch block (LBBB) demonstrate leftward displacement of the interventricular septum during preejection, followed by rightward (paradoxical) motion.¹ This is in contrast to the normal heart, in which the septum has minimal motion during preejection and moves leftward and toward the center of the left ventricular (LV) cavity during ejection (Figure 1A). Because contractions in the normal ventricle are synchronized, a circular shape of the LV short axis is maintained throughout the cardiac cycle. During LBBB, however, LV shape is distorted during preejection as the result of flattening of the septal curvature and simultaneous lengthening of the late-activated lateral wall.² The abnormal motion of the septum during preejection has been referred to as septal beaking when imaged by M-mode echocardiography^{1,3} (Figure 1B) and septal flash in studies that have used myocardial velocity imaging.⁴ The mechanism of abnormal preejection motion of the septum in LBBB is not entirely clear. Studies that have

used right ventricular (RV) pacing as an analog to LBBB suggest that the septum is shifted leftward because the RV is activated first, causing RV pressure to transiently exceed LV pressure, creating a decrease in the left-to-right transseptal pressure gradient (P_{TS}), thereby pushing the septum leftward like a passive membrane at the very beginning of systole.^{3,5} Alternatively, the abnormal leftward motion is due to active septal contraction. The latter mechanism would be facilitated during LBBB because the LV lateral wall is late activated and therefore does not generate an opposing pressure. Distinction between the 2 mechanisms is clinically important when assessing LV dyssynchrony in patients: Preejection leftward motion caused by active contraction should be included when defining timing of septal activation, whereas passive motion should not be included. In most studies of dyssynchrony, however, preejection septal motion has been excluded from the assessments, evaluating the ejection phase only.⁶

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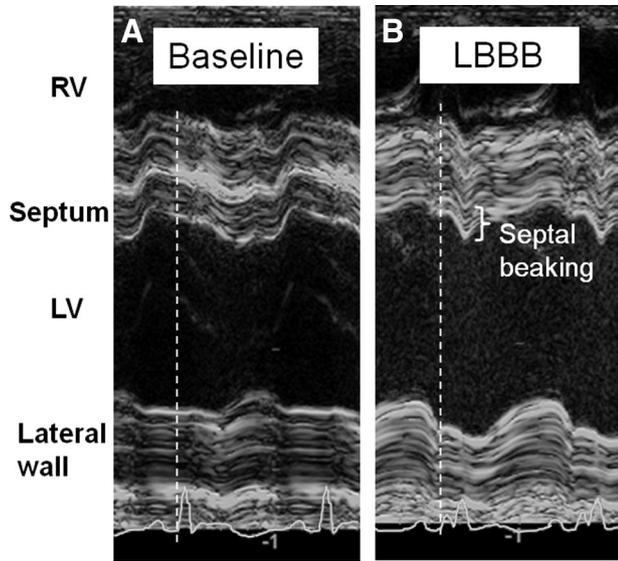


Figure 1. M-mode recordings from a representative experiment illustrating septal beaking during LBBB.

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The main objective of the present study was to determine mechanisms of preejection leftward motion of the interventricular septum during LBBB. For this purpose, we used an experimental model in which LBBB was induced by radio-frequency ablation and regional electromyograms were used to measure timing of electrical activation. To determine if the leftward motion was due to passive membrane responses, we related septal motion to the transseptal pressure gradient, and potential contributions from active septal contractions were assessed by LV pressure-dimension analysis. We also investigated determinants of systolic rightward motion of the septum during LBBB.

Methods

Animal Preparation

Eight mongrel dogs of either sex and body weight of 34 ± 2 kg were anesthetized, ventilated, and surgically prepared as previously described.⁷ This included partial splitting of the pericardium from apex to base and loose resuturing of the pericardial edges after completion of instrumentation. To enable load interventions, inflatable silicone occluders were placed around the proximal aorta and around both caval veins. A balloon catheter (131HF7, Edwards Lifesciences, Irvine, CA) was placed in the main pulmonary artery to induce selective right ventricular hypertension. The ECG was recorded from limb leads. Pacemaker leads were attached epicardially on the LV lateral wall and right atrium. The study was approved by the Norwegian Animal Research Authority. The animals were supplied by Center for Comparative Medicine, Oslo University Hospital, Oslo, Norway.

Hemodynamic Measurements

Aortic, left and right atrial, and left and right ventricular pressures were measured by micromanometers (MPC-500, Millar Instruments Inc, Houston, TX). Fluid-filled catheters, placed in the left and right atria, served as absolute pressure references for the micromanometers, which were zero-adjusted during a long diastole after an extrasystole induced at the end of each intervention. End diastole was defined as onset Q in ECG lead II.

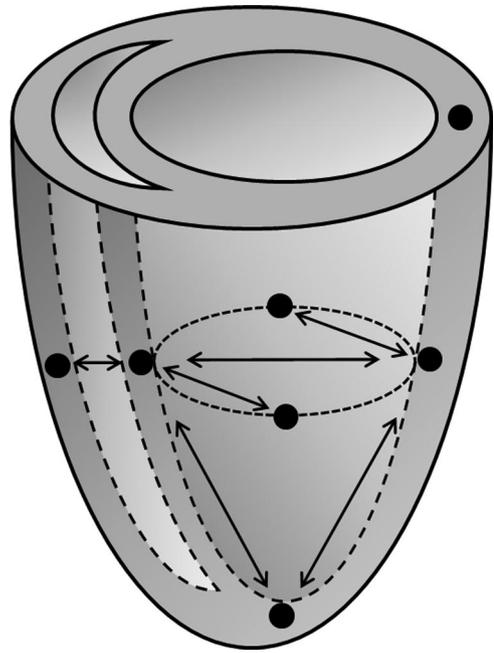


Figure 2. Schematic illustration of placement of the combined sonomicrometry crystals and IM-EMG-sensors. Arrows indicate which dimensions were measured. The basal LV crystal was included for volume measurements.

