Cardiac responses to left ventricular pacing in hearts with normal electrical conduction: beneficial effect of improved filling is counteracted by dyssynchrony

Espen Boe,1 Kristoffer Russell,1,2,4 Espen W. Remme,1,3 Ola Gjesdal,1,2 Otto A. Smiseth,1,2,3,4,5 and Helge Skulstad1,2,4

1Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway; 2Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; 3KG Jebsen Cardiac Research Center, University of Oslo, Oslo, Norway; 4Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Oslo, Norway; and 5Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway

Submitted 6 February 2014; accepted in final form 5 June 2014


Cardiac resynchronization therapy (CRT) has been proposed in heart failure patients with narrow QRS, but the mechanism of a potential beneficial effect is unknown. The present study investigated the hypothesis that left ventricular (LV) pacing increases LV end-diastolic volume (LVEDV) by allowing the LV to start filling before the right ventricle (RV) during narrow QRS in an experimental model. LV and biventricular pacing were studied in six anesthetized dogs before and after the induction of LV failure. Function was evaluated by pressures and dimensions, and dyssynchrony was evaluated by electromyograms and deformation. In the nonfailing heart, LV pacing gave the LV a head start in filling relative to the RV (P < 0.05) and increased LVEDV (P < 0.05). The response was similar during LV failure when RV diastolic pressure was elevated. The pacing-induced increase in LVEDV was attributed to a rightward shift of the septum (P < 0.01) due to an increased left-to-right transseptal pressure gradient (P < 0.05). LV pacing, however, also induced dyssynchrony (P < 0.05) and therefore reduced LV stroke work (P < 0.05) during baseline, and similar results were seen in failing hearts. Biventricular pacing did not change LVEDV, but systolic function was impaired. This effect was less marked than with LV pacing. In conclusion, pacing of the LV lateral wall increased LVEDV by displacing the septum rightward, suggesting a mechanism for a favorable effect of CRT in narrow QRS. The pacing, however, induced dyssynchrony and therefore reduced LV systolic function. These observations suggest that detrimental effects should be considered when applying CRT in patients with narrow QRS.

Cardiac resynchronization therapy (CRT) is an effective treatment option for heart failure (HF) patients with wide QRS (7). It has been shown that HF patients with narrow QRS may also benefit from CRT (5, 6, 23, 24). In large randomized studies, however, HF patients with narrow QRS did not benefit from CRT (3), and one study was terminated prematurely for futility and potential concerns about patient safety (20). In the recently published Echo-CRT trial, mortality was increased in patients with QRS < 130 ms and mechanical dyssynchrony receiving CRT treatment (15). This inconsistency between different trials may reflect methodological limitations of small nonrandomized studies. An alternative explanation is that there are subpopulations of HF patients with narrow QRS who benefit from CRT. The latter notion is supported by the study of Williams et al. (23), which suggested that left ventricular (LV) free wall pacing (LV pacing) improves LV filling and stroke work (SW) in patients with HF and narrow QRS by reducing the external forces that limit LV filling. These forces are commonly referred to as “external constraint” (2) and consist of pericardial and right ventricular (RV) diastolic pressures limiting distension of the LV free wall and interventricular septum, respectively. One of the proposed mechanisms for improvement of LV function by pacing is that LV end-diastolic volume (LVEDV) increases during LV pacing at the expense of RV volume, as the two ventricles compete for a limited space within the pericardium (4, 21, 23). It is speculated that during LV pacing, the early activated LV starts filling before the RV and can therefore occupy a larger volume within the pericardium (4, 18, 21, 23).

The present study explored hemodynamic responses to LV and biventricular pacing in hearts with narrow QRS and aimed to determine the mechanisms of the pacing-induced change in LVEDV and LV function. We tested the hypothesis that an earlier onset of LV compared with RV filling increases the left-to-right transseptal pressure gradient (P_{TS}), which causes a shift of the septum toward the RV, thereby increasing LVEDV. We investigated these responses in anesthetized dogs instrumented with ventricular pressure catheters, flat fluid-containing pericardial balloons, implanted myocardial ultrasonic crystals, and intramyocardial (IM) electromyograms (EMGs) before and after the induction of acute LV failure.

