Myocardial Infarction Does Not Preclude Electrical and Hemodynamic Benefits of Cardiac Resynchronization Therapy in Dyssynchronous Canine Hearts

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Background—Several studies suggest that patients with ischemic cardiomyopathy benefit less from cardiac resynchronization therapy. In a novel animal model of dyssynchronous ischemic cardiomyopathy, we investigated the extent to which the presence of infarction influences the short-term efficacy of cardiac resynchronization therapy.

Methods and Results—Experiments were performed in canine hearts with left bundle branch block (LBBB, n=19) and chronic myocardial infarction, created by embolization of the left anterior descending or left circumflex arteries followed by LBBB (LBBB+left anterior descending infarction [LADi; n=11] and LBBB+left circumflex infarction [LCXi; n=7], respectively). Pacing leads were positioned in the right atrium and right ventricle and at 8 sites on the left ventricular (LV) free wall. LV pump function was measured using the conductance catheter technique, and synchrony of electrical activation was measured using epicardial mapping and ECG. Average and maximal improvement in electric resynchronization and LV pump function by right ventricular LV pacing was similar in the 3 groups; however, the site of optimal electrical and mechanical benefit was LV apical in LBBB hearts, LV midlateral in LBBB+LCXi hearts and LV basal-lateral in LBBB+LADi hearts. The best site of pacing was not the site of latest electrical activation but that providing the largest shortening of the QRS complex. During single-site LV pacing the range of atrioventricular delays yielding ≥70% of maximal hemodynamic effect was approximately 50% smaller in infarcted than noninfarcted LBBB hearts (P<0.05).

Conclusions—Cardiac resynchronization therapy can improve resynchronization and LV pump function to a similar degree in infarcted and noninfarcted hearts. Optimal lead positioning and timing of LV stimulation, however, require more attention in the infarcted hearts. (Circ Arrhythm Electrophysiol. 2010;3:361-368.)

Key Words: cardiac pacing, artificial heart failure myocardial infarction

Cardiac resynchronization therapy (CRT) improves cardiac pump function and clinical status and reduces morbidity and mortality in patients with moderate-to-severe heart failure and left bundle branch block (LBBB).1–4 Several reports indicate that patients with ischemic etiology of heart failure, or ischemic cardiomyopathy (ICM), benefit less from CRT than patients with nonischemic heart failure, or dilated cardiomyopathy.5–8 The explanation for these observations is, as of yet, not clear. Some studies found that the presence of scar in the posterolateral wall is a negative predictor of CRT response, especially if left ventricular (LV) pacing occurs within a scarred region (usually the posterolateral wall).7–9 In the case of pacing outside a scarred region, no study has systematically explored whether the site of LV stimulation influences the response to CRT and whether CRT can be equally effective in infarcted and noninfarcted hearts.

We hypothesized that because in most hearts the scar constitutes only a minor part of the ventricles, CRT can resynchronize and recoordinate the remaining majority of viable myocardium and, thus, be effective, albeit potentially using other optimal site and timing of stimulation than in nonischemic ventricles. To investigate this hypothesis, we have used a novel canine model of experimental LBBB with myocardial infarction (MI) created in the territories of the left anterior descending (LAD) and left circumflex (LCX) coronary arteries.
Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation (Wet op de Dierproeven) and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Animal Experimental Committee of our institution.

Experimental Setup

Experiments were performed on adult mongrel dogs of either sex and unknown age, weighing 28.8±3.5 kg. In 19 dogs, LBBB was induced. In 18 other dogs, MI was created in either the LAD or the LCX territory, followed 4 weeks later by induction of LBBB [LBBB+LAD infarction (LADi), n=11; LBBB+LCX infarction (LCXi), n=7]. All interventions and measurements were performed using pentothal induction, and maintenance of anesthesia by ventilation with O2 and N2O (1:2) in combination with IV infusion of midazolam (0.25 mg/kg/h) and IV sufentanyl (3 μg/kg/h).

Severe transmural MI was created by embolization using a suspension of ~1-mL dry volume polyvinyl alcohol foam particles (particle size, 300 to 500 μm) diluted in 15 mL of a 50:50 mixture of contrast material and saline. To prevent arrhythmias during and after the embolization procedure, dogs were administered amiodarone (200 mg tablet) orally at a dose of 400 mg/d for 3 days before the induction of MI. LBBB was created by radiofrequency ablation.

