Factors determining the magnitude of the pre-ejection leftward septal motion in left bundle branch block

Espen W. Remme¹²³⁴*, Steven Niederer⁵, Ola Gjesdal¹³, Kristoffer Russell¹³, Eoin R. Hyde⁵, Nicolas Smith⁵, and Otto A. Smiseth¹²³⁴

¹Institute for Surgical Research, Oslo University Hospital, 0372 Oslo, Norway; ²Centre for Cardiological Innovation, Oslo University Hospital, Oslo, Norway; ³Department of Cardiology, Oslo University Hospital, Oslo, Norway; ⁴KG Jebsen Cardiac Research Centre, University of Oslo, Oslo, Norway; and ⁵Department of Imaging Sciences and Biomedical Engineering, King’s College London, London, UK

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Aims
An abnormal large leftward septal motion prior to ejection is frequently observed in left bundle branch block (LBBB) patients. This motion has been proposed as a predictor of response to cardiac resynchronization therapy (CRT). Our goal was to investigate factors that influence its magnitude.

Methods and results
Left (LVP) and right ventricular (RVP) pressures and left ventricular (LV) volume were measured in eight canines. After induction of LBBB, LVP and, hence, the transmural septal pressure ($P_{LV-RV} = LVP - RVP$) increased more slowly ($P < 0.01$) during the phase when septum moved leftwards. A biventricular finite-element LBBB simulation model confirmed that the magnitude of septal leftward motion depended on reduced rise of $P_{LV-RV}$. The model showed that leftward septal motion was decreased with shorter activation delay, reduced global or right ventricular (RV) contractility, septal infarction, or when the septum was already displaced into the LV at end diastole by RV volume overload. Both experiments and simulations showed that pre-ejection septal hypercontraction occurs, in part, because the septum performs more of the work pushing blood towards the mitral valve leaflets to close them as the normal lateral wall contribution to this push is lost.

Conclusions
Left bundle branch block lowers afterload against pre-ejection septal contraction, expressed as slowed rise of $P_{LV-RV}$, which is a main cause and determinant of the magnitude of leftward septal motion. The motion may be small or absent due to septal infarct, impaired global or RV contractility or RV volume overload, which should be kept in mind if this motion is to be used in evaluation of CRT response.

Keywords
Left bundle branch block • Septal beaking • Dyssynchrony • Computer modelling • Ventricular function

Introduction
In left bundle branch block (LBBB), the septum tends to move leftwards into the left ventricle (LV) at onset of systole followed by a rightward motion towards the right ventricle (RV).¹ This abnormal septal motion has been referred to as both septal beaking, based on observations in echocardiographic M-mode images²⁻³ (Figure 1), and more recently as septal flash⁴ based on a characteristic colour pattern in tissue Doppler images. In the latter study and in a more recent study,⁵ 89 and 88%, respectively, of the patients with this septal motion responded to cardiac resynchronization therapy (CRT). However, the underlying mechanisms that determine the magnitude of the early systolic septal motion in LBBB are not fully understood. An improved mechanistic understanding underpinning this motion is of clinical interest due to its potential as a predictor for CRT response.

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* Corresponding author. Tel: +47 23070000/23071413; fax: +47 23071397. E-mail address: espen.remme@medisin.uio.no

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The position of the inactivated septum and septal segment length have been shown to be determined by the right (RVP) and left ventricular (LVP) pressures at end diastole (ED). \textsuperscript{5-8} Previous studies, where RV apical pacing was used as a model for LBBB, reported a reversal of the transmural septal pressure ($P_{LVP-RVP}$) at onset of systole due to the earlier RV than LV activation, thus suggesting a pressure mediated pre-ejection leftward motion of the septum.\textsuperscript{3,7} We recently proposed that the septum actively contracts into the LV as most of the leftward motion occurs during a rise in $P_{LVP-RVP}$ as seen in canines with LBBB.\textsuperscript{9} Even though there is a rise in $P_{LVP-RVP}$ during leftward motion, the rate of rise may be slower than normal, which effectively reduces the instantaneous afterload to the contracting septum. The relation between early systolic rise in $P_{LVP-RVP}$ and leftward septal motion in LBBB is not known. Since a reduction in afterload increases shortening velocity, we hypothesize that the magnitude of the leftward motion depends on the reduction in the rise of $P_{LVP-RVP}$.

