Cardiac resynchronization therapy (CRT) has been proposed as an adjunct therapy in patients with drug-refractory heart failure (HF) (1–3). Initial studies demonstrated acute improvement in hemodynamics immediately after CRT (4). Other studies have demonstrated the sustained clinical benefit of CRT at longer follow-up, evidenced by improvement in HF symptoms, quality of life, exercise capacity, and left ventricular (LV) systolic performance (1–3,5–7). However, it has also become clear that 20% to 30% of patients do not respond to CRT (1–3). Therefore, interest has shifted toward identification of potential responders to CRT before implantation of the pacemaker (8–14). It is hypothesized that LV dyssynchrony is the most important determinant of response to CRT, and various techniques to detect and quantify LV dyssynchrony are currently under investigation (8–14). However, no large studies have focused on the prediction of benefit from CRT based on the degree of LV dyssynchrony. More important, it is unclear whether patients with LV dyssynchrony who respond to CRT have a better prognosis than patients without dyssynchrony.

Accordingly, we have related the extent of LV dyssynchrony before implantation of the CRT device (assessed by tissue Doppler imaging [TDI]) to clinical outcome and LV reverse remodeling after CRT in 85 consecutive patients. The accuracy of this approach (and the cutoff value for LV dyssynchrony) to predict outcome was determined using receiver-operating characteristic (ROC) curve analysis. Finally, the most important issue was addressed: would identification of responders before pacemaker implantation translate to a favorable prognosis during follow-up?

**METHODS**

**Patients and study protocol.** Eighty-five consecutive patients with end-stage HF, scheduled for implantation of a biventricular pacemaker, were included in the current study. The patients were selected according to the established selection criteria for CRT: 1) severe HF (New York Heart Association [NYHA] functional class III or IV), 2) severely depressed LV ejection fraction (LVEF ≤35%), and 3) QRS exhibiting left bundle branch block configuration with a duration ≥120 ms (1–3). Patients with atrial fibrillation or with a previously implanted pacemaker were excluded.

The study protocol was as follows: before pacemaker implantation, resting two-dimensional (2D) and color Doppler transthoracic echocardiography were performed to measure LVEF and LV volumes and analyze the severity of mitral regurgitation (MR). Next, myocardial TDI was...
Mitral regurgitation was characterized as: mild

tional parasternal long-axis and apical four-chamber images.

semiquantitatively from color-flow Doppler in the conven-
Simpson’s rule (17). The severity of MR was graded

color images by offline analysis.

interest, and pulse repetition frequencies between 500 Hz to
120 frames/s depending on the sector width of the range of
color Doppler frame rates varied between 100 and
QRS complex, were saved in cineloop format. For TDI,
color Doppler data (3 consecutive beats), triggered to the
two-chamber and four-chamber images). Standard 2D and
obtained using a 3.5-MHz transducer, at a depth of 16 cm
using a commercially available system (Vivid Seven; General
Hospitalization for HF and survival were assessed during
one-year follow-up after pacemaker implantation.
Echocardiography and data acquisition/analysis. Patients
were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven; General Electric-Vingmed, Milwaukee, Wisconsin). Images were
tained using a 3.5-MHz transducer, at a depth of 16 cm
in the parasternal and apical views (standard long-axis,
two-chamber and four-chamber images). Standard 2D and
color Doppler data (3 consecutive beats), triggered to the
QRS complex, were saved in cineloop format. For TDI,
color Doppler frame rates varied between 100 and
120 frames/s depending on the sector width of the range of
interest, and pulse repetition frequencies between 500 Hz to
1 KHz, resulting in aliasing velocities between 16 and
32 cm/s. Tissue Doppler parameters were measured from
color images by offline analysis.

The LV volumes and the LVEF were calculated from the
apical two- and four-chamber images using the biplane
Simpson’s rule (17). The severity of MR was graded
semi-quantitatively from color-flow Doppler in the conven-
tional parasternal long-axis and apical four-chamber images.
Mitr al regurgitation was characterized as: mild = 1 + (jet
area/left atrial area <10%), moderate = 2 + (jet area/left
atrial area 10% to 20%), moderately severe = 3 + (jet
area/left atrial area 20% to 45%), and severe = 4 + (jet
area/left atrial area >45%) (18).