ECG and Hemodynamic Measurements

Surface ECG, right ventricular (RV) pressure and LV pressure-volume relations (conductance catheter) were measured and analyzed as described previously.11–13 Electrical activation of the ventricles was mapped using two flexible multielectrode bands with a total of 108 electrodes and an octapolar electrode catheter placed transvenously at the RV septum and analyzed as described earlier.12

CRT Protocol

Measurements were performed between a few hours to 4 weeks after induction of LBBB. Data from measurements performed at these variable times were combined after verifying that the effects of pacing were independent from the duration of LBBB. Electrodes on the epicardial bands were used to stimulate at the anterior, lateral, and posterior sites of basal and mid levels of the heart. Additional pacing leads were positioned at the epicardium of the LV apical and LV apicolateral wall. Additionally, pacing leads were positioned transvenously in the RV septum and analyzed as described earlier.12

Electric Mapping at Baseline

Local impulse conduction velocity in the myocardium was quantified as conduction time over the first 2 cm of LV epicardium from an LV pacing site (Figure 2, left). Conduction time was similar in the myocardium of LBBB hearts and in noninfarcted myocardium of infarcted LBBB hearts (~37 versus ~40 milliseconds [ms], respectively). In contrast, conduction time was significantly prolonged within or across an infarcted region (~55 ms).

Despite the slower conduction in the infarctions, total electrical activation time in the ventricles was not significantly different between the LBBB group and the combined LBBB+MI groups during atrial pacing (93 and 88 ms, respectively) and BiV pacing (both 81 ms) (Figure 2, right). Similarly, QRS duration did not differ between LBBB and LBBB+MI hearts at baseline and during BiV pacing (Table).

Pump Function at Baseline

During baseline RA pacing, RV end-diastolic and end-systolic pressure and end-diastolic LV pressure were significantly elevated in the LBBB+MI hearts. In addition, at baseline stroke volume and stroke work were 20% to 30%
lower in the LBBB+MI hearts than in the LBBB hearts (Table 1).

**General Effects of BiV Pacing on Resynchronization and Pump Function**

Figure 3 depicts that BiV pacing reduced total activation time by approximately 10% in both the LBBB and LBBB+MI groups. Similarly, BiV pacing increased the maximal rate of LV pressure rise (LV dP/dtmax) by ~13% in both groups. The mean increase in stroke work due to BiV pacing was larger in the LBBB group (~30%) than in the LBBB+MI group (~20%), but this difference was not statistically significant (P=0.36).

**Spatial Distribution of the Electrical and Hemodynamic Benefits of CRT**

Figure 4 shows the mean percent increase in electrical resynchronization (top row), LV dP/dtmax (middle row), and stroke work (bottom row) as a function of pacing location on the LV wall on a schematic 3D model of the ventricles. In all 3 groups of animals, pacing at almost all LV sites resulted in a favorable electrical and hemodynamic response to CRT, as indicated by the light blue, yellow, and red. In the LBBB group, maximal electrical resynchronization and hemodynamic improvement (dark red) occurred when pacing the apical LV regions, whereas in the LBBB+LADi group, the basolateral LV wall yielded the largest benefit. In
LBBB and LCXi hearts, pacing at the LV midlateral wall resulted in the maximum electrical and hemodynamic response. The similar intensity of red in corresponding maps of the 3 groups indicates that there was no significant intergroup difference in the maximal increase in resynchronization, LV dP/dtmax, or stroke work.

Figure 5 (top) presents the same data numerically, especially for the 4 sites along the LV lateral wall. The asterisks indicate the site with the largest increase in LV dP/dtmax in the 3 groups. The similar intensity of red in corresponding maps of the 3 groups indicates that there was no significant intergroup difference. The similar intensity of red in corresponding maps of the 3 groups indicates that there was no significant intergroup difference.

