Left Ventricular Endocardial Pacing Improves Resynchronization Therapy in Canine Left Bundle-Branch Hearts

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Background—We investigated the benefits of the more physiological activation achieved by left ventricular (LV) endocardial pacing (ENDO) as compared with conventional epicardial (EPI) LV pacing in cardiac resynchronization therapy.

Methods and Results—In 8 anesthetized dogs with experimental left bundle-branch block, pacing leads were positioned in the right atrium, right ventricle, and at 8 paired (EPI and ENDO) LV sites. Systolic LV pump function was assessed as LVdP/dtmax and stroke work and diastolic function as LVdP/dtmin. Electrical activation and dispersion of repolarization were determined from 122 epicardial and endocardial electrodes and from analysis of the surface ECG. Overall, ENDO-biventricular (BiV) pacing more than doubled the degree of electrical resynchronization and increased the benefit on LVdP/dtmax and stroke work by 90% and 50%, respectively, as compared with EPI-BiV pacing. During single-site LV pacing, the range of AV intervals with a >10% increase in LV resynchronization (79±31 versus 32±24 ms, P<0.05) and LVdP/dtmax (92±29 versus 63±39 ms) was significantly longer for ENDO than for EPI pacing. EPI-BiV but not ENDO-BiV pacing created a significant (40±21 ms) transmural dispersion of repolarization.

Conclusions—Data from this acute animal study indicate that the use of an endocardial LV pacing electrode may increase the efficacy of resynchronization therapy as compared with conventional epicardial resynchronization therapy. (Circ Arrhythmia Electrophysiol. 2009;2:580-587.)

Key Words: bundle-branch block ■ electrophysiology ■ hemodynamics ■ pacing

Cardiac resynchronization therapy (CRT) has become a valuable therapy for patients with heart failure and conduction abnormalities. Yet, the search to improve this therapy continues because at least 30% of selected patients show no recognizable improvement.1

Clinical Perspective on p 587

In virtually all patients, CRT is delivered using epicardial pacing electrodes, because conventional access for lead positioning (transvenous, thoracotomy) results in an epicardial location of the left ventricular (LV) pacing electrode. However, physiological electrical activation originates in the endocardium and spreads to the epicardium. Moreover, on a theoretical basis, endocardial left placement would have the advantages that the path length for impulse conduction is shorter along the endocardium as compared with the epicardium and that conduction velocity is faster in the endocardium than in the epicardium.2 Another reason to consider endocardial LV pacing is that epicardial LV pacing not only reverses the transmural direction of electrical activation but potentially that of repolarization. The latter may create a substrate for life-threatening ventricular arrhythmias.3

The aim of this study was to investigate the potential benefit of endocardial compared with epicardial LV pacing in CRT. The study was performed in an established animal model of cardiac dyssynchrony,4–8 allowing comparison of endocardial and epicardial CRT at multiple sites and AV intervals with extensive physiological measurements. It was hypothesized that greater electrical resynchronization and hemodynamic improvement could be achieved from endocardial compared with epicardial pacing sites (for LV and biventricular [BiV] pacing). In addition, this study investigated whether repolarization was improved when using endocardial rather than epicardial pacing.
sure measurements for corresponding epicardial (EPI) and endocardial (ENDO) sites were performed in a consecutive sequence. Baseline measurements were repeated at each pacing site. Recording of measurements commenced 30 seconds after initiation of pacing at a site and/or AV interval, to achieve hemodynamic stability. Data were then acquired for 15 seconds to analyze at least 10 heart beats, that is, over more than 1 respiratory cycle.

Data Analysis
Data analysis was performed using custom made software. From the LV and RV pressure signals, the following parameters were derived: systolic and end-diastolic pressure, dP/dtmax, and dP/dtmin. LV volume was determined using the conductance data, recorded on a Leycom Sigma SDF signal conditioner processor (CDLeycom, Zoetermeer, The Netherlands).6 Mechanical interventricular asynchrony (MIVA) was assessed from the time difference of the upstroke of LV and RV pressures.6 Total and LV electrical activation times were calculated as the maximal difference in activation time between all RV and LV electrodes and all LV (including septal) electrodes, respectively. Total dispersion of repolarization was quantified from the time between the peak and end of the T wave on the surface ECG (Tp-e)9 as well as from the maximum time difference in repolarization, derived from the time of peak positive deflection of all 122 electrodes.10

