Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure

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Aims Cardiac resynchronization therapy (CRT) is an effective treatment for refractory congestive heart failure (CHF). However, up to 30% of patients do not respond to CRT. The aim of this study was to identify clinical and electrocardiographic (ECG) predictors of a positive response to CRT.

Methods and results This retrospective study included 139 consecutive patients successfully implanted with a CRT device (mean age, 68 ± 9 years, 113 men). At baseline, 69% of patients were in New York Heart Association (NYHA) functional class III, and 31% in class IV, mean left ventricular ejection fraction was 21 ± 6%, and mean QRS duration was 188 ± 28 ms. In each patient, left and right ventricular leads were placed to attain the shortest QRS duration during biventricular stimulation. Patients were classified at 6 months as responders to CRT (n = 100) if they were alive, they had not been re-hospitalized for management of CHF, and the NYHA class had decreased by 1 point, and/or peak VO₂ or 6 min walk increased by 10%. All others were classified as non-responders (n = 38; one patient was lost to follow-up). Uni- and multivariate logistic regression analyses were performed to detect a pre- or intra-operative predictor of a positive response to CRT. Among multiple demographic, clinical, and ECG variables, the amount of QRS shortening (ΔQRS) associated with biventricular stimulation was the only independent predictor of a positive (37 ± 23 ms) vs. negative (11 ± 23 ms) response to CRT (P < 0.001).

Conclusion A positive response to CRT was observed in 73% of patients at 6 months and predicted only by ΔQRS.
Predictors of response to CRT

Randomized studies have demonstrated a benefit conferred by CRT on symptoms of CHF and exercise capacity. Although this treatment is effective in the majority of patients, up to 30% of patients are considered 'non-responders'. Identifying reliable predictors of effectiveness of CRT remains a major challenge in clinical practice, particularly from the perspective of patient selection. Few studies have examined the intra-operative criteria of mid- to long-term effectiveness of this therapy. We performed this analysis to identify simple baseline predictive factors of a positive response to CRT.

Methods

Inclusion criteria

All patients who underwent successful implantations of biventricular stimulation systems between August 1994 and July 2001 were retrospectively included in this analysis. Criteria for implantation of a CRT system included: (i) CHF and NYHA functional class III or IV refractory to optimal medical management as defined by current guidelines, (ii) LVEF <35% and LVEDd >60 mm measured echocardiographically, and (iii) intraventricular conduction defects, manifest as a surface ECG QRS duration >150 ms in patients with spontaneous ventricular activation, or ≥200 ms in patients previously paced in the right ventricle.

Implantation techniques

An endovenous LV lead was implanted in a coronary sinus tributary in all cases, with a view to achieve permanent epicardial stimulation from a lateral or posterolateral vein or, when it was unattainable, from the mid- or great cardiac vein. The right ventricular (RV) lead was then implanted whether at the RVOT, the septum, the anterior wall, or the apex, according to the result of intra-operative biventricular pace mapping looking at the shortest biventricular paced QRS duration. Final lead positioning was assessed from post-operative chest X-ray in anterio-posterior and lateral view.

Patients in sinus rhythm received an atrio-biventricular pulse generator programmed in DDD(R) mode and interfaced with a bipolar right atrial and both ventricular leads. The atrio-biventricular delay was optimized individually on the basis of Doppler echocardiographic measurements of transmural flow. Patients in permanent atrial fibrillation received a dual chamber pulse generator programmed in DDD(R) mode, with the LV lead interfaced with the atrial channel and the RV lead with the ventricular channel. The AV, i.e. interventricular delay was programmed at a minimal interval of 30 ms to achieve the greatest degree of biventricular fusion. Radiofrequency atrioventricular junctional ablation was performed at the time of CRT system implantation to guarantee complete and permanent biventricular capture.

