Outcome of Patients Treated by Cardiac Resynchronization Therapy Using a Quadripolar Left Ventricular Lead

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Background: Not all heart failure (HF) patients benefit from cardiac resynchronization therapy (CRT). We assessed whether choosing the site of left ventricular (LV) pacing by a quadripolar lead may improve response to CRT.

Methods and Results: We prospectively randomized 23 patients with HF (67±11 years; 21 males) to CRT with a quadripolar LV lead (group 1, with the LV pacing site chosen on the basis of QRS shortening using simultaneous biventricular pacing), and 20 patients (71±6 years; 16 males) to a bipolar LV lead (group 2, with devices programmed with a conventional tip-to-ring configuration). New York Heart Association (NYHA) class and LV ejection fraction (EF) by 2D echocardiography were assessed at baseline and after 3 months. The baseline EF was not different between the 2 groups (25±6% group 1 vs. 27±3% group 2; P=0.22), but after 3 months EF was higher in group 1 (35±13% group 1 vs. 31±4% group 2; P<0.001). A reduction in at least 1 NYHA class at 3 months was observed in 22 (96%) and 12 (60%) of group 1 and group 2 patients, respectively (P<0.05).

Conclusions: CRT with a quadripolar LV lead was associated with an improvement of EF greater than that observed in patients receiving a bipolar LV lead. In devices with a quadripolar lead, CRT programming based on the best QRS shortening is reliable and effective. (Circ J 2016; 80: 613–618)

Key Words: Cardiac resynchronization therapy; Heart failure; Mortality; Multipolar pacing; Quadripolar lead

Cardiac resynchronization therapy (CRT) is a well-established therapy for treatment of heart failure (HF) with severely impaired left ventricular (LV) systolic function and evidence of ventricular dyssynchrony.1,2 Although advances in technology and clinical indications have increased the success rate,3,4 a sizable proportion of patients fail to show clinical or echocardiographic response to this treatment.5,6

Response to biventricular pacing may vary according to the site of pacing; in particular, the mid-ventricular and basal portions of the lateral LV wall were recently associated with the best response.7,8 Recently, quadripolar LV leads have been designed in order to provide more options for LV pacing.9–15 This new lead integrates 4 pacing electrodes that allow a higher number of pacing configurations in device programming as compared with traditional bipolar LV leads. Recent studies suggest that CRT with quadripolar LV lead is associated with a higher implantation success rate and low rates of dislocation and phrenic nerve stimulation (PNS).10,12,14 In this study, we tested if choosing the pacing configuration associated with best QRS shortening among those allowed by quadripolar lead can result in a better response to CRT compared with use of a traditional bipolar lead.

Methods

Study Population

From January 2010 to January 2012, 43 consecutive patients (mean age 69±9 years; 37 male), referred to our Center for CRT, were prospectively enrolled and randomized using a computer-generated table of random numbers. Of them, 23 patients (mean age 67±11 years; 21 male) were implanted with a quadri-polar LV lead (group 1) and 20 patients (mean age 71±6 years; 16 male) with a bipolar LV lead (group 2). Patients with a preexisting pacemaker or ICD device were excluded. Indications for CRT implantation were based on the European Society of Cardiology guidelines for HF recommendations.1 In particular, all patients had an ejection fraction (EF) <35% and QRS duration ≥130 ms with left bundle branch block (LBBB) morphology.
portion of the free LV wall (P4-M2). In each patient, the pacing configuration associated with the shortest QRS duration was programmed at the end of CRT device implantation; biventricular pacing was simultaneous: the V-V interval was programmed to 0 ms and no change was allowed during follow-up; in both study groups the AV interval was optimized by automatic AV programming, based on an algorithm (QuickOpt) provided by the ICD. In patients with a bipolar lead, a conventional pacing configuration (tip to ring) was programmed; other possible configurations, using the right ventricular lead as the anode (ie, left tip to right ring of left ring to right ring) were also tested but were associated with a wider QRS in all patients. Patients were blinded to the type of LV lead they received.

