Improvement of Left Ventricular Function After Cardiac Resynchronization Therapy Is Predicted by Tissue Doppler Imaging Echocardiography

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Background—Cardiac resynchronization therapy was shown to reverse left ventricular (LV) remodeling in patients with congestive heart failure (CHF). However, the prediction of benefit is controversial. We aimed to investigate predictive factors of LV functional recovery and reversed remodeling after biventricular pacing.

Methods and Results—Forty-nine consecutive patients with CHF and a wide QRS complex (182±32 ms) were studied by echocardiography before resynchronization. Intraventricular and interventricular asynchrony and their combination were assessed by pulsed-wave tissue Doppler imaging from measurements of regional electromechanical coupling times in basal segments of the right and left ventricle. At 6-month follow-up, responders were defined by a relative increase in LV ejection fraction ≥25% compared with baseline (n=27). Receiver operating curve analysis revealed the degree of intraventricular asynchrony (area under the curve 0.77), interventricular asynchrony (area under the curve 0.69), and their combination (area under the curve 0.84) as the best predictors of functional recovery after resynchronization. In addition, the degree of intraventricular and interventricular asynchrony correlated significantly with the improvement of LV ejection fraction (r=0.73, P<0.0001), end-diastolic diameter (r=−0.59, P<0.0001), and end-systolic diameter (r=−0.48, P<0.001) at follow-up. QRS duration and conventional echo-Doppler indices were not predictive of reversed LV remodeling.

Conclusions—In patients with CHF, the degree of intraventricular and interventricular asynchrony and their combination are the best predictive factors of LV functional recovery and reversed remodeling after cardiac resynchronization therapy. (Circulation. 2004;109:978-983.)

Key Words: pacing ■ heart failure ■ imaging ■ remodeling

Cardiac resynchronization therapy (CRT) with biventricular pacing (BP) was shown to improve symptoms, quality of life, and exercise tolerance in patients with refractory systolic heart failure and a wide QRS complex of left bundle-branch block–like morphology.1–6 Previous studies used the morphology and duration of the QRS complex for selection of patients for CRT. However, the accuracy of QRS duration in predicting left ventricular (LV) functional recovery after BP is controversial.2,3,5,6–11

The extent of mechanical asynchrony and its reduction by BP was proposed as the main mechanism underlying LV functional recovery.7–9,12–16 Thus, the assessment of mechanical asynchrony may be crucial to predict effects of CRT on LV remodeling and function. In this regard, tissue Doppler imaging (TDI) has emerged as a technique that allows accurate assessment of the regional timing of mechanical events relative to the phases of the cardiac cycle.7,9,12,16–18 However, data on the value of TDI-derived indices of asynchrony to predict reversed LV remodeling after long-term BP are limited. In the study by Søgaard et al,7 the extent of myocardium with delayed longitudinal contraction was predictive of LV functional recovery and reversed remodeling after CRT.

Mechanical asynchrony can also be assessed from the comparison of time intervals between the onset of the QRS complex and the regional velocity of myocardial systolic shortening as a surrogate of regional electromechanical coupling. We therefore hypothesized that assessment of intraventricular and interventricular mechanical asynchrony with TDI-derived electromechanical coupling times would be superior to ECG or conventional echocardiographic parameters to predict LV functional recovery and reversed remodeling after BP.

Methods

Patients

Fifty-five consecutive patients undergoing BP were prospectively selected with the following criteria: (1) congestive heart failure (New
defined as E/A
views.21 At pulsed-wave TDI (Acuson Sequoia C256), velocities of filling pattern was assessed from the transmitral flow in apical parasternal long-axis view. LV end-diastolic dimension (LVEDd) was measured at the onset of the QRS complex, and LV end-systolic dimensions were measured from M-mode echocardiography in the basal to mid posterolateral wall in all patients.