We also hypothesize that the magnitude of leftward septal motion depends on other factors such as changes in regional and global contractility including septal infarction, LV septal-to-lateral wall activation delay, and RV volume overload where the septum is already displaced into the LV at ED. Furthermore, if the septum moves into the LV during the isovolumic contraction phase, other structures have to stretch. Previous studies have suggested that this motion of the septum is made possible by the simultaneous stretching of the late-activated LV lateral wall.\textsuperscript{9,10} However, there may also be stretching of other LV regions that facilitate the leftward septal motion which has not been previously considered. During the pre-ejection phase, the mitral valve leaflets are pushed closed and moved towards the left atrium until they reach their final closed position when the papillary muscles and chordae tendineae become completely taut, implying that there is blood moving behind the closing leaflets. We previously found that $\sim5\%$ of the volume from apex to equator was pushed towards the valve plane during mitral valve closure in the normally electrically activated LV.\textsuperscript{11} The septal as well as anterior, lateral, and posterior LV regions all shortened during this phase. Hence, only a small amount of shortening was needed in each of these regions to push $5\%$ of the blood from apex to base. We hypothesize that due to late activation, the LV free wall contribution to this push is lost in LBBB and that a component of the abnormally large leftward septal motion is the earlier activated septum moving further leftwards to compensate for this loss as septum mostly alone pushes all the blood required to move the leaflets to their closed position.

The aim of this study was to investigate factors that influence the magnitude of the abnormal pre-ejection leftward septal motion in left bundle branch block including the role of ventricular pressures, changes in contractility, septal infarction, activation delay, right ventricular (RV) volume overload, and the closing motion of the mitral valve leaflets.

- The magnitude is highly dependent on slowed early systolic rise in left ventricular pressure (LVP) and hence slowed rise of transmural septal pressure ($LVP-RVP$).
- The magnitude is reduced with a decrease in septal to left ventricular lateral wall activation delay, septal infarct, impaired global or RV contractility, or RV volume overload.
- The pre-ejection septal hypercontraction occurs, in part, because it does more of the work to push blood towards the closing mitral valve leaflets during the phase when the leaflets are pushed towards the atrium, as the normal lateral wall contribution to this push is lost.

**What’s new?**

- This study investigates in detail factors that influence the magnitude of the abnormal pre-ejection leftward septal motion in left bundle branch block including the role of ventricular pressures, changes in contractility, septal infarction, activation delay, right ventricular (RV) volume overload, and the closing motion of the mitral valve leaflets.
- The magnitude is highly dependent on slowed early systolic rise in left ventricular pressure (LVP) and hence slowed rise of transmural septal pressure ($LVP-RVP$).
- The magnitude is reduced with a decrease in septal to left ventricular lateral wall activation delay, septal infarct, impaired global or RV contractility, or RV volume overload.
- The pre-ejection septal hypercontraction occurs, in part, because it does more of the work to push blood towards the closing mitral valve leaflets during the phase when the leaflets are pushed towards the atrium, as the normal lateral wall contribution to this push is lost.

**Methods**

**Experimental study**

We analysed measurements from a previously performed acute experimental study on eight mongrel canines ($34 \pm 2$ kg).\textsuperscript{9} The study was performed in a controlled manner.
into the LV. Pentobarbital was reduced to half the dose after 4 h of infusion. The an- 

ing (MVC) phase, which is seen as the c-wave in the LA pressure trace 

image in 

mitral leaflets towards the LA, which temporarily increases LA pressure.14 

dium to 

2 

8 

mm. The transmural fibre orientation was interpolated linearly 

dimensions representative of a typical dog heart: LV short- and long-axis 

the geometry was modified to a generic circular LV shape ( 

article describes the mathematical modelling concepts in detail. In short, 

LBBB was obtained after 5–20 ablations (50 

C/30 W) at a location 

animals were supplied by Centre for Comparative Medicine, Oslo 

University Hospital, Oslo, Norway. The animals were anesthetized 

bolus of thiopental 25 mg kg, followed by continuous infusion 

morphine (3.5 mg kg \(-1\) h \(-1\)) and pentobarbital (2 mg kg \(-1\) h \(-1\)). Pentobarbital was reduced to half the dose after 4 h of infusion. The an-

