Diastolic Asynchrony Is More Frequent Than Systolic Asynchrony in Dilated Cardiomyopathy and Is Less Improved by Cardiac Resynchronization Therapy

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OBJECTIVES
To compare the incidence of diastolic and systolic asynchrony, assessed by tissue Doppler imaging (TDI), in patients with congestive heart failure (CHF) and severe left ventricular (LV) dysfunction, and to assess TDI changes induced by cardiac resynchronization therapy (CRT).

BACKGROUND
Thirty percent of CRT candidates are nonresponders. Besides QRS width, the presence of echographic systolic asynchrony has been used to identify future responders. Little is known about diastolic asynchrony and its change after CRT.

METHODS
Tissue Doppler imaging was performed in 116 CHF patients (LV ejection fraction 26 ± 8%).

RESULTS
The CHF group consisted of 116 patients. Diastolic asynchrony was more frequent than systolic, concerning both intraventricular (58% vs. 47%; p < 0.0004) and interventricular (72 vs. 45%; p < 0.0001) asynchrony. Systolic and diastolic asynchrony were both present in 41% patients, but one-third had isolated diastolic asynchrony. Although diastolic delays increased with QRS duration, 42% patients with narrow QRS presented with diastolic asynchrony. Conversely, 27% patients with large QRS had no diastolic asynchrony. Forty-two patients underwent CRT. Incidence of systolic intraventricular asynchrony decreased from 71% to 33% after CRT (p < 0.0001), but diastolic asynchrony decreased only from 81% to 55% (p < 0.0002). Cardiac resynchronization therapy induced new diastolic asynchrony in eight patients.

CONCLUSIONS
Diastolic asynchrony is weakly correlated with QRS duration, is more frequent than systolic asynchrony, and may be observed alone. Diastolic asynchrony is less improved by CRT than systolic. Persistent diastolic asynchrony may explain some cases of lack of improvement after CRT despite good systolic resynchronization. (J Am Coll Cardiol 2005;46:2250–7) © 2005 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is now an accepted treatment of patients with drug-refractory congestive heart failure (CHF) (1). Widened QRS is considered as the landmark of cardiac asynchrony and this criterion has been used in most controlled studies on CRT (1,2). In addition, QRS width ≥130 ms is used in current American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology (ACC/AHA/NASPE) guidelines for biventricular pacemaker implantation (3). However, QRS width has been shown to be a weak predictor of clinical or echocardiographic improvement (4,5) and recent studies suggest that the presence of a systolic asynchrony as determined by tissue Doppler imaging (TDI) may have the potential to better identify future responders to CRT (6–8).

A number of systolic mechanical indices of asynchrony have been proposed, either between the left and the right ventricles (interventricular asynchrony) (9) or between the left ventricular (LV) walls (intraventricular asynchrony) (10–15). Most of these studies focused only on systolic synchronicity, whereas little is known about the existence of diastolic asynchrony.

Diastolic function plays a major role in symptoms and pathophysiology of CHF (16) and left bundle branch block (LBBB) has been shown to shorten LV diastolic filling time (17), to directly impair diastolic function (18–20), and to cause diastolic as well as systolic asynchrony (17). In addition, ventricular interaction in diastole has been described in one-half of patients with CHF, especially in those with increased LV filling pressures (21). Finally, the mechanisms responsible for the benefits of CRT in CHF patients are not...
fully understood. Systolic resynchronization probably explains in part the benefit derived from CRT, but other mechanisms, such as reduction of mitral regurgitation and improved diastolic filling, are probably also involved (22). However, no data exists concerning the role of diastolic resynchronization in these patients.

For these reasons, we performed a prospective study whose objectives were: 1) to compare the respective incidence of diastolic and systolic asynchrony, assessed by TDI, in a large population of patients with CHF with or without LBBB; and 2) to assess CRT-induced changes of systolic and diastolic asynchrony parameters in a population of patients with LBBB.