Protocol
Data were collected at baseline and at 6-month follow-up. LV dimensions were measured from M-mode echocardiography in the parasternal long-axis view. LV end-diastolic dimension (LVEDd) was measured at the onset of the QRS complex, and LV end-systolic dimension (LVESt) was defined by the smallest LV cavity.20 LV volumes and LVEF were quantified by the Simpson method.20 LV filling pattern was assessed from the transmural flow in apical views.21 At pulsed-wave TDI (Acuson Sequoia C256), velocities of long-axis wall motion were assessed in apical views during end-expiratory apnea, with sample volume of 5 mm positioned in the center of the analyzed segment. Care was taken to keep the incidence angle between the direction of the Doppler beam and the analyzed vector of myocardial motion as small as possible. The spectral Doppler signal filters were adjusted to obtain Nyquist limits between 15 and 20 cm/s with the lowest wall filter settings and the optimal gain to minimize noise. Sweep speed was set at 150 mm/s. All studies were saved on super-VHS videotapes and analyzed by an experienced echocardiographer. The average value from 3 to 5 consecutive beats was taken for each measurement. All echocardiographic analyses were performed by observers not involved in clinical follow-up and were blinded at all times to the clinical data. Atrioventricular delay was optimized at 3 days after implantation, another patient had permanent implantable cardioverter-defibrillator (Contak CD, Guidant) as described previously,19 and placed in the basal to mid posterolateral wall in all patients.

Implantation of Biventricular Pacemaker
All leads were implanted transvenously (Easytrak lead, Guidant Corp), connected to a biventricular pacemaker (Contak TR, Guidant) or implantable cardioverter-defibrillator (Contak CD, Guidant) as described previously,19 and placed in the basal to mid posterolateral wall in all patients.

Data Analysis
Brain natriuretic peptide (BNP) levels were determined from whole blood with a rapid BNP assay.22 Restrictive LV filling pattern was defined as E/A ≥2 or 1.5 < E/A < 2 and E-wave deceleration time ≤160 ms.21 Mitral regurgitation was graded on a 0-to-4-point scale with a visual estimate of regurgitant color-coded jet.23 A grade ≥3 for mitral regurgitation was considered significant.

Cardiac asynchrony was assessed from measurements of time intervals between the onset of the QRS complex and the beginning of regional velocity of myocardial systolic shortening, considered as a surrogate for regional electromechanical coupling intervals (Figure 1). Time intervals were measured in basal LV segments and basal lateral right ventricular (RV) segments (Figure 1). Intra-ventricular (LV) asynchrony was determined as the difference between the longest and shortest electromechanical coupling times in the basal septal, lateral, and posterior segments of the LV.17-19 Intra-ventricular (LV-RV) asynchrony was determined as the difference between electromechanical coupling times in the basal lateral segment of the RV and in the most delayed LV segment. Moreover, the combined index of intraventricular and interventricular mechanical asynchrony was calculated by adding both numbers: sum asynchrony = LV asynchrony + LV-RV asynchrony.

For statistical analysis, a cutoff value of 70% was used for the relative increase in LVEF ≥25% versus baseline. This cutoff value is ≥2 SD above the changes of both parameters observed after administration of placebo in randomized trials with β-blockers.24-26

Statistical Analysis
Data are presented as mean ± SD. Paired and unpaired t test, Fisher’s exact test, and Pearson test were used when appropriate. Receiver operating characteristic curves were derived to assess the predictive value of individual parameters. Statistical significance was defined at P < 0.05.

Results
Implantation of the device was successful in 96% (53/55) of patients. One patient died of massive cerebral bleeding a few hours after implantation. Another patient had permanent diaphragmatic stimulation. Two patients died due to ventricular fibrillation 3 and 4 months after implantation, respectively. The remaining 49 individuals entered the study. At 6-month follow-up, 27 patients showed a significant increase in LVEF (responders). The remaining 22 patients were classified as nonresponders.

