Background: Left ventricular dyssynchrony (LVD) has become a therapeutic target using biventricular pacing in selected heart failure patients. Recent advances in 3-dimensional echocardiography (3DE) and automated border detection (ABD) techniques have simplified quantification of global LVD. However, the accuracy and reproducibility of 3DE with ABD for measuring LVD have not been evaluated before.

Methods: The 3DE data for 50 patients were analyzed offline by 2 independent observers. Systolic dyssynchrony index (SDI) was determined by 3-dimensional ABD (3ABD) and 2-dimensional ABD (2ABD) with different imaging planes (2, 4, 6, 8, 12, 16 and 32). Data for 2-, 4-, 6-, 8-, 12-, 16- and 32-plane assessments were compared to those for 3ABD approach and repeat measurements.

Results: Biplane, 4-plane, and 6-plane assessment tended to overestimate SDI. As measured by 8-, 12-, 16- and 32-plane methods, SDI exhibited no significant difference and excellent correlation. The 3DE with 3ABD produced lower intra-observer and inter-observer variability (intra-observer: 7.9% and 14.8%; inter-observer: 9.8% and 16.4% for 3ABD and 8-plane, respectively). Total time for 3ABD approach (3.1 ± 0.6 min) was shorter than conventional 8-plane (14.4 ± 1.2 min, P < 0.001) approach.

Conclusion: Accurate quantification of SDI can be obtained from 3DE using 3ABD or 2ABD with as few as 8 planes. To assess SDI, 3DE using 3ABD exhibited better reproducibility than 3DE using 2ABD. Therefore, 3DE assessment using 3ABD is the preferred approach when evaluating global LVD is necessary. Further prospective study is necessary to demonstrate whether this SDI by 3ABD is a predictor of cardiac resynchronization therapy outcome or not.

Key Words: Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Three-dimensional echocardiography

Cardiac resynchronization therapy (CRT) is an established therapy for advanced heart failure patients with prolonged QRS complexes. Although the clinical benefits of CRT have been confirmed by several randomized controlled studies, one third of patients who received CRT are unresponsive. Evolving data suggest that directly assessing left ventricular dyssynchrony may help identify responders. Several echocardiographic tools help clinicians to quantify left ventricular dyssynchrony, and the quantity of dyssynchrony has been reported to correlate with the improvements in cardiac function after CRT, such as tissue Doppler imaging, real-time 3-dimensional (3D) echocardiography and radial strain by speckle tracking imaging.
Real-time 3D echocardiography allows functional evaluation of all left ventricle segments.\textsuperscript{11,13} Quantifying left ventricular dyssynchrony with 3D echocardiography takes all myocardial segments into account by examining the composite effects of radial, circumferential, and longitudinal contraction.\textsuperscript{11,14-16} The degree of dyssynchrony can be derived from 3D data sets by calculating the difference of the time taken to reach the minimum regional volume for each segment of the left ventricle.\textsuperscript{11,14-16} Previous studies have demonstrated that the number of 2-dimensional image planes for 3D reconstruction can affect the accuracy of 3D measurements.\textsuperscript{17-21} The influence of image-plane number on the accuracy and reproducibility of left ventricular dyssynchrony measurements has not been studied before. Moreover, recent advances in the 3D automated border detection (3ABD) technique simplify the process of 3D parameter measurement and allow easy and fast analysis of left ventricular dyssynchrony.\textsuperscript{22} The accuracy and reproducibility of this new method for assessing dyssynchrony has not been examined before. Accordingly, the purpose of this study was to evaluate the relationship between the number of image planes for 3D reconstruction and the resultant accuracy of dyssynchrony measurement. The feasibility, accuracy, and reproducibility of using the 3ABD algorithm for dyssynchrony assessment were also examined.

\section*{METHODS}

\subsection*{Study population}

The study population consisted of 25 consecutive systolic heart failure patients and 25 normal subjects with no apparent heart disease, as assessed by 2-dimensional echocardiography. All exhibited normal sinus rhythm and satisfactory transthoracic image quality. Those in whom 2 or more segments could not be visualized by conventional echocardiography were excluded. Other exclusion criteria included unstable clinical conditions, cardiac arrhythmia, severe dyspnea precluding breath-holding for at least 10 seconds and pacemaker implantation. Each patient gave written informed consent, and the hospital’s ethics committee approved the study protocol.