We investigated if the leftward and rightward septal preejection motion was sensitive to alterations in load induced by aortic, pulmonary, and caval constrictions.

Sonomicrometry and Regional Electromyograms

In each dog, 2-mm sonomicrometry crystals (Sonometrics Corporation, London, Ontario, Canada) with bipolar electrodes for measuring intramyocardial electromyograms (IM-EMG) were implanted in the inner third of the LV wall, as illustrated (Figure 2). This enabled simultaneous assessment of myocardial deformation and timing of regional electrical activation. Timing of regional electrical activation was defined as onset of first deflection from baseline in each IM-EMG trace. Data were digitized at 200 Hz.

The position of the septum relative to the RV and the LV was expressed as the ratio between the LV septum-to-lateral wall diameter and the distance from the RV lateral wall to the LV lateral wall (D_{LV}/D_{LV+RV}).

Echocardiography

A Vivid 7 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) was used for echocardiographic recordings. Two-dimensional gray-scale images (frame rate, $63 \pm 13 \cdot s^{-1}$) of the left ventricle were recorded in apical 4- and 2-chamber views and in the equatorial short-axis view. The radius of the curvature in short axis was calculated for the septum and LV lateral wall, based on diameters obtained from anatomic M-mode images in the parasternal short-axis view.⁸

Induction of LBBB

LBBB was induced by radiofrequency ablation (Celsius Catheter, Biosense Webster, Inc) at a location with a large left-bundle potential, two-thirds from the atrial and one-third from the ventricular signal. Stable LBBB was obtained after 5 to 20 ablations ($50^\circ\text{C}/30$ W), and energy was delivered for 30 additional seconds after induction of LBBB.

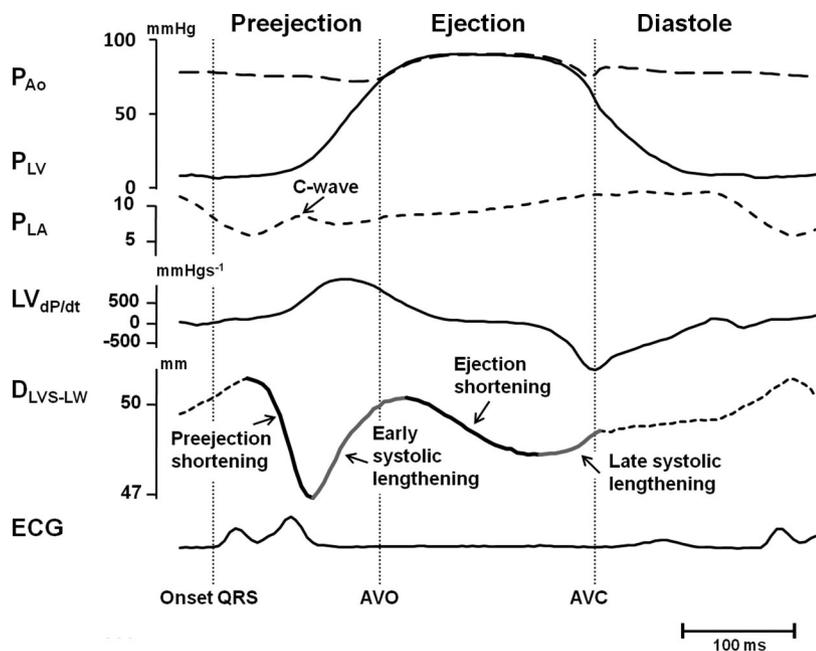


Figure 3. Representative recording during LBBB with definitions: Preejection shortening and lengthening in the LV septum-to-lateral wall trace correspond to the septal beaking pattern by M-mode echocardiography (Figure 1). $P_{Ao/LV/LA}$ indicates aortic/LV/left atrial pressure; $LV_{dp/dt}$, time derivative of P_{LV} ; D_{LVS-LW} , LV septum-to-lateral wall diameter; AVO, aortic valve opening; and AVC, aortic valve closure.

Mechanism of Leftward Septal Motion

To differentiate between the 2 proposed mechanisms, we used 2 different analytic approaches. First, we investigated if there was a reduction in P_{TS} near end diastole and during preejection caused by more rapid rise in P_{RV} than in P_{LV} , which would be consistent with a passive membrane response.

Second, we performed LV pressure-dimension analysis to determine if there were signs of active contraction of septal myocardium during the leftward motion. As a first step in this analysis, we related myocardial shortening to LV pressure and applied the concept that shortening against rising LV pressure would indicate active contraction. To further investigate if the myocardium developed active force, we compared the pressure-segment length relationship during preejection to the diastolic pressure-segment length relationship (passive curve) for the same segment. This was done for longitudinal and circumferential segments and also for LV septum-to-lateral wall diameter. Passive curves were constructed by plotting end-diastolic pressure-dimension coordinates from multiple beats during caval constriction. An upward shift from the passive curve would indicate myocardial stiffening caused by active contraction.⁹ In a segment that is entirely passive, however, the pressure-segment length coordinates will move along the passive curve.

To adjust for the influence of RV pressure, we performed the pressure-dimension analysis using either LV pressure or LV minus RV pressure (P_{TS}) to represent septal distending pressure.¹⁰ The true physiological septal passive elastic curve will be found in between these 2 curves.

If preejection leftward motion of the septum is a result of active septal contraction with delayed activation of the LV lateral wall, the motion pattern should be opposite when the LV lateral wall is activated earlier than the septum. Thus, we investigated if a beaking pattern was induced in the LV lateral wall by performing LV lateral wall pacing with a short AV delay (sensed AV delay of 58 ± 16 ms).