To investigate the sensitivity of electrical activation and hemodynamics to variations in timing of LV pacing with respect to intrinsic activation, the range of AV intervals was determined that provided an increase in LV dP/dtmax of at least 10% as compared with baseline. This criterion for improved LV resynchronization was based on that used previously in the canine LBBB model.4,8

Statistical Analysis
Continuous data are described as mean±SD and discrete variables as absolute values and percentages. A series of generalized linear regression models was used to compare epicardial and endocardial pacing sites for the primary and secondary end points, with identity, logistic, or Poisson link function according to the dependent variable assessed. To account for intradog correlation of measurements (pane-data), we calculated Huber-white robust standard errors. No missing data imputation was performed. Stata 9.2 (StataCorp, College Station, Tex) was used for computation. A 2-sided probability value ≤0.05 was considered statistically significant. The Bonferroni correction was used for post hoc comparisons.

Results
In each of the 8 experiments, 8 ENDO-EPI pairs of LV pacing sites were evaluated during BiV pacing and during LV pacing at various AV intervals. Due to occasional dislodgment of the endocardial electrode, unstable hemodynamic conditions and other technical problems, ultimately 49 of the possible 64 paired datasets (BiV+LV pacing for both ENDO and EPI) were successfully acquired.

During baseline atrial pacing (after LBBB), electrical activation spread from the RV endocardial wall through the septum and gradually over the LV lateral wall, the LV being activated ≈80 ms later than the RV (Figure 2). During BiV pacing, 2 regions of earliest activation were apparent, especially during epicardial BiV pacing. BiV pacing reduced the mean time difference between RV and LV activation as compared with atrial pacing, but ENDO-BiV pacing reduced the total activation time more than EPI-BiV pacing (Figure 2). ENDO-LV pacing with short AV intervals resulted in fairly synchronous LV activation, whereas during EPI-LV pacing, large differences in electrical activation times occurred, as observed by the large number of isochronal lines. Also noteworthy is the green isochronal zone at the antero-

Methods
Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The protocol was approved by the Animal Experimental Committee of Maastricht University.

The experiments were performed on 8 adult mongrel dogs of either sex and unknown age, weighing 28.0±0.5 kg. After pentothal induction, anesthesia was maintained by ventilation with O2 and N2O (1:2) in combination with infusion of midazolam (0.25 mg/kg/h IV) and sufentanil (3 μg/kg/h IV). Left bundle-branch block (LBBB) was created by radiofrequency ablation.4 After thoracotomy, 2 multi-electrode catheters were introduced into the carotid artery and jugular veins, respectively. After thoracotomy, 2 multi-electrode catheters were introduced into the carotid artery and jugular vein, respectively. After thoracotomy, 2 multi-electrode catheters were introduced into the carotid artery and jugular vein, respectively. Also noteworthy is the green isochronal zone at the antero-

Protocol
After instrumentation and after hemodynamic stabilization, electrical mapping and hemodynamic measurements were acquired simultaneously. The following sequence was used:

During the entire protocol, the atrium was paced at a constant rate, approximately 10% above intrinsic rhythm. For testing at each of the 8 pairs (endocardial and epicardial) RV pacing sites, baseline (atrially paced) measurements were followed by measurements during BiV pacing and by single-site LV pacing at 8- to 10-AV intervals. The AV intervals were chosen to provide a range with various degrees of fusion between pacing-induced activation and intrinsic (right bundle-branch–derived) activation, where optimal fusion was defined as the AV interval at which resynchronization was largest (electrical activation time shortest as derived from epicardial mapping). Measurements for corresponding epicardial (EPI) and endocardial
lateral wall, the result of breakthrough of activation from the endocardium.

