Optimal Left Ventricular Endocardial Pacing Sites for Cardiac Resynchronization Therapy in Patients With Ischemic Cardiomyopathy

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Objectives
We sought to investigate the impact of left ventricular (LV) pacing site on mechanical response to cardiac resynchronization therapy (CRT) in patients with ischemic cardiomyopathy (ICM).

Background
CRT reduces morbidity and mortality in patients with dyssynchronous LV failure; however, variability in response, particularly in ICM patients, poses ongoing challenges. Endocardial biventricular (BiV) stimulation may provide more flexibility in LV site selection and yield more natural transmural activation patterns. Whether this applies to ICM and whether optimal LV endocardial pacing locations vary among ICM patients remain unknown.

Methods
Peak rate of LV pressure increase (dP/dtmax) was measured at baseline, during VDD pacing at the right ventricular apex, and during BiV pacing from the right ventricular apex and 14 different LV endocardial sites in patients with ICM (n = 11). Seven patients already had an epicardial LV lead (CRT) in place, allowing comparison of epicardial BiV stimulation with that using an endocardial site directly transmural to the CRT-coronary sinus lead tip. Electroanatomic 3-dimensional maps with color-coded dP/dtmax response defined optimal pacing regions delivering ≥85% of maximal increase in dP/dtmax.

Results
Endocardial BiV pacing improved dP/dtmax over right ventricular apex pacing in all patients (mean increase 241 ± 38 mm Hg/s; p < 0.0001). In patients with pre-existing CRT leads, LV endocardial versus epicardial pacing at transmural sites yielded equivalent dP/dtmax values. However, dP/dtmax at the best endocardial site exceeded that achieved with the pre-implanted CRT device (mean increase 111 ± 25 mm Hg/s; p = 0.004). An average of −2 optimal endocardial sites were identified for each patient, located at the extreme basal lateral wall (8 of 11 patients) and other regions (9 of 11). Standard mid-LV free wall pacing yielded suboptimal LV function in 73% of patients. Optimal pacing sites were typically located in LV territories remote (9.3 ± 3.6 cm) from the infarct zone.

Conclusions
CRT delivered at best LV endocardial sites is more effective than via pre-implanted coronary sinus lead pacing. The location of optimal LV endocardial pacing varies among patients with ICM, and individual tailoring may improve CRT efficacy in such patients. (J Am Coll Cardiol 2010;56:774–81) © 2010 by the American College of Cardiology Foundation

Left ventricular (LV) systolic dysfunction is frequently compounded by dyssynchronous ventricular activation, resulting in an array of hemodynamic, structural, and molecular changes that worsen clinical outcomes in affected patients (1–5). Cardiac resynchronization therapy (CRT) reverses many of these derangements (6,7), and reduces morbidity and mortality in patients with dyssynchronous LV failure (8–10). Although clinically effective in most patients, CRT confers little or no therapeutic benefit to a substantial minority (20% to 50%) (11).

Failure of CRT may be due to a variety of factors, including inappropriate patient selection, inability to place an LV pacing lead due to unfavorable coronary sinus (CS)...
anatomy, or implantation of the CS lead at a suboptimal position. Traditionally, CRT has been delivered by LV pacing through a lead placed in a posterolateral tributary of the CS. Patients with ischemic cardiomyopathy (ICM) are less likely to benefit from CRT compared with their nonischemic counterparts (12–14), due perhaps to the effects of scar burden and variable distribution of optimal LV pacing sites in ischemic patients. Data regarding the ideal location for CS lead placement remain limited, with published studies performed predominantly in experimental models or in patients with nonischemic cardiomyopathy (15–17).

We hypothesized that patients with ICM may demonstrate a high degree of interpatient heterogeneity in LV pacing site locations yielding maximal CRT efficacy, and that optimal pacing sites may frequently occur in regions other than the posterolateral left ventricle. To test this hypothesis, we studied the acute CRT effect in a series of patients with ICM, performing biventricular (BiV) pacing from the right ventricular apex (RVA) coupled with ~50 different LV endocardial pacing sites in each patient. As endocardial pacing has itself been recently suggested to enhance a BiV stimulation effect over traditional LV endocardial stimulation (18), we further compared the two at the same location in a subset of patients with a pre-existing CS lead.

Methods

Patient selection. All patients included in the study were required to have ICM, severe LV systolic dysfunction (ejection fraction <35%) despite appropriate medical management, and evidence of dysynchronous ventricular activation. All patients were referred for LV tachycardia or premature ventricular complex ablation, with the pacing protocol performed in conjunction with electrophysiological study and anticipated ablation, thereby allowing catheter placement in the left ventricle. All patients consented to the investigation, and the protocol was approved by the Johns Hopkins institutional review board.