Determinants of Rightward Septal Motion

Abnormal septal motion during LBBB includes lengthening of the septal myocardium both during early and late systole.¹¹ In the present study, the 2 phases of septal lengthening are referred to as early and late systolic lengthening, respectively (Figure 3). We investigated the temporal relationship between systolic lengthening and LV lateral wall shortening and the relationship between septal early systolic lengthening and radius of curvature of the septum and lateral wall. Furthermore, we investigated the temporal relationship

between interruption of preejection septal shortening and the time of mitral valve closure, defined as the peak of the c-wave in the left atrial pressure trace.^{12,13}

Statistics

Values are expressed as mean \pm SD. Differences between groups were analyzed with the paired *t* test or repeated measures ANOVA *F* test, with Bonferroni correction for comparison to end-diastolic values. Associations between septal position and transseptal pressure gradient during pressure interventions were analyzed by linear regression in each individual.

For all statistical comparisons, $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS version 17 (SPSS version 17, SPSS Inc, Chicago, IL).

Results

Baseline and LBBB characteristics are displayed in Table 1. Induction of LBBB increased time from onset QRS to onset lateral wall IM-EMG from 10 ± 5 to 55 ± 11 ms ($P < 0.01$), indicating delay in electrical activation of the LV lateral wall, whereas time to onset septal IM-EMG remained constant at < 9 ms. QRS duration increased from 56 ± 8 to 112 ± 4 ms after induction of LBBB ($P < 0.01$).

In each dog, M-mode echocardiography demonstrated septal beaking after induction of LBBB, that is, preejection leftward motion and subsequent rightward motion of the septum (Figure 1). As shown in Figure 3, a similar beaking pattern was observed in the LV septum-to-lateral wall diameter trace (D_{LVS-LW}). The beaking pattern in the M-mode and the diameter traces coincided with preejection shortening and lengthening of the septal circumferential and longitudinal segments (Figure 4). The data describing the preejection shortening and early systolic lengthening are included in Table 1.

Early systolic lengthening ended during the early phase of LV ejection and was followed by a second shortening of the septal segments. Thereafter, a second phase of septal lengthening (late systolic lengthening) was observed before aortic

Table 1. Hemodynamic Variables at Baseline and LBBB

	Baseline (n=8) Mean±SD	LBBB (n=8) Mean±SD	P
Pressures, mm Hg			
P _{LV-Peak}	99.4±11.9	90.4±9.9	0.01
P _{RV-Peak}	25.2±7.6	23.7±7.2	0.08
P _{LV-ED}	9.1±3.2	8.7±3.0	0.67
P _{RV-ED}	7.5±2.4	6.5±1.5	0.19
P _{TS-ED}	1.7±1.4	2.2±2.2	0.41
LV dp/dt _{max} , mm Hg · s ⁻¹	1311±300	978±99	<0.01
End-diastolic segment length, mm			
Septum _{Longitudinal}	38.2±6.6	38.4±6.2	0.78
Septum _{Circumferential}	31.2±10.6	31.4±10.7	0.51
Lateral wall _{Longitudinal}	44.7±6.0	44.8±6.5	0.81
Lateral wall _{Circumferential}	32.5±6.5	32.6±6.3	0.92
End-diastolic D _{LVS-LW} , mm	46.7±7.7	47.2±8.5	0.31
Preejection shortening, %			
D _{LVS-LW}	0.9±1.3	7.5±3.6	<0.01
Septum _{Longitudinal}	0.7±0.9	3.2±2.0	<0.01
Septum _{Circumferential}	1.5±1.9	9.1±4.4	<0.01
Early-systolic lengthening, %			
D _{LVS-LW}	1.3±1.4	7.1±4.8	<0.01
Septum _{Longitudinal}	1.9±1.7	6.6±3.7	<0.01
Septum _{Circumferential}	0.5±0.6	4.8±3.9	<0.01
Heart rate, min ⁻¹	113±15	119±14	0.18
Stroke volume, mL	18.6±3.2	15.7±3.1	0.02

valve closure (Figure 3 and Figure 4). Thus, during LBBB, the septal myocardium had 2 phases with systolic shortening, during preejection and midejection, each one followed by relengthening. At end systole, the longitudinal septal segment was, on average, slightly stretched beyond end-diastolic length, whereas the circumferential segment was shortened by 6.4±4.7% ($P<0.01$). The lateral wall longitudinal and circumferential segments, however, were shortening throughout the entire LV ejection period.

There was no significant change in end diastolic P_{TS} after induction of LBBB (Table 1), and end-diastolic septal position, measured as D_{LV}/D_{LV+RV}, remained unchanged. During LBBB, the end-diastolic P_{TS} was altered by aortic constriction (+2.1±1.7 mm Hg) or pulmonary artery constriction (-2.6±2.3 mm Hg, both $P<0.05$), displacing the septum rightward or leftward at end diastole, respectively. The association between P_{TS} and septal position in each experiment was reflected in a strong correlation between P_{TS} and D_{LV}/D_{LV+RV} (r values for individual experiments between 0.89 and 0.99, all $P<0.01$).

Relationship Between Preejection Septal Shortening and Reduction in Transseptal Pressure Gradient

At end diastole and during preejection, P_{RV} briefly increased more rapidly than P_{LV}, which resulted in a decreasing P_{TS} (Figure 4). This was observed both during baseline and during

LBBB, but the P_{TS} decrease was larger during LBBB (1.5±0.8 versus 0.6±0.7 mm Hg, $P=0.01$). During LBBB, LV septum-to-lateral wall diameter decreased nonsignificantly (1.2±3.0%) during this phase, whereas shortening continued by 5.7±3.2% ($P<0.05$) when P_{TS} subsequently was rising. The septal longitudinal and circumferential segments shortened synchronously with LV septum-to-lateral wall diameter (Figure 4).

The relationship between change in P_{TS} and septal motion during LBBB was further investigated during loading interventions. In 4 experiments, the fall in P_{TS} disappeared and was converted to a continuous rise in late diastole and during preejection. Despite this, the preejection leftward motion remained present in each experiment, indicating that pressure was not the main causal component. The time from septal electrical activation to onset of septal shortening was 28±7 ms in these cases, relatively similar to the interval observed during LBBB and no loading (20±6 ms). Shortening occurred against rising P_{TS} and hence indicates that active contraction of the septum was initiated within this time interval.