\subsection*{Transthoracic 3D echocardiography}

The 3D echocardiographic imaging was performed from the apical window by a commercial scanner (SONOS 7500, Philips, Andover, Massachusetts, USA) equipped with a matrix-array transducer (X4, Philips). For acquisition of a full-volume data set, 4 smaller real-time volumes, acquired from alternate cardiac cycles, were combined to give a larger pyramidal volume (90° × 90°). The 3D datasets were acquired to include the entire left ventricular cavity then stored for offline data analysis. To optimize the frame rate of 3D datasets, depth was minimized to include only the left ventricle, mitral and aortic valves. In patients with an enlarged left ventricle, the scan line density was reduced to include the entire left ventricle. The 3D left ventricular image was analyzed offline by the software packages 4D LV-Analysis CRT 1.0 (TomTec, Gmbh, Unterschlessheim, Germany) and 4D LV-Analysis 2.0 (TomTec), to quantify left ventricular dyssynchrony.

\subsection*{Two-dimensional automated border detection (2ABD) algorithm}

Data analysis was performed offline using the software package 4D LV-Analysis CRT 1.0 (TomTec), for all 3D data sets. After extracting non-foreshortened apical views from the 3D data set, the number of image planes for 3D reconstruction (2, 4, 6, 8, 12, 16 or 32) was determined. The 2-dimensional endocardial borders of each plane were then traced semi-automatically; after first locating 3 landmarks (the apex, bilateral mitral annulus on each plane), overlaid ellipses were fitted to the endocardial borders at the end-diastolic and end-systolic phases, then adjusted as required (Figure 1). Adjustments to the automatically detected borders could be performed if necessary. After the endocardial borders of all component planes were delineated, 3D left ventricular volume changes with cardiac cycles were acquired. The entire left ventricular volume was divided into 16 sub-volumes corresponding to the 16 myocardial segments, as defined by the American Society of Echocardiography. The time to the point with minimum regional volume in each segment was taken to derive an index of left ventricular dyssynchrony. The systolic dyssynchrony index (SDI) was defined as the standard deviation of these timings and expressed as a percentage of the cardiac cycle to allow comparisons between patients with different heart rates.\textsuperscript{11} Higher SDI indicated greater left ventricular dyssynchrony.
Data analysis was performed using the revised software 4D LV-Analysis 2.0 (TomTec) with a 3ABD algorithm for all 3D data sets. First, non-foreshortened apical 2-, 3-, and 4-chamber views were extracted from the 3D data sets. The endocardial borders at the end-diastolic and end-systolic phases were then manually traced in 1 of the 3 apical views (Figure 2). After the tracing, the endocardial borders in the other 2 views were automatically delineated and adjusted if necessary. The software then automatically identified the 3D endocardial borders using a volume cast model. The automatically detected border was adjusted if necessary. After the endocardial borders of the full left ventricle were decided, 3D left ventricular volume changes with cardiac cycles were acquired. The SDI was derived using the 16-segment model in the same manner as the 2ABD algorithm.

SDI obtained by 2, 4, 6, 8, 12, 16 and 32 component image planes were compared with those obtained by 3ABD algorithm, which served as the reference standard. The bias (mean error ± SD) and maximum possible error (absolute value of the maximum error) were calculated for each data set. The reproducibility of the 2ABD- and 3ABD-derived SDI measurements was evaluated by calculating intra- and inter-observer variability.

Statistical analysis

The SDI values were expressed as means ± SD. The relationship between each measurement from 2ABD (2, 4, 6, 8, 12, 16 and 32 planes) and the reference standard (3ABD), was evaluated by linear regression analysis and Bland-Altman analysis. For normal subjects and heart failure patients, the biases (estimated value minus reference value) were calculated and compared between each method by one-way ANOVA. If ANOVA significantly differed across groups, the post hoc analysis (Dennett’s test) was compared between the group with the lowest bias and each of the other groups. A P-value of < 0.05 was considered statistically significant. In addition,
intra- and inter-observer variability was assessed for methods using 2ABD and 3ABD algorithms in heart failure patients.