PATIENTS AND METHODS

Patients. Baseline characteristics of the populations are summarized in Table 1.

CHF POPULATION. One hundred sixteen consecutive patients with LV dysfunction (mean left ventricular ejection fraction [LVEF] 26 ± 8%; left ventricular end-diastolic diameter [LVEDD] 73 ± 9 mm) were included, regardless of QRS duration (mean duration 168 ± 43 ms) or New York Heart Association (NYHA) functional class. The population was divided into three groups according to QRS duration: group 1, QRS <120 ms (n = 40); group 2, QRS 120 to 150 ms (n = 34); and group 3, QRS >150 ms (n = 42).

CRT POPULATION. Forty-two patients (out of the CHF population) underwent CRT. All patients had drug-refractory heart failure (NYHA functional class III or IV), severe LV dysfunction (LVEF 26 ± 7%; LVEDD 73 ± 9 mm), and QRS enlargement on the surface electrocardiogram (mean duration 168 ± 34 ms). Only patients with sinus rhythm were included, although five patients had a history of paroxysmal or persistent AF but were in sinus rhythm at the time of implantation and of echocardiographic examination. The presence of echocardiographic asynchrony was not an inclusion criterion. CRT patients were similar to CHF group 3 patients in QRS duration (168 ± 34 ms vs. 177 ± 17 ms, respectively; p = 0.08) and mean ejection fraction (26 ± 7% vs. 27 ± 7%, respectively; p = 0.8). However, only 18 (43%) CHF group 3 patients were in NYHA functional class III or IV (mean NYHA functional class 2.6 ± 0.8 vs. 3.4 ± 0.5 in CRT patients; p < 0.0001).

IMPLANTATION OF BIVENTRICULAR PACEMAKER. Biventricular pacemakers were implanted as previously described (23). The LV pacing lead was inserted by transvenous approach through the coronary sinus into the lateral or posterolateral cardiac vein. The biventricular devices used in patients with sinus rhythm were InSync III (Medtronic, Minneapolis, Minnesota) in 35 patients and biventricular cardioverter defibrillator Contak CD (Guidant, Minneapolis, Minnesota) in 7 patients. After implantation, the atrioventricular interval was optimized to obtain the maximal diastolic filling time without interruption of the A wave using pulsed Doppler analysis of the transmitral flow ac-

Table 1. Baseline Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 40)</th>
<th>CHF Patients (n = 116)</th>
<th>CRT Patients (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32 (80%)</td>
<td>91 (78%)</td>
<td>33 (79%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 11</td>
<td>61 ± 14</td>
<td>58 ± 13</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.6 ± 0.9</td>
<td>3.4 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>32 (28%)</td>
<td>14 (33%)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy*</td>
<td>84 (72%)</td>
<td>28 (67%)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>110 (95%)</td>
<td>42 (100%)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>107 (92%)</td>
<td>41 (98%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>89 (77%)</td>
<td>39 (93%)</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>50 (43%)</td>
<td>22 (52%)</td>
<td></td>
</tr>
<tr>
<td><strong>Electrocardiographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>85 ± 13</td>
<td>132 ± 43</td>
<td>168 ± 34</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>136 ± 13</td>
<td>161 ± 18</td>
<td>177 ± 38</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>40 (100%)</td>
<td>97 (84%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard echo data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>73 ± 6</td>
<td>26 ± 8</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>73 ± 9</td>
<td>73 ± 9</td>
<td></td>
</tr>
</tbody>
</table>

*1 idiopathic, 5 chemotherapy induced, 4 valvular, 3 alcoholic, 1 postpartum cardiomyopathy. Data are presented as the mean value ± SD or as the number (percentage) of controls or patients.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association.
cording to Ritter et al. (24). All biventricular devices were programmed to deliver simultaneous pacing of the right and left ventricle.