Pressure-Dimension Relationships During Preejection

Figure 5 and Figure 6 show LV pressure-dimension loops in representative experiments. The septal segments and LV septum-to-lateral wall diameter demonstrated shortening against rising P_{LV} and except for the first part of preejection, against rising P_{TS}, consistent with active myocardial contraction. This was further supported by the finding that electrical activation of the septum preceded onset of shortening (19±10 ms).

As shown in Figure 6, during preejection shortening the relationship between LV pressure and septal segment lengths was shifted upward relative to the passive curve, indicating stiffening of the septum, which is consistent with active contraction. The relationship between P_{TS} and septal segment lengths was also shifted upward, except for a brief period during the initial phase of preejection shortening (median duration, 5 ms; range, 0 to 48 ms). The online-only Data Supplement Table shows the data for the upward shift in all animals for the 2 septal segments and the diameter.

Determinants of Septal Systolic Lengthening

An active preejection septal shortening implies that the septum is active also during the following early systolic lengthening. Therefore, the extrinsic pulling forces must exceed the intrinsic septal contracting forces. As shown in Figure 4, interruption of septal shortening or onset of early systolic lengthening coincided with onset of shortening in the LV lateral wall (4±9 ms) and also with the c-wave in the left atrial pressure trace, which was used as a marker of timing for the end of mitral valve closing motion (1±10 ms).

At onset of early systolic lengthening, the septum was significantly flattened relative to the lateral wall, as indicated by increased septal radius of curvature (Table 2). The LV cross section became more circular when LV pressure increased during isovolumic contraction, and at the time of aortic valve opening, the septal and lateral wall radii of curvature were more equal.

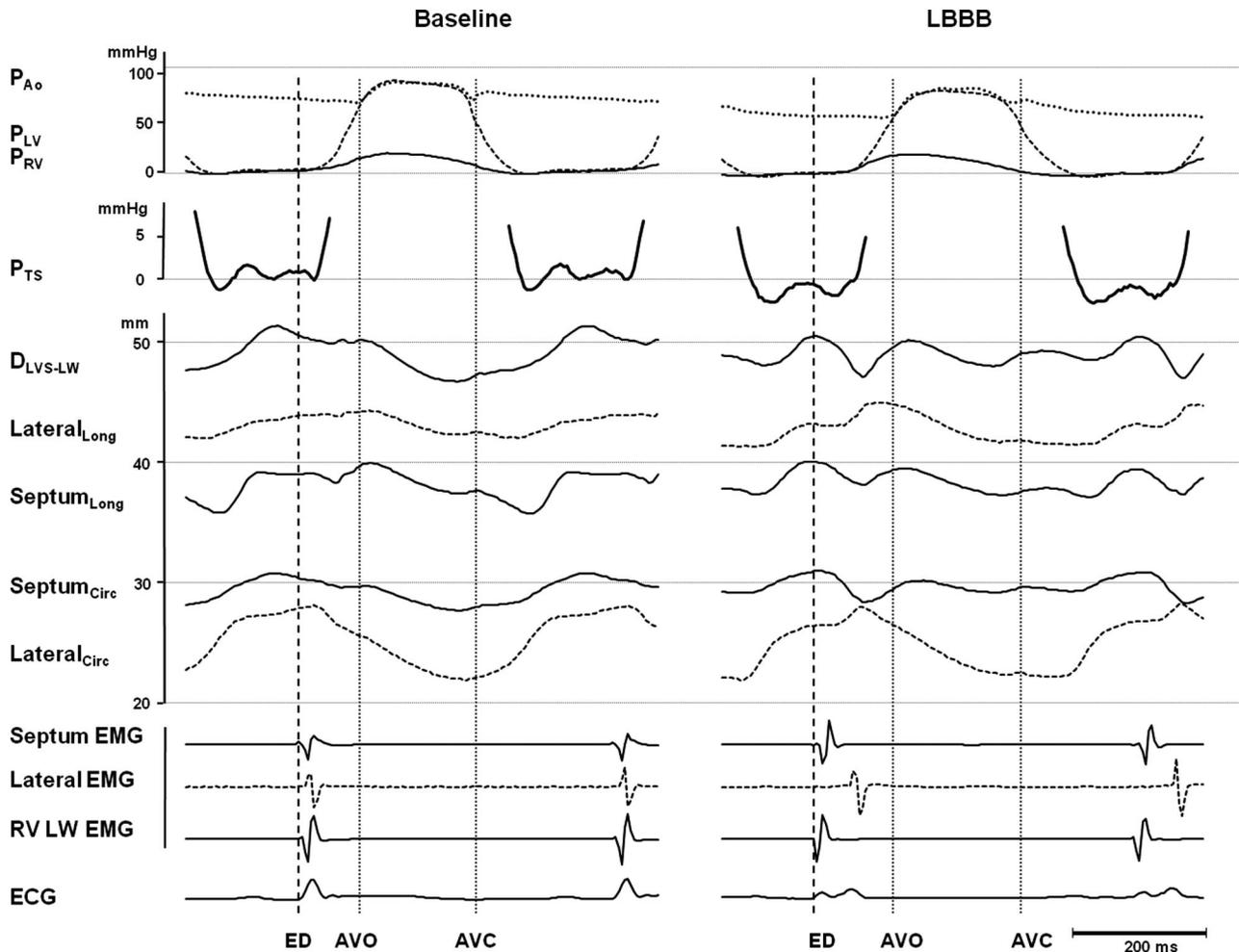


Figure 4. Pressures, segment lengths, and EMG recordings from a representative experiment during baseline and LBBB. D_{LVS-LW} indicates LV septum-to-lateral wall diameter; P_{TS} , transseptal pressure gradient; ED, end diastole; AVO, aortic valve opening; AVC, aortic valve closure; and RV LW, right ventricular lateral wall.

The late systolic lengthening of the 2 septal segments started, on average, 54 ± 34 ms before aortic valve closure, at a time when P_{LV} was falling. This time difference compares well with the delay in electrical activation of the LV lateral wall relative to the septum, which was 53 ± 10 ms.

