Real-Time Three-Dimensional Echocardiography
A Novel Technique to Quantify Global Left Ventricular Mechanical Dyssynchrony

S. Kapetanakis, MBBS; M.T. Kearney, MD; A. Siva, PhD; N. Gall, MD;
M. Cooklin, MD; M.J. Monaghan, PhD

Background—Left ventricular (LV) mechanical dyssynchrony (LVMD) has emerged as a therapeutic target using cardiac resynchronization therapy (CRT) in selected patients with chronic heart failure. Current methods used to evaluate LVMD are technically difficult and do not assess LVMD of the whole LV simultaneously. We developed and validated real-time 3D echocardiography (RT3DE) as a novel method to assess global LVMD.

Methods and Results—Eighty-nine healthy volunteers and 174 unselected patients referred for routine echocardiography underwent 2D echocardiography and RT3DE. RT3DE data sets provided time-volume analysis for global and segmental LV volumes. A systolic dyssynchrony index (SDI) was derived from the dispersion of time to minimum regional volume for all 16 LV segments. Healthy subjects and patients with normal LV systolic function had highly synchronized segmental function (SDI, 3.5±1.8% and 4.5±2.4%; P=0.7). SDI increased with worsening LV systolic function regardless of QRS duration (mild, 5.4±0.83%; moderate, 10.0±2%; severe LV dysfunction, 15.6±1%; P for trend <0.001). We found that 37% of patients with moderate to severe LV systolic dysfunction had significant dyssynchrony with normal QRS durations (SDI, 14.7±1.2%). Twenty-six patients underwent CRT. At long-term follow-up, responders demonstrated reverse remodeling after CRT with a significant reduction in SDI (16.9±1.1% to 6.9±1%; P<0.0001) and end-diastolic volume (196.6±17.3 to 132.1±13.5 mL; P<0.0001) associated with an increase in LV ejection fraction (17±2.2% to 31.6±2.9%; P<0.0001).

Conclusions—RT3DE can quantify global LVMD in patients with and without QRS prolongation. RT3DE represents a novel technique to identify chronic heart failure patients who may otherwise not be considered for CRT. (Circulation. 2005;112:992-1000.)

Key Words: bundle-branch block ■ heart failure ■ pacing ■ echocardiography ■ echocardiography, three-dimensional

More than half a million new cases of chronic heart failure (CHF) are diagnosed each year in the United States alone.¹ Recent data from Sweden have demonstrated that although mortality in patients with CHF is improving,² patients admitted to hospital with a principal diagnosis of heart failure still have a mortality of 25% at 1 year, a mortality worse than those associated with many cancers.³ Moreover, recent trials of what could now be considered optimal pharmacological therapy for CHF have shown that despite this therapy, mortality is still >25% at 3 years, and >25% of patients will have an admission to hospital with decompensated heart failure during that time.⁴,⁵ Therefore, developing new strategies to improve both morbidity and mortality in patients with CHF is an important goal.

It is now well established that at least 20% of patients with CHF have conduction system disease,⁴,⁶,⁷ which is manifest by prolongation of the QRS complex on a 12-lead ECG. Recently, the abnormal ventricular activation and contraction (left ventricular [LV] mechanical dyssynchrony [LVMD]) has emerged as a therapeutic target in CHF patients with moderate to severe symptoms and substantial LV dysfunction (LVD). These patients often benefit from a pacing modality known as cardiac resynchronization therapy (CRT). Recent studies have shown that CRT improves functional capacity and quality of life in selected CHF patients.⁸–¹¹ Moreover, data suggest that CRT alone may confer a mortality benefit.¹² Currently, only patients with QRS prolongation are recommended to receive CRT.⁹–¹¹,¹³–¹⁵ Some studies, however, have demonstrated that QRS duration is a poor indicator of mechanical dyssynchrony.¹⁶–¹⁸ Furthermore, complex echocardiographic studies have suggested that a significant proportion of CHF patients with normal QRS durations may have LVMD.¹⁶,¹⁸

It seems important to identify new markers of LVMD independently of the QRS duration because it may open new
avenues of treatment for patients not responding to pharmacological therapy. In addition, because a significant proportion of patient receiving CRT do not benefit, identifying these nonresponders is also important.14,15,19,20 The present report describes a novel utility for real time 3D echocardiography (RT3DE). This imaging modality allows functional assessment of all 16 individual segments of the LV. By integrating the function of all of these segments, we have developed a simple, reproducible method of quantifying global LV dyssynchrony.