For TDI analysis, the digital cineloops were analyzed
using commercial software (Echopac 6.1, General Electric-
Vingmed) by two independent observers blinded to the
clinical outcome. The sample volume was placed in the LV
basal portions of the anterior, inferior, septal, and lateral
walls (using the two- and four-chamber images) and, per
region, the time interval between the onset of the QRS
complex and the peak systolic velocity was derived. Left
ventricular dyssynchrony was defined as the maximum delay
between peak systolic velocities among the four walls within
the LV (most frequently observed between the interventric-
ular septum and the lateral wall) (19). Interventricular
dyssynchrony was assessed by comparing the delay between
peak systolic velocity of the right ventricular (RV) free wall
and the LV lateral wall (8). The time required to analyze the
tissue Doppler data was 10 to 15 min.

Pacemaker implantation. The LV pacing lead was in-
serted transvenously via the subclavian route. First, a coro-
nary sinus venogram was obtained using the balloon cath-
eter. Next, the LV pacing lead was inserted via the coronary
sinus using an 8-F guiding catheter and positioned prefer-
ably in a (postero-)lateral vein (82 patients, 96%). In the
remaining three patients, the LV lead was positioned in the
anterior position.

The right atrial and ventricular leads (with separate
connectors) were positioned conventionally. The atrioven-
tricular delay was optimized by 2D echocardiography so that
it provided the longest filling time for completion of the
end-diastolic filling flow before LV contraction (20). A
dedicated resynchronization device was used in all patients.
When a conventional indication for an ICD existed, a
combined device was implanted.

Statistical analysis. Results are presented as mean values ±
SD. Data were compared using paired or unpaired Student
\( t \) test when appropriate. Proportions were compared using
chi-square analysis with Yates correction. Optimal cutoff
values of parameters to predict response to CRT were
determined by ROC curve analysis. The optimal cutoff
value was defined as that providing the maximal accuracy to
distinguish between responders/nonresponders.

Differences in cardiac event rates (death and hospitaliza-
tion for HF) over time were analyzed by the method of
Kaplan-Meier and log-rank test. For all tests, a \( p \) value
<0.05 was considered significant.

RESULTS

Study population. Eighty-five patients were included. The
patient characteristics are summarized in Table 1. Patients
had severe LV dysfunction (mean LVEF 23 ± 7%, range
9% to 34%), with extensive dilation (LV end-diastolic
volume 258 ± 56 ml). Approximately equal numbers of
patients had HF of ischemic and nonischemic etiology. The
QRS duration was prolonged, ranging from 120 to 240 ms.

The mean LV dyssynchrony was 73 ± 49 ms (range 0 to
221 ms) before CRT. The site of latest activation was the
lateral wall in 89% of patients; in the remaining 11%, the
site of latest activation was the septum (n = 4, although this
may also be due to passive motion rather than true late
activation), anterior wall (n = 2), or the inferior wall (n =
3). The mean RV-LV dyssynchrony was 47 ± 38 ms.

Thirty-seven patients received a resynchronization pace-
Table 1. Patient Characteristics (n = 85)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n = 59)</th>
<th>Nonresponders (n = 21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 12</td>
<td>66 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>64/21</td>
<td>14/7</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>27 (46)</td>
<td>9 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class III/IV</td>
<td>81%/29%</td>
<td>90%/10%</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>33 (56%)</td>
<td>11 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>26 (44%)</td>
<td>10 (48%)</td>
<td>NS</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>174 ± 29</td>
<td>171 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>6-MWT</td>
<td>291 ± 122</td>
<td>279 ± 155</td>
<td>NS</td>
</tr>
<tr>
<td>QoL score</td>
<td>40 ± 15</td>
<td>43 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 ± 6</td>
<td>22 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>254 ± 57</td>
<td>272 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>197 ± 55</td>
<td>214 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Severe MR</td>
<td>12 (20%)</td>
<td>7 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>RV-LV dyssynchrony (ms)</td>
<td>47 ± 34</td>
<td>49 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>LV dyssynchrony (ms)</td>
<td>87 ± 49</td>
<td>35 ± 20</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