The time delay in activation in 3 principal directions was compared during single-site pacing from the basal lateral EPI-LV and ENDO-LV electrodes at short AV intervals. During atrial pacing, a large septal-to-lateral delay was present, consistent with LBBB, whereas there was no significant delay in activation between base and apex and between endocardium and epicardium due to collision of activation wave fronts coming from 2 sides around the LV circumference (Figure 3, see also Figure 2). ENDO-LV pacing markedly shortened the delay in activation between lateral and septal electrode (lateral-septal) and, more pronounced, between base and apex, as compared with EPI pacing. The transmural conduction time between the EPI and ENDO electrodes was 7.7% versus 10.3% (Table). This larger increase in LVdP/dtmax during ENDO pacing was significant both in the BiV and LVopt pacing sites combined during BiV pacing, LV pacing at an short AV interval. Presented are mean values and standard deviations of 8 experiments. *P<0.05 compared with baseline; †P<0.05 ENDO compared with EPI.

In line with these observations, stroke work also increased more during ENDO BiV pacing than during EPI BiV pacing (33.2±25.5% versus 22.2±19.2%; Figure 5). BiV pacing did not affect LV systolic and end-diastolic pressures nor RV pressures, except for a small but significant increase in RVdP/dtmax during EPI-BiV pacing (Table).

During ENDO-LV pacing, the range of AV intervals at which electrical resynchronization and LVdP/dtmax increased by >10% as compared with baseline was significantly larger than during EPI-LV pacing (79±31 versus 32±24 ms and 92±29 versus 63±39 ms, respectively, Figure 6).

Figure 7A shows that at every ENDO pacing site, BiV pacing resulted in a significant improvement in electrical resynchronization compared with baseline. In contrast, at 3 sites (Bant, Bpost, and Mpost) EPI-BiV pacing did not significantly improve resynchronization compared with baseline. For the various individual pacing sites, the mean increase in LVdP/dtmax ranged from 5% to 16% for EPI-BiV pacing and from 14% to 24% for ENDO-BiV pacing. Data from basal and midventricular areas for anterior, lateral, and posterior sites and from the apical lateral and LV apical sites were combined to define anterior, lateral, posterior, and apical wall segments. For all 4 wall segments, ENDO-BiV pacing increased electrical resynchronization and LVdP/dtmax significantly more than EPI-BiV pacing. In 45 of 49 and 47 of 49 paired datasets, the increase in resynchronization and LVdP/dtmax, respectively, was larger during ENDO-BiV pacing than during EPI-BiV pacing.

In addition to the effects on electrical activation and mechanical contraction, ENDO-BiV pacing resulted in larger reductions in parameters of dispersion of repolarization compared with EPI-BiV pacing: both Tp-e and total dispersion of repolarization were reduced by ≈10% more during ENDO than during EPI-BiV pacing (Figure 8A). During EPI-BiV pacing, repolarization in the epicardium preceded that in the endocardium by ≈40 ms, whereas during baseline and ENDO-BiV pacing, no significant transmural difference in the timing of repolarization was found (Figure 8B).
Discussion

This acute animal study shows for the first time that compared with conventional LV epicardial pacing-based CRT, endocardial CRT produces more homogeneous and rapid ventricular electrical depolarization and repolarization and additional improvement in systolic LV pump function. With LV endocardial pacing, the beneficial effects of CRT with single-site LV pacing are less dependent on the timing and position of LV pacing than with an epicardial LV electrode.

As compared with epicardial CRT, endocardial CRT provides less transmural dispersion of repolarization.

Electrical Resynchronization

The crucial parameter underlying the acute hemodynamic benefit of endocardial CRT over conventional epicardial CRT probably is the electrical resynchronization. Several factors may explain the observed effects. First, the path length for the depolarization wave to reach all regions of the ventricles is smaller, because LV endocardial sites are more centrally located than LV epicardial sites. A second factor favoring more synchronous activation during endocardial CRT is the faster impulse conduction in endocardium compared with other layers. Theoretically, this faster impulse conduction could be due to conduction in Purkinje and non-Purkinje fibers. Because Purkinje fibers are electrically largely isolated from the surrounding working myocardium, they can only be activated by direct stimulation into these fibers. The observation that endocardial LV pacing consistently increased conduction velocity, whereas the Purkinje fibers form only a loose network in most of the LV endocardium, makes an important contribution of conduction through Purkinje fibers unlikely. Subendocardial non-Purkinje fibers conduct impulses faster than midmyocardial or epicardial fibers, especially in the longitudinal direction. Indeed, the large difference in base-to-apex conduction times between epicardial and endocardial CRT (Figure 3) suggests that more rapid spread of the activation wave front longitudinally may be an important component of endocardial CRT. A third factor contributing to faster activation during endocardial LV pacing is the more rapid transmural conduction from endocardium to epicardium than in the opposite direction. As a consequence of all these factors, within ~40 ms after the first LV activation a large portion of the LV wall is activated during endocardial BiV pacing, whereas it takes ~60 ms to activate
a similar region during epicardial BiV pacing. Consequently, the activation waves originating from the LV and RV electrode coalesce more rapidly during ENDO-BiV pacing than during EPI-BiV pacing.