Collection of outcome measures

From a review of medical records, the following variables were recorded at baseline and up to 6 months after CRT system implantation: (i) NYHA functional class, (ii) exercise capacity from the distance covered during a 6 min hall-walk and peak exercise O₂ consumption (peak VO₂), (iii) QRS duration and axis, (iv) echocardiography measurements of LVEF and LVEDd, (v) hospitalizations for decompensated CHF, (vi) vital status.

Study groups assignment

The study population was divided in two groups on the basis of the assessment of the clinical composite response, as currently applied by heart failure specialists. A positive response to CRT at 6 months included: (i) alive status, (ii) no interim hospitalization for decompensated CHF, and (iii) a ≥1 point decrease in NYHA functional class or, if NYHA was unchanged, a >10% increase in peak VO₂, in the distance covered during a 6 min walk, or in both.

Statistical analyses

Unless otherwise specified, results are presented as mean ± standard deviation (SD). Efficacy of CRT was examined by comparing variables at baseline vs. 6 months after implantation of the biventricular pacing system. Differences between baseline and 6 months were tested by the Student’s t-test for paired samples for comparisons of quantitative variables and by the McNemar test for comparisons of qualitative variables. A univariate, logistic regression analysis was used for identifying pre- and intra-operative variables to be predictive of a positive response to CRT, including age, underlying heart disease, absence vs. presence of prior permanent ventricular pacing, sinus rhythm vs. atrial fibrillation, QRS duration before and during biventricular stimulation and the difference between the two values (ΔQRS), NYHA class, LVEF, LVEDd, and RV and LV lead position. Only variables significant at the 0.25 level in the univariate analysis were included in the multivariable logistic regression. Then variables were selected according to a step-down stepwise procedure using likelihood ratio statistic (then interactions between these variables will be explored, if there are at least two variables in the final model). Finally, the goodness-of-fit was assessed with the Hosmer and Lemeshow’s test. P < 0.05 was considered statistically significant and all tests were two-sided. No correction of type 1 error for multiple tests was performed.

Results

Study population

During the study period, transvenous biventricular pacemaker implantation was attempted in 158 patients and successfully performed in 88% patients that constitute the study population. The implantation success rate increased progressively from the very preliminary experience (61% in 1994–96) to the latest (98% in 2000–01). Detailed technical data have already been reported.

The study population included 139 patients (mean age, 68 ± 9 years; 113 men). A non-ischaemic dilated cardiomyopathy was present in 54%, ischaemic heart disease in 35%, and miscellaneous disorders in 11% of patients (Table 1). At the time of CRT system implantation, 96 patients were in NYHA functional class III and 43 in class IV. Sinus rhythm was present in two-thirds and permanent atrial fibrillation in one-third of patients. A dual chamber permanent pacemaker had been previously implanted for conventional anti-bradycardia indications in 23 and a VVI pacemaker in 13 patients. QRS duration ranged from 150 to 260 ms (mean, 188 ± 28 ms) and
was significantly longer in previously paced (210 ± 25 ms) than non-paced (181 ± 25 ms) patients (P < 0.001). The LV lead was implanted in a lateral or a posterolateral vein in 73% of cases. The RV lead was positioned at the septum or the anterior wall in 72%. This relative proportion of apical and non-apical RV leads was not significantly different in previously paced patients (33 vs. 63%) when compared with patients with intrinsic conduction (23 vs. 77%).

Six month outcomes

During the 6 month period of observation, four patients died of endstage CHF, one died suddenly, and one patient died of a non-cardiac cause. Among the survivors (n = 133), the repartition of the NYHA functional class was very different, as shown in Figure 1 (P < 0.001), whereas peak VO₂ increased from 13.4 ± 3.5 to 16.1 ± 4.0 mL/kg/min (P < 0.001), distance covered in 6 min from 309 ± 105 to 370 ± 103 m (P < 0.001), and LVEF from 20 ± 6 to 27 ± 9% (P < 0.001). Biventricular stimulation shortened the mean QRS duration from 188 ± 28 to 159 ± 21 ms (P < 0.001), and shifted the frontal QRS axis from −32 ± 49 to +58 ± 69° (P < 0.001, Table 2).