imals were artificially ventilated through a cuffed endotracheal tube with 

room air and 20–50% oxygen. At completion of the experiment, the ani-

mals were euthanized by an overdose of pentobarbital injected directly 

The surgical preparation, instrumentation, and interventions have 

been described in detail previously.9 In brief, this was an open-chest 

model with loosely resutured pericardium following surgical instrumen-

tation of the heart. Left atrial and left and right ventricular and aortic 

pressures were measured by micromanometers (MPC-500, Millar 

Instruments, Inc., Houston, TX). Left ventricular dimensions and regional 

deformations were measured by sonomicrometry (Sonometrics 

Corporation, London, Ontario, Canada). Regional electrical activation 
times were recorded from implanted bipolar electrodes. Data were re-
corded at 200 Hz. Recordings were obtained at baseline and following 

induction of LBBB. Left bundle branch block was induced by radiofre-

quency ablation (Celsius Catheter, Biosense Webster, Inc.). Stable 

LBBB was obtained after 5–20 ablations (50°C/30 W) at a location 

with a large left bundle potential, two-thirds from the atrial and 
one-third from the ventricular signal. Energy was delivered for 30 add-
tional seconds after induction of LBBB. 

The LV volume from equator to apex was calculated using sonomi-
crometric crystals. Four crystals were placed subendocardially around 

equator (two-thirds the distance from apex to base) in the septum, 

anterior, lateral, and posterior LV walls and one at the apex. The average 

long-axis diameter from apex to these four equatorial crystals was 

assessed. This long-axis diameter and two short-axis diameters were 

used to calculate the apical two-thirds of the LV volume (LVV apical) 
as shown in the following equation:12 

\[
\text{LVV apical} = \pi/6 \times \text{septum-to-lateral wall diameter} 
\times \text{anterior-posterior wall diameter} \times \text{long-axis diameter}
\]

Strain was assessed between crystal pairs aligned in the circumferential 

and longitudinal directions in both septum and LV lateral wall. We further 
calculated leftward septal motion as the displacement of the septal equa-
torial crystal into the LV,13 qualitatively similar to tracking the displace-

ment of the LV endocardial septal border as shown in the M-mode 

image in Figure 1. We investigated deformations during early systole 

from onset Q in electrocardiogram (ECG) to the end of mitral valve 
closing (MVC) phase, which is seen as the c-wave in the LA pressure trace 
(Figure 2). The c-wave has been attributed to the closing motion of the 

mitral leaflets towards the LA, which temporarily increases LA pressure.14 

Mathematical model study

We applied the RV and LV FE modelling framework previously applied 
to a study of human hearts with LBBB.15 The online supplement of that 
article describes the mathematical modelling concepts in detail. In short, 
the geometry was modified to a generic circular LV shape (Figure 3) with 
dimensions representative of a typical dog heart: LV short- and long-axis 
diameters of 4 and 6 cm, respectively, and an LV equatorial wall thickness 
of 8 mm. The transmural fibre orientation was interpolated linearly 

from 90° with respect to the circumferential orientation at the endocar-
dium to −60° at the epicardium, in qualitatively agreement with 

measured data.16 Electrical activation was simulated using the monodo-

main equations with initial stimulation sites in the subendocardial region 

around the mid third below the equator of both ventricles for normal 
activation and only in the RV for LBBB activation. Conduction velocity 

was adjusted to fit the septal to LV lateral wall activation delay at equator 
to the measured delay between electrodes at these two sites during 
LBBB in the animals (Figure 3). 

Passive elastic properties were defined by a transversely isotropic ma-

terial law aligned to the fibre orientation using similar stiffness parameters 
as in the previous study.15 Furthermore, we applied the same length- 

time-dependent active tension model where we adjusted the parameter 

for peak isometric tension to 100 kPa, giving a maximum LV dP/dt of 

1500 mmHg/s consistent with measurements in the animals. Prior to ac-
tivation, the LV and RV were inflated to end diastolic pressures of 9.0 and 

7.5 mmHg, respectively. Following activation, the cavity volumes were 

kept constant as active fibre stress was increased according to the active 
tension model and regional activation times. At the time when LV and RV 
pressures exceeded 57 mmHg (average aortic pressure at onset ejection 
in the animals during LBBB) and 20 mmHg, respectively, ejection was 
simulated by Windkessel models providing the pressure–volume rela-
tions.15 The leftward septal motion occurred during the beginning of iso-

volumic contraction. Thus, simulation of ejection and the reminder of the 

cardiac cycle was of limited interest for this study.
A specified time is equivalent to a change in the rise of \( P \) in a steady-state model; thus, it is not dependent on the time course of \( P \). ward septal motion was quantified as the displacement of an LV endocardial plane. Leftward septal motion was quantified as the displacement of the septal node towards the LV centre as indicated. For peak isometric tension in the active tension model \(^{15} \) to 50 or 150 kPa in the free wall elements. Changes in contractility were implemented by adjusting the parameter \( \tau \) to mimic assessment of this motion in M-mode images (Figure 3). Changes in contractility were quantified as the displacement of the septal node towards the LV centre as indicated.