Pacing protocol. CATHETER PLACEMENT. All patients underwent placement of standard electrophysiological pacing catheters at the high right atrium and RVA, as well as placement of a roving ablation catheter with a 3-dimensional position sensor (ThermoCool, Biosense Webster, Inc., Diamond Bar, California) in the left ventricle. Right atrial and right ventricular catheters were introduced through 6-F venous sheaths, and the roving catheter was advanced transseptal approach and advanced across the mitral valve (n = 1). The Millar catheter was linked to a custom-designed data acquisition platform for collection of LV pressure and digital calculation of peak rate of left ventricular pressure increase (dP/dt_max).

VENTRICULAR PACING. The right atrial, right ventricular, and LV catheters were connected to a temporary pacemaker capable of VDD pacing (Medtronic, Inc., Minneapolis, Minnesota). Pacemaker output was delivered through a customized splitter that allowed for simultaneous pacing through the right ventricular apical catheter and the roving LV catheter. Pacing was typically performed at 5 mA, although higher outputs for pacing in regions of diseased myocardium were occasionally required. A single fixed atrioventricular (AV) delay was used throughout the study; the ideal AV delay was determined at the onset of the study, and was defined as the longest AV delay that allowed for ventricular pacing without evidence of fusion with native conduction. Values for dP/dt_max were recorded during baseline rhythm (normal sinus rhythm in 10 of 11; atrial fibrillation in 1 of 11), and during VDD-RVA pacing at study onset, study conclusion, and 1 to 2 times during the protocol to document stable LV function over the course of the investigation. dP/dt_max values were recorded during VDD-BiV pacing (atrial-sensed, RVA, and LV paced) at approximately 50 different LV sites (51 ± 14 sites). At each LV pacing site, endocardial bipolar electrogram voltage data were collected, and LV capture through the roving catheter was confirmed for 8 to 10 beats before initiation of BiV pacing and collection of dP/dt_max data (collected over 15 to 20 beats). In patients with a CRT system in place, dP/dt_max values were also obtained during CRT pacing through the device at identical AV delays used in the study protocol. In those patients, endocardial sites directly transmural to the distal pole of the CS lead were identified, and dP/dt_max was assessed at those points as well.

Map generation. An electroanatomic mapping system (Carto XP) was used to collect 3-dimensional location and display hemodynamic data at each LV site. Bipolar voltage, activation, and dP/dt_max maps were generated. Values for dP/dt_max were converted to a color-coded scale, allowing customized high-density mapping of LV systolic function versus endocardial pacing site. At each point, dP/dt_max values were derived from an averaged series of paced beats (typically 15 to 20) using customized software.

Analysis of scar and optimal pacing site locations. Infarct, optimal pacing region, and total LV areas were measured (Carto XP). Scar was defined by endocardial
bipolar voltage assessment, with cutoff values of 1.5 and 0.5 mV for diseased tissue and dense scar, respectively. Optimal pacing regions were defined as those regions yielding ≥85% of the peak achievable increase in dP/dt max over baseline RVA pacing (i.e., [(dP/dt max site) − (dP/dt max RVA)]/[(dP/dt max peak) − (dP/dt max RVA)] >0.85). Distances between pacing sites and the infarct center were determined using curvilinear measurements over the LV endocardial surface (Carto XP) and expressed both as linear surface distance (in centimeters) and as a percentage of the total LV circumference in the plane of measurement.

**Statistical analysis.** Data are presented as mean ± SD. Comparisons of dP/dt max values between pacing modes (baseline RVA pacing, BiV pacing, device-based epicardial LV pacing) were performed with paired 2-tailed Student t tests. The coefficient of variation for baseline dP/dt max measurements was calculated for each patient as (SD/mean)·100.

**Results**

Eleven patients (all male, age 68 ± 5 years) were studied between February 2006 and September 2009. Baseline clinical data are provided in **Table 1**. All had dysynchronous LV systolic failure due to ICM (mean ejection fraction 18 ± 5%), with symptoms from New York Heart Association functional class I to III despite optimal medical therapy. Patients were referred for mapping and ablation of monomorphic ventricular tachycardia (10 of 11 patients) or symptomatic premature ventricular complexes (1 of 11 patients). The determination of LV dyssynchrony was based on surface electrocardiography with or without tissue Doppler imaging. Nine patients had left bundle branch block (QRS duration 178 ± 26 ms), 1 had an interventricular conduction delay pattern with mechanical dyssynchrony noted on echocardiography (QRS duration 131 ms; tissue Doppler imaging >80 ms between septal and lateral wall activation), and 1 had right bundle branch block (QRS duration 200 ms). Seven patients had a CRT BiV pacing system in place at the time of study enrollment.