Methods

Study Population
We recruited 89 healthy subjects and 174 unselected patients referred for routine echocardiography. Subjects were excluded from further analysis if it was not possible to obtain adequate 2D or 3D data sets for analysis. A 2D data set was considered unsuitable if it was not possible to obtain correct parasternal M modes, pulsed-wave Doppler at the mitral valve and LV outflow tract, or 2D images of any of the 3 apical views of the LV. A 3D data set was considered unsuitable for analysis if >2 segments could not be visualized or if it contained visible translation artifacts. The study was approved by the Medical Research and Ethics committees at King’s College Hospital, and all patients gave written consent before participation.

2D Echocardiography
We performed 2D echocardiography using a Sonos 7500 (Philips) with an S3 transducer. LV dimensions, fractional shortening, and septo-posterior wall motion delay (SPWMD) were obtained with M mode from the parasternal long-axis view.21 Apical 4- and 2-chamber views were acquired for calculation of the LV ejection fraction (LVEF) with the biplanar method of disks. Pulsed Doppler was used to calculate the myocardial performance index (MPI).22

Tissue Doppler Imaging
Tissue Doppler imaging was performed with the Sonos 7500 and S3 transducer. Narrow sector angle acquisitions of each LV wall were performed in the apical 4-, 2-, and 3-chamber views with color tissue Doppler (minimum frame rate, 90 Hz). Data from reconstructed curved color M modes were averaged from 3 cardiac cycles. The times to isometric contraction (Ti), maximum sustained systolic velocity (Ts), minimum strain (Te), and early and late diastolic velocities (Te and Ta) were measured in each of the 12 nonapical segments. Dyssynchrony indexes were calculated from each of these parameters as the SD from each of the 12 examined segments on the basis of previously described methods.23–25 To enable comparisons to acquisitions with different heart rates and 3D-derived data, timings were expressed as percentages of the averaged cardiac cycle duration.

Real-Time Transthoracic 3D Echocardiography
RT3DE uses the X4 matrix array transducer to obtain a pyramidal volume in real time. This second-generation matrix array transducer features 3000 active elements sending and receiving simultaneously; images are rendered in real time. These volumes have a relatively narrow sector width (30°×50°). For acquisitions of larger volumes, as is necessary to visualize the entire LV, full-volume acquisition (FVA) is used. For acquisition of a full-volume data set, 4 smaller real-time volumes, acquired from alternate cardiac cycles, are combined to provide a larger pyramidal volume (up to 90°×90°; Figure 1). FVA is performed during breathhold and requires a relatively stable R-R interval to minimize translation artifacts between the 4 acquired subvolumes.

Apical FVAs of the LV were obtained in all patients. To optimize the frame rate of acquisition, depth was minimized to include only the mitral and aortic valves, the positions of which are required for spatial orientation in subsequent analyses. In patients with a significantly dilated LV, the scan line density was reduced to produce a larger pyramidal volume of acquisition.

Quantitative analysis involves defining a number of 2D slices through the voxel-based 3D data set. In each of the slices, the endocardial border is traced with a semiautomated detection process, and a “cast” of the LV cavity is then created as a mathematical model, providing time-volume data for the entire cardiac cycle. By dividing this volume into pyramidal subvolumes based around a nonfixed central point, it is possible to gain an estimation of time-volume data corresponding to each of the 16 standard myocardial segments, as defined by the American Society of Echocardiography (Figure 1).

Developing an Index to Quantify LV Synchrony With RT3DE
We devised a dysynchrony index by calculating the time taken to reach minimum regional volume for each segment as a percentage of the cardiac cycle. The systolic dyssynchrony index (SDI) was defined as the SD of these timings. Higher SDI denotes increasing intraventricular dyssynchrony. To allow comparisons between patients with significantly different heart rates, SDI is expressed as a percentage of the duration of the cardiac cycle rather than in milliseconds.

Assessing the Effect of CRT on SDI
Patients undergoing CRT were examined before implantation and after device optimization, which occurred 2±1 days after implantation. AV delay was optimized with pulsed Doppler to maximize LV filling times and ejection times. Clinical follow-up was performed when possible ~2 months after implantation. For patients followed up in different institutions, a telephone interview was conducted. Patients were reexamined at 10±1 months with 2D echocardiography and RT3DE, and NYHA class was reassessed. A positive response to CRT was defined as a persistent reduction in NYHA class at long-term follow-up.