Clinical and ECG Data
At baseline, responders had a shorter duration of heart failure and longer QRS duration than nonresponders (Table 1). There

Figure 1. Example of assessment of cardiac asynchrony. In apical 4-chamber (A4C) and long-axis (ALAX) view, cardiac asynchrony was assessed from time interval between onset of QRS complex and onset of regional velocity of myocardial systolic shortening at TDI (right lower corner) as surrogate of regional electromechanical coupling time. Regional activation was measured at basal lateral (LV L), basal septal (LV S), and basal posterior (LV P) segments of LV and basal lateral (RV L) segment of RV (asterisks). Intra-ventricular asynchrony was calculated as difference between longest and shortest regional electromechanical coupling time in 3 basal LV segments (LV L, LV S, and LV P). Interventricular asynchrony was calculated as difference between regional electromechanical coupling time in RV L segment and most delayed from 3 LV segments (ie, longest regional electromechanical coupling time).
were no other differences between groups. At follow-up, both groups showed a significant reduction of NYHA class, QRS duration, and prevalence of severe mitral regurgitation.

**Echocardiographic Data**

At baseline, responders had lower E/A ratios and greater LV asynchrony, LV-RV asynchrony, and sum asynchrony than nonresponders (Table 2). Maximal LV asynchrony was present between the septal and posterior segments in 32 patients (65%) and between the septal and lateral segment in 17 patients (35%). All other parameters were similar in both groups.

At follow-up, LV volumes and dimensions decreased in responders but not in nonresponders. E-wave deceleration time was longer and the prevalence of restrictive LV filling decreased only in responders. Furthermore, responders showed a decrease in the extent of myocardium with postsystolic shortening and a reduction of all indices of cardiac asynchrony after BP. These parameters remained unchanged in nonresponders. E/A ratio and RV systolic pressure were reduced in both groups. Finally, responders had significantly lower BNP levels at follow-up than nonresponders ($P<0.01$).

**Predictors of Effects of BP on LV Function and Remodeling**

As shown in Figure 2, there was a large overlap in individual values of QRS duration between responders and nonresponders. In contrast, LV, LV-RV, and sum asynchrony had

**TABLE 1. Clinical and ECG Data of Both Groups at Baseline and at 6-Month Follow-Up**

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=27)</th>
<th>Nonresponders (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>Age, y</td>
<td>70±6</td>
<td>NA</td>
</tr>
<tr>
<td>Ischemic idiopathic, %</td>
<td>44/56</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of heart failure, y</td>
<td>4.0±2.9</td>
<td>NA</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.2±0.9</td>
<td>1.7±0.6†</td>
</tr>
<tr>
<td>BNP level, pg/mL</td>
<td>858±453</td>
<td>453±412§</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>ß-Blockers, %</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77±14</td>
<td>70±15</td>
</tr>
<tr>
<td>Sinus rhythm, %</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Atrioventricular delay, ms</td>
<td>195±29</td>
<td>133±11‡</td>
</tr>
<tr>
<td>QRS complex, ms</td>
<td>190±30</td>
<td>152±37‡</td>
</tr>
<tr>
<td>Significant mitral regurgitation, %</td>
<td>37</td>
<td>4¶</td>
</tr>
</tbody>
</table>

*P<0.001 for baseline responders vs baseline nonresponders; †P<0.0001, §P<0.01, ¶P<0.001, ¶¶P<0.05, vs baseline; ||P<0.01 for follow-up responders vs follow-up nonresponders.

**TABLE 2. Conventional and Tissue Doppler Echocardiographic Parameters of Both Groups at Baseline and at 6-Month Follow-Up**