Characteristics of responders vs. non-responders to CRT

A positive response was observed in 100 patients (72%), whereas 38 patients (27%) were not clinically improved by CRT. One patient was lost to follow-up. The baseline characteristics of the two groups were generally similar, including functional capacity and echocardiographic measurements (Table 3), as well as the sites of implantation of the LV and RV leads (Table 4). Comparisons of 6 months clinical characteristics between the two groups are shown in Table 5. Among all variables examined, the only significant differences detected were derived from the surface ECG. In univariate analysis, QRS duration before CRT was longer in responders (192 ± 27 ms) than in non-responders (180 ± 29 ms, P < 0.001), whereas it was shorter in responders (155 ± 20 ms) than in non-responders (169 ± 20 ms) during CRT (P < 0.001). Among responders, QRS duration during CRT decreased in 95%, increased in 2%, and remained unchanged in 3%. Among non-responders, QRS decreased in 60%, increased in 27%, and remained unchanged in 13%. Finally, the mean QRS shortening (ΔQRS) associated with CRT when compared with baseline was significantly greater among the responders (37 ± 23 ms) than the non-responders (11 ± 23 ms, P < 0.001, Table 4 and Figure 2). However, no clear-cut value could be found for separating responders and non-responders. This result was principally observed in patients with baseline intrinsic conduction (Table 6). A similar trend was also observed in the subgroup of previously paced patients, but did not reach statistical significance threshold probably owing to the small number of patients. No significant differences were observed between patients with normal sinus rhythm and patients with permanent AF even though an additional 30 ms interventricular delay was mandatory applied in AF patients.

A receiver operating characteristic curve analysis failed to identify a cut-off value of ΔQRS. ΔQRS was thus considered as a continuous variable and included in the logistic regression with a 20 ms step.

The univariate logistic regression showed that QRS duration during CRT and ΔQRS was significantly associated with response (P < 0.018 and P < 0.001).

The multivariable logistic regression showed that ΔQRS emerged as the only independent predictor of response to CRT (for a step of 20 ms: odds ratio 2.15, 95% confidence interval 1.46–3.17, P < 0.001)

Discussion

Since the first report, in 1994, of the implantation of a biventricular cardiac stimulator to improve the
In our comparison of responders vs. non-responders, the only predictor of a therapeutic benefit conferred by biventricular stimulation was the magnitude by which it decreased the QRS duration. Although, in this study, this observation was highly predictive, other studies reached different conclusions.\textsuperscript{14-16} They differed, however, from ours in two main respects. First, the criteria used by others to define responders have been variable and often limited to changes in NYHA functional class,\textsuperscript{14,15} whereas we applied a robust composite endpoint, combining a subjectively derived measurement (NYHA class) with objective outcomes, including mortality and heart failure hospitalization. We believe, as recommended by Packer,\textsuperscript{9} that this represents a more global assessment of the patient. Secondly, in the present study, the RV implantation site was selected on a patient-to-patient basis, to obtain the shortest QRS duration during biventricular stimulation, whereas, in other studies, the RV lead was generally implanted at the apex.\textsuperscript{14-17}

On the basis of the known pathophysiology of electromechanical disorders, the change in QRS duration produced by biventricular stimulation should represent the quality of electrical resynchronization and indirectly reflect the degree of correction of electromechanical abnormalities. Though their observation remains controversial, Kim et al.\textsuperscript{18} reported that the decrease in QRS duration was correlated with an increase in systolic ejection volume, via a decrease in LV end-diastolic volume. This has a direct intra-operative impact on the choices of LV and RV ventricular pacing sites, which should aim at attaining the narrowest QRS possible. Although there is general agreement regarding the lateral position of the LV lead, there is no consensus for the placement of the RV lead. Pending the validation of this recommendation by dedicated prospective studies, it appears important, for the time being, to implant the RV lead at a site associated with the shortest QRS duration during biventricular pacing.