**Echocardiographic protocol.** Standard measurements, including Doppler parameters, were performed using a System Five ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with a 3-MHz phased array probe. LV systolic and diastolic dimensions were measured by two-dimensional guided M-mode method. Ejection fraction was assessed by Simpson’s rule using conventional apical four- and two-chamber views. Time velocity integral and duration of ejection were measured on the aortic Doppler signal. Diastolic function was evaluated on the transmitral Doppler signal (peak E and A, E/A ratio, diastolic filling time). The TDI recordings were acquired during end-expiratory apnea in the apical four- and two-chamber views to assess the long-axis motion of the ventricles. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. Sector size and depth were optimized for the highest frame rate. 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. At least three consecutive beats were digitized. In the CRT population, measurements were performed the day after implantation, at baseline (pacemaker turned off), and after at least 10 min of biventricular pacing. All TDI recordings were performed by the same two authors.

**DATA ANALYSIS.** Regional myocardial pulsed-Doppler velocity profiles were reconstituted and computer analyzed offline (EchoPac 6.3.6; GE Vingmed Ultrasound) by positioning the sample volume in the middle of the basal portion of four different LV wall segments (septal, lateral, anterior, and inferior) and in the basal lateral right ventricular (RV) segment. With use of the QRS as a reference point, the systolic electromechanical delay (EMD) was measured as the time to the onset of the systolic velocity curve. Similarly, diastolic EMDs were obtained using the onset of the diastolic E-wave (Fig. 1). The average of at least three consecutive beats was used for comparison. Interventricular (inter-V) asynchrony was calculated as the difference between the systolic or diastolic EMDs of the lateral free wall of the right ventricle and of the most delayed LV segment. Intraventricular (intra-LV) asynchrony was defined as the time difference between the shortest and longest EMD among the four LV walls. A combined index of asynchrony was calculated as the sum of interventricular and intraventricular delays (7).

**Statistical analysis.** All data are expressed as mean value ± SD. Comparisons of data were performed using the Student t test for paired and unpaired data when appropriate. Linear regression analysis was used to calculate the correlation between electrical and echocardiographic parameters. A value of p < 0.05 was considered statistically significant.

To minimize the variability of the measurements, all TDI recordings were analyzed by the same author. The intraobserver variability assessed in 10 consecutive patients was 4.3% for diastolic intra-LV, 4.1% for diastolic inter-V, 4.4% for systolic intra-LV, and 4.0% for systolic inter-V delays. Finally, systolic and diastolic asynchrony indices were evaluated in a control group of 40 healthy control subjects (32 men, 8 women; mean age 56 ± 15 years) with no history of cardiovascular disease in order to define threshold values for the different asynchrony parameters. They had normal physical, electrocardiographic, and standard echocardiographic examination (LVEF 73 ± 6%; QRS duration 85 ± 13 ms). Asynchrony delays obtained in the control popula-
tion were used to characterize the range of normal intra-LV and inter-V delays for diastolic and systolic asynchrony. Gaussian’s distribution of the control variables was verified by the Shapiro and Wilk test. The statistical alpha risk was fixed at 0.05, so that 95% of the control group was included among patients displaying significant systolic intra-LV asynchrony, the lateral wall was the most delayed in 66%, the inferior wall in 15%, the anterior wall in 15%, and the septal wall in 4% of patients. For diastolic intra-LV asynchrony, the distribution was 62%, 16%, 17%, and 5% respectively.

**RESULTS**

One hundred eight patients (93%) in the CHF population had complete TDI analysis. Incomplete data were due to very low velocity profiles or to technical problems. In the CRT population, biventricular pacemaker implantation was successful in all patients. TDI recordings were adequate for analysis in all patients as well as in the control population.