We ran series of simulation cases within which model parameters were adjusted to quantify their effect on septal motion during early systole. Leftward septal motion was quantified as the displacement of an LV endocardial septal node towards the centre of the LV at the equatorial plane (Figure 3) to mimic assessment of this motion in M-mode images (Figure 1).

**Reference simulations**

Initially, we ran simulations with normal activation and LBBB activation where the ventricular volumes were enforced to be isovolumic from onset of activation (time \( t = 0 \)).

**Transmural septal pressure**

In the experiments, we observed that \( P_{LV-RV} \) had risen to a lower value at the time of peak leftward septal motion during LBBB compared with the same phase at baseline. In the simulation model, we investigated the magnitude of leftward motion with respect to variations in the level of \( P_{LV-RV} \) at time of peak leftward motion. The model is a steady-state model; thus, it is not dependent on the time course of \( P_{LV-RV} \) to a given level at a given time. Therefore, changing \( P_{LV-RV} \) at a specified time is equivalent to a change in the rise of \( P_{LV-RV} \) to this time point. \( P_{LV-RV} \) at the time of peak leftward motion of the reference simulation was altered by changing RVP, while LVP was adjusted accordingly to maintain constant LV volume. This ensured that a potential increase or decrease in leftward septal motion would be caused by a change in \( P_{LV-RV} \) and not by a change in LV volume. However, the change in RVP changed RV volume during this isovolumic contraction phase. It must therefore be regarded as a hypothetical simulation case designed to illustrate the principle of the impact of \( P_{LV-RV} \) on magnitude of leftward septal motion.

**Changes in contractility**

In order to investigate the effect of changes in \( P_{LV-RV} \) while maintaining both cavity volumes constant during the isovolumic contraction phase, we performed four simulations where either RV or LV free wall contractility was changed by \( \pm 50\% \). Mainly, the pressure rise in the ventricle with altered contractility would change, affecting rise in \( P_{LV-RV} \). Changes in contractility were implemented by adjusting the parameter for peak isometric tension in the active tension model \(^{15} \) to 50 or 150 kPa in the free wall elements.

In order to investigate the effect of globally reduced or increased contractility, we performed two additional simulations with a similar \( \pm 50\% \) contractility change in both ventricles including septum.

**Septal infarction**

We investigated the influence of septal infarction and varying infarct size. The infarcted region was modelled by stiff, isotropic properties that did not generate active fibre stress as explained previously. \(^{15} \) The septal wall consisted of four rows of elements from base towards apex (Figure 3). Four simulation cases were run. In the first, the most apical septal row of elements was infarcted; in the second, the two most apical septal rows were infarcted; in the third, the three most apical rows were infarcted; and in the final, all four rows (i.e. the entire septum) were infarcted.

**Activation delay**

The conduction velocity of electrical activation was initially estimated, so the LV septal-to-lateral wall activation delay was 55 ms for the reference LBBB simulation, consistent with the measured delay in the animals. We investigated the relation between magnitude of leftward septal motion and LV septal-to-lateral wall activation delay running simulation cases where this delay was altered from 20 to 90 ms by varying the electrical conduction velocity.

**Right ventricular volume overload**

We then investigated if the magnitude of pre-ejection leftward septal motion was reduced if the septum was already pre-displaced leftwards at ED, which occurs in RV volume overload when ED RVP is increased and hence ED \( P_{LV-RV} \) decreased. In different simulation cases, ED RVP was increased in steps of 0.75 mmHg, so ED \( P_{LV-RV} \) changed from 1.5 mmHg at the reference simulation to \( \pm 5.25 \) mmHg. This displaced the ED septal position leftwards as ED RV volume was increased.