Data Analysis
The 2D, M-mode, and Doppler images were stored digitally and analyzed on an EnConcert server (version B.2.2, Philips). Tissue Doppler images were stored digitally and analyzed with Qlab.
Nominal variables were compared by use of the chi-square test. Significance of trend across LV groups in continuous and nominal variables was tested with Somer’s D test for ordered groups. Correlations were performed with linear regression and Pearson’s coefficient. Interobserver agreement and intraobserver agreement were assessed with linear regression, Bland-Altman method, intraclass correlation coefficient (ICC), and the average difference between readings corrected for their mean. A value of P<0.05 was considered significant.

Results

Patient Characteristics
The 89 healthy volunteers and 174 unselected patients underwent 2D echocardiography and RT3DE. In 36 subjects (36.9%), it was not possible to perform qualitative analysis of LV volume on 3D echo because of either suboptimal apical acquisitions or significant translation artifacts. In 24 subjects, it was not possible to obtain all 2D, M-mode, and Doppler measurements. A total of 42 subjects (16%)—8 (10.3%) normal subjects and 34 (19.5%) patients—were excluded from further analyses.

Of the 143 patients, 63 (36%) had a history of cardiovascular disease but normal LV systolic function with LVEF >50% by biplane Simpson’s method. Of the 80 patients (36.2%) with LVD, 40 (18.1%) had QRS duration >120 ms. Patients with cardiovascular history were separated into 4 groups by 2D LVEF (biplane method of disks): group 1, LVEF >50% (n=63, 44%); group 2, LVEF 40% to 49% (n=18, 12.6%); group 3, LVEF 30% to 39% (n=18, 12.6%); and group 4, LVEF <30% (n=44, 30.8%).

Thirty-one patients with atrial fibrillation were imaged. Multiple FVAs were acquired in each of these subjects until a satisfactory data set could be obtained. In 22 patients (71%), it was possible to obtain at least 1 FVA of the LV without visible translation artifacts.

Clinical characteristics of these patients are summarized in Table 1.

Patients With and Without QRS Prolongation
There were no statistically significant differences in gender, cause of heart failure, prevalence of atrial fibrillation, medical therapy, biochemical profile, or interventricular septal thickness between patients with QRS duration >120 ms and those with QRS duration >120 ms. In patients with prolonged QRS duration, the mean age was higher (P<0.0001) and 2D echocardiographic indicators of LV function were significantly worse, in keeping with the higher prevalence of left bundle-branch block in patients with LVD.

In patients with LVD, prolonged QRS duration was associated with significantly higher serum sodium, LV end-diastolic internal diameter (but not volume), and MPI.

There was, however, no statistically significant difference in SPWMD and SDI compared with patients with LVD and normal QRS duration. Table 2 summarizes the comparisons between patients with systolic LVD and narrow or broad QRS complexes.

LVEF Findings
The LVEF derived by the biplane method of disks on 2D echo demonstrated an excellent correlation with LVEF derived by volumetric analysis of the RT3DE data set (regression coefficient 0.865; 95% CI, 0.813 to 0.917). Bland-Altman analysis of the 2 methods revealed that the 2D biplane estimation of LVEF produced a systematic overestimation of 3.6±0.5% (95% CI, −10 to 17.4) compared with RT3DE.

Mechanical Dyssynchrony
The SDI demonstrated significant differences between patients with normal systolic function and various degrees of LVD. For normal subjects, the mean SDI was 3.5±1.8%. Patients with cardiovascular disease and normal LVEFs had a mean SDI of 4.5±2.4%. For mild, moderate, and severe systolic dysfunction, the mean SDIs were 5.4±0.8%, 10.0±2.2%, and 15.6±1%, respectively (P for trend <0.001; Figure 2).

The logarithmic correlation between LV systolic function (LVEF, fractional shortening) and SDI persisted regardless of QRS duration (r=0.79 and r=0.77 for LVEF in patients with broad and narrow QRS, respectively; Figure 3). In contrast, there was a weak correlation between QRS duration and SDI (r=0.284; Table 3). There was a moderate correlation between SDI and 2D measures of LVMD (r=0.46 for SPWMD; r=0.52, P<0.0001 for all comparisons).

