Maximal Electric Separation–Guided Placement of Right Ventricular Lead Improves Responders in Cardiac Resynchronization Defibrillator Therapy

Rodrigo I. Miranda, MD; Michael Nault, MD*; Amer Johri, MD; Christopher S. Simpson, MD; Kevin A. Michael, MB, ChB; Hoshiar Abdollah, MB, ChB; Adrian Baranchuk, MD; Damian P. Redfearn, MD

Background—Cardiac resynchronization therapy is widely used for the treatment of heart failure. Recent data suggest that electric separation during left ventricular pacing varies within the right ventricle (RV). We hypothesized that placement of the RV lead guided by maximal electric separation (MES) would improve response to cardiac resynchronization therapy compared with standard apical placement.

Methods and Results—A single-blind, randomized controlled trial was conducted. Patients eligible for cardiac resynchronization therapy-D were enrolled. Left ventricular lead placement was performed at the coronary sinus branch. The RV outflow tract, septum, and apex were mapped during left ventricular pacing and MES recorded. Patients were randomized to receive either apical placement or RV lead placement at the site mapping MES. Left ventricular ejection fraction, 6-minute walk distance, and New York Heart Association functional class were recorded at baseline and 3 months by blinded observers. Response was defined as at least one of the following: 5% absolute increase in ejection fraction, 50 m increase in 6-minute walk distance, or an increase by >1 functional class. Primary end point was improvement in ejection fraction at 3 months. Fifty patients were randomized (25 MES-guided and 25 apical). Baseline characteristics were similar in the 2 groups. Electric separation was lower in the apex (143±23 versus 168±25 ms in MES group; P=0.01). MES was most commonly septal and rarely apical (4/50 patients). Responders in the MES-guided versus apical group are as follows: Echo 21 versus 13 patients (P=0.032), 6-minute walk distance 19 versus 12 patients (P=0.079), and functional class 22 versus 15 patients (P=0.051). No dislodgment or reposition for suboptimal defibrillation tests was reported.

Conclusions—MES-guided placement of the RV lead improves cardiac resynchronization therapy responders compared with standard apical placement. (Circ Arrhythm Electrophysiol. 2012;5:927-932.)

Key Words: devices for heart failure  heart failure  pacing  electric separation

Cardiac resynchronization therapy (CRT) is an established treatment for drug-refractory heart failure (HF) and left ventricular (LV) mechanical dyssynchrony because of conduction delay.1-3 However, 20% to 40% of patients are nonresponders to CRT therapy.4 Several variables, including cause of HF,5,6 pattern of mechanical dyssynchrony,9,10 and site of LV pacing,11,12 have been investigated as predictors of response.

Published reports have suggested that a posterolateral or lateral branch of the coronary sinus (CS) generally provides the optimal LV pacing site.11-13 Furthermore, the placement of the LV lead is limited by the anatomic distribution of tributaries of the CS.13

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Given that the goal of CRT is to improve ventricular synchrony by coordinating LV and right ventricular (RV) contraction, the suggestion has been made that ideal lead positioning includes maximal RV to LV electrode separation.14-18 Furthermore, recent data suggest that greater interlead physical separation14,15 and greater electric separation (ES)16-18 correlate with better clinical outcomes.

The position of the RV lead has traditionally been apical; however, recent information suggests deleterious effects in RV-LV synchrony during RV apical pacing.19-22

Interlead ES varies in different positions within the RV.23 Indeed, the place of maximal ES (MES) was found usually at the septum and rarely at the apex.23

Optimal placement of the RV lead during biventricular pacing has not been assessed. We hypothesized that MES-guided placement of the RV lead will increase the number of CRT responders compared with standard apical placement.

Methods

The study was a prospective, randomized, single-blind trial comparing clinical outcomes in a CRT population randomized to standard...
apical lead placement of the RV lead or guided placement to the site of MES. The study was approved by the local ethics board.

Patients
Consecutive patients with conventional indications for CRT were recruited. The indication for CRT was standard according to current clinical guidelines: symptomatic HF despite optimal medical therapy, LV ejection fraction (EF) <35%, sinus rhythm, and QRS >120 ms with left bundle branch block morphology. Exclusion criteria were preexisting devices attending for upgrades, atrial arrhythmia, or inability to place the LV lead (Figure 1).