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=27)</th>
<th>Nonresponders (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>73±7</td>
<td>67±8*</td>
</tr>
<tr>
<td>LVESd, mm</td>
<td>61±6</td>
<td>52±7*</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>289±72</td>
<td>251±79*</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>224±63</td>
<td>159±58*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24±5</td>
<td>37±8*</td>
</tr>
<tr>
<td>E/A of mitral inflow</td>
<td>1.57±0.97</td>
<td>1.28±0.73§</td>
</tr>
<tr>
<td>E-wave deceleration time, ms</td>
<td>155±53</td>
<td>196±55*</td>
</tr>
<tr>
<td>Patents with restrictive LV filling, %</td>
<td>44</td>
<td>19§</td>
</tr>
<tr>
<td>Extent of myocardium with postsystolic shortening, %</td>
<td>72±25</td>
<td>45±25¶</td>
</tr>
<tr>
<td>RV systolic pressure, mm Hg</td>
<td>37±13</td>
<td>26±8¶</td>
</tr>
<tr>
<td>LV asynchrony, ms</td>
<td>84±33</td>
<td>34±15*</td>
</tr>
<tr>
<td>LV-RV asynchrony, ms</td>
<td>84±37</td>
<td>43±17*</td>
</tr>
<tr>
<td>Sum asynchrony, ms</td>
<td>167±57</td>
<td>75±21*</td>
</tr>
</tbody>
</table>

LVEDV indicates LV end-diastolic volume; LVESV, LV end-systolic volume.

*P<0.0001, §P<0.05, ¶P<0.001 vs baseline; ||P<0.05, #P<0.0001 for baseline responders vs baseline nonresponders; †P<0.01, ¶¶P<0.001 for follow-up responders vs follow-up nonresponders.
smaller overlaps of individual values. As shown in Figure 3, all 3 parameters of TDI asynchrony had a larger area under the receiver operating characteristic curve than the QRS duration, with the largest area for the combined index of intraventricular and interventricular asynchrony. The value of sum asynchrony with the optimal predictive accuracy (the highest sensitivity and specificity) was 102 ms. When this cutoff value was used, all but 6 patients (12%) were correctly identified with sensitivity, specificity, and accuracy of 96%, 77%, and 88%, respectively.

Moreover, the sum asynchrony correlated closely with improvements in LVEF, LVEDd, and LVESd after resynchronization (Figure 4). QRS duration did not show a significant association with any parameter.

Reproducibility
In 10 study subjects, interobserver variability was 9.6% for the measurement of LVEF, 7.9% for LVEDd, 8.2% for LVESd, 8.5% for LV asynchrony, and 7.2% for LV-RV. Intraobserver variability was 8.2% for LVEF, 5.5% for LVEDd, 6.3% for LVESd, 6.8% for LV asynchrony, and 6.1% for LV-RV asynchrony.

Discussion
The present study investigated clinical, ECG, and echocardiographic factors associated with LV functional recovery and remodeling after CRT. The main findings are as follows: (1) Clinical, ECG, and conventional echocardiographic parameters did not enable the identification of responders to CRT. (2) In contrast, TDI-derived indices of intraventricular and interventricular asynchrony accurately predicted positive LV remodeling in response to CRT. (3) Reversed LV remodeling in responders was associated with improvement of the LV restrictive filling pattern and a decrease in BNP levels.

LV Remodeling Versus Symptoms After BP: Clinical Perspective
The beneficial effects of CRT have been related to clinical parameters such as NYHA class, quality of life, and exercise tolerance. We also observed a decrease in NYHA class after CRT in nearly all patients. However, improvement in NYHA class may not always represent a better outcome. In contrast, other parameters, such as the response of BNP levels or persistent restrictive LV filling pattern despite optimal medical therapy, bear prognostic information in heart failure patients. In the present study, the restrictive LV filling pattern improved and BNP levels decreased in responders but not in nonresponders. Furthermore, improvements in LV filling pattern and BNP levels were associated with a reduction of LV volumes and dimensions. It is of note that previous trials with β-blockers indicated that reversed LV remodeling correlates with improved survival. This suggests that despite a similar decrease in NYHA class, the observed reversed LV remodeling, larger decrease in BNP levels, and improvement of restrictive LV filling pattern in responders may be associated with better prognosis than in nonresponders. Accordingly, identification of predictive factors for reversed LV remodeling after BP may be of value for the clinical management of heart failure patients.