The cause of heart failure was obtained from the clinical history of each patient. In patients with LVD, there was no statistically significant difference in age, LVEF, wall motion score index, MPI, QRS duration, or SDI between those with ischemic and nonischemic heart failure. In patients with akinetic/scarred segments, the only significant difference was in wall motion score index (P=0.0003); there was no significant difference in SDI (P=0.94). There was no difference in SDI in patients with normal QRS duration with and without ischemic heart disease (SDI, 9.5±1.3% and 7.5±0.8%, respectively; P=0.2). In patients with prolonged QRS durations, there was no difference in SDI between those with and without a history of ischemic heart disease (SDI, 13.2±2.3% versus 11.4±1.7%, P=0.6).

We defined an arbitrary cutoff for significant mechanical dyssynchrony as an SDI >3 SD above the mean for normal subjects (8.3%). The following values were also considered abnormal: MPI ≥0.7, SPWMD ≥80 ms, end-diastolic volume (EDV) ≥130 mL, and QRS ≥120 ms. SPWMD >130 ms has been shown to correlate to reverse remodeling after CRT.23 We selected a lower cutoff to enable comparisons with lesser degrees of LVMD. In patients with moderate or severe LVD, the MPI and SPWMD identified ~75% of the patients with significant dyssynchrony (76.2% and 72.2%, respectively), whereas a QRS duration of >120 ms identified just 46% of patients in all groups of LV function with significant dyssynchrony by our criteria as assessed by RT3DE.

In patients with moderate or severe LVD, 46.8% had prolonged QRS durations, and 71.1% had significant dysyn-
chrony. Of these patients with QRS durations ≥120 ms, 18 (62%) had significantly elevated SDI. In the patients with QRS durations <120 ms, 26 (78.8%) had significant dysynchrony by our criteria (mean SDI, 14.7±1.2%). In patients with moderate or severe LVD, 36.8% were found to have both narrow QRS durations and significant dysynchrony.

### Reproducibility

Twenty subjects were selected for reliability analyses between 2 observers. The selected subjects had a maximum of 1 missing segment on the 3D data set, with adequate acoustic windows. There was excellent correlation with the Bland-Altman method, with mean±SD for SDI, LVEF, and EDV of 0.47±1.43%, 1.75±2.99%, and 3.6±11.9 mL, respectively. The ICC and variability were 0.954 and 6.4%, 0.982 and 5.6%, and 0.973 and 3.4% for SDI, LVEF, and EDV, respectively.

The results derived from the 3D analyses by observer 1 were compared with results calculated by the same interpreter from a period ranging from 12 to 18 months previously. The intraobserver variability was excellent, with average differences of 0.63±2.46% for SDI, 1.0±3.84% for LVEF, and 0.9±21.26 mL for EDV. ICC and variability for SDI were 0.932 and 8.1%, 0.987 and 2.5% for LVEF, and 0.973 and 0.6% for EDV.