**Closing of the mitral valve**

During the beginning of systolic contraction, there is an LV intracavitary redistribution of blood from the apical to basal region as the mitral valve leaflets move towards the atrium during valve closure. The simulation model did not include the mitral valve leaflets. Thus, we could not directly simulate the closing motion of the leaflets. However, the effect of mitral valve closure could be simulated by changing LV apical volume accordingly. Incorporating a 5% reduction of the volume from apex to equator during the beginning of contraction infers a reciprocal increase in the volume encapsulated within the basal segments and hypothetical mitral leaflets as they would move in the direction of the left atrium. Consistent with our experimental measurements, we reran the normal
Table 1 Changes during interval from onset Q in ECG to end of mitral valve closure (n = 8)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LBBB</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of interval, ms</td>
<td>65 ± 8</td>
<td>83 ± 15*</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>ΔLVP, mmHg</td>
<td>18.0 ± 7.1</td>
<td>8.9 ± 4.5*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔP_{LV – RV}, mmHg</td>
<td>14.3 ± 6.6</td>
<td>3.6 ± 2.6*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔLVV apical, %</td>
<td>−5.0 ± 2.6</td>
<td>−4.2 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Septal circ strain, %</td>
<td>−3.0 ± 2.2</td>
<td>−7.7 ± 5.6*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Septal long strain, %</td>
<td>0.4 ± 2.1</td>
<td>−2.1 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>LV lateral wall circ strain, %</td>
<td>−2.7 ± 1.4</td>
<td>3.2 ± 3.1*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV lateral wall long strain, %</td>
<td>−0.9 ± 1.2</td>
<td>2.1 ± 1.7*</td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; LVP, LV pressure; P_{LV – RV}, transmural septal pressure; LVV apical, LV volume from apex to equator; circ, circumferential; long, longitudinal. *P < 0.02.

and LBBB activation reference simulations incorporating a 5% reduction of the LV volume from equator to apex. Implementation of the early systolic apical volume reduction was achieved by controlling the pressure relative to the volume: active myocardial fibre tension increases for each new time step. To maintain a constant volume, the cavity pressure must increase correspondingly, while a smaller pressure increase will result in a volume reduction. Left ventricular pressure was controlled to follow a specified linear pressure–apical volume relation with a 5% apical volume reduction as LVP rose from 9 to 22 mmHg, similar to the experimental findings. During the remaining time steps of the pre-ejection phase, LVP was increased to maintain global LV isovolumic conditions. We further performed a series of simulations with LBBB activation where the magnitude of this volume reduction was varied to investigate its relation to the magnitude of leftward septal motion.

Statistics
Experimental results are presented as mean ± SD. For comparisons between values from baseline and LBBB, we applied a two-tailed, paired Student’s t-test, where P < 0.05 was considered significant.

Results

Experimental canine study
Induction of LBBB caused electrical dysynchrony and abnormal deformation as shown in Figure 2. There was an increase in QRS duration (112 ± 4 vs. 59 ± 8 ms at baseline, P < 0.01). The LV lateral wall was activated 53 ± 10 ms after septum, which was significantly different from the delay at baseline (9 ± 5 ms, P < 0.01). Both during baseline and LBBB, there was an early systolic contraction of the LV apical volume that was interrupted when the mitral valve finished its closing movement (c-wave in LAP trace). As shown in Figure 2 and Table 1, this interval was prolonged and LVP rise was slowed with LBBB, consistent with less efficient global LV contraction. While both the septum and LV lateral wall shortened moderately during this phase at baseline, the LV lateral wall lengthened during LBBB while shortening in the septum increased substantially (Table 1). The early systolic reduction in LV apical volume was relatively similar during baseline and LBBB. This indicates that the septum is doing more of the work, i.e. increased septal shortening, to push blood from the apical LV region towards the valve plane during mitral valve closure.

Table 1

<table>
<thead>
<tr>
<th>Time (ms)</th>
<th>Septal beaking (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Figure 4 Simulation results: early systolic leftward displacement of the septum, mimicking septal beaking M-mode traces as shown in Figure 1. Left bundle branch block activation resulted in substantial leftward motion. As indicated by the downward arrows, the leftward motion was increased in the simulation cases when LV apical volume was reduced by 5% to simulate the blood volume that is pushed towards the basal region during the MVC phase. As can be seen, this increase was larger during LBBB activation than normal activation, despite the displaced blood volume being identical. The larger increase in leftward motion is thus consistent with the septum doing more of the work to push this blood volume towards the closing mitral valve in LBBB.

Mathematical model study

Reference simulations
In the LBBB activation simulation case, the model reproduced the typical early systolic septal leftward motion followed by rightward motion. Figure 4 shows septal motion for normal and LBBB activation.

