Tissue Doppler Imaging and Strain Doppler Imaging as Modalities for Predicting Clinical Improvement in Patients Receiving Biventricular Pacing

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Background The purpose of this study was to determine the utility and efficacy of tissue Doppler imaging (TDI) and strain Doppler imaging (SDI) for evaluating ventricular synchrony and function, and for predicting the long-term clinical improvement in patients undergoing biventricular pacing (BVP).

Methods and Results TDI and SDI were performed before and <1 month after initiating BVP in 17 patients with advanced heart failure. An intraventricular conduction delay between the left ventricular (LV) septal and lateral walls was measured by TDI. The average LV strain (LV-strain) was calculated from data obtained at the center of 6 regions of the LV (base and mid-point between the basal and apical portions, and the mid-point between these 2 points on the septal and lateral walls). During a 23±7 month follow-up period, 12 patients improved clinically and did not require re-hospitalization for heart failure (responder group), but the remaining 5 did not improve (nonresponder group). Before BVP, the intraventricular conduction delay was greater in the responder group than in the nonresponder group (p<0.01), but after BVP, it did not differ between the 2 groups. LV-strain improved after BVP in the responder group but not in the nonresponder group (p<0.05).

Conclusion A high intraventricular conduction delay before BVP and decreased strain shortly after BVP may predict long-term clinical improvement in patients undergoing this treatment. (Circ J 2005; 69: 194–200)

Key Words: Biventricular pacing; Dyssynchrony, Heart failure; Myocardial strain; Tissue Doppler Imaging

Biventricular pacing (BVP) is currently indicated for the treatment of patients with medially refractory heart failure and electrical dyssynchrony;1–4 but it is becoming increasingly clear that QRS duration is an inadequate predictor of the response to BVP therapy.5–6 Because the improvement in mechanical dyssynchrony after BVP correlates with improvement in clinical status and reverse remodeling5–12 there are ongoing investigations to determine the most accurate and efficient method of detecting mechanical dyssynchrony. Echocardiography, including tissue Doppler imaging (TDI), is simple, easy and ideal for evaluating regional wall motion.2–13 Furthermore, recent advances in TDI and strain Doppler imaging (SDI) have enhanced the ability to evaluate ventricular synchrony and regional myocardial function.5–16 However, the utility and efficacy of TDI and SDI for evaluating ventricular synchrony and function and for predicting long-term clinical improvement in patients undergoing BVP have not been sufficiently determined. The purpose of this study was to clarify this point.

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Study Population
This study included 17 patients with advanced heart failure and a wide QRS complex who received a pacemaker or an implantable cardioverter defibrillator (ICD) providing BVP. There were 12 men and 5 women, and their mean age was 66±9 years: 13 patients had idiopathic cardiomyopathy, 2 had ischemic heart disease, and the remaining 2 had valvular heart disease; 11 patients were in New York Heart Association (NYHA) functional class IV, and the remaining 6 were in class III despite maximal pharmacologic therapy at the time of pacemaker implantation. The QRS interval was >140 ms and the left ventricular (LV) ejection fraction determined by echocardiography was <40% in all the patients.

Patients were divided into 2 groups according to their clinical status at the end of the follow-up period (23±7 months; range: 14–37 months): the responder group (n=12) and the nonresponder group (n=5; Table I). The clinical status of each patient was determined at the end of the follow-up period by 2 cardiologists who did not have any information concerning the BVP status of the patients. A responder was defined as a patient who improved clinically to NYHA functional class I or II during the follow-up period and a nonresponder was one who did not. There was no significant difference between the 2 groups in the NYHA classification before the initiation of BVP (p=0.9; Table I).
Device Implantation

At the time of implantation of the pacemaker, 11 patients were in sinus rhythm and had left bundle-branch block, and the remaining 7 were in chronic atrial fibrillation with bradycardia and had already received right ventricular (RV) pacing. These 7 patients underwent a procedure to revise the RV pacing system to allow BVP, and all ventricular activation occurred through the pacing leads after initiation of this type of pacing. In 11 patients who were in sinus rhythm at the time of BVP initiation, an atrial lead was implanted in the right atrial appendage, and a RV lead was placed at the RV apex. In the 7 patients in chronic atrial fibrillation who underwent revision of the RV pacing system to a BVP system, the LV lead was connected to the atrial port of the pacemaker, and the RV lead was attached to the ventricular port. The atrioventricular delay was programmed to its minimal value (10 ms or 30 ms), so that BVP consisted of LV pacing followed 10 ms or 30 ms later by RV pacing.

The LV pacing lead was inserted by the transvenous approach through the coronary sinus, and placed in the left marginal or postero-lateral cardiac vein in 15 patients. The remaining 2 patients had the epicardial pacing wires placed in the anterolateral portion of the LV. The RV pacing lead was placed in the RV apex in all the patients.