New York Heart Association (NYHA) functional class and 2D echocardiography data were obtained at baseline and at 3-month follow-up in all patients by a physician blinded to the patient’s treatment group.

### Implantation Procedure and Lead Characteristics

Technical aspects of leads and device implantation were described in detail previously. Briefly, the coronary sinus (CS) was cannulated from a subclavian entry site using a commercially available long peelable guiding sheath. In both groups, the LV lead was preferentially positioned in a lateral or posterolateral branch. A different branch was chosen only when venous anatomy, stimulation thresholds, lead stability, or diaphragmatic stimulation prevented lead delivery into the primary site. The final position of the LV pacing lead was assessed by fluoroscopy. Lead positioning at the apex of the lateral wall was avoided. PNS was tested in all patients, starting from the maximum pacing system analyzer output.

The quadripolar LV pacing lead used in this study was the Quartet™ lead (St. Jude Medical, Sylmar, CA, USA), a 4.7F, over-the-wire, steroid-eluting LV lead with 4 pacing poles (with electrodes designated, distally to proximally, as D1, M2, M3, and P4), connected to a dedicated CRT defibrillator (Unify Quadra™ or Promote Quadra™, St. Jude Medical). Four possible pacing configurations were assessed: the distal poles (D1-M2), the basal poles (P4-M2) and 2 intermediate dipoles (M2-P4 and M3-P4), stimulating the distal portion (D1-M2), the mid-ventricular portion (M2-P4 and M3-P4) or the basal portion of the free LV wall (P4-M2). In each patient, the pacing configuration associated with the shortest QRS duration was programmed at the end of CRT device implantation; biventricular pacing was simultaneous: the V-V interval was programmed to 0 ms and no change was allowed during follow-up; in both study groups the AV interval was optimized by automatic AV programming, based on an algorithm (QuickOpt) provided by the ICD. In patients with a bipolar lead, a conventional pacing configuration (tip to ring) was programmed; other possible configurations, using the right ventricular lead as the anode (ie, left tip to right ring of left ring to right ring) were also tested but were associated with a wider QRS in all patients. Patients were blinded to the type of LV lead they received.

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### 2D Echocardiography

Transthoracic echocardiography was performed according to the recommendations of the European Society of Echocardiography by a single expert operator (C.C.), blinded to clini-

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**Table 1. Clinical Characteristics of the 2 Study Groups of Patients Indicated for Cardiac Resynchronization Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Quadripolar lead group (n=23)</th>
<th>Bipolar lead group (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±11</td>
<td>71±6</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>21/2</td>
<td>16/4</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (73%)</td>
<td>16 (80%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (48%)</td>
<td>6 (30%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10 (43%)</td>
<td>11 (55%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6 (26%)</td>
<td>4 (20%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>12 (52%)</td>
<td>10 (50%)</td>
<td>1</td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy</td>
<td>11 (48%)</td>
<td>10 (50%)</td>
<td>0.76</td>
</tr>
<tr>
<td>History of paroxysmal atrial fibrillation</td>
<td>11 (48%)</td>
<td>5 (25%)</td>
<td>0.20</td>
</tr>
<tr>
<td>EF (%)</td>
<td>25±6</td>
<td>27±3</td>
<td>0.22</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>12/11</td>
<td>11/9</td>
<td>0.19</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>165±21</td>
<td>162±11</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**Table 2. Pre-Implantation Echocardiographic Data of Study Patients Indicated for Cardiac Resynchronization Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Quadripolar lead group (n=23)</th>
<th>Bipolar lead group (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>25±5</td>
<td>27±4</td>
<td>0.22</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>233±111</td>
<td>195±62</td>
<td>0.18</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>169±95</td>
<td>140±51</td>
<td>0.24</td>
</tr>
<tr>
<td>MVR</td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; EF, ejection fraction.