**Control population and definition of threshold values.** Interventricular and intraventricular systolic and diastolic delays obtained in the control group are presented in Table 2, as well as values for the combined interventricular plus intraventricular index. Threshold values for significant asynchrony were 36 and 35 ms for systolic interventricular and intraventricular delays, respectively, and 35 and 36 ms for diastolic interventricular and intraventricular delays, respectively. Therefore, a delay exceeding 40 ms was used to define systolic and diastolic interventricular and intraventricular asynchrony. Similarly, a threshold value of 80 ms was used for the combined index (sum of inter- and intraventricular delays).

**CHF population. Electromechanical TDI delays.** The analysis of electromechanical TDI delays showed that among patients displaying significant systolic intra-LV asynchrony, the lateral wall was the most delayed in 66%, the inferior wall in 15%, the anterior wall in 15%, and the septal wall in 4% of patients. For diastolic intra-LV asynchrony, the distribution was 62%, 16%, 17%, and 5% respectively.

**RELATIVE INCIDENCE OF SYSTOLIC AND DIASTOLIC ASYNCHRONY.** Diastolic intra- and interventricular delays were significantly longer than systolic delays (intra: \( p < 0.0001 \); inter: \( p < 0.0001 \); sum inter+intra: \( p = 0.0002 \) (Table 2). Moreover, using the pre-defined thresholds for significant asynchrony, the incidence of diastolic asynchrony was higher than the incidence of systolic asynchrony for all parameters (Table 3) (intra: \( p = 0.0004 \); inter: \( p < 0.0001 \); sum inter+intra: \( p < 0.0001 \)). Figure 2 shows the repartition of systolic and diastolic asynchrony in the CHF population. Among patients with CHF, 41% presented with both systolic and diastolic asynchrony, one-third had isolated diastolic asynchrony, and very few (8%) had isolated systolic asynchrony.

**INCIDENCE OF ASYNCHRONY ACCORDING TO QRS DURATION.** Table 2 displays inter- and intraventricular delays according to QRS duration. Both systolic and diastolic interventricular and intraventricular delays increased with increasing

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**Table 2. Systolic and Diastolic Interventricular and Intraventricular Delays (ms) in Controls, in the CHF Population According to QRS Duration, and in the CRT Population at Baseline and During Biventricular Stimulation**

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic Intra</th>
<th>Systolic Inter</th>
<th>Sum Systolic</th>
<th>Diastolic Intra</th>
<th>Diastolic Inter</th>
<th>Sum Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 40)</td>
<td>17.4 ± 9.1</td>
<td>12.5 ± 11.5</td>
<td>29.9 ± 15</td>
<td>16.6 ± 9.4</td>
<td>13.3 ± 11.2</td>
<td>29.9 ± 14.8</td>
</tr>
<tr>
<td>CHF (n = 108)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n = 36)</td>
<td>35 ± 29</td>
<td>30 ± 26</td>
<td>66 ± 51</td>
<td>39 ± 28</td>
<td>53 ± 39</td>
<td>92 ± 55</td>
</tr>
<tr>
<td>Group 2 (n = 32)</td>
<td>47 ± 43</td>
<td>44 ± 38</td>
<td>90 ± 74</td>
<td>55 ± 51</td>
<td>68 ± 50</td>
<td>123 ± 82</td>
</tr>
<tr>
<td>Group 3 (n = 40)</td>
<td>60 ± 51</td>
<td>62 ± 44</td>
<td>122 ± 79</td>
<td>76 ± 50</td>
<td>95 ± 59</td>
<td>171 ± 89</td>
</tr>
<tr>
<td>All patients (n = 108)</td>
<td>48 ± 44</td>
<td>46 ± 39</td>
<td>94 ± 73</td>
<td>58 ± 47</td>
<td>73 ± 53</td>
<td>131 ± 84</td>
</tr>
<tr>
<td>CRT (n = 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>73 ± 42</td>
<td>63 ± 51</td>
<td>137 ± 82</td>
<td>101 ± 91</td>
<td>89 ± 69</td>
<td>190 ± 135</td>
</tr>
<tr>
<td>Biv stimulation</td>
<td>36 ± 34</td>
<td>30 ± 33</td>
<td>66 ± 61</td>
<td>75 ± 60</td>
<td>66 ± 42</td>
<td>141 ± 93</td>
</tr>
</tbody>
</table>

Biv = biventricular; Inter = interventricular; Intra = intraventricular; other abbreviations as in Table 1.