METHODS

Six mongrel dogs of either sex and body weight of 37 kg (range: 33–39 kg) were prepared, and pressure measurements were recorded as previously described (10). To monitor pericardial pressure, flat fluid-containing balloons were inserted over the RV and LV lateral walls (19). In each dog, eight 2- to 3-mm sonomicrometric crystals (Sonometrics, London, Ontario, Canada) were implanted subendocardially (Fig. 1). Five of the crystals also had IM-EMGs. Data were digitized at 200 Hz.

Pacemaker leads were attached epicardially on the middle third of the LV lateral wall, endocardially on the basal septum in the RV outflow tract, and on the posterior wall of the right atrium. Constrict-
Animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Rikshospitalet, Oslo, Norway). The National Animal Experimentation Board approved the study. Animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Rikshospitalet, Oslo, Norway).

Interventions

Pacemaker programming. Two modes of ventricular pacing were used: 1) LV pacing (isolated pacing in the LV lateral wall) and 2) biventricular pacing (pacing in both ventricles). LV pacing was performed to delay RV activation and filling relative to LV activation and filling. Atrioventricular intervals between 30 and 120 ms were initially tested. We found that a short atrioventricular delay (50 ms) and atrial pacing achieved our goal of delaying RV pacing relative to LV pacing. This pacing modality consistently activated the septum from the LV lateral wall, preventing fusion of the activation wave from the pacing site with the normal activation wave. Atrioventricular delays above 50 ms lead to inconsistent activation sequences and therefore limited delays in RV filling relative to LV filling. We also performed the more commonly used biventricular pacing, with an atrioventricular delay of 80 ms and an interventricular delay of 4 ms, to examine its hemodynamic effects in hearts with normal electrical conduction.

Pulmonary artery constriction. Inflation of the constrictor increased peak RV pressure (RVP) significantly during baseline and HF (Table 1). The inflation was held constant during pacing interventions and transient caval constrictions.

Acute HF by coronary microembolization. Acute LV global ischemia was induced by repeated injections of a 55-μm microspheres (Distrilab, Leusden, The Netherlands) into the left main coronary artery (17). The embolization procedure was ceased once acute HF was evident, as indicated by increased mean left atrial pressure and reduced RV peak pressure (RVP) significantly during baseline and HF (18).

Experimental Protocol

Measurements were obtained during baseline and during baseline with pulmonary artery constriction. Acute HF was subsequently induced by repeated injections of a 55-μm microspheres (Distrilab, Leusden, The Netherlands) into the left main coronary artery (17). The embolization procedure was ceased once acute HF was evident, as indicated by increased mean left atrial pressure and reduced RV peak pressure (RVP) significantly during baseline and HF (18).

Fig. 1. Schematic illustration of ultrasound crystal placements in the myocardium. Five of the crystals included bipolar electrodes for measurements of intramyocardial electromyograms (IM-EMGs). RV, right ventricle; LV, left ventricle.

Table 1. Hemodynamic variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 6)</th>
<th>Change during LV Pacing (n = 5)</th>
<th>Change during LV Pacing Before pacing</th>
<th>Change during LV Pacing After pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, ml</td>
<td>87 (73–105)</td>
<td>5 (3–7)</td>
<td>77 (68–88)</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>0.4 (0.2–0.6)</td>
<td>0.6 (0.4–0.8)</td>
<td>7.2 (5.8–8.4)</td>
<td>6.6 (4.7–7.7)</td>
</tr>
<tr>
<td>LV dP/dt, mmHg/s</td>
<td>881 (74.9)</td>
<td>40 (36.1)</td>
<td>81 (74.9)</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>PTS, mmHg</td>
<td>0.8 (0.5–2.4)</td>
<td>1.2 (0.8–1.6)</td>
<td>4.9 (3.5–8.3)</td>
<td>4.3 (3.0–7.9)</td>
</tr>
<tr>
<td>Maximum RV pressure, mmHg</td>
<td>28 (22–28)</td>
<td>42 (36.1)</td>
<td>81 (74.9)</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>LV peak filling, ml/s</td>
<td>0.8 (0.5–1.3)</td>
<td>1.2 (0.8–1.6)</td>
<td>4.9 (3.5–8.3)</td>
<td>4.3 (3.0–7.9)</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>87 (73–105)</td>
<td>5 (3–7)</td>
<td>77 (68–88)</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>0.4 (0.2–0.6)</td>
<td>0.6 (0.4–0.8)</td>
<td>7.2 (5.8–8.4)</td>
<td>6.6 (4.7–7.7)</td>
</tr>
<tr>
<td>RV peak filling, ml/s</td>
<td>0.8 (0.5–1.3)</td>
<td>1.2 (0.8–1.6)</td>
<td>4.9 (3.5–8.3)</td>
<td>4.3 (3.0–7.9)</td>
</tr>
<tr>
<td>RV end-diastolic volume, ml</td>
<td>87 (73–105)</td>
<td>5 (3–7)</td>
<td>77 (68–88)</td>
<td>42 (32–51)</td>
</tr>
<tr>
<td>RV end-diastolic pressure, mmHg</td>
<td>0.4 (0.2–0.6)</td>
<td>0.6 (0.4–0.8)</td>
<td>7.2 (5.8–8.4)</td>
<td>6.6 (4.7–7.7)</td>
</tr>
</tbody>
</table>