EDV, end-diastolic volume; ESV, endsystolic volume; MVR, mitral valve regurgitation. Other abbreviation as in Table 1.
Smirnov test. Continuous variables were compared by unpaired t-test. Variables that showed a distribution significantly different from normal were compared by Mann-Whitney U-test. Fisher’s exact test was used to compare categorical variables. Data are reported as mean ± standard deviation or proportions. A 2-tailed P value <0.05 was considered as statistically significant. Data were analyzed by the SPSS 20.0 statistical software (SPSS Italia, Inc, Florence, Italy).

**Results**

Clinical characteristics and echocardiographic findings at baseline were similar in the 2 study groups (Tables 1,2).

All patients underwent CRT device implantation without complications. In group 1, the CS branch for LV lead location...
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Discussion

In this prospective randomized study of patients undergoing CRT, we compared the response to CRT in patients implanted with a bipolar or quadripolar LV lead. We found that, by programming the pacing configuration associated with the shortest QRS among the multiple pacing configurations allowed by utilization of a quadripolar lead, improvement in LVEF at 3-month follow-up can be higher than in patients implanted with a bipolar LV lead.

Currently, a sizable proportion of patients do not benefit from CRT. Many factors have been associated to a poor response, including pacing from areas of scar, enrolling patients with only slightly enlarged QRS (<150 ms), LV lead positioning in an anterior branch of the CS. Recently, data from the MADIT-CRT trial suggested that the response to biventricular pacing may vary according to the site of pacing, with the mid-ventricular and basal portions of the lateral wall generally associated with a better response compared with apical sites.

Although most of the available devices allow many configurations of LV pacing (tip to ring, ring to tip, tip to coil, etc), the pacing site remains substantially unchanged. However, the quadripolar lead allows personalization of the LV pacing site. Although it is well recognized that changes in the pacing vectors can be associated with a lower pacing threshold or with avoidance of PNS, whether they allow also a better response of LV function to CRT is presently unproven. Our study provides early evidence that this is the case.

The main hypothesis of our study was that pacing from different sites of the LV lateral wall (as allowed by a quadripolar catheter) can be associated with a different response in terms of LV function. We found that, by programming the pacing configuration associated with the shortest QRS among the multiple pacing configurations allowed by utilization of a quadripolar lead, improvement in LVEF at 3-month follow-up can be higher than in patients implanted with a bipolar LV lead.
of improvement of LVEF at mid-term follow-up. Although the indication to CRT is now based on LBBB morphology and QRS width, QRS shortening as a prognostic indicator after CRT implantation is still debated. However, in our study, the pacing configuration was chosen on the basis of QRS shortening, because of some evidence in support of its role in predicting the response.21–23 By choosing the left pacing configuration (and consequently the site of LV pacing) on the basis of the shortest QRS width achieved, we were able to obtain a better CRT response in patients implanted with quadripolar leads as compared with patients with bipolar leads programmed with a conventional tip-to-ring configuration.

Study Limitations
First, a small number of patients was enrolled in our single-center study and therefore our data need to be confirmed in larger populations and multicenter studies. Second, our study was not double-blind, although objective measurements were obtained by blinded operators. Third, echocardiographic measurements were done by a single operator, whereas concordant findings from at least 2 operators might have made the results stronger; however, the echocardiographer was a very expert cardiologist with more than 10 years of daily experience in the field and there was a high intraobserver reproducibility of echocardiographic data. Echocardiographic quantification of LV dyssynchrony was not routinely tested, because its presence is no longer required for the indication of CRT in patients with LBBB,1 so its role in predicting response cannot be evaluated in this study.24–26 Finally, we obtained data only at mid-term follow-up (3 months), and therefore future studies should assess whether the results are maintained over a longer follow-up time.27

In conclusion, our data showed that utilization of a quadripolar lead was associated with a better functional outcome compared with a standard bipolar lead, if confirmed in large controlled randomized studies, this finding might substantially change our approach to CRT.

Author Contributions

Conflicts of Interests
None.

References
5. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: The magnitude of the problem and the issues. Circ J

Figure 4. LV ejection fraction (EF) before and after cardiac resynchronization therapy (CRT) in group 1 and group 2.