Load Dependency of Preejection Septal Motion

Preejection septal shortening and early systolic lengthening responded differently to load alterations, but both remained present even during extreme loading conditions. Preejection shortening was maximal at intermediate septum positions and was reduced when septum was shifted leftward as the result of reduction in P_{TS} but also when septum was shifted rightward as the result of increase in P_{TS} . Systolic lengthening, however, was maximal when septum was in the extreme leftward position and decreased progressively and linearly when septum was shifted rightward. These relationships are displayed for individual experiments in Figure 7.

LV Lateral Wall Pacing

Early and unopposed activation of the LV lateral wall by pacing the lateral wall resulted in delayed electrical activation

of the septum by 57 ± 7 ms relative to the LV lateral wall ($P < 0.01$), thus creating an opposite LV electrical activation pattern compared with that seen during LBBB. This introduced an LV lateral wall beaking pattern. Figure 8 shows a continuous M-mode recording in a dog with LBBB as LV pacing was turned on. Septal beaking is seen in the beats before pacing. Lateral wall beaking was initiated by pacing, and there was simultaneous loss of septal beaking.

Discussion

In the present study, we used an experimental model that reproduced the abnormal preejection leftward motion and paradoxical rightward motion, which have been observed in patients with LBBB.¹ As demonstrated by pressure-dimension analysis, leftward displacement of the interventricular septum during preejection was attributed mainly to active contraction of septal myocardium. In addition, during the initial part of the leftward motion, the transseptal pressure gradient decayed, which may have contributed to this motion. However, the time of onset septal shortening reflected onset of active contraction, as shown in experiments in which we abolished the passive component. Furthermore, the transsep-

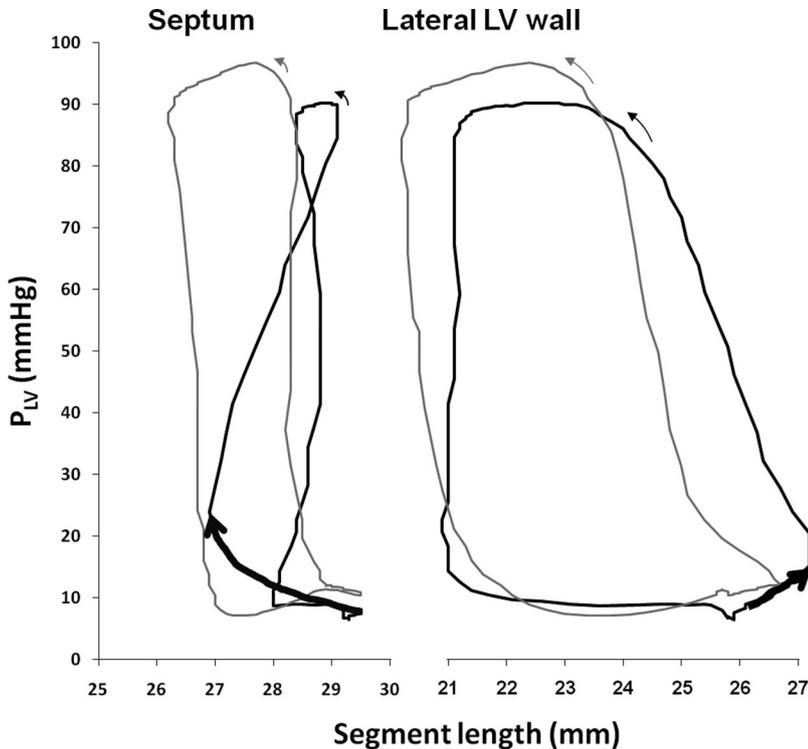


Figure 5. Pressure-dimension loops during baseline (gray) and LBBB (black) for representative septum and lateral LV wall short-axis segments. The preejection septal shortening in the septum and the simultaneous stretching in the lateral wall during LBBB are indicated by thick black arrows. During LBBB, the loop area, which corresponds to segmental stroke work, is reduced and has become negative (dominantly clockwise rotation) in the septum while it is slightly increased in the lateral wall. Thin arrows indicate loop directions.

tal pressure gradient modified the magnitude of leftward septal motion through its effect on end diastolic septal position. Thus, preejection septal motion was maximal at intermediate septal positions but decreased when end-diastolic septal position was shifted either leftward or rightward. In addition to shortening during preejection, the septum was shortening during the midphase of LV ejection. Each of the 2 phases of septal shortening during LBBB was followed by systolic lengthening. The early systolic lengthening was attributed to septal flattening and LV lateral wall shortening, whereas the late systolic lengthening was probably a reflection of earlier deactivation of the septum than of the LV lateral wall.

Mechanism of Leftward Septal Motion

At end diastole when the ventricles are fully relaxed, the septum behaves like a passive membrane, and its position is determined by the pressure gradient between the left and the right ventricles (P_{TS}),^{5,14} which was confirmed in the present study. Tanaka et al¹⁴ studied patients with pulmonary hypertension and demonstrated rapid leftward motion of the inter-ventricular septum during atrial systole and showed that this was caused by reversal of P_{TS} , which was due to forceful contraction of the right atrium. Because leftward motion of the septum and reduction in P_{TS} occurred in diastole, they concluded that the septum was moved leftward by a passive mechanism. During LBBB, however, the leftward motion occurs at a time when the septum may be activated. Therefore, in the present study, we explored the potential contributions from active myocardial contraction as well as passive motion caused by reduction in P_{TS} .

To determine if preejection septal shortening was caused by active contraction, we analyzed septal pressure-segment

length loops and observed that septal myocardium was shortening against rising LV pressure, consistent with actively contracting myocardium. A passive myocardial segment, on the contrary, would lengthen during rising pressure. Furthermore, the relationship between LV pressure and septal segment lengths was shifted upward relative to the passive curve for these segments. Thus, the segments were stiffer than predicted by the diastolic pressure-dimension relationship, which implies active myocardial contraction. Results were similar for the relationship between LV pressure and LV septum-to-lateral wall diameter.