CRT devices were implanted as previously described. Briefly, a 6947 dual-coil, high-voltage lead (Medtronic Inc, Minneapolis, MN) was placed at the RV apex to provide back-up pacing in the event of inadvertent ativoventricular block during CS lead placement. The LV lead was sited in the posterolateral branch (first option), lateral branch (second option), or middle cardiac vein (third option) of the CS. After satisfactory positioning of the LV lead, a deflectable catheter (Polaris, Boston Scientific, Natick, MA) was used to map the RV from RV outflow tract (RVOT) to apex, with care to avoid the anterior free wall. After completion of the protocol, this catheter was removed and replaced with a 5076 or 4076 active fixation pacing lead (Medtronic Inc, Minneapolis, MN) placed in the right atrial appendage.

Mapping the RV
After placement of the LV lead, a roving deflectable catheter was used to map the RV. The catheter was placed in the septal RVOT, high septum, inflow septum, mid-septum, apical septum, and apex; the definitions for these site are shown in Figure 1A. For the RVOT and septum, care was taken to ensure that the catheter was torqued in a posterior fashion to avoid the anterior wall. Once a stable position was obtained, the position of the catheter was confirmed by fluoroscopy in both left anterior oblique 40° and lateral anterior oblique 10° by experienced operators. During constant LV pacing at a cycle length of 600 ms, median ES was recorded for 10 to 15 beats at each site within the RV.

Electric Separation
A standard ventricular pacing output of 5.0 V/0.5 ms was programmed to ensure complete ventricular capture. The electric delay to the recording electrode within the RV was assessed using the device programmer/analyzer (model 2090, Medtronic Inc). Intracardiac measurements were calculated with reference to the markers of the paced and sensed events recorded at a sweep speed of 50 mm/s. The distance between the paced and sensed events was calculated in milliseconds (Figure 1B). Traces were carefully inspected for noncapture or fusion, and such beats were eliminated from analysis.

At this point, patients were randomized to either apical placement of the RV lead or at the place of MES.

All patients had subsequent posterior-anterior and lateral chest x-ray (CXR) to confirm positioning of the pacing leads. Digital calipers were used to calculate the physical separation on the lateral CXR, this was recorded for subsequent correlation with the final recorded ES.

End Points
Echocardiogram, 6-minute walk distance test (6MWD), functional class, and serum biomarkers B-type natriuretic peptide and high-sensitivity C-reactive protein (CRP) were recorded at baseline and 3 months by blinded observers.

Definition of Response
Response to CRT was defined by a 5% absolute increase in EF by Echo, a 50-m increase in 6MWD, or an increase by >1 in New York Heart Association functional class. Super-responders were defined as patients with improvements in all 3 criteria.

The primary end point was objective evidence of reverse LV remodeling as evidenced by improvement in EF at 3 months.

Safety End Points
Defibrillation threshold was performed with a 10-J safety margin. RV lead dislodgment and complications related to the procedure were collected.

The devices were manufactured by Medtronic (Minneapolis, MN) (Concerto models). All patients received simultaneous LV and RV pacing. The ativoventricular interval was programmed to secure permanent biventricular pacing.

Statistical Analysis
The analysis was performed using an intention-to-treat basis. Normality was assessed using the Anderson-Darling test; comparisons between sites were performed using a paired Student t test and between groups with a 2-tailed, unpaired Student t test for normally distributed data and Mann-Whitney test for skewed data. Fisher exact test was used for categorical data. The Pearson correlation was used to correlate ES and physical interlead distance. Repeated-measures ANOVA test was used to compare ES within the RV, and Wilcoxon rank-sum tests were applied. For all analyses, P<0.05 was considered to be statistically significant. Data are presented as mean±SD, unless otherwise stated.

Results
Sixty consecutive patients meeting inclusion criteria were approached; 5 declined and 2 were enrolled in other studies. Of the 53 remaining patients, 3 were excluded: 1 patient did not have the procedure and in 2 patients the duration of the procedure negated the study protocol before randomization (in 1 case, multiple LV lead dislodgment was cited as the reason for increased procedure time). Thus, data are available on 48 patients (39 men; mean age 67.1±7.3 years), 28 with ischemic cause of cardiomyopathy (Figure 2).

The patients were mostly in New York Heart Association functional class III (90%), with wide QRS (163.7±22.6 ms) and low LV ejection fraction (24.2±5.9%). Most patients were
taking angiotensin-converting enzyme inhibitors or angiotensin receptors blockers (90%), β-blockers (92%), diuretics (92%), and aldosterone antagonists (70%).