To further examine the reproducibility of this technique, another 15 unselected patients were studied on 2 occasions within a 24-hour period by observer 1. The ICC and variability for EDV, LVEF, and SDI were 0.99 and 1%, 0.98 and 3.7%, and 0.88 and 4.6%, respectively. To examine the effect of different line densities on 3D quantification, an additional 16 patients were examined with both normal and low line density acquisitions. The ICCs for EDV, LVEF, and SDI were 0.85, 0.97, and 0.89, respectively.
TABLE 2. Clinical and Echocardiographic Parameters in LVD (LVEF <50%) Patients With Prolonged (≥120 ms) or Normal (<120 ms) QRS Duration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Narrow QRS (n=43)</th>
<th>Broad QRS (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>27 (62.8)</td>
<td>27 (77.1)</td>
<td>0.172</td>
</tr>
<tr>
<td>Age, y</td>
<td>64±18.2</td>
<td>71.3±8.6</td>
<td>0.670</td>
</tr>
<tr>
<td>Ischemic LVD, n (%)</td>
<td>23 (53.5)</td>
<td>18 (51.5)</td>
<td>0.856</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>8 (18.6)</td>
<td>7 (20.0)</td>
<td>0.876</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>80.9±18.7</td>
<td>78.7±16.7</td>
<td>0.617</td>
</tr>
<tr>
<td>Biochemistry, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>137.5±4.6</td>
<td>139.5±2.9</td>
<td>0.041</td>
</tr>
<tr>
<td>Creatinine</td>
<td>142.4±134.5</td>
<td>130.5±70.5</td>
<td>0.650</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide, mg/d</td>
<td>34.4±54.9</td>
<td>28.6±28.4</td>
<td>0.570</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>20 (46.5)</td>
<td>23 (65.7)</td>
<td>0.089</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>24 (55.8)</td>
<td>24 (65.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>16 (37.2)</td>
<td>14 (40)</td>
<td>0.801</td>
</tr>
<tr>
<td>Calcium antagonist, n (%)</td>
<td>4 (9.3)</td>
<td>1 (2.9)</td>
<td>0.248</td>
</tr>
<tr>
<td>Antiplatelet agents, n (%)</td>
<td>22 (51.2)</td>
<td>16 (42.1)</td>
<td>0.632</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>10 (23.3)</td>
<td>8 (22.9)</td>
<td>0.967</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>23 (53.5)</td>
<td>18 (51.4)</td>
<td>0.856</td>
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<tr>
<td>Insulin, n (%)</td>
<td>5 (11.6)</td>
<td>2 (5.7)</td>
<td>0.363</td>
</tr>
<tr>
<td>Oral hypoglycemic, n (%)</td>
<td>2 (4.6)</td>
<td>0 (0)</td>
<td>0.196</td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>LVSD, cm</td>
<td>1.27±0.3</td>
<td>1.24±0.33</td>
<td>0.620</td>
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<tr>
<td>LVWd, cm</td>
<td>5.9±0.8</td>
<td>6.5±1.2</td>
<td>0.007</td>
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<tr>
<td>EDV, mL</td>
<td>153.5±74.5</td>
<td>171.0±71.8</td>
<td>0.29</td>
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<tr>
<td>FS, %</td>
<td>17.3±7.7</td>
<td>15.1±6.9</td>
<td>0.214</td>
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<tr>
<td>EF, %</td>
<td>31.3±11.3</td>
<td>27.4±11.6</td>
<td>0.132</td>
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<tr>
<td>MPI</td>
<td>0.705±0.303</td>
<td>0.893±0.00349</td>
<td>0.017</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.08±0.58</td>
<td>2.3±0.48</td>
<td>0.077</td>
</tr>
<tr>
<td>Dyssynchrony</td>
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</tr>
<tr>
<td>SPWMD, ms</td>
<td>118.2±77.6</td>
<td>129.2±73.6</td>
<td>0.579</td>
</tr>
<tr>
<td>SDI, %</td>
<td>10.3±6.9</td>
<td>12.1±8.3</td>
<td>0.290</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

**Tissue Doppler Imaging**

Of the 50 patients studied, 57.5% had QRS duration ≥120 ms; 64.8% of patients had a moderate or severe reduction in LVEF (mean LVEF, 37±2.9%). Although the selected patients were considered to have optimal windows for tissue Doppler imaging studies, it was not possible to image 2 myocardial segments in 8 (16%) and 1 segment in 12 (24%). The indexes of dyssynchrony were derived as the SD of all observed timings, as described above.

The SDI in this subgroup showed a very good logarithmic correlation to LVEF, regardless of QRS duration (r=0.785 for all patients; r=0.799 for QRS ≥120; and r=0.782 for QRS <120 ms). There was no statistical difference between these groups (10.6±1.5% versus 6.9±1.2%; P=0.07).

**Strain**

The SD of time to minimum strain (SD-Te) showed a moderate correlation with ejection fraction (r=0.53, P=0.008 for all patients; r=0.44, P=0.04 for broad QRS duration; and r=0.62, P=0.008 for narrow QRS duration). There was a significant difference in SD-Te between patients with prolonged or normal QRS duration (11.9±1.2% versus 16.8±1.3% respectively; P=0.008). There was a moderate correlation between SD-Te and SDI in patients with prolonged and normal QRS duration (r=0.47, P=0.001 for all patients; r=0.5, P<0.04; and r=0.49, P<0.04, respectively).

**Systolic Velocities**

There was a moderate correlation between the SD of times to isometric contraction (SD-Ti) and SDI, which was greater in patients with normal QRS durations (r=0.48, P=0.008 for all patients; r=0.29, P=0.18 for prolonged QRS duration; and r=0.82, P<0.0001 for normal QRS duration). There was a moderate correlation with LVEF for patients with broad and narrow QRS complexes (r=0.42, P=0.003; and r=0.54, P=0.01, respectively).

