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

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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, Oslo, Norway

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

Boe E, Russell K, Remme EW, Gjesdal O, Smiseth OA, Skulstad H. Cardiac responses to left ventricular pacing in hearts with normal electrical conduction: beneficial effect of improved filling is counteracted by dyssynchrony. Am J Physiol Heart Circ Physiol 307: H370–H378, 2014. First published June 6, 2014; doi:10.1152/ajpheart.00089.2014.—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.

Address for reprint requests and other correspondence: H. Skulstad, Dept. of Cardiology, Oslo Univ. Hospital, Rikshospitalet, PO Box 4950 Nydalen, Oslo 0424, Norway (e-mail: helge.skulstad@rikshospitalet.no).
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) performed to delay RV activation and filling relative to LV activation. This pacing modality consistently activated the septum from the pacing site with the normal activation wave. Atrioventricular delay of 80 ms and an interventricular delay of 4 ms, therefore limited delays in RV filling relative to LV filling. We also initially tested. We found that a short atrioventricular delay (50 ms) performed to delay RV activation and filling relative to LV activation. This pacing modality consistently activated the septum 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 activation.

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 microsphere solution (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 peak LV pressure (LVP) and stroke volume (SV).

Experimental Protocol

Measurements were obtained during baseline and during baseline with pulmonary artery constriction. Acute HF was subsequently

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**Table 1. Hemodynamic variables**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Baseline (n = 6)</th>
<th>Baseline with Pulmonary Artery Constriction (n = 6)</th>
<th>Heart Failure with Pulmonary Artery Constriction (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume, ml</td>
<td>21.1 (17.2–25.3)</td>
<td>23.2 (17.5–32.7)</td>
<td>19.5 (15.2–23.7)</td>
</tr>
<tr>
<td>Stroke work, mmHg·ml</td>
<td>1,404 (1,372–2,087)</td>
<td>1,740 (1,520–2,274)</td>
<td>1,244 (810–1,296)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>111 (90–130)</td>
<td>10 (5–14)*</td>
<td>113 (101–130)</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>2.4 (2.2–2.6)</td>
<td>2.9 (2.6–3.2)*</td>
<td>2.5 (2.2–3.2)*</td>
</tr>
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<td>Stroke volume, ml</td>
<td>21.1 (17.2–25.3)</td>
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</tbody>
</table>

Values are given as medians with interquartile ranges in parentheses. n, number of animals/group; LV, left ventricular; RV, right ventricular; P<0.05 compared with values during baseline; †P<0.05 compared with values 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.** PTs 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: [LV volume = (π × longitudinal diameter × anteroposterior diameter × septum-to-LV free wall diameter)/6]. 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.

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**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 (τ) 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 Pτs during baseline and HF (Table 1). Pulmonary artery constriction resulted in a leftward and up-

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**Fig. 3.** Representative traces showing the time shift of LV relative to RV filling with LV lateral wall pacing. **Left** (pacing off): there was synchronous activation of the LV and RV as indicated by the near simultaneous onset of R-waves in LV and RV lateral wall IM-EMGs (bottom). In this case, the onset of RV filling preceded onset of LV filling by 10 ms. **Right** (pacing on): during LV pacing, there was earlier electrical activation of the LV lateral wall than of the RV lateral wall. The delay in activation of the RV is represented by the time difference between the red (LV) and blue (RV) vertical lines in the bottom. The onset of LV filling now preceded RV filling by 10 ms, as indicated by the vertical lines in the top. Hence, LV pacing induced an interventricular time shift of onset filling of 20 ms. Please note that the end-diastolic transseptal pressure gradient increased once LV pacing was turned on. LVP, LV pressure; LAP, left atrial pressure; RVP, RV pressure; RAP, right atrial pressure.
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<sub>TS</sub>

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<sub>TS</sub> increased during LV pacing (Fig. 3), and there was a significant correlation between changes in LVEDV and P<sub>TS</sub> (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<sub>TS</sub>, pericardial pressures (both before pacing), and the interventricular time shift of onset filling. P<sub>TS</sub> 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 τ and LV dP/dt<sub>min</sub>. Similar changes were seen in HF during LV pacing but failed to reach statistical significance.