The final LV lead location was posterolateral vein in 39, lateral in 9, and middle cardiac vein in 2 patients. All patients recorded a high percentage of biventricular pacing at 3-month follow-up (95±4%). Table 1 showed the ES mapped in 6 places within the RV during LV pacing in all patients. ES measured during LV pacing was consistently and significantly lower in the RV apex (143.9±23.6 ms; \( P = 0.01 \)) compared with the apical group (153.3±24.2 ms; \( P = 0.01 \)) (4 patients). There is a positive correlation between ES and physical interlead distance in the CXR (\( r = 0.67, P = 0.0001 \)) (Figure 3).

Table 1 showed the ES mapped in 6 places within the RV during LV pacing in all patients. ES measured during LV pacing was consistently and significantly lower in the RV apex (143.9±23.6 ms; \( P = 0.01 \)). The place of MES was most commonly found in the mid-septum (19 patients; \( P = 0.03 \)) and only rarely in the apex (4 patients).

There is a positive correlation between ES and physical interlead distance in the chest x-ray (\( r = 0.67; P = 0.0001 \)) (Figure 3).

Baseline characteristics were similar in the 2 groups (Table 2). Patients had well-treated moderate or severe HF and major LV systolic dysfunction. Final measured ES was 167.9±24.8 ms in the MES-guided group and 143.1±21.4 ms in the apical group (\( P = 0.0001 \)).

### Secondary End Points

#### 6MWD Test
In the MES-guided group, the 6MWD improved from 275.1±127 to 351±137 m (\( P = 0.01 \)) and in the apical group from 274±121 to 330±126 m (\( P = 0.01 \)). The number of responders was 19 patients in the MES-guided group versus 12 in the apical group (\( P = 0.079 \)).

#### Functional Capacity
The number of responders was 22 in the MES-guided group versus 15 in the apical group (\( P = 0.051 \)).

#### Biomarkers
There were significant changes in serum levels of B-type natriuretic peptide and CRP in both groups (Table 5). The

### Primary End Points
Compared with the apical group, patients in the MES-guided placement of the RV lead had higher number of echo responders (21 versus 13 patients; \( P = 0.032 \)) (Table 3). At 3-month follow-up, there was improvement in EF in both groups, but the delta was higher in the MES-guided group (9.5±3.9%) compared with the apical group (5.1±8.4%) (\( P = 0.03 \); Table 4). At 3 months, there is evidence of reverse LV remodeling, with improvement of the LV end-diastolic volume in both groups. The delta was significantly greater in the MES-guided (23±6 mL) versus apical (11±4 mL) (\( P = 0.03 \)) group.

### Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline</th>
<th>MES Guided (n=25)</th>
<th>Apical (n=25)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value Age, y/o</td>
<td>67.2±9.6</td>
<td>67.3±6.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Male sex</td>
<td>19</td>
<td>20</td>
<td>0.46</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>15</td>
<td>14</td>
<td>0.55</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>163.5±23</td>
<td>164.9±25</td>
<td>0.74</td>
</tr>
<tr>
<td>LVEF (echo, %)</td>
<td>23.6±7.3</td>
<td>25.1±6.1</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEDV (echo, mL)</td>
<td>183±48</td>
<td>182±42</td>
<td>0.3</td>
</tr>
<tr>
<td>Six-minute walk distance, m</td>
<td>275±127</td>
<td>280±119</td>
<td>0.33</td>
</tr>
<tr>
<td>NYHA FC III, patients</td>
<td>23</td>
<td>22</td>
<td>0.4</td>
</tr>
<tr>
<td>β-blockers</td>
<td>23</td>
<td>23</td>
<td>0.52</td>
</tr>
<tr>
<td>% biventricular pacing</td>
<td>95.1±3.9</td>
<td>95.9±4.3</td>
<td>0.33</td>
</tr>
<tr>
<td>Electric separation, ms</td>
<td>167.9±24.8</td>
<td>143.1±21.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MES indicates maximal electric separation; LVEF, left ventricular ejection fraction; LVEDV, LV end-diastolic volume; NYHA FC, New York Heart Association functional class.

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**Figure 2.** Diagram of the study. CRT indicates cardiac resynchronization therapy; LV, left ventricular; MES, maximal electric separation; RVOT, right ventricular outflow tract; 6MWD, 6-minute walk distance test; FC, functional class.