**Table 3. Percentage of Patients With Systolic and Diastolic Interventricular and Intraventricular Asynchrony in Controls, in the CHF Population According to QRS Duration, and in the CRT Population at Baseline and During Biventricular Stimulation**

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic Intra</th>
<th>Systolic Inter</th>
<th>Sum Systolic</th>
<th>Diastolic Intra</th>
<th>Diastolic Inter</th>
<th>Sum Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 40)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CHF (n = 108)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n = 36)</td>
<td>33</td>
<td>28</td>
<td>31</td>
<td>42</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Group 2 (n = 32)</td>
<td>50</td>
<td>44</td>
<td>44</td>
<td>59</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>Group 3 (n = 40)</td>
<td>58</td>
<td>63</td>
<td>70</td>
<td>73</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>All patients (n = 108)</td>
<td>47</td>
<td>45</td>
<td>49</td>
<td>58</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>CRT (n = 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>71</td>
<td>60</td>
<td>69</td>
<td>81</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>Biv stimulation</td>
<td>33</td>
<td>31</td>
<td>31</td>
<td>35</td>
<td>55</td>
<td>64</td>
</tr>
</tbody>
</table>

p (baseline vs. Biv stimulation) <0.0001 <0.0001 <0.0001 0.0002 0.0002 0.0002

Abbreviations as in Tables 1 and 2.
QRS duration. However, both systolic and diastolic delays were weakly correlated with QRS duration (systolic intra: \( r = 0.29; p < 0.002; \) inter: \( r = 0.33; p < 0.0001; \) sum intra+inter: \( r = 0.41; p < 0.0001\); diastolic intra: \( r = 0.37; p < 0.0001\); inter: \( r = 0.32; p = 0.0008; \) sum intra+inter: \( r = 0.41; p < 0.0001\)).

Similarly, the number of patients with significant asynchrony increased with QRS duration (Table 3, Fig. 3). However, as shown in Figure 3, a significant number of patients with narrow QRS (group 1) displayed echocardiographic intraventricular asynchrony; one-third of these patients had significant asynchrony during systole and even more during diastole. Conversely, some patients with very large QRS (group 3) had no mechanical asynchrony. Forty-two percent of these patients did not present with systolic asynchrony, and 27% had no diastolic asynchrony despite the presence of typical LBBB on the surface electrocardiogram.

**CRT population. Electrocardiography.** QRS duration significantly shortened from 168 ± 34 ms to 118 ± 23 ms after CRT (\( p < 0.0001 \)). The PR interval was reduced from 177 ± 38 ms to 134 ± 15 ms (\( p < 0.0001 \)). Heart rate was not significantly different between baseline and CRT (69.7 ± 12 vs. 70 ± 6; \( p = 0.74 \)).

**STANDARD ECHOCARDIOGRAPHY.** Ejection fraction did not improve significantly after biventricular pacing (26.8 ± 7.4% vs 27.4 ± 7.4%; \( p = 0.1 \)). Aortic velocity time integral (11.1 ± 2.1 cm vs. 12.8 ± 2.3 cm; \( p < 0.0001 \)) and duration of the ejection period (247 ± 52 ms vs. 269 ± 56 ms; \( p < 0.0001 \)) increased significantly. Diastolic E- and A-wave velocities were not significantly different between baseline and CRT mode (86 ± 32 cm/s vs. 81 ± 29 cm/s; \( p = 0.2 \); and 63 ± 31 cm/s vs. 65 ± 33 cm/s; \( p = 0.6 \)). LV diastolic filling time (319 ± 80 vs. 396 ± 89; \( p < 0.0001 \)) and deceleration time (186 ± 41 vs. 200 ± 53; \( p < 0.0001 \)) increased after pacing.