Table. Electrophysiological and Hemodynamic Variables During Baseline Atrial Pacing and During BiV Pacing in the LBBB and LBBB+MI Groups

<table>
<thead>
<tr>
<th></th>
<th>LBBB</th>
<th>LBBB+MI</th>
<th>%ΔLBBB-%ΔLBBB+MI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>BiV</td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Paced HR, bpm</td>
<td>116.5±10.5</td>
<td>117.4±11.1</td>
<td>125.6±14.8</td>
<td>1.25</td>
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<tr>
<td>QRS width, ms</td>
<td>116.3±7.88</td>
<td>99.9±11.7*</td>
<td>114.6±12.2</td>
<td>1.17</td>
</tr>
<tr>
<td>MIVA, ms</td>
<td>−26.5±6.6</td>
<td>−15.9±10.7*</td>
<td>−16.2±6.4*</td>
<td>−20.20</td>
</tr>
<tr>
<td>LVPmax, mm Hg</td>
<td>89.9±9.3</td>
<td>89.2±11.3</td>
<td>86.9±13.9</td>
<td>−3.31</td>
</tr>
<tr>
<td>LV dP/dtmax, mm Hg/s</td>
<td>1,504±207</td>
<td>1,693±283*</td>
<td>1,650±321*</td>
<td>0.36</td>
</tr>
<tr>
<td>LV dP/dtmin, mm Hg/s</td>
<td>−1353±212</td>
<td>−1408±285</td>
<td>−1551±340</td>
<td>2.85</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>6.0±2.1</td>
<td>5.4±3.1</td>
<td>13.3±5.9†</td>
<td>9.98</td>
</tr>
<tr>
<td>SV, mL</td>
<td>31.4±6.9</td>
<td>34.2±9.8</td>
<td>21.7±8.5†</td>
<td>5.23</td>
</tr>
<tr>
<td>SW, mm Hg x mL</td>
<td>1,877±413</td>
<td>2,410±995*</td>
<td>1,420±684*‡</td>
<td>8.65</td>
</tr>
<tr>
<td>RPmax, mm Hg</td>
<td>21.4±9.1</td>
<td>22.8±8.4</td>
<td>29.4±5.5</td>
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<tr>
<td>RV dP/dtmax, mm Hg/s</td>
<td>499±92.1</td>
<td>569±107.6</td>
<td>543±138</td>
<td>14.28</td>
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<tr>
<td>RV dP/dtmin, mm Hg/s</td>
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<td>−268±59.8</td>
<td>−311±85</td>
<td>−0.46</td>
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<tr>
<td>RVEDP, mm Hg</td>
<td>0.40±4.9</td>
<td>0.30±7.1</td>
<td>7.3±4.9†</td>
<td>−25.06</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, unless otherwise indicated. Pooled data from 160 paced measurements in 18 LBBB+MI hearts and 19 LBBB hearts. The difference between relative changes in the 2 groups (%ΔLBBB−%ΔLBBB+MI) was estimated from a general linear model with identity link, including the site of pacing. To account for intraclass correlation of measurements (panel data), Huber-White robust standard errors were calculated; thus, no assumptions were made on the correlation structure. HR indicates heart rate; LV dP/dtmax, maximal rate of LV pressure rise; LVEDP, LV end-diastolic pressure; LV dP/dtmin, maximal rate of LV pressure decline; RV dP/dtmax, maximal RV pressure; MIVA, mechanical interventricular asynchrony; RV dP/dtmin, maximal rate of RV pressure rise; RV dP/dtmin, maximal rate of RV pressure decline; RVEDP, RV end-diastolic pressure; RPmax, maximal RV pressure; SV, stroke volume; SW, stroke work.

*P<0.05 versus corresponding baseline.
†P<0.05 versus LBBB baseline.
‡P<0.05 versus LBBB BiV.

Figure 3. Percent increase in resynchronization (equals reduction in total activation time), LV dP/dtmax, and stroke work during BiV pacing in LBBB and LBBB+MI hearts. Data from all sites combined. *P<0.05 versus baseline.
groups) (Figure 6, middle). At the best pacing site for each heart (Figure 6, right), we determined during single-site LV pacing the range of AV delays at which \( \geq 70\% \) of maximal LV dP/dtmax could be achieved. This AV delay range was significantly smaller in LBBB/LADi (\( \approx 40 \) ms) and LBBB/LCXi (\( \approx 45 \) ms) than in LBBB hearts (\( \approx 70 \) ms).