**Figure 3.** Positive correlation between electric separation and physical interlead distance in the chest x-ray.

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**Table 1. ES and Place of MES Mapped in 6 Places Within the RV During LV Pacing**

<table>
<thead>
<tr>
<th>Place of MES</th>
<th>ES, ms</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVOT</td>
<td>153.2±24.6</td>
<td>3</td>
</tr>
<tr>
<td>High septum</td>
<td>156.7±24.6</td>
<td>6</td>
</tr>
<tr>
<td>Inflow septum</td>
<td>158.1±27.7</td>
<td>9</td>
</tr>
<tr>
<td>Mid-septum</td>
<td>159.2±24.4</td>
<td>19*</td>
</tr>
<tr>
<td>Apical septum</td>
<td>153.3±24.2</td>
<td>8</td>
</tr>
<tr>
<td>Apex</td>
<td>143.9±23.6</td>
<td>4</td>
</tr>
</tbody>
</table>

ES indicates electric separation; MES, maximal electric separation; RV, right ventricle; LV, left ventricle; RVOT, RV outflow tract.

*Mid-septum is the most common place of MES (\( P = 0.03 \)).

†Mean ES is lower in the apex (\( P = 0.01 \)).
level of CRP was significantly lower at 3-month follow-up in the MES-guided group versus apical group (P=0.005).

Analysis of subgroups separated by cause of HF is shown in Table 6. There is a trend toward higher number of responders in patients with dilated cardiomyopathy and MES-guided placement of the RV lead.

### Safety End Points
There was 1 patient with acute LV lead dislodgment during attempts at mapping the RV, with successful reposition. Defibrillation threshold was performed in 21 of 25 patients in the MES-guided group and in 15 of 25 patients in the apical group. The device senses and defibrillates (25 J) successfully in all cases. There were no RV lead dislodgments.

### Discussion
The major finding of this randomized study was that MES-guided placement of the RV defibrillator lead improves the number of CRT responders compared with standard apical placement. The MES-guided group had a higher number of responders in terms of EF (84% versus 52%; P=0.032), 6MWD test (76% versus 48%; P=0.079), and functional class (88% versus 60%, P=0.051), compared with conventional apical placement. Furthermore, super-responders, patients with improvement in all 3 parameters, were significantly more prevalent in the MES-guided group (62% versus 32%; P=0.046). In addition, a significant reduction in inflammatory markers was observed only in the MES group (Table 5).

A reliable method to evaluate optimal lead positioning in CRT is still awaited. LV lead placement is limited by the tributaries of the CS and epicardial access.25–27 Little attention has been given to RV lead placement, perhaps because of the assumption of less impact on cardiac synchrony.

Previous trials have demonstrated a positive correlation between ES and clinical outcomes in CRT. Sassone et al16 reported that ES between RV-LV leads correlates with interlead distance and CRT responders. Heist et al14 reported that interlead distance in lateral CXR correlates with acute CRT response by echo. Merchant et al15 reported that interlead distance and electric delay predict reverse remodeling in CRT. The place of MES represents the latest activation point in the RV during LV pacing. Mapping ES within the RV showed that ES was lower in the apex compared with the RVOT and septal locations (P=0.001). Indeed, the place of MES was most commonly found in the septum and only rarely in the apex (4/50 patients).21

RV pacing from the place of MES secures earliest activation of the latest point in the RV, improving interventricular synchrony.25–27 Furthermore, the place of MES was most commonly found in the septal locations, a site not commonly used in CRT-D. Septal placement of the implantable cardioverter defibrillator lead has good evidence for safety.24 In our series, there were no implantable cardioverter defibrillator lead dislodgments, and the defibrillator test was successfully performed.

In pacemakers, septal pacing has shown benefits over apical pacing in terms of LV function and synchrony.19,20 Long-term apical pacing has been associated with interventricular dys-synchrony and HF.21,22 However, in our study, of the 3 patients in the MES-guided group where MES was observed at the apex and thus apical placement occurred, the primary end point of echo response was seen in all 3.

There is evidence of positive correlation between physical interlead distance and CRT responders. Heist et al14 reported that interlead distance in lateral CXR correlates with acute CRT response by echo. Merchant et al15 reported that interlead distance and electric delay predict reverse remodeling in CRT. We found a positive correlation between ES and physical interlead distance in the CXR (r=0.67; P=0.01). This information

### Table 3. Main Results

<table>
<thead>
<tr>
<th>Value at 90 d</th>
<th>MES Guided</th>
<th>Apical</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta EF, %</td>
<td>9.5±3.9</td>
<td>5.1±8.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Delta LVEDV, mL</td>
<td>23±6</td>
<td>11±4</td>
<td>0.03</td>
</tr>
<tr>
<td>Delta 6MWD, m</td>
<td>79±74</td>
<td>62±68</td>
<td>0.12</td>
</tr>
<tr>
<td>Delta FC (grades)</td>
<td>0.92±0.4</td>
<td>0.72±0.3</td>
<td>0.21</td>
</tr>
<tr>
<td>Delta ORS, ms</td>
<td>24±21</td>
<td>25±21</td>
<td>0.78</td>
</tr>
</tbody>
</table>

MES indicates maximal electric separation; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; 6MWD, 6-minute walk distance test; FC, functional class.