6-MWT = 6-minute walk test; QoL = quality of life; RV-LV = right ventricular-left ventricular; other abbreviations as in Table 1.

maker (Contak TR [n = 27], Guidant, St. Paul, Minnesota, or InSync III [n = 10], Medtronic Inc., St. Paul, Minnesota) and 48 for a combined CRT-ICD device (Contak CD [n = 15] or Contak Renewal [n = 30], Guidant, Minnesota, and InSync III CD [n = 3], Medtronic Inc., Minnesota). Two types of LV leads were used (Easytrack 4512-80 [n = 73], Guidant, Minnesota, or Attain-SD 4189 [n = 12], Medtronic Inc., Minnesota). The procedure was successful in all patients and no procedure-related complications were observed.

After CRT, the QRS duration was reduced from 178 ± 36 ms to 155 ± 22 ms (p < 0.01). The optimized atrioventricular delay was 115 ± 32 ms.

Within six months after CRT, five patients died of worsening HF. Because these patients did not have the six-month follow-up assessment, they could not be included in the prediction of response to CRT, but they were included in the prognostic evaluation.

**Clinical improvement after CRT.** At baseline and six months follow-up, the clinical status of the patients was assessed. New York Heart Association functional class improved from 3.2 ± 0.4 to 2.1 ± 0.7 (p < 0.01). In addition, the Minnesota score decreased from 42 ± 16 to 29 ± 16 (p < 0.01), and the 6-min walking distance increased from 278 ± 132 m to 399 ± 149 m (p < 0.01). The LVEF demonstrated a modest improvement (from 23 ± 7% to 28 ± 8%, p < 0.05), with a reduction in LV end-diastolic volume (259 ± 57 ml to 237 ± 58 ml, p < 0.05) and end-systolic volume (201 ± 54 ml to 173 ± 53 ml, p < 0.05). Mitral regurgitation improved by at least one grade in 12 of 19 (63%) patients with severe regurgitation (2 patients of the 21 patients with severe MR at baseline died before echocardiographic follow-up).

**Responders and nonresponders.** The patients were subsequently divided into responders and nonresponders, based on an improvement in NYHA functional class by ≥1 score and an improvement by ≥25% in 6-min walking distance (Tables 2 and 3). In the responders, the mean NYHA functional class improved from 3.2 ± 0.4 to 1.7 ± 0.5, whereas it remained unchanged in the nonresponders (by definition). The 6-min walking distance improved from 291 ± 122 m to 438 ± 116 m and remained unchanged in the nonresponders (279 ± 155 m vs. 254 ± 175 m) (by definition).

At baseline, no significant differences were observed between responders and nonresponders, except that the nonresponders tended to have larger LV end-diastolic and end-systolic volumes, although these differences were not significant (Table 2). The only variable that was significantly different between the two groups was the LV dys-
synchrony, which was extensive in the responders and minimal in the nonresponders (Table 2). Of note, RV–LV dyssynchrony was not different between responders and nonresponders.

The responders showed a significant improvement in clinical parameters after CRT (Table 3), whereas none of the clinical parameters improved in the nonresponders after CRT. Furthermore, the LVEF improved in the responders and reverse remodeling was observed after CRT. In the nonresponders, the LVEF did not improve and the LV volumes did not decrease after CRT.

In the responders, 12 patients had severe MR and 11 (92%) patients improved in MR by at least one grade after CRT. In the nonresponders, seven patients had severe MR, and only one (14%, p < 0.05 vs. responders) improved at least one grade after CRT.

To define the optimal cutoff value to predict clinical response, ROC curve analysis was performed. When responders were defined as patients exhibiting an improvement in NYHA functional class ≥1 score and an improvement ≥25% in 6-min walking distance, an optimal sensitivity and specificity of 80% were obtained at a cutoff level of 65 ms for LV dyssynchrony (Fig. 1).