For SD-Ti and SD-Ts, a moderate correlation with SDI was found only for patients with narrow QRS complexes (r=0.38, P=0.009 for all patients; r=0.06, P=0.79 for QRS duration ≥120 ms; and r=0.57, P=0.02 for QRS duration <120 ms). Similar correlations were noted for LVEF (r=0.39 for all patients, r=0.17 and r=0.5 for prolonged and normal QRS duration, respectively). Using a cutoff for 33 ms for SD-Ts not corrected for R-R interval and the arbitrary cutoff of 8.3% for SDI as described above, there was agreement in 56.5% of patients with broad QRS complex for the presence of LVMD and 41.2% of patients with narrow QRS complex. When there was no agreement between methods, SD-Ts was abnormal in 38% of cases and SDI was abnormal in 8%. However, in the absence of a gold standard method for defining LVMD, it is not possible to assess the accuracy of each method.

**Diastolic Velocities**

The SD of times to early and late diastolic velocities (SD-Te, SD-Ta) showed similar correlations to LVEF and SDI. For SD-Te, correlations with LVEF showed r=0.4 for all patients, r=0.16 for prolonged QRS duration, and r=0.58 for narrow QRS duration. Correlation with SDI showed r=0.37, r=0.26, and r=0.32 for all patients and those with prolonged and normal QRS duration, respectively.
CRT Outcomes
Twenty-six patients (age, 67.5 ± 6.1 years; 86% male) fulfilled the criteria for CRT at our institution: QRS duration ≥130 ms, left ventricular internal diameter (diastolic) ≥6 cm, LVEF <35%, and symptomatic heart failure on maximum achievable medical therapy. Twelve patients (46.2%) had ischemic cardiomyopathy. Optimization of AV delay was performed 2 ± 1 days after implantation with Doppler echocardiography in all but 3 patients who had a history of chronic atrial fibrillation. RT3DE was performed before and after optimization. Patients were followed up routinely at ~2 and 10 months after implantation.

At short-term follow-up, 5 patients (19.2%) did not report symptomatic improvement. All others reported a reduction in NYHA functional class, and in these 21 patients, the pre-CRT SDI was significantly higher (15.8 ± 1.2% versus 9 ± 1%; P = 0.0005) and preimplantation LVEF was lower (18.1 ± 1.7% versus 26.9 ± 1.9%; P = 0.04).

At long-term follow-up (10 ± 1 months), 23 patients were reinvestigated, with 3 patients lost to follow-up. All patients were reassessed for NYHA class and underwent repeated echocardiography. Patients with persistent symptomatic improvement at long-term follow-up were classified as responders. Six patients (26.1%) reported no improvement or deterioration in symptoms. Two patients died of progressive heart failure after the follow-up period. One of the nonresponders had concurrent severe aortic stenosis severe coronary disease but had declined surgical intervention and remained symptomatic despite echocardiographic improvement. Two of the nonresponders reported initial symptomatic improvement at 2 months with subsequent deterioration, reflecting possible disease progression or initial placebo effect.

Responders differed significantly in SDI and LVEF before implantation, with higher SDI (16.6 ± 1.1% versus 7.1 ± 2%; P = 0.0005) but similar LVEF (18.6 ± 2.8% versus 23.9 ± 2.4%; P = 0.4) and NYHA class (3.4 ± 1.8 versus 3.0 ± 1.7; P = 0.09). Clinical and echocardiographic characteristics of responders and nonresponders are summarized in Table 4.

At long-term follow-up, responders demonstrated a significant reduction in SDI, whereas nonresponders demonstrated an increase in dyssynchrony (~9.5 ± 5.5% versus 4.3 ± 4.8%; P = 0.008; Figure 4). Responders demonstrated evidence of reverse LV remodeling, with an increase in LVEF (ΔLVEF, 14.4% ± 1.6% versus 0.07 ± 1.1%; P < 0.0001) and a reduction in EDV (ΔEDV, −17.9 ± 1.3 versus 12.5 ± 4.1 mL; P = 0.04; Figure 4). These patients reported a significant reduction in NYHA class, whereas nonresponders reported no change in NYHA class (ΔNYHA, −1.2 versus 0.2; P < 0.0001).