RESULTS

Table 1 shows the clinical characteristics of the 50 enrolled patients. Analysis of 3D SDI was feasible in the enrolled subjects. Calculating one SDI value using the 3ABD algorithm required 3.1 min, range 12-18 min, P < 0.001) and the 12-plane algorithm (mean 18.5 ± 2.0 min, range 14.5-24 min, P < 0.001). Adjustment of the detected endocardial surface using the 3ABD algorithm was necessary in 9 (36%) normal subjects and 15 (60%) heart failure patients. Patients with a wide QRS or left bundle branch block had significantly elevated SDI as compared to normal subjects (mean: 14.1 ± 6.7%; 15.6 ± 6.7%, both P < 0.001).

Comparisons with reference values

The SDI measurements correlated highly and significantly with the reference values in heart failure patients using the 2ABD and 3ABD algorithms (r: 0.98, all P < 0.001), and in normal subjects using the 2ABD algorithms with image planes larger than 8 (r: 0.64-0.74, all P < 0.001) (Table 2). Despite considerable biases, correlation coefficients remained high in the 2- and 4-plane assessments (r: 0.94, 0.96) for heart failure patients because they reflected the variability from the correlation line rather than the identity line. Using the 2ABD algorithms with image planes less than 8, positive biases were observed in normal subjects (2-plane 0.53%, P = 0.021; 4-plane 0.47%, P = 0.033) and heart failure patients (2-plane 2.80%, 4-plane 2.06%, both P < 0.01; 6-plane 2.0%, P = 0.012), indicating overestimation by limited planes for 3D dyssynchrony assessment. The bias in SDI measurements was relatively constant with at least 8 image planes and increased progressively and significantly with less than 8 image planes (Figure 3).

Figure 4 depicts the results for the linear regression and agreement analyses between the reference values and the measured SDI by the 8-plane and 32-plane assessments. When all subjects were analyzed, the measurements of SDI correlated with the reference values equally well when using the 8-plane and 32-plane algorithms (r: 0.96 and 0.98, respectively, all P < 0.001).

Table 2. Accuracy of SDI quantification by 2ABD with different image planes compared with 3ABD algorithms

<table>
<thead>
<tr>
<th>No. of image planes</th>
<th>Regression equation</th>
<th>r value</th>
<th>Bias (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>y = 3.04 + 0.55x</td>
<td>0.28</td>
<td>0.53 ± 2.17</td>
<td>0.021</td>
</tr>
<tr>
<td>4</td>
<td>y = 1.18 + 0.87x</td>
<td>0.44</td>
<td>0.47 ± 2.0</td>
<td>0.033</td>
</tr>
<tr>
<td>6</td>
<td>y = 2.56 + 0.55x</td>
<td>0.32</td>
<td>0.03 ± 1.87</td>
<td>NS</td>
</tr>
<tr>
<td>8</td>
<td>y = 0.81 + 0.83x</td>
<td>0.64</td>
<td>-0.16 ± 1.14</td>
<td>NS</td>
</tr>
<tr>
<td>12</td>
<td>y = -0.33 + 1.0x</td>
<td>0.70</td>
<td>-0.31 ± 1.11</td>
<td>NS</td>
</tr>
<tr>
<td>16</td>
<td>y = -1.30 + 1.12x</td>
<td>0.74</td>
<td>-0.62 ± 1.15</td>
<td>NS</td>
</tr>
<tr>
<td>32</td>
<td>y = -0.90 + 1.03x</td>
<td>0.74</td>
<td>-0.75 ± 1.05</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure (n = 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>y = 0.26 + 1.22x</td>
<td>0.94</td>
<td>2.80 ± 2.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>y = 0.10 + 1.17x</td>
<td>0.96</td>
<td>2.06 ± 2.13</td>
<td>0.009</td>
</tr>
<tr>
<td>6</td>
<td>y = -1.34 + 1.23x</td>
<td>0.96</td>
<td>2.00 ± 2.45</td>
<td>0.012</td>
</tr>
<tr>
<td>8</td>
<td>y = 0.39 + 1.08x</td>
<td>0.95</td>
<td>1.29 ± 1.87</td>
<td>NS</td>
</tr>
<tr>
<td>12</td>
<td>y = -1.34 + 1.15x</td>
<td>0.95</td>
<td>0.36 ± 2.22</td>
<td>NS</td>
</tr>
<tr>
<td>16</td>
<td>y = -1.31 + 1.13x</td>
<td>0.98</td>
<td>0.21 ± 1.41</td>
<td>NS</td>
</tr>
<tr>
<td>32</td>
<td>y = -2.37 + 1.22x</td>
<td>0.98</td>
<td>0.14 ± 1.79</td>
<td>NS</td>
</tr>
</tbody>
</table>