Receiver-operating characteristic curve analysis was also performed to define the optimal cutoff value for LV dyssynchrony to predict reverse LV remodeling. At a cutoff value of 65 ms for LV dyssynchrony a sensitivity and specificity of 92% were obtained to predict a reduction of ≥15% LV end-systolic volume (Fig. 2).

Figure 1. Receiver-operating characteristic curve analysis demonstrated a sensitivity and specificity of 80% to predict response to cardiac resynchronization therapy defined as an improvement in New York Heart Association functional class ≥1 score and an improvement ≥25% in 6-min walking distance at a cutoff level of 65 ms for left ventricular (LV) dyssynchrony.

Figure 2. Receiver-operating characteristic curve analysis demonstrated a sensitivity and specificity of 92% to predict reverse left ventricular (LV) remodeling after cardiac resynchronization therapy defined as an improvement in LV end-systolic volume ≥15% at a cutoff level of 65 ms for LV dyssynchrony.
if LV dyssynchrony increased further, no further reduction in LV end-systolic volume occurred (as evidenced by the horizontal line, $y = 55$) (Fig. 3).

**Prediction of prognosis.** Follow-up was performed during one year after implantation. A total of 16 events occurred in the 80 patients, including 7 deaths (1 noncardiac death, 6 worsening HF) and 9 hospitalizations for decompensated HF. The event rate in responders was significantly lower than in nonresponders (8% vs. 52%, $p < 0.01$).

Moreover, when patients were divided according to the presence/absence of LV dyssynchrony (using a 65 ms cutoff value), only three events (6%) occurred in the 49 patients with dyssynchrony as compared with 13 (33%) in the 31 patients without dyssynchrony. None of the five patients who died before the six-month follow-up assessment had LV dyssynchrony; inclusion of these patients resulted in a 50% event rate during the one-year follow-up in the patients without dyssynchrony (Fig. 4).

Moreover, 6 of 48 (13%) patients with a combined CRT-ICD device experienced adequate shocks (for ventricular arrhythmias) during the one-year follow-up; all of these patients were nonresponders.

**DISCUSSION**

The findings in the current study can be summarized as follows: 1) all baseline characteristics are comparable in responders and nonresponders to CRT, except for the LV dyssynchrony, which was larger in responders; 2) baseline LV dyssynchrony of 65 ms or more has a sensitivity and specificity of 80% to predict clinical response and 92% to predict reverse LV remodeling; 3) patients with extensive dyssynchrony who undergo CRT have an excellent prognosis (6% event rate), whereas patients who do not have dyssynchrony and undergo CRT have a poor prognosis (event rate 50%).

**Benefit of CRT.** In the entire study population, an improvement in all clinical parameters was observed, in line with previous studies concerning CRT (5–7). Comparable to recent randomized clinical trials (Multicenter InSync Randomized Clinical Evaluation [MIRACLE], Multisite Stimulation in Cardiomyopathies Study [MUSTIC], Pacing Therapies for Congestive Heart Failure [PATH–CHF]), reductions in NYHA functional class and quality of life score were noted and an increase in 6-min walking distance was observed (5–7). Moreover, in the present study a modest improvement in LVEF was shown, comparable to results of the MIRACLE trial (6). In addition, significant reverse remodeling was demonstrated, also in line with data from the MIRACLE trial (21).

However, not all patients responded equally to CRT, and when patients were divided into responders and nonresponders, based on improvement in NYHA functional class, it became evident that an improvement in clinical parameters was observed only in the responders. Moreover, improvements in LVEF and reverse remodeling were also observed only in the responders. When individual results were analyzed, it became clear that 21 patients (26%) did not respond to CRT. When the five patients who died before the six-month follow-up were also included, the percentage of nonresponders was 31%. This observation is in agreement with previous studies (8–14). For example, in the MIRACLE trial, 20% of patients did not experience an improvement in symptoms and 32% did not improve in NYHA functional class (6). Similarly, Reuter et al. (22) demonstrated that 18% of 102 consecutive patients undergoing CRT did not improve in NYHA functional class and quality-of-life score.