More rapid impulse conduction, resulting in broader activation wave fronts, facilitates the achievement of sufficient fusion between intrinsic conduction and/or RV pacing and LV pacing derived wave fronts. Broader activation wave fronts during endocardial LV pacing is a likely explanation of why resynchronization was less dependent on the exact site of LV pacing. As shown in Figure 6, epicardial BiV pacing did not resynchronize significantly when pacing at basal anterior or posterior or the midventricular posterior sites, whereas all endocardial pacing sites resulted in significant resynchronization.

Similarly, broader activation wave fronts can provide an explanation for the larger range of AV intervals where >10% resynchronization was achieved during LV pacing. Single-site LV pacing at various AV intervals results in different degrees of fusion between intrinsic (right bundle) activation and LV pacing activation,8 comparable to different timing of RV and LV pacing (V-V interval). Therefore, these data also suggest that resynchronization would be less dependent on the V-V interval during BiV pacing.

**Hemodynamic Benefit**

Previous studies from this laboratory using the nonfailing canine LBBB model and testing a range of epicardial LV pacing sites and AV intervals have shown that the maximum hemodynamic effect was achieved when LV electrical resynchronization was largest (minimal differences in intraventricular activation times).4 The present study extends this observation, showing that endocardial pacing improves electrical resynchronization to a greater degree than epicardial CRT and also further increases the hemodynamic benefit. Similarly, the lesser dependency of resynchronization on the LV pacing site also translates into less dependency of hemodynamic benefit on LV pacing site and timing.

During epicardial BiV pacing, the hemodynamic effects were larger when pacing at apical sites than pacing at basal and most midventricular sites (Figure 6). This is in agreement with earlier studies indicating that the hemodynamic effect of pacing is also dependent on the sequence of activation.13,14 The data from the present study suggest that with largely similar activation sequences during epicardial and endocar...
Several groups have implanted endocardial leads into the LV via a transseptal approach to provide CRT in cases of unsuitable or unsuccessful coronary sinus lead implantation. One small study has compared the effectiveness of endocardial and epicardial CRT. Garrigue et al. studied 8 patients receiving LV endocardial CRT using the atrial transseptal approach and compared them with 17 patients receiving conventional epicardial CRT. After 6 months of therapy, echocardiography revealed that endocardial BiV pacing provided more homogenous intraventricular resynchronization than epicardial BiV pacing, associated with better LV filling and systolic performance. Preliminary data in patients also showed that endocardial CRT provided LVdP/dtmax values equal to or greater than epicardial CRT. These data are all consistent with findings in the present study.

Possible Clinical Implications

The hemodynamic benefit of endocardial LV pacing for CRT, evidenced by this study and supported by the aforementioned small patient studies, may translate to an increased effectiveness of CRT. In patients who are judged to be responders based on functional improvement and/or reverse remodeling, endocardial BiV pacing may confer even greater benefit. In addition, in patients in whom a lack of response to CRT is due to suboptimal pacing site and/or electrical activation time, endocardial CRT could result in these patients becoming responders. This idea is based on the observations in the present study that the number of sites without electrical and/or mechanical benefit (<10%) with epicardial pacing were reduced considerably with endocardial pacing and that the range of AV intervals at which a beneficial effect was achieved during LV pacing was considerably larger. Also, in many nonresponders, ventricular activation occurs more heterogeneously and thus restoration of a more physiological (endocardium to epicardium) activation may be more beneficial. However, a prospective clinical study should test the hypothesis that endocardial CRT can increase the rate of responders or the magnitude of response.