Values are given as medians with interquartile ranges in parentheses; *P < 0.05 compared with values with the pacemaker turned off; †P < 0.05 compared with values with the pacemaker turned off; ‡P < 0.05 compared with values during baseline. LV dP/dt, maximum rate of change in LV pressure; PTS, transeptal pressure gradient; P0, peak RV pressure; Pp, pericardial pressure; Ph, pressure during heart failure; LVEDV, LV end-diastolic volume; LVEDP, LV end-diastolic pressure; Pp, peak systolic pressure; Pp, pericardial pressure; Ph, pressure during heart failure.
induced, and measurements were repeated without pulmonary artery constriction and finally with pulmonary artery constriction (Table 1). During each of the experimental conditions, recordings were performed with and without pacing.

**Definitions and Data Analysis**

**Timing.** The timing of regional myocardial electrical activation was defined as onset R in EMGs. Since LV pacing caused regional differences in the timing of electrical activation, there were also regional differences in the onset of systole. We therefore defined end diastole as the point in time when 50% of the LV was electrically activated according to IM-EMGs (activation of two EMGs) in the equatorial plane (Fig. 1). Peak negative LV dP/dt defined end systole.

**Pressures.** P_{Ts} was calculated as LVP – RVP measured at end diastole. LV transmural pressure was calculated as LVP – LV pericardial pressure. Pericardial pressures were measured in diastole as their mean values during the time interval from minimum LVP to end diastole (16).

**Data analysis.** Values represent the mean of three consecutive heart cycles recorded with the respirator turned off. LV volume was calculated by sonomicrometry using a three-axis ellipsoid model as follows: 

\[
\text{LV volume} = \left( \pi \times \text{longitudinal diameter} \times \text{anteroposterior diameter} \times \text{septum-to-LV free wall diameter}/6 \right)
\]

Improvements in filling were assessed by increases in LVEDV at similar intracavitary end-diastolic pressures (EDPs). In about two-thirds of cases, LVEDP was unaltered by pacing, and the change in LVEDV could be extracted directly from recordings when the pacemaker was turned on or off at similar LVEDPs. In the remaining cases, the change in LVEDV at a given LVEDP was measured by comparing the end-diastolic pressure-volume curves before and during pacing (Fig. 2, A, B, and D). This was necessary to exclude a load-mediated change in LVEDV.

Areas of LV pressure-segment length loops were used as indexes of regional work. SW was calculated as follows: (maximal LVP – EDP) × SV (8).

The onset of LV and RV filling was defined as the first diastolic crossover between atrial and ventricular pressures. A shift in the onset of filling was quantified as the change in timing of LV filling relative to RV filling (Fig. 3).

LV electrical and mechanical dyssynchrony was assessed using five IM-EMGs and six to eight crystal segments representing circumferential and longitudinal myocardial contraction. Dyssynchrony was quantified as the SD of time between onset R in the ECG and onset R.