As an alternative measure of septal distending pressure, we used P_{TS} ; for this pressure, the analysis indicated an active mechanism. During a brief period (median, 5 ms) at onset of preejection shortening, however, the relationship between P_{TS} and septal segment lengths was not shifted. Observations in the 4 experiments in which the fall in P_{TS} was abolished by loading interventions indicate that active contraction contributes also during the initial phase of preejection shortening. Furthermore, abolishing the passive component (no fall in P_{TS}) caused no significant change (<10 ms) in time from onset septal IM-EMG to onset septal shortening, indicating that onset shortening reflects timing of septal activation. These observations suggest that septal preejection shortening is caused predominantly by active myocardial contraction and that onset of preejection shortening may serve as a marker of septal activation. A passive mechanism probably contributed to preejection shortening but appeared to play a minor role.

Our conclusion regarding the role of active septal contraction is consistent with the observation of Dillon et al¹ that septal beaking was absent in patients with LBBB caused by septal infarctions. The findings in previous studies that have used RV outflow tract pacing to simulate LBBB are in

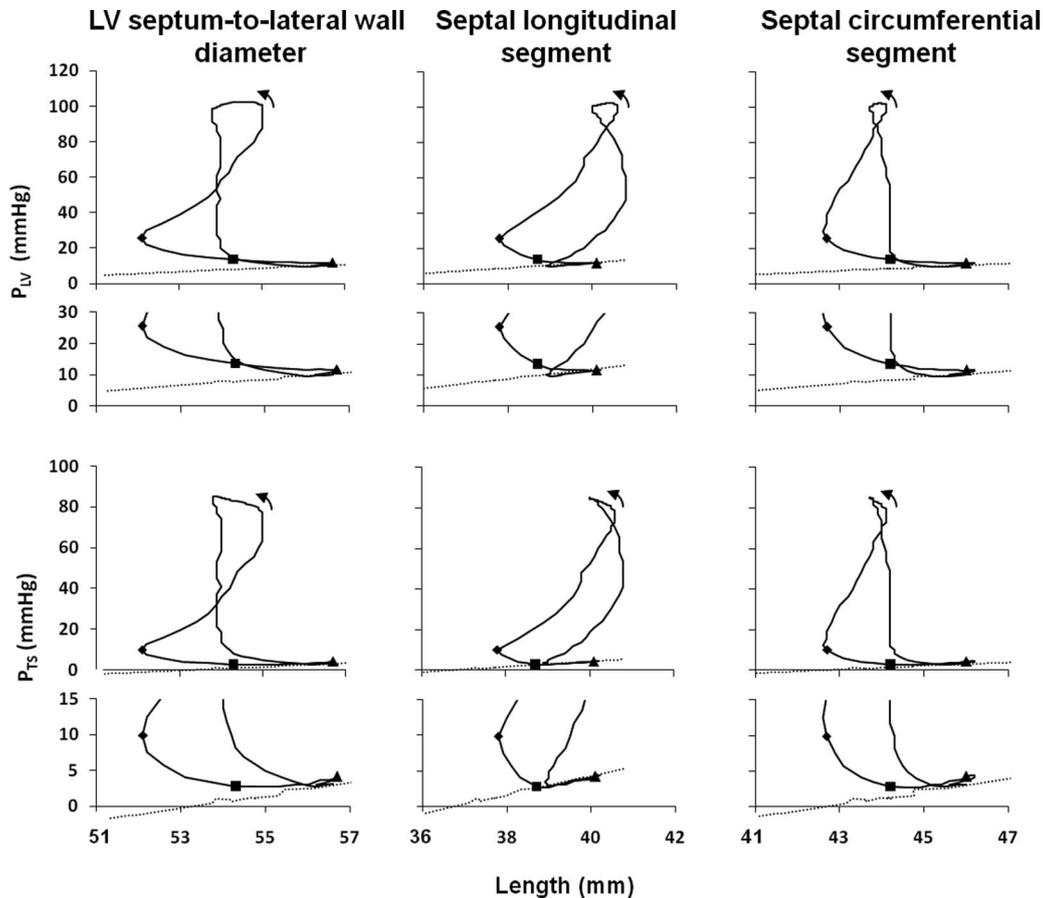


Figure 6. Pressure-dimension loops during LBBB: Relationships between P_{LV} and P_{TS} and passive curves (dotted lines) are displayed with low and high gain. Onset of preejection shortening (triangle), interrupted septal shortening (diamonds), and the midpoint between the 2 (squares) are indicated.

apparent conflict with the present study.^{3,5} The difference, however, may reflect that the RV pacing model differs from LBBB with regard to relative timing of RV and LV activation. Possibly, there may be more delay in activation of the left relative to the right ventricle in the RV pacing model than during LBBB. It is also possible that a different methodological approach in these studies might have revealed a contribution from an active component.

Mechanism of Rightward Septal Motion

A most unfavorable mechanical feature of abnormal septal motion during LBBB is systolic lengthening, which reduces the contribution from the septum to stroke volume. In cases in which the septum is lengthened beyond its end-diastolic

length, it even makes a negative contribution to LV stroke volume similar to the function of an aneurysm. The negative contribution of septal segments to LV stroke work is evident by considering pressure-segment length loops during LBBB, as illustrated in Figures 5 and 6. However, the reduced septal work is partly compensated for by increased shortening of the LV lateral wall.²

Abnormal systolic lengthening of the septum during LBBB reflects interactions with the LV lateral wall caused by the conduction delay. In the normal ventricle, septal and LV free wall segments shorten during the beginning of the isovolumic contraction phase, as reflected in positive velocity spikes during preejection, causing displacement of blood toward the LV base, thereby moving the mitral valve leaflets toward closure.¹⁵ The normal preejection shortening is arrested when the mitral valve has reached its final closure position, which corresponds to the c-wave in the left atrial pressure trace, and thereafter true isovolumic conditions exist. We suggest that during LBBB, the preejection shortening of the early activated septum is enhanced because it alone moves blood toward the mitral valve, resulting in full valve closure, and the septum also pushes blood against the late activated lateral wall, which is passively stretched. When the lateral wall is activated, true isovolumic conditions prevail and forceful contraction of the prestretched lateral wall causes septal lengthening. The observation that the left atrial pressure

Table 2. Radii of Circumferential Curvatures for Septum and LV Lateral Wall

	Onset QRS	Interrupted Septal Shortening	Aortic Valve Opening
Septum, cm	2.2±0.3	2.3±0.4*	2.0±0.3*
Lateral wall, cm	2.2±0.3	2.1±0.3*†	1.9±0.3*†
Relative, septum/lateral	1.00±0.01	1.26±0.14*	1.13±0.10

* $P \leq 0.05$ versus onset QRS.