**ASYNCHRONY PARAMETERS (TABLE 2).** All systolic intraventricular delays were significantly reduced after CRT. Diastolic delays were less improved than systolic delays. The incidence of diastolic asynchrony remained high during biventricular pacing (Table 3, Fig. 4). Nearly one-third of the patients still displayed systolic asynchrony, and more than half still had diastolic asynchrony. In 11 patients without intra-LV asynchrony at baseline, CRT induced de novo asynchrony: in 3 patients during systole and in 8 during diastole (mean increase in delays 64 and 76 ms, respectively).

There was no significant correlation between QRS shortening after CRT and the improvement of any of the systolic or diastolic asynchrony parameters. Similarly, no correlation was found between PR interval reduction and the improvement of diastolic intra- or interventricular asynchrony (\( p = 0.62 \) and 0.69, respectively).

Finally, there was no significant difference between “TDI responders” (suppression of significant systolic and diastolic asynchrony) and “TDI nonresponders” during CRT concerning the benefit in terms of EF (27.5 ± 6% vs. 27.3 ± 7%; \( p = 0.4 \)), aortic velocity time integral (12.9 ± 2.4 cm vs. 12.6 ± 2.2 cm; \( p = 0.2 \)) or diastolic filling time (379 ± 76 ms vs. 416 ± 82 ms; \( p = 0.09 \)) in this acute study. The programmed AV delay was similar between TDI responders and nonresponders (106.4 ± 19 ms vs. 105.5 ± 20 ms; \( p = 0.5 \)).

**OPTIMIZATION OF THE VV-DELAY.** Optimization of the VV-delay was performed under echocardiographic and TDI guidance in a subgroup of 15 patients in whom resynchronization was judged unsatisfactory by post-implantation TDI study. The main objective of this adjustment was to
Diastolic asynchrony is frequently observed by TDI in
The main results of this study are as follows:

DISCUSSION
The main results of this study are as follows:
1. Diastolic asynchrony is frequently observed by TDI in
   patients with dilated cardiomyopathy and is weakly
correlated with QRS duration.
2. Diastolic is more frequent than systolic asynchrony in
   these patients and may be observed alone.
3. Diastolic asynchrony is less improved by CRT than
   systolic asynchrony.

Echocardiographic evaluation of cardiac resynchronization
therapy. Although a QRS duration $\geq 130$ ms is part of
the ACC/AHA/NASPE guidelines for implantation of
pacemakers and antiarrhythmic devices (3), 20% to 30% of
patients do not respond to CRT (5,8) and convincing
evidence exists that asynchrony may be absent in patients
with large QRS (25) or present in patients with narrow
QRS (26).

Various echocardiographic approaches have been proposed
to evaluate mechanical asynchrony and select future responders
to CRT, including M-mode echocardiography (10), automatic
endocardial LV border detection (11), measurement of time
difference between left and right pre-ejection intervals (9), as
well as several TDI methods (12–15,25–27). However, none
of the proposed asynchrony parameters has been validated
in a large controlled trial and thus should be used in clinical
practice for patient selection. Tissue Doppler imaging was
the most frequently used technique in past studies. The
rationale for using TDI techniques includes the fact that
pulsed-wave TDI has a high sampling rate, resulting in a
high temporal resolution with the potential to investigate
cardiac episodes of short duration, and that it has been
shown to be accurate to assess regional timing of not only
systolic but also diastolic cardiac events (14). However,
these studies suffer from several limitations: First, they used
different TDI modes, some authors measuring delays on
myocardial velocity curves (“live” measurements of myocar-
dial velocities by pulsed-wave TDI [6,15,27]), others using
off-line analysis of TDI tracings derived by post-processing
of the velocity curves (11–15,25,26), and other authors
using TDI curves to derive strain and strain rate (28) or
tissue tracking; second, the method of measurement of
EMDs varies among studies, some authors using the time
difference between QRS and the onset of the systolic
velocity curve (26) and others using the peak velocity (26);
finally, different definitions of what a significant asynchrony
is have been reported (14,25,27) and no consensus exists on
this point.