**Fig. 2.** Representative LV end-diastolic pressure-volume curves recorded before and during LV lateral wall pacing. The curves were constructed during transient caval constriction. A: LV pacing during baseline produced a rightward shift of the end-diastolic pressure-volume relation, which implies that LV volume was larger at any given LV end-diastolic pressure. B: LV pacing during heart failure (HF) did not change the end-diastolic pressure-volume relation. C: Pulmonary artery constriction caused a leftward and upward shift of the end-diastolic pressure-volume curve demonstrating impaired filling of the LV. D: LV pacing during HF with pulmonary artery constriction caused a rightward shift of the end-diastolic pressure-volume curve, similar to the response in A.
in IM-EMGs for electrical events (ElecDysSD) and the SD of time from onset R in the ECG to peak segmental shortenings for mechanical events (MechDysSD).

The time constant of the exponential LVP decay ($\tau$) during isovolumic relaxation was calculated and indicates the rate of LV relaxation (22). The peak rapid filling rate was measured as the maximum time derivative of the volume calculation during early filling.

**Statistical analysis.** Values are expressed as medians (interquartile ranges). Significance for median difference was assessed using Wilcoxon paired test. For multiple comparisons, Friedman’s two-way analysis (SPSS 18.0, SPSS, Chicago, IL) was used. $P < 0.05$ was considered significant. Linear regression was used to assess changes induced during pacing and to determine possible predictors of the observed increase in LVEDV during LV pacing. The residuals were normally distributed in these latter analyses.

**RESULTS**

The hemodynamic status of the animals is shown in Table 1. Coronary microembolisation induced acute LV failure as evident by increased LVEDP and reduced SV. The elevated LVEDP was accompanied by an increase in PTS. Pulmonary artery constriction resulted in an increase in RV peak systolic pressure and caused a reduction in LVEDV during baseline and HF (Table 1). The reduction in LVEDV was due to leftward displacement of the interventricular septum, as indicated by a significant reduction in septum-to-LV free wall diameter and increase in septum-to-RV free wall diameter. This was associated with reductions in Prs during baseline and HF (Table 1).

Pulmonary artery constriction resulted in a leftward and up-
ward shift of the LV end-diastolic pressure-volume relationship (Fig. 2C).

Pericardial pressures increased significantly and uniformly over both ventricles during HF (Table 1).

**Timing of Electrical Activation and Filling**

Electrical activation of the two ventricles was nearly simultaneous during spontaneous heart rhythm. As predicted, LV pacing resulted in delayed activation of the RV lateral wall (Fig. 3).

During spontaneous heart rhythm, the onset of LV and RV filling occurred almost simultaneously (−5 ms (interquartile range: −15 to 14 ms), not significant (NS)). The change in electrical activation during LV pacing led to an earlier onset of LV compared with RV filling by 19 ms (interquartile range: 14–24 ms, \( P < 0.05 \)) for all four experimental conditions. A representative example is shown in Fig. 3.

Biventricular pacing had only a modest effect on the timing of electrical activation and caused no significant changes in the time shift of onset filling (5 ms (interquartile range: −4 to 5 ms), NS).

**LV Filling and \( P_{TS} \)**

LV pacing resulted in an increase in LVEDV in all situations except in HF alone (Table 1). The increase in LVEDV was attributed to a significant increase \( (P < 0.01) \) in the septum-to-LV lateral wall diameter (1.9% (interquartile range: 0.7–2.7%)) and a reduction \( (P < 0.01) \) in the septum-to-RV lateral wall diameter (−2.4% (interquartile range: −4.8 to −1.0%)), indicating a rightward shift of the septum during LV pacing.

There was a good correlation between changes in LVEDV and changes in the septum-to-RV lateral wall diameter \( (R = 0.63) \) and septum-to-LV lateral wall diameter \( (R = 0.66; \) Fig. 4, A and B). No significant changes in the combined LV and RV transverse diameter (LV lateral wall to RV lateral wall), LV anteroposterior diameter, or LV long-axis diameter were observed. Thus, the increased volume during LV pacing was due to a shift of the septum toward the RV.

\( P_{TS} \) increased during LV pacing (Fig. 3), and there was a significant correlation between changes in LVEDV and \( P_{TS} \) (Fig. 4C).

Biventricular pacing caused no significant change in LVEDV (Table 3). There were no significant changes in pericardial pressures or LV transmural pressures during LV or biventricular pacing.