**Discussion**

The main findings of this study in the novel canine model of LBBB combined with MI indicate that infarcted hearts as well as noninfarcted hearts with LBBB can benefit from CRT. Achieving the maximal benefit in infarcted hearts, however, requires accurate positioning of the LV pacing lead and more precise timing of LV stimulation. The presence and location of the infarction determines the best pacing site. This best site does not coincide with the region of latest activation but can be recognized as the site providing the most profound reduction in QRS duration.

**Influence of Presence and Location of MI on CRT Response**

The finding that the position of the LV lead where optimal benefit of CRT is achieved varies with presence and location of the infarction is novel. In all hearts studied, an LV lateral position was optimal, but the longitudinal position varied depending on the presence and location of the infarct. In the noninfarcted LBBB group, pacing the LV apex provided optimal resynchronization and hemodynamic response similar to that in hearts with normal ventricular conduction.15.16 This finding may be attributable to the fact that epicardial LV apical stimuli are conducted rapidly toward the endocardium and in a basal direction, providing rapid activation of the entire LV endocardium.16 The optimal LV pacing position in infarcted hearts appears to be determined by the fastest pathway of impulse conduction that provides collision of wavefronts originating from the RV and LV pacing sites. In hearts with an apically located infarction, as present in the LBBB/LADi group, impulse conduction can bypass the infarction easiest when pacing the LV basal wall. In contrast, the midlateral position is best in the case of LCX infarctions because from this position, the wavefront can easily proceed over the anterior wall as well as over the LV apex.

These patterns of electric resynchronization also translate into the extent of hemodynamic benefit. Accordingly in all hearts, the site providing the most pronounced electrical resynchronization also resulted in the best hemodynamic improvement. The easiest estimation of such a site is to assess the site resulting in the most pronounced QRS reduction. The latter is in agreement with a subanalysis of the Cardiac Resynchronization in Heart Failure trial,17 indicating that not QRS duration at baseline but QRS duration at 3 months predicted outcome of CRT. Indeed, 2 studies showed that the amount of QRS complex shortening by BiV pacing was a good predictor of CRT response.18,19

The data indicate that there is no optimal distance between pacing site and infarction because the best pacing site in the case of LADi is remote from the infarct area, whereas it is close to the infarct area in case of LCXi. More surprising, the site of latest electrical activation appears not to be the best pacing site. This finding contrasts with several studies report-
ing that concordance of LV pacing site and latest activated region is a prerequisite for CRT response.20–22 However, these studies compared only a limited number of pacing sites and regions and did not discriminate between basal and apical regions. Further, in the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure trial, LV lead location was not a major determinant of response to CRT.23

Another effect of infarction is that the timing of LV stimulation is more critical in infarcted hearts. This finding can be derived from the measurements during single-site LV pacing with various AV intervals. LV pacing at varying AV delays results in varying degrees of fusion between intrinsic activation and the activation wave generated by the LV pacing electrode. The observation that in the LBBB+MI hearts the range of AV delays at which ≥10% increase in resynchronization can be obtained is narrower than in the LBBB hearts indicates that, in the case of previous MI, the timing of RV and LV stimulation (∼VV interval) is more critical.14 This finding may be explained by the fact that the more complicated conduction path in infarcted hearts required a more precise timing of stimulation. Thus, although a similar improvement can be achieved in LBBB and LBBB+MI hearts, the latter may require more precise optimization to achieve this improvement.

Comparison With the Literature

In the present study, we avoided positioning the pacing leads in the infarction; therefore, this study especially addresses the issue of how the presence of an infarction influences the responsiveness to CRT. On the basis of our results and presuming that an acute hemodynamic response is an important determinant for long-term reverse remodeling and clinical benefits (discussed later), it can be understood that often poorer responses to CRT are found in patients with MI. After all, in clinical practice it may not always be possible to explore which pacing site and timing is optimal. The Multicenter InSync Randomized Clinical Evaluation study4 showed that echocardiographic reverse remodeling was less in patients with ICM than in patients with dilated cardiomyopathy. This finding was corroborated by some,5,8,24–26 but not all studies.6,27–30 At least part of the explanation for a poor response in patients with ICM may be that pacing (usually LV posterolateral) within the scar hampers CRT response,7,9 but this finding is not confirmed by other studies.31,32

In many studies, the position of the scar, of the pacing lead, and the combination of the two is not exactly known. Moreover, only a few studies indicated having used optimization of AV delay, VV interval, or both.27,28,31,32 Interestingly, these latter studies did not find a negative influence of infarction, including a study from the group that reported the negative effect of scar on CRT response in nonoptimized
patients. Therefore, our findings are consistent with observation in human studies, showing that pacing outside the infarct in patients with an LV free wall infarct still carries a benefit. The extent of this benefit may well depend on the size of the scar, as shown by several studies. In our preparation with infarct size ranging from 14% to 32%, a hemodynamic benefit could be reached that was similar to that in noninfarcted LBBB hearts. It is possible that this benefit may not be achieved in the case of larger infarctions; however, the relation between pacing site and infarct location, as shown here, may still hold.