There are several ways to achieve endocardial CRT. With currently available pacing systems and tools, a transseptal approach is possible, as is practiced in a few centers. However, potential adverse effects of this approach include the requirement for long-term anticoagulation, the risk of thromboembolic events, the potential for lead dislodgment, and the worsening of mitral regurgitation. Another possibility would be to reach the endocardium transmurally from the epicardium via surgical access. Finally, endocardial CRT will become more feasible when the technology of leadless pacing becomes available. Clearly, the applicability of endocardial CRT in humans will depend on tools allowing safe and effective long-term LV pacing.

Limitations

The present study was performed in a model of acute LBBB in the canine, nonfailing heart. Obviously, many circumstances in this model differ from the clinical situation in patients with heart failure. However, with regard to the effects of LBBB and electrical resynchronization, several studies have shown at least qualitatively comparable results to those of patients with conduction abnormalities. Also, in...
this canine LBBB model we have previously shown that acute hemodynamic benefit using epicardial BiV pacing is associated with chronic reverse remodeling. A possible limitation is that in the model of acute LBBB, electrical remodeling is incomplete. In LBBB hearts, electrical remodeling causes a decrease in action potential duration and in conduction velocity in the latest activated (LV lateral wall) regions. Changes in action potential duration relate to “cardiac memory,” which develops within half an hour of inducing electrical dyssynchrony with ventricular pacing but may develop further during subsequent weeks of dyssynchronous pacing. However, chronic LBBB has little effect on the transmural difference in action potential duration.

Changes in conduction velocity in chronic LBBB might influence the benefit of ENDO-CRT. Although in normal hearts as well as in the LV anterior wall of chronic LBBB hearts conduction is faster in endocardial than epicardial tissue, the opposite gradient is observed in the latest activated LV lateral wall. Therefore, when pacing at the LV lateral wall, a likely site during CRT, the benefit of endocardial pacing may be reduced, but further, on the anterior wall, the endocardial conduction will become more rapid again. Moreover, as discussed above, the benefits of ENDO-CRT may also arise from the smaller pathlength and a more normal physiological (endocardial to epicardial) activation sequence. The latter 2 factors are hardly influenced by the remodeling process. The benefit of the shorter pathlength is as large as that of the transmural difference in conduction velocity. Assuming an LV having an inner radius of 3 cm and wall thickness of 1 cm, it can be calculated that endocardial circumference is ≈30% smaller. Therefore, the data from the present study are promising and, to some extent, supported by clinical observations, but require further confirmation in animals and/or patients with chronic dysynchrony.

Conclusions
The data from the present study in the canine model of acute LBBB demonstrate that the transmural location of the LV pacing site adds another dimension to CRT, since endocardial CRT considerably improves resynchronization of activation and systolic LV pump function as compared with conventional epicardial CRT. In addition, the benefits were less dependent on pacing site and timing of stimulation, indicating a greater likelihood of achieving a positive CRT response for endocardial than for epicardial CRT. Therefore, this study indicates that it would be worthwhile to investigate the potential benefits of endocardial CRT in animal models of heart failure combined with LBBB as well as in CRT patients.

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References
CLINICAL PERSPECTIVE

Conventionally, cardiac resynchronization therapy (CRT) is applied using a left ventricular (LV) pacing electrode, positioned at the LV epicardium (either in an epicardial vein or surgically screwed into the myocardium). However, physiological electrical activation originates in the endocardium and spreads to the epicardium. In the present study in the canine model of acute left bundle-branch block, we showed that pacing at an endocardial rather than epicardial LV pacing electrode provides more pronounced electrical resynchronization and hemodynamic benefit and prevents transmural dispersion of repolarization. Moreover, these CRT benefits are also less dependent on proper timing and site of stimulation. The present study therefore provides the proof of principle that endocardial CRT has the potential to improve efficacy of CRT. Whether this is indeed achieved in CRT patients depends on whether the responses are the same in hearts with heart failure and chronic left bundle-branch block. Practical application of endocardial CRT will depend on the availability of reliable techniques and tools to implant the LV lead into the LV endocardium. Possible options are a transatrial-septal approach, a longer screw electrode using a surgical approach, and the novel technique of leadless pacing.
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