Linear regression analysis was used to assess possible predictors of improved filling (increased LVEDV) related to pacing. These predictors included \( P_{TS} \), pericardial pressures (both before pacing), and the interventricular time shift of onset filling. \( P_{TS} \) before pacing was the only variable that had a significant \( (P < 0.05) \) correlation with the change in LVEDV.

LV pacing led to a significant impairment in global LV relaxation, as shown by the increase in both \( \tau \) and LV \( dP/dt_{\text{min}} \). Similiar changes were seen in HF during LV pacing but failed to reach statistical significance.

**Pacing-Induced LV Dyssynchrony**

LV pacing induced significant increments in ElecDysSD, QRS width, and MechDysSD during baseline, indicating substantial electrical and mechanical dyssynchrony, respectively (Table 2).

After the induction of HF, there was unaltered synchronous electrical activation of the LV, as shown by the unchanged low values of ElecDysSD and QRS width (Table 2). The induction of HF changed mechanical events significantly with an increase in MechDysSD, indicating mechanical dyssynchrony (Table 2). LV pacing of the failing LV caused a significant increase in ElecDysSD and QRS width, demonstrating electrical dyssynchrony, and a further increase in MechDysSD (NS; Table 2).

Biventricular pacing increased ElecDysSD in each experiment, except for one experiment during baseline. The increase was of small magnitude (Table 2) and did not reach statistical significance. There was no significant increase in MechDysSD during biventricular pacing.
Systolic Function During Pacing

LV pacing induced heterogeneous contraction patterns. The most striking changes were a reduction in regional work in the early activated LV lateral wall and increased work in the late-activated septum (Fig. 5). On average, LV pacing reduced regional work in the lateral wall by −75% (interquartile range: −107% to −59%) during baseline (P < 0.05) and by −70% (interquartile range: −122% to −38%) during HF (P < 0.05). The septum, however, demonstrated an increase in work by 15% (interquartile range: −3% to 62%) during baseline (NS) and by 38% (interquartile range: −14% to 78%, P < 0.05) during HF.

LV pacing led to reductions in SV, LV dP/dtmax, and SW during baseline and HF (Table 1 and Fig. 6) in all four experimental conditions. RV systolic function was also reduced; however, these changes were not significant during all interventions. Biventricular pacing led to significant reductions in global systolic function of the LV during baseline with a rightward shift of the septum. There was, however, no improvement in cardiac output since the expected preload-mediated increase in SW was counteracted by pacing-induced dyssynchrony.

Biventricular pacing caused no significant difference in timing of filling of the two ventricles or increase in LVEDV. Similar to LV pacing, however, biventricular pacing reduced LV systolic function. This was most likely caused by the induction of slight electrical dyssynchrony, which resulted in some degree of contractile heterogeneity. Importantly, the negative effects on systolic function with biventricular pacing were less marked than with LV pacing.

Mechanism of the Increase in LVEDV During LV Pacing

LV pacing led to electrical activation of the LV before the RV. This resulted in an earlier onset of filling of the LV relative to the RV, consistent with the hypothesis. During baseline conditions, LV pacing increased Prs, which explains the rightward shift of the septum. Thus, LVEDV increased at the expense of RV volume. This was reflected in a rightward shift of the LV end-diastolic pressure-volume relationship (Fig. 2A). There was no suggestion that the LV dilated as a consequence of the reduced LV systolic function, as there was no change in LVEDP or LV transmural EDP when we compared measurements before and after pacing. We did not observe a reduction in pericardial pressure to explain the improvement in filling. A similar response was also observed during LV pacing of the failing heart after RVPs had been elevated by pulmonary artery constriction (Fig. 2D).

DISCUSSION

We investigated potential mechanisms of improved cardiac function during pacing in hearts with a narrow QRS. The present study was performed in a dog model during baseline conditions and during acute LV failure. LV pacing gave the LV a head start in filling relative to the RV, which resulted in a moderate increase in LVEDV. This increase was attributed to a rightward shift of the septum. There was, however, no improvement in cardiac output since the expected preload-mediated increase in SW was counteracted by pacing-induced dyssynchrony.