† $P \leq 0.05$ versus septum.

All ANOVA, $P \leq 0.05$.

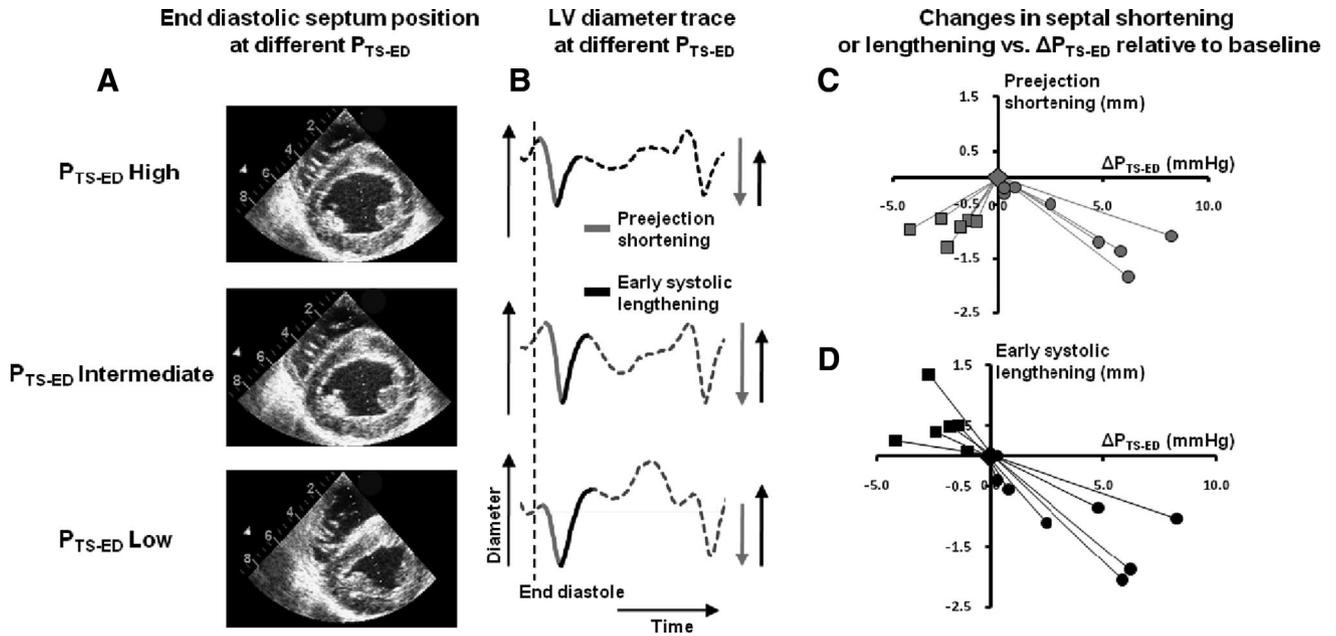


Figure 7. Left panels (A) show short-axis echocardiographic images at different transseptal pressure gradients (P_{TS-ED}). Mid panels (B) display LV septum-to-lateral wall diameter traces at P_{TS-ED} corresponding to A. Graphs to the right display changes in preejection shortening (C) and early systolic lengthening (D) as function of change in P_{TS-ED} from baseline conditions during LBBB (ΔP_{TS-ED}). Measurements at peak positive (circles) and peak negative change (squares) during load interventions during LBBB were compared with baseline conditions (diamonds) during LBBB.

c-wave coincided with onset of septal lengthening is consistent with this proposed mechanism.

As shown by Prinzen et al,² dyssynchrony leads to increased shortening in late activated areas due to increased local preload. We suggest that early systolic lengthening of the septum is due to forceful contraction of the hyperextended, late activated LV lateral wall (Starling effect), which results in rise in the transseptal pressure gradient that pushes the septum rightward. The stretching of the activated septum is further enforced by preejection flattening of septal curvature (increased radius), which increases the distending load on the septum according to the law of Laplace. Furthermore,

as proposed by Little et al,³ reduction in RV volume (because RV ejection starts before LV ejection) may contribute to rightward motion of the septum.

Before aortic valve closure, the septal segments demonstrated a second phase of systolic lengthening (late systolic lengthening), whereas the LV lateral wall segments continued shortening until aortic valve closure. The late systolic lengthening may reflect that the early activated septal segments start relaxing earlier than the late activated lateral wall segments.³ This mechanism was supported by the observation that the time from onset of late systolic lengthening to aortic valve closure was similar to the delay in electrical activation of the LV lateral wall relative to the septum. This second phase of lengthening of septal myocardium enhances the mechanical disadvantage of LBBB because the net contribution of septal contraction to LV stroke volume was further reduced.