SDI, systolic dyssynchrony index; x, SDI by 32-plane approach; 2ABD, 2-dimensional automated border detection; 3ABD, 3-dimensional automated border detection; p-value, post hoc comparisons with the group with the lowest bias.
The 95% limits of agreement for the 8-plane and 32-plane algorithms were similar when compared to that for the 3ABD algorithm (2SD: 3.3 and 3.0, respectively).

Intra- and inter-observer variability

Linear regression analyses of repeat measurements in heart failure patients resulted in high correlation coefficients for 8-plane, 32-plane and 3ABD algorithms (intra-observer: 0.97, 0.98 and 0.98; inter-observer: 0.96, 0.96 and 0.98, respectively). The intra- and inter-observer variability values for heart failure patients were lower for the 3ABD-derived SDI compared with the 2ABD-derived SDI values (7.9%, 14.8% and 11.6% for intra-observer and 9.8%, 16.4% and 12.4% for inter-observer in 3ABD, 8-plane and 12-plane, respectively) (Table 3).

DISCUSSION

This study demonstrated that currently available 3D echocardiography and 3ABD techniques enable rapid and accurate quantification of global left ventricular dyssynchrony with good reproducibility. Accurate evaluation of left ventricular dyssynchrony can also be obtained using 2ABD algorithm with at least 8 planes for 3D reconstruction. The shortcomings of the conventional 8-plane approach are increased time spent and
variability in comparison to the novel 3ABD approach.

Accurate assessment of systolic dyssynchrony can help identify patients likely to benefit from CRT. LV dyssynchrony actually is a three-dimensional phenomenon. Several recent studies have demonstrated the potential of real-time 3D echocardiography in this field because it enables the evaluation of left ventricular dyssynchrony in a comprehensive way.11,14,16 Up till now, only one preliminary report suggested SDI derived from 3-dimensional echocardiography predicted response to CRT in a pilot group of 26 patients.15 Poor temporal resolution (14-17 frames/s) compared with 2-dimensional or tissue Doppler echocardiography prevents precise measurement of timing and may result in failure to detect LV dyssynchrony.

Prior studies of 3D echocardiography for assessing LV dyssynchrony did not fully utilize 3D volumetric information, because they were still based on tracing of endocardial borders on multiple 2-dimensional planes extracted from the 3D data.11,13-18,21 Such analyses are basically 2-dimensional, and the results can be inaccurate, because small areas of abnormality are more difficult to identify if an inadequate number of planes is analyzed. The results in this study demonstrated limited-plane assessment tends to overestimate SDI. In this regard, the recently developed 3ABD algorithm allows direct detection of endocardial borders in the 3D domain and resolves many of the limitations associated with the conventional analysis.22 This study is the first to examine whether direct detection of the 3D endocardial borders can accurately and reliably measure left ventricular dyssynchrony. The 3ABD approach offers accuracy comparable to the conventional method and additional advantages of time-saving, better reproducibility, and reduced reliance on geometric assumptions of left ventricular shape.22

Previous 3D echocardiographic reconstruction studies have demonstrated that at least 8 to 12 2-dimensional planes are needed for accurate assessments of left atrial volume, left ventricular volume, left ventricular ejection fraction, and left ventricular mass.18-21,23 Our results are consistent with data of previous similar studies and extend their findings to include clinical assessment of left ventricular dyssynchrony. Assessment by inadequate number of 2-dimensional planes tends to underestimate left ventricular volume18 and overestimate left ventricular dyssynchrony. The present study suggests that more than 8 image planes add negligible incremental accuracy and decrease measurement variability at the expense of increased analysis time. For clinical purposes, when multiple 2-dimensional planes are used in 3D reconstruction, 8 planes suffice for accurately assessing left ventricular dyssynchrony.