In the current study and in most of the large clinical trials, the selection criteria included severe HF (NYHA functional class III or IV) with severely depressed LVEF ($\geq 35\%$), and wide QRS complex ($\geq 120$ ms). Thus, additional selection
criteria are needed to reduce the high number of nonresponders.

**Left ventricular dyssynchrony to select candidates for CRT.** When baseline characteristics were compared between responders and nonresponders (Table 2), the only variable that was different between the two groups was the LV dyssynchrony (whereas the RV-LV dyssynchrony was also not different). This finding was not unexpected, as various studies have recently emphasized the importance of LV dyssynchrony for the response to CRT (8–14). Pitzalis et al. (23) have used M-mode echocardiography to assess LV dyssynchrony by measuring the septal-to-posterior wall motion delay. Although this is an elegant and simple method to assess LV dyssynchrony, in patients with ischemic heart disease and previous anterior infarction assessment of septal movement is frequently not possible. Recent studies have therefore focused on TDI applications to assess dyssynchrony. Sogaard et al. (10) have used tissue tracking in 25 patients to detect regions with delayed longitudinal contraction. The authors demonstrated that the extent of delayed longitudinal contraction predicted response to CRT. Breithardt et al. (11) used strain rate imaging in 18 patients to assess dyssynchrony. More recent studies have focused on timing of peak systolic velocities of different myocardial regions to assess LV dyssynchrony. Yu et al. (12) have evaluated 30 patients before and after CRT with TDI and demonstrated that LV dyssynchrony allowed separation between patients with and without LV remodeling as expressed by a reduction in end-systolic volume by more than 15%. Assessment of dyssynchrony was comparable to the present analysis, with the exception that 12 segments were used, instead of 4 segments in the present study.

Receiver-operating characteristic curve analysis demonstrated a sensitivity and specificity of 80% for prediction of clinical status and 92% for the prediction of reverse LV remodeling. Receiver-operating characteristic curve analysis identified the cutoff value of 65 ms as optimal. Of interest, Gorcsan et al. (13) have recently evaluated a small group of patients and also reported a similar value (65 ms) as optimal cutoff value to predict response to CRT. This cutoff level may now be used in further studies to prospectively select patients for CRT.

**Prognostic value of CRT and LV dyssynchrony.** The typical patients who are eligible for CRT (HF, depressed LVEF, and wide QRS complex) have a poor prognosis when treated conservatively (1–3). Moreover, Bader et al. (19) have recently shown that in these patients the presence of LV dyssynchrony is an important predictor of poor outcome.

Prognostic studies in patients undergoing CRT are still scarce. Various studies have evaluated patients after CRT; the initial studies have reported the acute benefit (4), other studies have demonstrated response after six months to one year, and preliminary data have shown sustained benefit over time (5–7). A recent meta-analysis of the 11 published studies of 4 randomized trials (including 1,634 patients) demonstrated a short-term (six-month) survival benefit after CRT as compared with optimized medical therapy (24).

However, none of the studies have evaluated the relation between baseline dyssynchrony in patients undergoing CRT and prognosis. In the current study, one-year follow-up was obtained and the results demonstrated a low event rate (6%) after CRT in patients with LV dyssynchrony at baseline as compared with patients without dyssynchrony (50% event rate). This observation further supports the hypothesis that the degree of LV dyssynchrony is not only predictive of response to CRT but is also related to favorable prognosis when treated by CRT.

It is most likely that both patients with and without LV dyssynchrony have a poor prognosis if untreated, and possibly the patients with LV dyssynchrony have an even worse prognosis. If treated by CRT, the hemodynamic improvements observed after CRT in responders (i.e., the patients with LV dyssynchrony) may result in an improved prognosis, as observed in the current study. The patients without LV dyssynchrony do not improve in hemodynamics, resulting in poor long-term survival.

**Conclusions.** Patients with extensive LV dyssynchrony responded well to CRT. Using a cutoff level of 65 ms, a sensitivity and specificity of 80% were obtained to predict clinical response and of 92% to predict reverse LV remodeling. Moreover, patients with LV dyssynchrony ≥65 ms had an excellent prognosis after CRT, in contrast to patients with <65 ms who had a high event rate (50%) during one-year follow-up.

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