**Hemodynamic response.** Mean resting dP/dt max was 680 ± 115 mm Hg/s in native rhythm and 677 ± 178 mm Hg/s during RVA pacing. dP/dt max during RVA pacing remained stable throughout the protocol (average coefficient of variation of 7.6%), showing that other comparisons were being made under steady-state conditions.

Resynchronization with BiV VDD pacing from the RVA and LV endocardial sites improved LV mechanical function in all patients (Fig. 1), with an average peak increase in dP/dt max of 36% (+241 ± 38 mm Hg/s) compared with baseline RVA pacing alone (p < 0.0001). In the 7 patients with CRT systems already in place, we found that dP/dt max values arising from pacing at LV endocardial sites yielding peak results were higher than those from pacing through the implanted CRT system (13% increase; +110 ± 65 mm Hg/s; p = 0.0042).

One potential reason for the disparate effects of endocardial BiV pacing versus implanted CRT (CS pacing) was the LV surface being paced rather than the LV region being paced. To test this, we compared the hemodynamic effect of LV endocardial pacing using a site immediately transmural to the CS lead tip with the effect from device-based epicardial LV pacing (Fig. 2). The dP/dt max response was similar whether LV pacing was endocardial or epicardial (923 ± 234 mm Hg/s vs. 877 ± 278 mm Hg/s, respectively [p = 0.5]), suggesting that the maximal enhanced response seen with endocardial stimulation was more likely due to accessing ideal LV pacing sites rather than to endocardial stimulation per se.

**Mapping the optimal site.** Classically, CRT has been thought best achieved through lateral or posterolateral free-wall LV pacing. We found, however, that pacing at traditionally accepted LV pacing sites (mid-lateral LV) resulted in suboptimal LV systolic function in the majority of patients (8 of 11) (Fig. 3A). Rather, the most reproducible spot for optimization of LV function (i.e., sites yielding ≥85% peak increase in dP/dt max) appeared to be immediately below the mitral valve ring, typically in the anterolateral or lateral wall (8 of 11 patients) (Fig. 3B). Rather than a single pacing site, 9 of 11 patients had ≥2 contiguous sites yielding optimal hemodynamic results (Fig. 3A). Optimal pacing regions had an average area of 13 ± 13 cm² or 5.2 ± 4.4% of total LV endocardial surface area. dP/dt max and voltage maps from all patients are presented in the Online Appendix.

Systematic analysis of optimal pacing site location was performed by schematically segmenting the LV into 9 regions: anterior, lateral, inferior, and septal base; anterior, lateral, inferior, and septal mid-wall; and apex. Among the

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<th>Table 1 Clinical Characteristics</th>
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<td><strong>Male</strong></td>
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Values are mean ± SD or n (%).

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11 patients, a total of 24 regions were found to include sites yielding optimal function. These sites were located predominantly but not exclusively at lateral and anterior regions (Fig. 4, Online Appendix). Optimal pacing sites were never found on the inferior LV wall.

**Scar versus optimal site location.** To determine the influence of infarct size and location on the corresponding effectiveness and location of optimal LV endocardial pacing sites, scar area and scar-pacing site distance were measured using CartoXP software. The average infarct size was 227.6 ± 43 cm² or 25.8 ± 14.9% of the total LV endocardial area. Optimal pacing sites were typically located far from infarct centers (9.3 ± 3.6 cm; 37% of coplanar LV circumference) and were located in healthy myocardium (bipolar voltage >1.5 mV) in 10 of 11 patients. In the 7 patients with CRT leads in place, distance from the lead tip to the scar center was similarly large (8.3 ± 3.2 cm; 34% of coplanar circumference), suggesting that distance alone did not result in peak achievable dP/dt max. There was no effect of scar size on dP/dt max response to BiV pacing (either peak dP/dt max achievable or peak increase over baseline) or on the size and number of optimal LV endocardial pacing sites.