Transmural septal pressure
The magnitude of leftward septal motion was highly dependent on the simultaneous rise in P_{LV – RV}. Figure 5A shows the relation between the magnitude of P_{LV – RV} at the time of peak leftward septal motion and magnitude of the septal motion for the simulation cases where P_{LV – RV} at time of peak leftward motion was adjusted. Septal leftward motion was 1.1 mm in the reference simulation. From the slope of the relation in Figure 5A, it can be inferred that leftward motion was increased by ~0.2 mm per 1 mmHg reduced rise in P_{LV – RV}.

Changes in contractility
Reduced RV free wall contractility slowed RVP rise, increasing the rise in P_{LV – RV} by 3.3 mmHg during the first 70 ms, thus decreasing leftward septal motion. The effect was opposite for increased RV contractility. Reduced contractility in the LV free wall slowed the rise in P_{LV – RV} by 3.0 mmHg and hence increased leftward septal motion and vice versa (Figure 5A).

Global 50% reduced contractility decreased leftward septal motion to 0.8 mm (i.e. 27% decrease), while it was increased to 1.3 mm
(18% increase) with 50% increased contractility. The time to peak leftward motion was prolonged with reduced contractility, but the rise in \( P_{LV-RV} \) was slower, resulting in a similar \( P_{LV-RV} \) at this time point.

### Septal infarction

In all three simulation cases when the equatorial septal elements were infarcted, leftward motion was decreased (Figure 5B). However, when only the most apical row of septal elements was infarcted (25% septal infarction), there was a slight increase in the equatorial leftward septal motion, which was located more basal than the infarct region. The loss of contractile force in the apical part of septum resulted in these elements being pushed rightwards when the more basal part of septum actively contracted. Thus, the equatorial septum was allowed to move further leftward, pushing blood towards the stretching apical septal region in this simulation case. The rise in \( P_{LV-RV} \) was gradually reduced to only 1 mmHg with 100% septal infarct region. Despite this reduced afterload against leftward septal motion, leftward motion decreased as active septal contraction was gradually abolished by increasing septal infarct size.

### Activation delay

Increased activation delay in the LV lateral wall relative to the septum, increased leftward septal motion (Figure 5C). When activation delay was increased from 20 to 90 ms, the leftward septal motion increased from 0.7 to 1.4 mm, and at the same time, the rise in LVP was slowed down, resulting in a reduced rise of \( P_{LV-RV} \) by 6.3 mmHg.

### Right ventricular volume overload

In simulation cases with increasing ED RVP and ED RV volume, the septum was substantially shifted into the LV at ED (Figure 5D). This resulted in a corresponding reduction in the subsequent pre-ejection leftward septal motion. In the cases with the most extreme ED leftward position of septum, there was practically no pre-ejection leftward motion following ED. In these cases, the septum started moving rightwards.

### Closing of the mitral valve

As seen in Figure 4, leftward septal motion was increased when a 5% apical LV volume reduction was included to simulate the MVC phase both during normal and LBBB activations. However, as seen in the figure, this increase in leftward motion was 0.3 mm during normal activation, while the increase was 0.5 mm during LBBB activation, consistent with the septum contributing more to the mitral valve closure during LBBB. The reduction in LV apical volume and increased leftward septal motion were related to a reduced rise in LVP. This further reduced the rise in \( P_{LV-RV} \) by 2.3 and 4.9 mmHg for normal and LBBB activations, respectively, consistent with reducing afterload during this phase, thus allowing for more septal contraction. Figure 5E shows the relation between the magnitude of apical volume reduction during the MVC phase and magnitude of leftward septal motion.

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**Figure 5** Pre-ejection leftward septal motion as a function of five different variables in the simulation model. The bullet point represents the reference LBBB simulation case in all panels. (A) The transmural septal pressure \( (P_{LV-RV}) \) at the time of peak leftward septal motion was varied. The two square points are the simulation cases when RV free wall contractility was reduced or increased by 50%. The two diamond points are the cases for similar changes in LV free wall contractility. (B) Simulation cases when a septal infarct was included in the model and infarct region was stepwise increased to cover the most apical row of septal elements (25%), the 2 most apical rows (50%), the 3 most apical rows (75%), and all 4 rows (100%). (C) Simulation cases where activation delay between septum and LV lateral wall was varied. (D) End diastolic (ED) position of the septum was shifted leftwards by increasing ED RV pressure and volume. (E) Left ventricular apical volume was reduced to different degrees to simulate the MVC phase. The square point is the simulation case when this volume was reduced by 5%, which was similar to the average volume reduction in the animals. In the default LBBB simulation case (bullet point), the global LV volume is constant. Still there is a slight reduction in apical volume (1.8%), which is explained by this volume being pushed from apex to the late-activated basal region that stretches during this phase.
Discussion