Pacing-Induced LV Dyssynchrony

LV pacing induced significant increments in ElecDys<sub>SD</sub>, QRS width, and MechDys<sub>SD</sub> 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 ElecDys<sub>SD</sub> and QRS width (Table 2). The induction of HF changed mechanical events significantly with an increase in MechDys<sub>SD</sub>, indicating mechanical dyssynchrony (Table 2). LV pacing of the failing LV caused a significant increase in ElecDys<sub>SD</sub> and QRS width, demonstrating electrical dyssynchrony, and a further increase in MechDys<sub>SD</sub> (NS; Table 2).

Biventricular pacing increased ElecDys<sub>SD</sub> 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 MechDys<sub>SD</sub> during biventricular pacing.

![Fig. 4](http://ajpheart.physiology.org/)

Fig. 4. Linear regression analysis of the changes induced by LV pacing showing a significant relationship between the LV end-diastolic volume versus RV diameter (A), LV diameter (B), and transseptal pressure gradient (C).
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/dt max, 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).

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.

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.
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 P\textsubscript{TS} during HF causing a rightward displacement of the septum before pacing. When HF was combined with elevation of pulmonary artery pressure, which reduced P\textsubscript{TS} and shifted the septum leftward, LV pacing caused an increase in LVEDV. The dependency of septal position on P\textsubscript{TS} 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 P\textsubscript{TS} 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\textsubscript{max} and \( \tau \), 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

**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 (\text{-2.2 to -0.3})^*)</td>
<td>(-1.0 (\text{-1.7 to -0.1}))</td>
<td>(-0.4 (\text{-1.5 to 0.2}))</td>
<td>(-0.6 (\text{-1.0 to 0.3}))</td>
</tr>
<tr>
<td>Stroke work, mmHg/ml</td>
<td>(-159 (\text{-220 to -49})^*)</td>
<td>(-126 (\text{-214 to -68})^*)</td>
<td>(-46 (\text{-168 to -2}))</td>
<td>(-69 (\text{-106 to 0}))</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>(-1 (\text{-2 to 0}))</td>
<td>(0 (\text{-2 to 2}))</td>
<td>(0 (\text{-1 to 2}))</td>
<td>(0 (\text{-2 to 0}))</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>(0.1 (\text{-0.2 to 0.1}))</td>
<td>(0.0 (\text{-0.1 to 0.1}))</td>
<td>(0.0 (\text{-1.0 to 1}))</td>
<td>(0 (-0.3 to 0.1))</td>
</tr>
<tr>
<td>LV dP/dt\textsubscript{max}, mmHg/s</td>
<td>(-60 (\text{-102 to -18})^*)</td>
<td>(-83 (\text{-97 to -9}))</td>
<td>(-39 (\text{-66 to 2}))</td>
<td>(-50 (\text{-63 to -28}))</td>
</tr>
<tr>
<td>RV dP/dt\textsubscript{max}, mmHg/s</td>
<td>(-12 (\text{-30 to 3}))</td>
<td>(-21 (\text{-26 to -11})^*)</td>
<td>(-15 (\text{-33 to 14}))</td>
<td>(-11 (\text{-25 to -6}))</td>
</tr>
<tr>
<td>Maximum LV pressure, mmHg</td>
<td>(-3 (\text{-5 to 0})^*)</td>
<td>(-4 (\text{-7 to -2})^*)</td>
<td>(-2 (\text{-4 to 1}))</td>
<td>(-2 (\text{-5 to -2})^*)</td>
</tr>
<tr>
<td>Maximum RV pressure, mmHg</td>
<td>(-1 (\text{-1 to 0}))</td>
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<td>(0 (\text{-1 to 0}))</td>
<td>(-1 (\text{-1 to 1}))</td>
</tr>
<tr>
<td>LV dP/dt\textsubscript{min}, mmHg/s</td>
<td>(82 (\text{55-119})^*)</td>
<td>(136 (\text{64-193})^*)</td>
<td>(53 (\text{12-82}))</td>
<td>(52 (\text{37-85})^*)</td>
</tr>
<tr>
<td>RV dP/dt\textsubscript{min}, mmHg/s</td>
<td>(12 (\text{3-24})^*)</td>
<td>(18 (\text{13-43})^*)</td>
<td>(9 (\text{2-41}))</td>
<td>(9 (\text{7-13}))</td>
</tr>
<tr>
<td>(\tau), ms</td>
<td>(0 (\text{1 to 3}))</td>
<td>(0.0 (\text{0.2 to 2}))</td>
<td>(2 (\text{-3}))</td>
<td>(1 (\text{-2}))</td>
</tr>
<tr>
<td>Peak rapid filling rate, ml/s</td>
<td>(-7 (\text{-35 to -2}))</td>
<td>(0 (\text{-10 to 8}))</td>
<td>(-6 (\text{-12 to -4}))</td>
<td>(-3 (\text{-4 to 0}))</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>(-0.7 (\text{-1.1 to -0.4}))</td>
<td>(-0.2 (\text{-1.3 to 0.1}))</td>
<td>(-0.5 (\text{-1.3 to 0.2}))</td>
<td>(-0.3 (\text{-0.9 to 0.1}))</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>(-0.1 (\text{-0.3 to 0.2}))</td>
<td>(0.0 (\text{-0.5 to 0.0}))</td>
<td>(-0.4 (\text{-0.9 to 0.3}))</td>
<td>(-0.1 (\text{-0.4 to 0.3}))</td>
</tr>
<tr>
<td>P\textsubscript{ts}, mmHg</td>
<td>(-0.1 (\text{-0.1 to 0.2}))</td>
<td>(-0.2 (\text{-1.0 to 0.0}))</td>
<td>(-0.2 (\text{-0.7 to -0.1}))</td>
<td>(-0.1 (\text{-0.3 to 0.0}))</td>
</tr>
<tr>
<td>LV P\textsubscript{cP}, mmHg</td>
<td>(-0.4 (\text{-0.8 to 0.0}))</td>
<td>(0.0 (\text{-0.2 to 0.2}))</td>
<td>(-0.2 (\text{-0.5 to 0.1}))</td>
<td>(-0.1 (\text{-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.
interaction (11). In particular, it is possible that pericardial pressure may be more elevated in chronic HF, which would strengthen ventricular interactions during LV pacing. This could result in a larger pacing-induced increase in LVEDV than observed in the present study.