From our results, it can be understood that pacing with 2 LV leads as opposed to 1 has beneficial effects. After all, the chance of pacing from the optimal site with 2 LV leads is larger than from a single site. In a post hoc analysis of the Triple Resynchronization in Paced Heart Failure study, of those patients who initially were nonresponders (reduction in LV end-systolic volume >10%) on conventional BiV pacing, ~40% became responders to dual-site LV pacing.

**Clinical Implications**

The results from the present study indicate that infarcted hearts can benefit from CRT as well as noninfarcted hearts with LBBB. Clinical studies need to demonstrate whether the best pacing sites in patients correspond to those in dogs; however, in many patients, the exact location of the infarction may not be known. It may not be feasible to do scar-imaging studies before implantation of the LV lead. In that case, acute hemodynamic testing could help to optimize CRT. If such testing is not feasible, another finding in the present study may be useful: The site providing maximal hemodynamic benefit relates closely to the site where BiV pacing leads to the largest reduction in electrical activation, as measured in terms of the QRS duration. Therefore, an elegant and feasible approach could be to move the pacing lead around while searching for the site with the narrowest QRS complex.

**Limitations**

This study was performed in canine hearts with LBBB and MI. As far as we are aware, this novel model approaches the condition of ICM in patients more than any other experimental model published until now. Besides the infarction and the LBBB, the hearts had compromised pump function, as can be derived from the elevated RV end-diastolic and end-systolic pressures as well as the LV end-diastolic pressure in combination with 25% to 30% reduction in stroke volume and stroke work compared to hearts with isolated, acute LBBB. Nevertheless, there still may be several differences between this animal model and patients with infarction, such as the kind (proximal or distal) and duration of LBBB and the age of the infarction. However, with regard to the effects of LBBB and electrical resynchronization, several studies in the animal model of LBBB have shown at least qualitatively similar results as in patients with LBBB, such as that concerning acute hemodynamic benefit and chronic reverse remodeling.

An important difference between our animal model and the condition in many patients with ICM is that we induced complete (nearly transmural) MI and maintained severe ischemia by embolization. We did not allow reperfusion, and the contribution of collateral blood flow was most likely limited, which may well differ in humans in whom subendocardial extensions of infarcts are more likely to arise because of collateralization. We opted for this model in order to create a worst-case scenario for electrical conduction. One large, massive infarction is presumably a bigger obstacle for electrical conduction than smaller, nontransmural, and patchy infarctions. The infarct size in the present study (ranging from 14% to 32%) seems to be in the same range as that in the study by Ypenburg et al., where ~20% of segments had transmural scar. However, in some patients, scar size may be as large as 60% to 70% of LV mass.

LV lead placement in patients depends on the cardiac venous system. It may not be technically feasible to position the pacing lead at the high basal level. Similarly, it may be difficult to find a suitable vessel just near scar tissue.

**Conclusions**

This study in canine hearts with LBBB indicates that the presence or the location of MI does not reduce the maximal extent of electrical resynchronization and hemodynamic benefit from CRT. However, achieving the optimal effect of CRT requires more precise positioning of the LV lead and more accurate timing of LV stimulation in hearts with MI than in those without.

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Dr Klersy served as a statistical consultant for Medtronic Italy and Boston Scientific Italy. Dr Leyva received research grants from Medtronic and St Jude Medical and received honoraria from Medtronic and Sorin. Dr Auricchio received research grants from Medtronic, Boston Scientific, and St Jude Medical; received honoraria from Biotronik, Sorin, and Medtronic; and served as a consultant for EBR Systems, Medtronic, and Sorin. Dr Prinzen received research grants from Medtronic, Boston Scientific, and EBR Systems and is an advisor to Medtronic.

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