The reproducibility of SDI measurements is important for clinical applications in routine dyssynchrony analysis. If the method of calculating SDI exhibits unacceptable variability, additional measurements must be calculated and averaged to obtain a reliable result. This increased time spent for 3D data processing is impractical for routine analysis. Compared with a previously published study using multiple planes to quantify left ventricular dyssynchrony, the present results showed higher inter- and intra-observer variability when using 8 image planes for 3D reconstruction (Table 3).11 In the study of Kapetanakis et al, the intra- and inter-observer variabilities for SDI were only 4.6% and 6.4% compared to 14.8% and 16.4%, respectively, in our study.11 This discrepancy has several possible explanations. First, in our study, reproducibility was examined in selected patients with better acoustic windows or by more than 8 image planes. Variability in SDI measurements would be higher in routine analysis. Second, measurement variability would be lower for patients with higher SDI values. If variability analysis is evaluated in high-SDI patients, variability in measurements is reduced. Similar problems were noted in the recently-published prospective, multicenter (PROSPECT) trial to test the performance of 12 echocardiographic dyssynchrony parameters for predicting CRT response.24

The value of a true 3D solution for clinically assessing left ventricular volume and function has been demonstrated previously. Semi-automated detection of the 3D left ventricular endocardial borders from real-time 3D data allows rapid, accurate and reliable measurements of left ventricular volume and function.22 This method not only solves the problems of inaccuracy and higher variability inherent to traditional 2-dimensional estimations of left ventricular volumes but also avoids the tedious and lengthy process of conventional 3D data analysis by manual or semi-automated tracing of the endocardial borders in multiple 2-dimensional planes.22 The new 3ABD technique employed in this study sig-
nificantly improves dyssynchrony assessment over the conventional 3D approach by minimizing intra- and inter-observer variability and reducing the time required for 3D data analysis. This approach offers accurate and reliable results and is practical for routine clinical use.

Although accurate and reproducible results can be achieved rapidly, the novel 3ABD process applied in this study still requires offline analysis and export of 3D data to an external computer for data processing. Rapid online quantification of left ventricular volume from real-time 3D echocardiographic data has been validated previously.22 The recently commercially available echocardiographic machines can perform the analysis of LV dyssynchrony on cart without data transfer and offline analysis. However, the accuracy and reproducibility of online measurements of left ventricular dyssynchrony from real-time 3D data requires further confirmation.

Further limitations of this study are the choice of the reference standard and the frame rate of 3D echocardiography. Although cardiac magnetic resonance has been used extensively as a standard for comparing 3D parameters due to its superior endocardial definition,21-22,25-27 no single standard for quantitative analysis of 3D dyssynchrony has been widely accepted. The 3ABD assessment may not be the ideal standard for comparison and higher frame rate of 3D echocardiography is needed for the accurate assessment of LV dyssynchrony.

On the other hand, 3D SDI represents global dyssynchrony, not regional. Some heart failure patients have significant regional dyssynchrony between septal and lateral walls and may benefit by CRT, but their global dyssynchrony parameters may be small by averaging with all segments. To date, there are still technical demands and inter-observer variations in most of the echo parameters developed for CRT.28-29 In ACC/AHA/HRS 2008 guidelines for device-based therapy, there is no single echo criteria included to select patients for CRT, neither regional nor global dyssynchrony index. Efforts aimed at decreasing variability arising from technical and interpretative issues may solve this problem.

CONCLUSION

Accurate quantification of left ventricular dyssynchrony can be obtained using 3D echocardiography with a 3ABD approach or 2ABD algorithms with as few as 8 image planes. The 3ABD approach dispenses with the need for geometric assumptions and exhibits less measurement variability than the conventional 3D method using multiple 2-dimensional planes. Beyond this, the 3ABD approach is faster and more user-friendly. Therefore, 3ABD approach is better than two-dimensional echocardiography with 3D reconstruction for routinely evaluating LV dyssynchrony in heart failure patients. Whether the SDI by 3ABD can predict CRT outcome or not needs further prospective work-up.

ACKNOWLEDGEMENT

Part of the contents has been presented in the Scientific Session 2006 of the American Heart Association in Nov, 2006 in Chicago, USA.

This work was supported by Grant NSC 96-2314-B-182A-137 from the National Science Council, Taipei, Taiwan and CMRPG 350951 from Chang Gung Memorial Hospital, Taipei, Taiwan.

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3D Automated Contour Detection for Dyssynchrony Measurements