In our previous study, we found that in LBBB the septum actively contracted into the LV as opposed to being passively pushed in by the RVP rising faster than LVP. Furthermore, we found that the magnitude of this motion depended on the end diastolic $P_{LV-RV}$. In the present study, we investigated a number of additional factors that could influence the magnitude of early systolic septal leftward motion in LBBB, which is important if it is to be used as a clinical predictor of response to CRT. In particular, it would be of clinical interest to understand what factors could reduce or abolish this motion despite the presence of LBBB. We identified that the magnitude of this motion is highly dependent on slowing of the rise of LVP and $P_{LV-RV}$ which is consistent with the slowed rise in $P_{LV-RV}$ representing a reduced instantaneous afterload to contraction of the septum into the LV. We also showed that increased septal to LV lateral wall activation delay increases leftward septal motion, while reduced global or RV contractility or septal infarction reduces it, and that an already leftward displaced septum at ED due to RV volume overload reduces the pre-ejection leftward motion following ED. Previously, it has been suggested that the abnormally large septal motion into the LV is facilitated by stretching of the late-activated LV lateral wall. However, we demonstrated that the closing motion of the mitral leaflets towards the atrium also facilitates increased leftward septal motion. This is due to the septum almost alone is doing the work to close the valve: the septum pushes all the blood from the apex towards the valve leaflets in order to push them to their closed position with limited or even paradoxical contribution to this push from the LV free wall.

Transmural septal pressure

Late activation of the LV lateral wall delays active contraction in this region, which temporarily impedes its contribution to increasing LVP. In the animals, we found that the abnormally large leftward septal motion occurred as the simultaneous rise in LVP and $P_{LV-RV}$ was significantly reduced. This reduced rise in $P_{LV-RV}$ offered reduced instantaneous afterload against septal contraction and leftward motion compared with the quicker rise in $P_{LV-RV}$ during normal activation. It is important to note that instantaneous afterload here refers to the afterload during the beginning of systole when LVP is typically $<30$ mmHg, and not afterload in the more conventional sense as peak LVP during ejection. Model simulations confirmed the high sensitivity of leftward septal motion to alterations in $P_{LV-RV}$ during the same interval. Thus, leftward septal motion is not a response to a reversal of $P_{LV-RV}$ as previously proposed, but rather a reduced rise of $P_{LV-RV}$.

Changes in contractility

Left bundle branch block is often associated with cardiomyopathy with reduced contractility. In the simulation model, reduced global contractility reduced leftward septal motion and vice versa. Instantaneous afterload ($P_{LV-RV}$) at the time of peak leftward motion was unaltered; hence, the changes in motion reflected changes in contractility consistent with an active contraction component to the leftward septal motion.

Skeletal infarction

The distinct early systolic leftward motion of the septum may not be seen in all LBBB patients. As the majority of the septal leftward motion is caused by active septal contraction, skeletal infarction, which impairs active septal contraction, should reduce leftward septal motion. This was supported by the simulation model results where the leftward motion was reduced when skeletal infarction was included. These findings are consistent with inspection of the septal fibre shortening traces shown by Leenders et al. in their Figure 4 where they reduced septal contractility in the CircAdapt model. It is also noteworthy that in one of the original studies of septal motion and LBBB, Dillon et al. reported that the characteristic abnormal pre-ejection septal motion was observed in all LBBB cases with the exception of the two patients who also had coronary artery disease.

Activation delay

We found that increased LV septal-to-lateral wall activation delay increased leftward septal motion. Leenders et al. did not explicitly investigate the magnitude of leftward septal motion; however, they varied mechanical activation delay in their CircAdapt mathematical model of an LBBB heart. In Figure 3 in their paper, increased septal fibre shortening can be seen with increasing delay, consistent with our findings.