Discussion
The principal findings of this study, the first to explore the feasibility of using RT3DE in assessing the synchronicity of contraction are the following. First, acquisition is clinically practical and reproducible. Second, with RT3DE, it is possi-

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**TABLE 3. Correlation of the SDI Derived by RT3DE With Other Echocardiographic Parameters and QRS Duration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>0.794</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FS</td>
<td>0.635</td>
<td>&lt;0.0001</td>
</tr>
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<td>WMSI</td>
<td>0.547</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MPI</td>
<td>0.520</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SPWMD</td>
<td>0.406</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDV</td>
<td>0.580</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS</td>
<td>0.264</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>SD-Ti*</td>
<td>0.330</td>
<td>0.0205</td>
</tr>
<tr>
<td>SD-Ts*</td>
<td>0.264</td>
<td>0.0640</td>
</tr>
<tr>
<td>SD-Te*</td>
<td>0.169</td>
<td>0.2466</td>
</tr>
<tr>
<td>SD-Ta*</td>
<td>0.334</td>
<td>0.0203</td>
</tr>
<tr>
<td>SD-P*</td>
<td>0.470</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

FS indicates fractional shortening; WMSI, wall motion score index; SD-Ti, SD of times to isometric contraction; SD-Ts, SD of times to maximum systolic velocity; SD-Ta, SD of times to early and late diastolic peak velocities; and SD-Te, SD of times to minimum strain.

*Tissue Doppler parameter comparison performed in a subgroup of 50 patients.

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**TABLE 4. Clinical and Echocardiographic Characteristics of Symptomatic Responders and Nonresponders to CRT Before Implantation of Biventricular Pacemaker**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>19 (73.1)</td>
<td>6 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>15 (78.9)</td>
<td>6 (85.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.4 ± 0.6</td>
<td>3.0 ± 1.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischemic LVD, n (%)</td>
<td>9 (45)</td>
<td>3 (50)</td>
<td>0.83</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>18.6 ± 9.1</td>
<td>23.9 ± 6.7</td>
<td>0.2</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>190.2 ± 69.5</td>
<td>151.1 ± 52.4</td>
<td>0.3</td>
</tr>
<tr>
<td>SDI, %</td>
<td>16.1 ± 5.1</td>
<td>7.1 ± 3.6</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD when appropriate.
ble to integrate the function of all 16 LV segments into an index that can be used to quantify the severity of LV dyssynchrony. Third, this index significantly improves in patients treated with CRT and identified responders in our cohort. Fourth, with RT3DE, it is possible to identify patients with CHF and normal QRS duration who have substantial dyssynchrony of LV systolic contraction.

**Current Techniques Used to Quantify LV Synchrony**

Quantification of intraventricular mechanical dyssynchrony has become increasingly important as CRT establishes itself as an effective therapy in patients with CHF. Currently, QRS duration on the 12-lead ECG is used to select patients for CRT; although quantification of LVMD by a number of methods has been proved superior in identifying responders to CRT. Visual estimation of dyssynchrony with 2D echocardiography is crude and often difficult; delays ≤70 ms cannot be detected with the human eye. Even in the presence of longer delays, dyskinetic segments may appear hypokinetic or akinetic in certain views. The 2D echocardiographic measures such as SPWMD have been shown to have value in predicting subsequent reverse remodeling in patients undergoing CRT. With this and similar methods, however, only 2 opposing walls can be assessed at any one time, and spatial resolution as low as only 1 point in each wall is compared.

Tissue Doppler methods for qualitatively and quantitatively assessing intraventricular dyssynchrony have been shown to be useful in selecting and monitoring patients for CRT. Using dyssynchrony indexes based on tissue velocity measurements, Yu et al and Bax et al demonstrated high predictive value for both symptomatic improvement and long-term prognosis after CRT. Breithardt et al demonstrated that strain measurements based on tissue velocity normalize after CRT, whereas segmental tissue velocities do not. However, Yu and colleagues have shown regional tissue velocities to be more predictive of reverse remodeling after CRT.

The widespread adoption of these techniques, however, has been limited by aspects of acquisition and analysis that may lead to low reproducibility. With tissue Doppler imaging, spatial resolution is also low because it depends on 1D (pulsed Doppler) or 2D (color Doppler) imaging of the 3D heart and multiple acquisitions are required to image all segments, resulting in nonsimultaneous comparisons of segmental coordination. Moreover, tissue Doppler analysis relies on correct axis acquisition because misaligned images produce velocity curves consisting of not only the longitudinal but also the radial velocities. Additionally, translation may occur in >1 plane, producing further artifacts. In patients with suboptimal image quality, color tissue Doppler acquisitions frequently may contain significant artifacts, making interpretation difficult. In many subjects, apical segments cannot be analyzed because of the orientation of the segments and near-field artifacts.