In the multivariable analysis, we found no reliable preoperative predictor of a positive response to CRT,
including the baseline QRS complex duration even if there was a significant trend in univariate analysis. Aurrichio et al. (19) and Kass et al. (20) found a QRS duration of 150 ms to be predictive of a haemodynamic improvement in the acute setting. In contrast, our observations suggest that, in a population of patients with a markedly prolonged QRS at baseline (a mean of nearly 190 ms in this study), a 10 or 20 ms decrease is not as reliable in its prediction of a favourable electromechanical response as in the presence of a QRS < 150 ms. Among other pre-operative variables, the quantification of intra- and interventricular asynchrony by new echocardiographic imaging methods appears promising. Using Doppler echocardiographic techniques, Yu et al. (21) identified the homogenization of regional ventricular contraction to be the main mechanism behind effective cardiac resynchronization, and Pitzalis et al. (16) found responders to CRT to have a significantly longer septal-to-posterior wall motion delay at baseline than the non-responders.

Table 4 | Comparisons of baseline electrocardiographic data in responders vs. non-responders to CRT

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 100)</th>
<th>Non-responders (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm/atrial fibrillation (n)</td>
<td>69/31</td>
<td>24/13</td>
<td>0.2</td>
</tr>
<tr>
<td>LBBB or non-specific IVCD/RBBB</td>
<td>94/4</td>
<td>35/2</td>
<td>0.7</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>236 ± 49</td>
<td>254 ± 71</td>
<td>0.6</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-implantation of CRT system</td>
<td>192 ± 27</td>
<td>180 ± 29</td>
<td>0.018</td>
</tr>
<tr>
<td>Post-implantation of CRT system</td>
<td>155 ± 20</td>
<td>168 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQRS (ms)</td>
<td>37 ± 23</td>
<td>11 ± 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frontal QRS axis (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-implantation of CRT system</td>
<td>−36 ± 40</td>
<td>−25 ± 63</td>
<td>0.3</td>
</tr>
<tr>
<td>Post-implantation of CRT system</td>
<td>55 ± 64</td>
<td>70 ± 79</td>
<td>0.3</td>
</tr>
<tr>
<td>LV lead position (% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>74</td>
<td>73</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>RV lead position (% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septum or anterior</td>
<td>74</td>
<td>69</td>
<td>0.6</td>
</tr>
<tr>
<td>Apex</td>
<td>26</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Unless specified otherwise, values are mean ± SD. LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction defect. ΔQRS = QRS duration before − QRS duration after CRT implantation.

Table 5 | Comparisons of the 6 month clinical outcomes in responders vs. non-responders to CRT

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 100)</th>
<th>Non-responders (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional classes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td>0</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>85</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Distance covered in 6 min walk (m)</td>
<td>395 ± 86</td>
<td>269 ± 108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak VO2 (mL/kg/min)</td>
<td>16.8 ± 4</td>
<td>14 ± 3.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Unless specified otherwise, values are mean ± SD.
they remain to be validated in larger patient populations over longer periods of observation. The ongoing CARE-HF trial, which uses echocardiographic dyssynchrony as one of its criteria for the selection of candidates for CRT, should provide information in this regard.

Study limitations

As our study was retrospective, some data were not available in all patients. So this study is based on an intra-patient comparison.

Patient heterogeneity (stable sinus rhythm vs. permanent AF; intrinsic conduction vs. paced rate) may have influenced the results. Furthermore, our population included patients treated as long as 10 years ago, much before publication of echocardiographic evaluations of mechanical dyssynchrony, limiting our collection of truly comparable data. However, despite the growing emphasis put on several echocardiographic criteria of cardiac dyssynchronization, they all remain to be prospectively validated in randomized studies.

Conclusions

This analysis provides further confirmation of the intermediate-term benefits conferred by CRT which, based on a set of robust clinical criteria, was effective in the 1998 Pacemaker Guidelines. J Am Coll Cardiol 2002;40:1703–1719.

References