Right ventricular volume overload

When end diastolic RVP, and consequently volume, was increased, the septum was displaced leftwards at ED. This resulted in a flattening of the septal wall, i.e. increased septal radius of curvature. In our previous experimental study, we constricted the pulmonary artery to create RVP overload; however, this also resulted in ED RVP increase and an ED leftward shift and flattening of the septum. Leftward septal motion following ED was reduced in that case, consistent with the simulation results in the current study. The wall stress in a circular LV wall generates a perpendicular traction acting on the surface, which is in equilibrium with the cavity pressure. As active wall stress increases, the wall contracts and moves or squeezes inward, increasing cavity pressure which maintains this equilibrium. A flatter septum will generate a lower surface traction, in keeping with Laplace’s law. Inward septal contraction will be resisted with a lower cavity pressure, hence reducing the magnitude of leftward motion. When the septum is flattened (has a large radius of curvature) relative to the LV free wall, the cavity pressure will increase faster than the surface stress developed by active contraction in this septal configuration. The septum will move rightwards becoming more curved (lower radius of curvature), so the surface traction matches the cavity pressure. We believe that this principle also explains the subsequent rightward septal motion (or the so-called rebound stretch) that normally follows the initial leftward motion and flattening of the septum in LBBB.

Closing of the mitral valve

Our study shows that leftward septal motion is not only facilitated by LV lateral wall stretch but also by the closing motion of the mitral valve, a factor that, to our knowledge, has not been proposed before. Analogous to how late activation of the lateral wall increases
effective chamber compliance during early systole and hence reduces LV pressure rise, early systolic flexible motion of the mitral leaflets also effectively increases chamber compliance, reducing the rate of pressure rise and afterload during this phase, as opposed to if they had been completely rigid. The closing motion of the leaflets towards the atrium implies that there is a volume of blood displaced behind the leaflets. Furthermore, displacement of blood implies a connected wall displacement. In the animals during normal activation, there was a small, synchronous shortening in the whole LV wall from apex to equator that reduced the apical volume by \( \approx 5\% \) during the closing motion of the mitral valve. This is consistent with activation of the basal segments and segments become completely tense and stop stretching. Hence, the early-activated septum pushed blood both against the LV lateral wall and towards the basal LV region. Thus, our results suggest that a contributing factor for early systolic septal hypercontraction during LBBB is that the septum does more of the work to move the blood required to close the mitral valve. It is important to note that the closing motion of the mitral valve does not imply there is retrograde flow into the atrium or that a given volume displacement from the apical region has the opposite effect. However, confounding factors with valve disease such as changes in loading or remodelling may counteract or obscure this predicted effect on septal motion. Pulmonary regurgitation may cause RV volume overload and ED septal flattening that will reduce pre-ejection leftward septal motion. Left bundle branch block may be a result of septal infarction. Thus, an infarct that causes LBBB may also be a factor that reduces the abnormal leftward septal motion, precluding the use of this motion as a diagnostic marker of LBBB. This study has been limited to abnormal septal motion during the pre-ejection phase in LBBB. However, there may also be abnormal septal motion during other phases in LBBB and also in other disease conditions such as pulmonary hypertension. Some of the factors investigated in the present study may be relevant to explain the abnormal septal motion also in those cases.

### Limitations

Though the FE model includes advanced mathematical descriptions of the myocardium, it is still a simplified representation of the in vivo heart and contains a number of assumptions. The details of the FE model and assumptions have been described previously. Consistent with experimental findings, we included simulation of 5% LV apical volume displacement towards the valve plane during the closing motion of the mitral valve leaflets. It is possible that a comparable volume displacement is also present in the RV during the closing motion of the tricuspid valve leaflets. No measurements are available to quantify the timing or magnitude of the change in RV volume during this phase. To test if the absence of this mechanism had a significant effect on septal motion, we performed a simulation with simultaneous 5% volume reduction in both RV and LV during this phase. The impact on the magnitude of leftward septal motion was small; the magnitude was 3% (0.05 mm) smaller compared with the simulation case (Figure 4, solid line) without only LV apical volume reduction.

### Conclusions

The magnitude of the early systolic leftward septal motion in LBBB is highly dependent on pressure rise in the ventricles, where slowed LV pressure rise offers an abnormal low instantaneous afterload against leftward septal motion. The late activation of the LV lateral wall makes it compliant and thus facilitates a hyper leftward septal motion by stretching when the septum contracts. Another factor contributing to the abnormal leftward motion is that the septum almost alone, with no or limited contribution from the LV free wall, having to push all the blood required to move the mitral valve leaflets into their final closed position. Increased LV septal-to-lateral wall activation delay increases early systolic septal motion. The motion may be small or absent in the presence of septal infarct, impaired global or RV contractility or RV volume overload. This should be kept in mind if the early systolic septal motion pattern is to be used in evaluation of CRT response.
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