### Table 5. Levels of Biomarkers at Baseline and 3-Month Follow-Up

<table>
<thead>
<tr>
<th>Value</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP, ng/L</td>
<td>1770 (IQR 1070)</td>
<td>899 (IQR 672)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.9±4.7</td>
<td>4.1±4.3</td>
</tr>
</tbody>
</table>

### Table 6. Subgroup Analysis: Ischemic vs DCM

<table>
<thead>
<tr>
<th>Value</th>
<th>Apex (n=25)</th>
<th>MES Guided (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Ischemic (n=14)</td>
<td>Ischemic (n=15)</td>
</tr>
<tr>
<td>DCM</td>
<td>DCM (n=11)</td>
<td>DCM (n=10)</td>
</tr>
<tr>
<td>ECHO responders</td>
<td>7 (50%)</td>
<td>6 (54%)</td>
</tr>
<tr>
<td>6MWD responders</td>
<td>7 (50%)</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>FC responders</td>
<td>8 (57%)</td>
<td>7 (63%)</td>
</tr>
<tr>
<td>Super-responders</td>
<td>4 (28%)</td>
<td>4 (36%)</td>
</tr>
</tbody>
</table>

DCM indicates dilated cardiomyopathy; MES, maximal electric separation; 6MWD, 6-minute walk distance test; FC, functional class.
supports use of interlead ES to optimize lead positioning during implant and improve CRT response.

Biomarkers have a prognostic role in patients with HF. Reduction in serum levels of high-sensitivity CRP has been associated with response to CRT therapy.25 We report that CRP levels were significantly lower in the MES-guided group compared with the apical group (P=0.005), in concordance with the clinical outcomes.

It is recognized that both ischemic and nonischemic dilated cardiomyopathy benefit from CRT implant.26,28 In this study, the subgroup analysis demonstrated benefit in both causes, with a trend toward a higher number of responders in the dilated cardiomyopathy group (Table 6).

Our work suggest that the septal region, particularly the mid-septum, demonstrated consistently greater ES than the apex in this cohort of cardiomyopathy patients.23 Because the number of patients with apical placement in the MES-guided group was small (Figure 2), it is not possible to differentiate the effect of septal pacing per se from the strategy of MES-guided therapy. The only study published to date to examine this was an observational study where the outcome was not different in septal or apical position.30 However, the septum is frequently ill-defined, and confounding can occur from RVOT or anterior wall placement. We found variability in ES in anatomically nearby septal locations; careful definitions and mapping of the RV mitigated this problem, and the study was driven by the MES, not simply septal location. In the ischemic cohort, the RV mapping may have more relevance as the location of scar in relation to LV lead placement will differ and thus intraoperative mapping of ES might be expected to have greater impact; further studies of this aspect are required. The outcome of the larger SEPTAL-CRT trial31 may inform as the utility of pursuing an MES-guided approach or simply adopting a septal position for all the CRT patients. Given that the MES is most often at the mid-septum, this location might be adopted pending further studies.

Limitations
The relatively small sample size and lack of consensus defining CRT response limit the interpretation. In our study, the response observed in the apical group was relatively low but was in keeping with similar studies using strict definitions for response.32–34 In addition, the use of blinded observers and significant improvement observed in all criteria support a true effect of the intervention. A larger study with longer follow-up would be valuable to evaluate a sustained clinical improvement associated with improvement in LV remodeling.

Conclusions
MES-guided placement of the RV defibrillation lead during CRT is both practical and feasible. The results of this randomized study clearly show the benefit in terms of clinical response and reverse LV remodeling that may be obtained with optimization of the RV lead pacing position.

Acknowledgments
Colleen Londry is acknowledged for her contribution to verification and quality of echocardiographic assessment.

Disclosures
None.

References
Cardiac resynchronization therapy is an established treatment for drug-refractory heart failure and left ventricular mechanical dyssynchrony because of conduction delay. However, 20% to 40% of patients are nonresponders to cardiac resynchronization therapy. Maximal electric separation–guided placement of the right ventricular defibrillation lead during cardiac resynchronization therapy is both practical and feasible. The results of this randomized study show the benefit in terms of clinical response and reverse left ventricular remodeling that may be obtained with optimization of the right ventricular lead pacing position.
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