Another possibility is that patients with chronic HF and narrow QRS have “concealed” electrical conduction delay that is partly corrected by CRT (12). Furthermore, the cutoff of 120 ms does not take into account characteristics such as sex or heart size.

Clinical Aspects

The present study showed that LV and biventricular pacing reduced LV function in hearts with narrow QRS. If these observations are valid for patients with HF, it implies that CRT has benefit primarily in patients with electrical dyssynchrony. These results may explain the disappointing findings in the Echo-CRT trial, which found higher mortality (11.1%) in the treatment group compared with the control group (6.4%) (15).

The concept of an earlier onset of filling of the LV could be an important factor in situations where there is abnormal conduction and a high degree of septal limitation of LV filling, such as in patients with left bundle branch block and pulmonar hypotension due to LV failure, in whom the septum is shifted leftward. This may be one of the reasons why LV pacing has shown to be as good as biventricular pacing in some patients in need of CRT (14). Theoretically, these patients may, in addition to the improvement in electrical dyssynchrony and systolic function, also benefit from improved filling during LV pacing. Further research is needed to explore this hypothesis.

Limitations

The present study used an experimental animal model in which pressure levels and ventricular function were modified by anesthesia and surgery. The pacing responses, however, were tested over a wide range of LV and RV diastolic pressures and were studied before and after the induction of HF. The model included a loosely resutured pericardium, which has shown to maintain pericardial constraint (16). Therefore, we believe the principle findings and conclusions with regard to ventricular interactions and pacing-induced dyssynchrony are valid, although the magnitude of the responses may differ in the heart in an otherwise intact organism.

This study only evaluates acute, short-term effects of pacing and increases 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 LV lateral wall activation could be concealed within a normal QRS duration. We were unable to study the effect of pacing in this situation, which requires regional ablation. This could be tested in future studies. However, our main findings should caution the use of CRT in patients without electrical dyssynchrony.

Pulmonary artery constriction led to a limited reduction in PTrs. In a model with chronic pulmonary hypertension, there could be a progressive and more marked increase in the end-diastolic RV pressure and therefore a more marked decrease in PTrs. In these situations, the positive effects of LV pacing could be potentiated. The same method of pulmonary artery constriction to induce pressure overload has been used in a previous study (13). Others methods to induce pulmonary pressure overload, such as clot infusion (1) or pharmacological agents, might be a better method to reflect normal physiology. The responses to these methods could, however, be difficult to control and are nonreversible.

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


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AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00089.2014 • www.ajpheart.org