Predictors of LV Remodeling After BP
In current practice, patient selection for CRT is based on duration of the QRS complex. Nevertheless, our data and previous data demonstrate that the degree of electrical asynchrony is a poor predictor of response to CRT. On the other hand, in the PAcing THERapies for Congestive Heart Failure (PATH-CHF) trial, the degree of baseline LV
remodeling determined the effect of CRT. In the present study, the degree of LV remodeling at echocardiography did not distinguish responders from nonresponders. Nevertheless, responders might have been less sick, which is supported by the lower E/A ratio and a shorter history of congestive heart failure. However, patients with greater systolic asynchrony (responders) have a significant extent of myocardium that exhibits postsystolic shortening that occurs during early diastole of the remaining segments. This may suppress early diastolic filling by a time shift in driving pressures with a relative reduction of early filling.31 Taken together, these data suggest that patients with greater asynchrony may have lower E waves and higher A waves, resulting in a lower E/A ratio than patients with less asynchrony despite a similar degree of LV dysfunction and comparable baseline BNP levels.

Recent studies suggested that the degree of LV asynchrony could identify patients responding to CRT.7,9,12–15 In the present study, we used simple measurements of time intervals between the beginning of the QRS complex and the onset of regional mechanical activation as surrogates of regional electromechanical coupling to assess the degree of both LV and RV asynchrony. An important issue is whether analysis of either intraventricular or interventricular asynchrony alone is sufficient to identify responders. In the present study, 4 responders had only mild to moderate intraventricular asynchrony despite severe interventricular asynchrony. Four non-responders with isolated intraventricular or interventricular asynchrony were identified only by using the combined index of asynchrony. Consequently, 22 patients were identified correctly only after both indices of cardiac asynchrony were combined. Another question is how to define interventricular asynchrony. In the present study, interventricular asynchrony was defined as the difference between the basal lateral segment of the RV and the most delayed LV segment. With these criteria, all 3 indices of mechanical asynchrony are superior to other parameters in predicting therapeutic effects of BP, with the highest predictive accuracy for the combined index.

Furthermore, the extent of intraventricular and interventricular asynchrony at baseline correlated with changes in indices of LV remodeling at follow-up. These beneficial effects on LV remodeling appeared to be independent of therapy with ACE inhibitors or β-blockers. This suggests that correction of mechanical asynchrony is sufficient to cause a reversal of negative remodeling in patients with congestive heart failure irrespective of concomitant medication.

Study Limitations
The reproducibility of LV volume measurements by echocardiography may be limited because of interindividual variability caused by variable degrees of LV shortening in apical views. Nevertheless, LV volume measurements were consistent with changes in LV dimensions that are less susceptible to interindividual variations. In addition, we used cutoff values of LVEF and LV dimensions for identification of responders above 2 SD of the reproducibility of measurements in our population of patients with severe LV dysfunction.

In contrast to color-coded TDI, pulsed-wave TDI does not allow simultaneous comparison of regional timing in different segments during 1 beat. Color-coded analysis may reduce patient scanning time and eliminate errors introduced by beat-to-beat variations in loading conditions or heart rate. Thus, the use of color-coded measurements may improve accuracy for assessment of cardiac asynchrony compared with the use of only pulsed-wave TDI analysis.

Apart from active contraction, regional systolic velocities may reflect passive motion of the segment due to heart
motion or tethering by adjacent segments. In the present study, none of the patients had RV volume overload or significant pericardial effusion. To minimize the effect of whole heart motion, all measurements were performed during end-expiratory apnea. To avoid the effect of tethering, the sample volume was always placed in the mid portion of each segment under study.

Conclusions
This study demonstrated that the combined index of intraventricular and interventricular asynchrony accurately predicts LV functional recovery and reversed remodeling after BP. The use of such a parameter may help to select patients who will benefit most from CRT. Its true clinical and prognostic significance remains to be confirmed in a large prospective trial.

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