**Using 3D Echocardiography to Assess LV Synchrony**

Quantification of mechanical dyssynchrony with RT3DE takes all myocardial segments into account by examining the composite effect of radial, circumferential, and longitudinal contraction. The SD of times to peak segmental contraction based on 3D regional volumetric analysis is reproducible with a variability of <10%. In a longitudinal study, we have demonstrated that it improves with the improvement in LV synchrony seen with CRT. Using RT3DE, we were able to identify and quantify dyssynchrony in patients with normal LV systolic function and those with varying degrees of systolic dysfunction, a finding consonant with previous studies showing that dyssynchrony varies significantly between patients with normal and abnormal LV function. Moreover and crucially, we were able to show highly significant differences in SDI associated with differences in LV systolic function.

Using RT3DE, we found that mechanical dyssynchrony is increasingly prevalent with worsening LV systolic function independently of QRS durations, a finding supported by the strong correlation between the dyssynchrony index and measures of LV systolic function such as ejection fraction, fractional shortening, and wall motion score index. Another important finding was that there was no correlation between the origin of LVD and the presence of scarred or aneurysmal segments, implying that ischemic cardiomyopathy or local areas of scarring do not cause significant dyssynchrony per se but that this is dependent on the overall LV systolic function.

As discussed, prolongation of the QRS complex is currently used as a marker of mechanical dyssynchrony to select...
patients for CRT. Most patients with bundle-branch block on the ECG exhibit marked lack of coordination in segmental contraction that may be visibly detected on 2D echocardiography. Using tissue Doppler, however, Yu and colleagues and Pitzalis et al have indicated that the presence of left bundle branch block may identify only about half of all patients with mechanical dyssynchrony. Consistent with this, in our study, 50% of patients with significant dyssynchrony had a normal QRS duration.

**CRT and 3D Echocardiographic Assessment of LV Dyssynchrony**

In patients who underwent CRT, SDI declined with biventricular pacing. Patients with a high SDI before implantation experienced the greatest reduction in mechanical dyssynchrony with CRT, and patients who did not experience symptomatic improvement had statistically lower SDI before implantation. Moreover, most responders demonstrated reverse remodeling of the LV at longer-term follow-up with a significant reduction in end-diastolic and end-systolic volumes and SDI that were associated with a significant increase in LVEF. This raises the intriguing possibility that our dyssynchrony index derived from 3D echocardiography may be a useful tool not only to quantify dyssynchrony but also to identify patients who may not benefit from CRT.

**Study Limitations**

Currently, a range of methods for quantification of intraventricular dyssynchrony is available, but a gold standard technique has yet to be accepted. The accuracy of our method for quantifying LVMD could have been established by using a control group consisting of individuals undergoing implantation of a biventricular pacemaker but with no active pacing. Given the duration of the follow-up period and the current level of evidence for efficacy of CRT in treatment of CHF, it would be difficult ethically to justify such a control group. In the absence of a gold standard, the clinical value of each technique must be compared to establish the accuracy and clinical utility of each technique. The present study did not examine the relative value of SPWMD and tissue Doppler methods in the subjects undergoing CRT, which warrants a further adequately powered, prospective study.

This study was designed to validate RT3DE as a method of quantifying intraventricular mechanical dyssynchrony in normal subjects, patients with cardiovascular disease, and patients undergoing CRT. A small number of studies have reported that selected patients with narrow QRS complexes may benefit from resynchronization therapy. However, in the absence of QRS prolongation, it is not clear how these patients should be selected. In this cohort, 22 patients (36.8%) with moderate or severe LVD were found to have QRS duration <120 ms and significant mechanical intraventricular dyssynchrony as assessed by 3D echo.

We did not assess the response of patients with normal QRS durations and dyssynchrony measured with RT3DE undergoing CRT, which warrants a prospective, adequately powered study comparing RT3DE with 2D echocardiographic methods. It would also be useful to correlate changes in dyssynchrony assessed using RT3DE with changes in functional status using measurements such as maximal oxygen uptake or 6-minute walk test; this also warrants further study.

**Conclusions**

RT3DE is a feasible and reproducible method to quantify LV function and intraventricular mechanical dyssynchrony. We have demonstrated that QRS duration is a poor marker of dyssynchrony because there was an increase in dyssynchrony with worsening LV systolic function, independently of QRS duration. The use of RT3DE has the potential to refine investigative and treatment strategies for patients with CHF and to open up new options for patients refractory to optimal medical therapy.

**Acknowledgment**

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**References**


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