In our study, both interventricular and intraventricular
delays were obtained from off-line analysis of TDI record-

Diastolic versus systolic asynchrony. Although several
studies focused on systolic asynchrony, data concerning
diastolic asynchrony are very scarce. However, diastolic
phenomena are probably as important as systolic in CRT.

First, several echocardiographic studies demonstrated
that LBBB causes marked diastolic function impairment
both in CHF patients (18,19) and in patients with normal
systolic function (17,20). Main diastolic abnormalities
cased by LBBB included reduced LV filling time, pro-
longed isovolumic contraction and relaxation times, altered
transmitral filling patterns, and prolonged duration of mitral
regurgitation in patients with LV dysfunction. Morris-
Thurgood et al. (29) found diastolic filling abnormalities to be
of crucial importance in CRT patients and proposed that part
of the benefit of CRT was probably related to better LV filling
rather than ventricular systolic resynchronization (29).

Second, ventricular interaction in diastole also plays a
potential role in CHF patients. Atherton et al. (21) docu-
mented that LV filling was impeded in one-half of CHF
patients by ventricular interaction in diastole from the raised
RV diastolic pressure and by external constraint from the
pericardium, especially in patients with increased LV filling
pressure. This diastolic interaction could explain the delayed
onset of mechanical diastolic motion in the LV (measured
by TDI), even in patients without systolic interventricular
asynchrony. The reduction of the ventricular interaction in diastole during LV pacing has also been proposed to be the dominant mechanism by which LV pacing may produce hemodynamic improvement in CHF patients (29,30).

Third, very few data exist concerning diastolic asynchrony itself (14,31). However, it has been shown for a long time that LBBB caused both systolic and diastolic asynchronies (17). More recently, in their study of 112 CHF patients, Yu et al. (14) found the incidence of systolic and diastolic asynchrony to be 51% and 46%, respectively, in patients with narrow QRS, and 73% and 69%, respectively, in patients with large QRS.

In our study, diastolic delays were significantly longer than systolic delays, and the incidence of diastolic asynchrony was higher than that of systolic asynchrony concerning both intra-LV (58% vs. 47%) and inter-V (72% vs. 45%) asynchrony. In a majority of CHF patients in our study, diastolic and systolic asynchronies were both present. This may be explained by the fact that diastole and systole are closely linked: A delayed contraction of a segment will result in a delayed relaxation in this segment. However, the main result of our study is that diastolic asynchrony was more frequently observed than systolic asynchrony. The reasons why diastolic is more frequent than systolic asynchrony are not clear. The length of diastole, which includes both isovolumic relaxation and contraction times, may make diastolic study more sensitive than systolic and allow an earlier identification of a delayed segment, before systolic asynchrony occurs. This was illustrated by the fact that diastolic asynchrony was observed alone in more than one-third of CHF patients in our study.

Finally, the lack of correlation between parameters of diastolic asynchrony and conventional Doppler parameters of diastolic function (E/A ratio, deceleration time, and LV diastolic filling time) may be explained by the fact that the latter parameters are highly dependent on LV filling pressure (which may vary widely in patients with CHF) and do not reflect only the diastolic coordination between LV walls.