Table 2. Electrical and mechanical indexes

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 6)</th>
<th></th>
<th>Heart Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pacing</td>
<td>LV pacing</td>
<td>Biventricular pacing</td>
</tr>
<tr>
<td>Electrical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS width, ms</td>
<td>53 (40–63)</td>
<td>114 (99–128)*</td>
<td>64 (49–90)</td>
</tr>
<tr>
<td>ElecDysSD, ms</td>
<td>7 (3–7)</td>
<td>25 (24–28)*</td>
<td>8 (5–11)</td>
</tr>
<tr>
<td>Mechanical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MechDysSD, ms</td>
<td>22 (6–35)</td>
<td>58 (39–88)*</td>
<td>12 (11–36)</td>
</tr>
</tbody>
</table>

Values are given as medians with interquartile ranges in parentheses; n, number of animals. ElecDysSD, SD of time between onset R in the ECG and onset R in intramyocardial electromyograms; MechDysSD, SD of time from onset R in the ECG to peak segmental shortenings. *P < 0.05 compared with values with the pacemaker turned off; †P < 0.05 compared with values during baseline.
When LV pacing was applied in the failing ventricle, there was no shift of the end-diastolic pressure-volume relationship (Fig. 2B). We propose that this was due to the high PTS during HF causing a rightward displacement of the septum before pacing. When HF was combined with elevation of pulmonary artery pressure, which reduced PTS and shifted the septum leftward, LV pacing caused an increase in LVEDV. The dependency of septal position on PTS is consistent with previous studies (9, 13). The pacing-induced increase in LVEDV was not related to a decline in LV systolic function but was a function of PTS and septal position before pacing.

**Mechanism of the Reduction in LV Function During LV Pacing**

There was an overall reduction in SW by LV and biventricular pacing despite the improved LV filling. Therefore, the positive effect of pacing on preload was offset by the reduction in systolic function. The negative effect on systolic function was most marked with LV pacing. This was attributed to induction of dyssynchrony in ventricles with an intact electrical conduction system. Biventricular pacing also had a negative effect on systolic function but to a lesser degree, consistent with the smaller effect on electrical synchrony. In contrast to normal electrical activation, which propagates rapidly to all parts of the myocardium, LV and biventricular pacing change the site of first electrical activation and cause an altered propagation of electrical impulse throughout the myocardium. The pattern of contraction during LV pacing was a mirror image of the pattern in left bundle branch block (Fig. 5) (9). LV pacing also increased LV dP/dt max and τ, indicating slowing of relaxation. Since there was an increase in LVEDV with an unaltered LVEDP, the slowing of relaxation did not appear to outweigh the positive effects of pacing on LV filling.

The discrepancy between the present experimental study and the clinical study by Williams et al. (23) may be explained by differences in the hemodynamic status of an acute open-chest animal model and patients with chronic congestive HF. The pericardium has a considerable additive effect on ventricular function before pacing.