Load Dependency of Septal Beaking

The magnitude of preejection septal shortening was load dependent, and the influence of load was primarily through its effect on end diastolic position of the septum.¹⁶ The beaking pattern, however, remained present despite load interventions, and no beaking was observed during pressure alterations at baseline, suggesting a modulating and not causative role of the pressure gradient. Maximum beaking was observed at intermediate septal positions. When P_{TS} was reduced and the septum was pushed into the LV at end diastole, there was a reduction in the amplitude of preejection shortening. This was probably a result of higher operating stiffness of the septum when it was already pushed leftwards at onset of systole. When P_{TS} was increased and the septum was pushed into the RV at end diastole, there was also a reduction

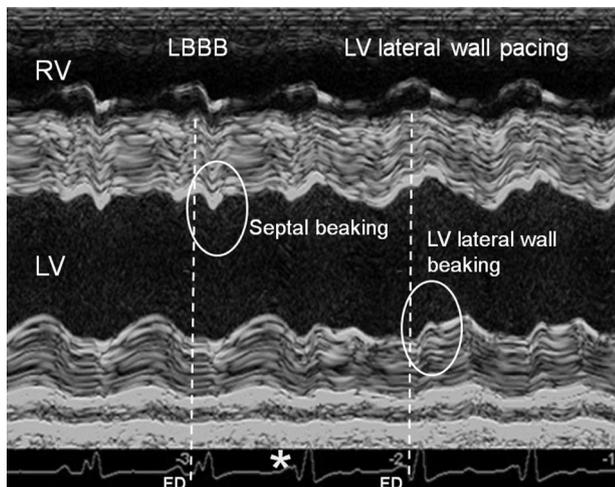


Figure 8. Continuous M-mode echocardiographic recording during transition from LBBB to pacing of the LV lateral wall. With onset of pacing, indicated by asterisk, the beaking pattern was moved from septum to the LV lateral wall.

in preejection shortening, probably because of the increased LV pressure acting as an increased afterload to preejection shortening. The early systolic lengthening had an entirely different relationship to septal position and increased progressively when the septum was moved from its extreme right position to extreme left position. This finding is consistent with the study of Pearlman et al,¹⁶ who showed that the direction and magnitude of septal motion during systole is determined by the position of the septum at end diastole.

Clinical Implications

In the present study, the average time from onset R in septal EMG to onset of septal shortening was <20 ms, suggesting that onset of septal shortening may be used as a marker of timing of septal activation. This time interval did not appear to be modified by changes in loading conditions because it was relatively unchanged when the preejection fall in P_{TS} was abolished. The present study indicates that septal shortening measured during LV ejection (ie, the second shortening occurring after the early systolic septal lengthening, Figures 3 and 4, right panel) may be misleading as marker of dyssynchrony because in most cases it started after onset of LV lateral wall shortening. It is therefore unlikely that measurements of timing that are limited to the ejection phase will provide accurate measures of delay in electrical activation of the lateral wall relative to the septum. Clinical studies, however, are needed to evaluate which marker of septal activation is the best predictor of success of CRT.

Limitations

The present study used a heavily instrumented animal model, and this preparation may not always represent normal physiology. The rather extensive surgery and the open-chest condition can explain why LV and RV systolic and diastolic pressures were in the lower range and why P_{TS} in some cases was slightly below zero at baseline. The relationship between preejection shortening and active septal contraction, however, was confirmed during loading interventions, which induced a wide range of pressure conditions, including elevated LV and RV systolic and diastolic pressures. 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 analysis of the relationship between LV pressure and septal segment length during preejection shortening did not take into account potential effects from changes in pressure external to the LV free wall (pericardial pressure).¹⁰ However, the observation that the relationship was shifted during beaking when using either P_{LV} or P_{TS} to represent septal distending pressure is compatible with an active mechanism of septal beaking. Furthermore, the essentially unchanged time from septal IM-EMG to onset of septal shortening when the fall in P_{TS} was abolished is consistent with an active mechanism.

Patients with LBBB and heart failure typically have extensive additional cardiac pathology. In our model, LBBB was present without additional heart failure except for that inherent in the model. This simplification of the true complexity of

LBBB in the clinical reality is a necessity, however, to be able to decipher the mechanisms involved in septal beaking.

In the clinical setting, LBBB can be caused by damage of the bundle branch at different levels, and the effect on septal activation might differ accordingly. In our model, ablation of the left bundle branch was performed close to the bundle of His. Despite this, the septal IM-EMG, located at the papillary muscle level in the LV third of the septal thickness, was activated rapidly after onset QRS in superficial ECG, indicating a close to normal activation of the interventricular septum.

The present study does not include data to explain the pathophysiology of dyssynchrony in RV apex or RV outflow tract-paced patients.

Conclusions

Abnormal systolic motion of the interventricular septum during LBBB includes 2 phases of myocardial shortening, 1 during preejection and 1 during midejection, which is followed by 2 phases of relengthening. As demonstrated in the present study, preejection septal shortening during LBBB is mainly a result of active septal contraction unopposed by the late-activated lateral LV wall. The magnitudes of preejection septal motions were modulated by end-diastolic RV and LV pressures. The finding that preejection septal shortening reflects active contraction suggests that the preejection phase should be included when assessing LV dyssynchrony in patients with LBBB.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In a majority of patients with left bundle-branch block, there is abnormal leftward motion of the interventricular septum during isovolumic contraction, often referred to as septal beaking and septal flash when applying M-mode echocardiography and tissue Doppler, respectively. It has not been definitely determined if this abnormal motion is due to active septal contraction or if it represents passive motion caused by an early rise in right ventricular pressure that pushes the septum leftward. The recent interest in quantification of dyssynchrony in patients who are candidates for cardiac resynchronization therapy has highlighted the importance of this distinction: If preejection septal motion is due to active contraction, it reflects timing of septal activation and should be included in left ventricular dyssynchrony assessment. If the motion is passive, however, it should not be used for timing of septal activation. The aim of this study was to differentiate between these mechanisms. In an animal model of left bundle-branch block, myocardial shortening was measured by sonomicrometry, electric propagation by implanted myocardial electrodes, and right and left ventricular pressures by micromanometers. The report concludes that the abnormal septal motion during preejection is a result of active septal contraction, unopposed by the late-activated left ventricular lateral wall. Whereas the magnitude of the preejection septal motion was modulated by changes in right and left ventricular loading, onset of septal shortening reflected septal activation regardless of loading conditions. These experimental data suggest that onset of preejection shortening rather than ejection phase indices should be used for timing of septal activation.