Mechanical versus electrical asynchrony. Another important result of our study is that although both interventricular and intraventricular delays increased with increasing QRS duration, the correlation between mechanical and electrical asynchrony was weak. Interestingly, the best correlation was observed for the combination of intraventricular and interventricular asynchrony (7). Moreover, a significant number of patients with large QRS presented without significant echocardiographic dysynchrony. Conversely, one-third of patients with narrow QRS presented with systolic and even more (61%) with diastolic asynchrony. These results are in agreement with those of Yu et al. (14), who found intraventricular asynchrony in only 73% patients with wide QRS, but also in 51% patients with narrow QRS. Similarly, Ghio et al. (25), using a delay of >50 ms to define intraventricular asynchrony, found a significant systolic asynchrony in 29.5% of patients with narrow QRS and in 71% of patients with large QRS. Our study not only confirmed these data but also showed that these results may be applicable to diastolic asynchrony.

Influence of CRT. Several studies showed that CRT was associated with a shortening of inter- and intraventricular systolic delays. For example, interventricular delay, as measured by pulsed Doppler, was reduced by 19% after CRT in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study (2). Similarly, systolic intraventricular resynchronization has been demonstrated after CRT using both M-mode echocardiography (10) and TDI techniques (6). More important, Penicka et al. (7), in a series of 49 patients studied by TDI before CRT, showed that the combination of intraventricular and interventricular asynchrony was the best predictor of LV functional recovery after CRT.

Moreover, no study focused on the influence of CRT on diastolic resynchronization. In our study, CRT was associated with a significant reduction of QRS width and systolic as well as diastolic delays. However, diastolic asynchrony was less improved by CRT than systolic. Moreover, in some patients, CRT was associated with worsening or new occurrence of systolic and/or diastolic asynchrony. Finally, optimization of the VV delay was performed under echocardiographic guidance in a subgroup of patients with unsatisfactory resynchronization and allowed a further decrease of the incidence of both systolic and diastolic asynchrony in these patients. These results underline the need to perform systematic measurements of both systolic and diastolic delays before and after CRT, and to try to optimize VV delay when resynchronization is judged unsatisfactory by post-implantation echographic study.

Besides resynchronization of the ventricles, another potential benefit of CRT in CHF may be related to the improvement of atrioventricular (AV) synchrony. The AV time delay has the potential to influence chamber mechanics and cardiac output (5) and to affect cardiac filling. In our series, all patients underwent AV delay optimization after pacemaker implantation. However, although DDD pacing alone may improve AV synchrony, it frequently results in a worsening of both interventricular and intraventricular synchrony; moreover, the benefits of LV pacing in patients with CHF and chronic RV pacing seem comparable to those of CHF patients without RV pacing, suggesting that CRT acts through ventricular resynchronization rather than optimization of the AV delay (32). Thus, associated LV stimulation is preferable in case of LV dysfunction in order to ensure AV and intraventricular and interventricular synchronization (32). We further need to evaluate which type of asynchrony (diastolic, systolic, atrioventricular, or intraventricular or interventricular) should be given priority when programming biventricular pacemakers.

Study limitations. Some limitations of our study are inherent to the TDI technique. Seven percent of patients among the CHF population had to be excluded because of very low velocity profiles or technical problems. In addition, apart from active contraction, regional systolic velocities
may reflect passive motion due to heart motion or tethering by adjacent segments. Although we tried to minimize this effect by performing measurements during end-expiratory apnea, strain rate techniques would have been more precise to identify the true wall contraction. Finally, the TDI method is angle dependent and can only assess longitudinal contraction.

Another limitation of our study is the heterogeneity of the studied population, including both ischemic and idiopathic cardiomyopathy. Our study was an acute study, and the long-term significance of our results has to be evaluated by specific longitudinal studies.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

Tissue Doppler imaging is a useful method for the assessment of systolic and diastolic asynchrony. Diastolic asynchrony is weakly correlated with QRS duration, is more frequent than systolic asynchrony, and may be observed alone in some patients. In addition, diastolic asynchrony is less improved by CRT than systolic asynchrony. Persistent diastolic asynchrony may explain in some cases the lack of clinical improvement after CRT despite good systolic resynchronization.

The prognostic value and clinical significance of diastolic asynchrony needs to be assessed in prospective longitudinal studies.

**REFERENCES**