---

**Table 3. Hemodynamic changes during biventricular pacing**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 6)</th>
<th>Baseline with Pulmonary Artery Constriction (n = 6)</th>
<th>Heart Failure (n = 6)</th>
<th>Heart Failure with Pulmonary Artery Constriction (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume, ml</td>
<td>1.7 (2.2 to 0.3)*</td>
<td>1.0 (1.7 to 0.1)</td>
<td>-0.4 (1.5 to 0.2)</td>
<td>-0.6 (1.0 to 0.3)</td>
</tr>
<tr>
<td>Stroke work, mmHg/ml</td>
<td>-159 (220 to 49)*</td>
<td>-126 (214 to 68)*</td>
<td>-46 (168 to 2)</td>
<td>-69 (106 to 0)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>-1 (2 to 0)</td>
<td>0 (2 to 2)</td>
<td>0 (1 to 2)</td>
<td>0 (2 to 0)</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>0.1 (0.2 to 0.1)</td>
<td>0.0 (0.1 to 0.1)</td>
<td>0.0 (1.0 to 1)</td>
<td>0.2 (1.0 to 0.1)</td>
</tr>
<tr>
<td>LV dP/dt max, mmHg/s</td>
<td>-60 (102 to 18)*</td>
<td>-83 (97 to 9)</td>
<td>-39 (66 to 2)</td>
<td>-50 (63 to 28)</td>
</tr>
<tr>
<td>RV dP/dt max, mmHg/s</td>
<td>-12 (30 to 3)</td>
<td>-21 (26 to 11)*</td>
<td>-15 (33 to 14)</td>
<td>-11 (25 to 6)</td>
</tr>
<tr>
<td>Maximum LV pressure, mmHg</td>
<td>-3 (5 to 0)*</td>
<td>-4 (7 to 2)*</td>
<td>-2 (-4 to 1)</td>
<td>-2 (-5 to 2)*</td>
</tr>
<tr>
<td>Maximum RV pressure, mmHg</td>
<td>-1 (1 to 0)</td>
<td>-1 (1 to 0)</td>
<td>0 (1 to 0)</td>
<td>-1 (1 to 1)</td>
</tr>
<tr>
<td>LV dP/dt min, mmHg/s</td>
<td>82 (35-119)*</td>
<td>136 (64-193)*</td>
<td>53 (12-82)</td>
<td>52 (37-85)*</td>
</tr>
<tr>
<td>RV dP/dt min, mmHg/s</td>
<td>12 (3-24)*</td>
<td>18 (13-43)*</td>
<td>9 (2-41)</td>
<td>9 (-7 to 13)</td>
</tr>
<tr>
<td>τ, ms</td>
<td>0 (0 to 2)</td>
<td>0 (0 to 2)</td>
<td>0 (2 to 3)</td>
<td>1 (2-3)</td>
</tr>
<tr>
<td>Peak rapid filling rate, ml/s</td>
<td>-7 (-35 to 1)</td>
<td>0 (10 to 8)</td>
<td>-6 (12 to 4)</td>
<td>-3 (-4 to 0)</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>-0.7 (1.1 to 0.4)</td>
<td>-0.2 (1.3 to 0.1)</td>
<td>-0.5 (1.3 to 0.2)</td>
<td>-0.3 (0.9 to 0.1)</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>-0.1 (0.3 to 0.2)</td>
<td>0.0 (-0.5 to 0.0)</td>
<td>-0.4 (0.9 to 0.3)</td>
<td>-0.1 (0.4 to 0.3)</td>
</tr>
<tr>
<td>PT, mmHg</td>
<td>0.1 (0.1 to 0.2)</td>
<td>0.2 (1.0 to 0.0)</td>
<td>-0.2 (0.7 to 0.1)</td>
<td>-0.1 (0.3 to 0.0)</td>
</tr>
<tr>
<td>LV Pp, mmHg</td>
<td>-0.4 (0.8 to 0.0)</td>
<td>0.0 (-0.2 to 0.2)</td>
<td>-0.2 (-0.5 to 0.1)</td>
<td>-0.1 (-1.4 to 0.2)</td>
</tr>
</tbody>
</table>

Values are given as medians with interquartile ranges in parentheses of changes with biventricular pacing; n, number of animals. *P < 0.05 compared with values with the pacemaker turned off.
artery constriction to induce pressure overload has been used in pacing could be potentiated. The same method of pulmonary end-diastolic RV pressure and therefore a more marked decrease in RVP by pulmonary constriction and does not account for long-term responses that may be modified by processes such as fibrosis and remodeling. In addition, delayed ventricular interactions and pacing-induced dyssynchrony are shown to maintain pericardial constraint (16). Therefore, we believe the principle findings and conclusions with regard to CRT in patients with narrow QRS in future clinical studies.

**Conclusions**

The present experimental study demonstrates that LV pacing can improve LV filling. This is related to early LV activation, which gives the LV a head start in filling and shifts the septum rightward. This occurs at a considerable cost, with reduction in systolic function due to pacing-induced dyssynchrony. This “double-edged sword” effect of pacing should be considered before applying CRT in patients with narrow QRS in future clinical studies.

**ACKNOWLEDGMENTS**

The authors thank Dr. Opdahl for reviewing the manuscript and A. Pamplona for surgical assistance.

**GRANTS**

E. Boe and K. Russell were recipients of research fellowships from The Norwegian Council of Cardiovascular Diseases and The University of Oslo, respectively. E. W. Remme was a recipient of a postdoctoral fellowship from KG Jebsen Cardiac Research Center.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