**Activation versus optimal site location.** To investigate whether baseline patterns of LV activation correlated with optimal LV pacing site location, endocardial LV activation maps were constructed for all patients (Online Appendix).
Activation maps were generated during sinus rhythm (n = 8), atrial fibrillation (n = 1), or RVA pacing (due to hemodynamically significant bradycardia; n = 2). LV activation duration in our series was prolonged (135 ± 44 ms), with latest activation at the left lateral free wall in 9 patients and at other regions in the remaining 2. In 8 of 11 patients, optimal pacing sites were located at regions other than the latest activated site (Online Appendix), whereas in 3 patients, optimal function was achieved by pacing the latest activated myocardium.

Discussion

To our knowledge, the current study presents the first systematic analysis of optimal endocardial LV pacing site location for CRT in patients with ICM. Our principal findings—that mid-left lateral free wall LV pacing resulted in suboptimal LV mechanical function in the majority of patients and that LV pacing at extreme basal positions was associated with a peak acute CRT response—have clear implications for how best to deliver resynchronization therapy in these patients. In addition, our report contributes to a growing body of data about the merits of endocardial versus epicardial LV pacing, the impact of scar burden on CRT response, and the impact of interpatient variability in optimal LV pacing site location.

Nonresponder rates to CRT continue to hover between 20% and 50%, depending on the metrics used to quantify CRT effect (11). Positioning of the CS lead is one important variable governing resynchronization response. Based on early work from Butter et al. (17), CRT typically is delivered through a lead positioned in a lateral or posterolateral CS tributary, midway between the base and apex of the ventricle. Our results suggest that in patients with ICM the traditionally accepted pacing site may not, in fact, yield the best mechanical results. The mid-lateral free wall of the LV, although better than baseline RV apical pacing, was consistently associated with suboptimal dP/dt_{max} values in our patient series. In contrast, pacing at the extreme base of the left ventricle, at a position adjacent to the mitral valve ring, was associated with superior mechanical results in 8 of 11 patients. This region provides logistical challenges for stable CS lead positioning. However, as active fixation CS leads become more widely used in clinical practice (19), placing leads in an extreme basal position may become more feasible.

Although extreme basal LV pacing gave good results in a clear majority of patients, stimulation at that site still gave poor results in 27% of our cohort, which (if extrapolated to long-term response) would do little to improve the CRT nonresponder rate. A striking finding in our series was the high degree of interpatient variability in optimal pacing site location. This finding was documented by Derval et al. (15) in a recent study of non-ICM patients using a protocol similar to ours and suggests that tailored CRT (i.e., patient-specific determination of optimal LV lead position at the time of device implantation) may be necessary to increase clinical response rates still further. One limitation to tailored therapy is the restriction imposed by CS tributary anatomy on lead positioning. This limitation, in part, has driven an interest in LV endocardial pacing for resynchronization therapy.

Our study contributes important new information about the feasibility of LV endocardial pacing for CRT (20–22). First and foremost, we demonstrate that LV endocardial pacing in patients with ICM is capable of dramatic improvements in LV systolic function when the optimal site is stimulated. The patients in our series had average baseline dP/dt_{max} values of 675 mm Hg/s, suggesting a series of
patients with particularly severe LV systolic dysfunction. Furthermore, scar burden in our patients was high, with an average scar area encompassing ~25% of the total LV area. Despite the severity of disease in this series, LV endocardial pacing resulted in an average improvement in dP/dt max of 36%, providing clear evidence that endocardial pacing is capable of delivering striking mechanical results, even in patients with very poor baseline function.

Some investigators have postulated that for any given lateral LV wall location, LV endocardial pacing may in fact

Figure 3 LV Maps of Voltage (Native Rhythm) and Systolic Function (Biventricular Pacing)

(A) Left ventricular (LV) voltage (top) and peak rate of left ventricular pressure increase (dP/dt max) (bottom) maps from a single patient in left anterior oblique (LAO) and left lateral (LL) projections. Voltage mapping shows a large inferior scar (red/gray), with viable anterolateral myocardium (purple). dP/dt max mapping shows 2 distinct pacing regions giving optimal dP/dt max values (purple), including 1 region at the extreme LV base (gray arrows). Pacing at the mid-LV free wall resulted in suboptimal LV mechanical function (orange/green, white arrows). Scale values in dP/dt max maps are expressed in mm Hg/s. Points tagged with colored balls were of clinical significance, but not relevant to the investigational protocol. (B) LV voltage (top) and dP/dt max (bottom) maps from 3 different patients, all in left lateral projection, showing optimal LV endocardial pacing sites at the extreme LV base. Note that this finding was independent of scar location (red) in the voltage maps. dP/dt max scale values are expressed in mm Hg/s. Points tagged with colored balls were of clinical significance, but not relevant to the study protocol. MVA = mitral valve annulus.
be superior to epicardial pacing for CRT (18). We did not find this to be the case. Seven of our patients had long-term CRT systems in place, allowing for direct comparison of endocardial versus epicardial pacing in patients with dys-synchronous failure. Our finding that the mechanical effect from LV endocardial and epicardial sites was comparable is more consistent with the work of Derval et al. (15) (who reported similar endocardial and epicardial results) than the work of van Deursen et al. (18) (who reported improved mechanical effects from endocardial pacing). The disparity between our results and those of van Deursen et al. (18) likely stems from the substrate being paced. Our investigation was performed in subjects with dysssynchronous heart failure, whereas van Deursen et al. (18) studied a canine model of dyssynchrony without superimposed LV systolic failure. We showed previously that dyssynchrony and heart failure independently have deleterious effects on parameters including expression of gap junction proteins (4), cell-cell coupling (5,23), and conduction velocity (5,23). These changes were most pronounced at the endocardial level in regions of latest myocardial activation. It is likely that pacing healthy endocardium may indeed result in more rapid and efficient LV myocardial activation, with attendant increases in dP/dt\textsubscript{max}. Our investigation, however, sheds light on the limitations of endocardial pacing in a diseased subject.

Using the Carto mapping system, we were able to delineate regions of scar and investigate whether scar burden or distribution had any appreciable effect on optimal pacing site location. We found that best pacing sites typically were located far from regions of dense scar; average optimal site location was frequently on the opposite LV wall from the infarct zone. However, pacing at regions distant from dense infarct zones was not sufficient for guaranteeing optimal LV mechanical response. Other endocardial sites, equally distant from the infarction, did not uniformly yield peak results. Furthermore, the CS lead position in the 7 patients studied with CRT systems in place was located far from regions of scar, but gave demonstrably worse results than the best LV endocardial sites. The mechanism by which certain LV endocardial sites yield optimal mechanical results does not appear to be simply a function of endocardial location per se or distance from the infarction. Rather, we suspect that there are variable patterns of conduction velocity, lines of conduction block, and pacing latency that dictate mechanical effects from stimulation at a certain site. These inputs, highly variable among patients, may explain in part the high rate of CRT non responders (particularly in patients with ischemic disease). As we show, however, searching out the optimal site(s) for CRT delivery makes these obstacles surmountable.

Intuitively it would appear that LV pacing at sites of latest activation should yield maximal mechanical response, but we did not find this to be the case. In the majority of patients, optimal pacing sites were located in regions activated neither extremely early nor late during ventricular excitation. The lack of correlation between latest endocardial activation sites and optimal pacing sites may reflect a disconnect between electrical and mechanical activation, the impact of regions of slow conduction and lines of conduction block on optimal pacing sites, or some combination of the two. From a practical standpoint, the dissociation between regions of late LV activation and best CRT response suggests that simply implanting a pacing lead at
zones of latest electrical activation would not be expected to achieve optimal mechanical results.

**Study limitations.** In the current study, we conducted our protocol only in patients referred for ventricular tachycardia or premature ventricular complex ablation (to justify catheter placement in the left ventricle). Our patient cohort, therefore, may not be representative of the general population of patients with ICM and dysynchronous LV failure. Because of the particular entry criteria and the intensive nature of the pacing protocol, only a small number of patients (with some variation in congestive heart failure symptom burden) were studied. In addition, various refinements of CRT pacing (including varying AV and interventricular delays) could not be investigated. Pacing was performed in the VDD mode, allowing for fixed AV delays during RVA and BiV pacing, but introducing fluctuations in heart rate as a variable. Finally, we compared the effects of endocardial and epicardial pacing in patients who had undergone long-term CRT, which may have introduced unknown effects on the mechanical response to pacing in that region. That our results are similar to those of Derval et al. (15) (who studied patients not subjected to long-term pacing) suggests that the effects of previous CRT in this comparison may be limited.

**Conclusions**

The LV pacing site is a principal determinant of acute CRT response in patients with ICM. LV endocardial pacing, by allowing access to heretofore inaccessible pacing sites, can yield substantial improvement in LV mechanics compared with traditional CS-based CRT. Until LV endocardial pacing schemes are available, CRT in patients with ICM is likely best delivered from a basal LV position.

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**REFERENCES**


**Key Words:** cardiac resynchronization therapy • heart failure • pacing.

**APPENDIX**

For supplemental data and figures, please see the online version of this article.