Tissue Doppler Imaging (TDI) and Strain Doppler Imaging (SDI)

TDI and SDI were performed before and shortly after (<1 month) initiating BVP in all the patients. LV dimensions were measured by M-mode echocardiography in the parasternal long-axis view. The LV end-diastolic dimen-

Table 1 Clinical Characteristics Before Biventricular Pacing

<table>
<thead>
<tr>
<th></th>
<th>Responder (n=12)</th>
<th>Non responder (n=5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65±10</td>
<td>68±8</td>
<td>0.6</td>
</tr>
<tr>
<td>M/F</td>
<td>8/4</td>
<td>4/1</td>
<td>1.0</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>6/6</td>
<td>2/3</td>
<td>0.9</td>
</tr>
<tr>
<td>Cause of chronic heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic/ischemic/valvular</td>
<td>10/1/1</td>
<td>2/2/1</td>
<td>0.29</td>
</tr>
<tr>
<td>No. of hospitalizations for heart failure</td>
<td>2.5±1.3</td>
<td>2.6±1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>4 (33%)</td>
<td>3 (75%)</td>
<td>0.4</td>
</tr>
<tr>
<td>QRS duration</td>
<td>184±29</td>
<td>161±11</td>
<td>0.11</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>49±9</td>
<td>47±4</td>
<td>0.6</td>
</tr>
<tr>
<td>End-diastolic dimension (mm)</td>
<td>66±10</td>
<td>67±6</td>
<td>1.0</td>
</tr>
<tr>
<td>End-systolic dimension (mm)</td>
<td>59±8</td>
<td>61±7</td>
<td>0.6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>27±12</td>
<td>20±7</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. No. of hospitalizations for heart failure was obtained during the period before biventricular pacing that was equal to the length of the follow-up period after biventricular pacing for each patient.

NYHA, New York Heart Association.
sion (LVEDd) was measured at the onset of the QRS complex, and the LV end-systolic dimension (LVESd) was defined by the smallest LV cavity. Pulsed-wave (PW) TDI and SDI were performed with a Vivid 7 echocardiography system (GE Vingmed Ultrasound, Horten, Norway) after completing conventional echocardiography. Images were obtained using a 1.5–4.0 MHz phased array transducer (M3S transducer; GE Vingmed Ultrasound) at a depth of 10–16 cm in the LV apical 4-chamber view. The image sector width was set as narrow as possible to allow a frame rate acquisition greater than 100 frames/s. At least 2 cine loops of raw TDI data, each containing 3 cardiac cycles, were stored online as digital scan-line data using the Vivid 7 scanner and were retrieved later and analyzed using the built-in analysis tools. Two experienced observers who were familiar with TDI and SDI and unaware of the clinical status of the patients analyzed the data.

Intraventricular conduction delays in the LV were measured by TDI. The region of interest (ROI) was positioned at the base of each of the septum and lateral wall of the LV, and the time from the onset of the QRS to the peak myocardial sustained systolic velocity was measured (Fig 1). The peak myocardial sustained systolic velocity was defined as the maximum velocity during systole, excluding the isovolumic contraction. The time difference between the 2 regions was defined as the intraventricular conduction delay in the LV. To avoid artifact, the peak myocardial sustained systolic velocity was examined in at least 2 cine loops. We confirmed that the regional myocardial velocity curves obtained by TDI were identical or nearly identical, and 2 beats were measured and averaged for each measurement.

As a measure of regional ventricular performance, we determined the peak myocardial strain at the center of 6 regions of the LV (base, mid-point between the basal and apical portions, and the mid-point between the 2 points on the septal and lateral walls; Fig 2) during a stable cardiac cycle, and the average LV strain (LV-strain) and coefficient of variation of the LV strain (CV-strain) were calculated as previously reported. The peak strain in each segment was determined as the difference in strain measured from the onset of the QRS complex to the nadir of the strain tracing. We also calculated the coefficient of variation for the time at which the maximum strain was recorded in each region (CV-time). As with the TDI measurements, 2 consecutive beats were measured and averaged for each measurement. We used an oval ROI (6×8 mm) with careful alignment of the cursor with the wall direction in any given region measured. The strain can be estimated by calculating the velocity gradient between the 2 points with the equation: strain = $\int_0^t \left( \frac{v(t) - v(t + \Delta t)}{\Delta t} \right) dt$. An offset of $\Delta t = 12$ mm was used in all studies.

Echocardiographic parameters, including TDI and SDI, were also obtained in 6 responders and 2 nonresponders 12±6 months after undergoing the BVP to assess its long-term effectiveness.

Other Measurements and Analysis

To determine the predictors of clinical improvement in patients undergoing BVP, the incidence of re-hospitalization for heart failure, QRS duration, and echocardiographic measurements shortly after BVP was initiated were also compared between the 2 groups.

Statistical Analysis

Continuous variables are expressed as the mean ±1 standard deviation. Student’s t-test was used to compare 2 groups. Analysis of variance (ANOVA) was used when comparisons involved ≥2 groups. When group differences were found, one-way ANOVA was followed by the Fisher’s protected least significant difference method to test the significance of the difference among means in all groups.
Categorical variables were compared using chi-squared analysis using the Yate’s correction if necessary. An overall chi-square test for a $2 \times n$ table was performed when comparisons involved $>2$ groups. A p-value <0.05 was considered significant.

**Results**

**Clinical Characteristics and Measurements Before BVP**

There were no significant differences in the mean age, gender, NYHA functional class, cause of heart failure, number of hospitalizations for heart failure prior to BVP, electrocardiographic indices, or echocardiographic measurements between the 2 groups before BVP (Table 1).

**Clinical Course and Measurements After BVP**

During the mean follow-up period after undergoing BVP, the 5 patients making up the nonresponder group had no change in their NYHA functional class, and all of them had to be re-hospitalized for worsening heart failure (average number of re-hospitalizations: $1.8\pm0.8$; range: 1–3), and 1 patient died of heart failure. In contrast, the 12 patients making up the responder group had an improvement in their NYHA functional class to I or II, and none of them was re-hospitalized.

There were no significant differences in the LVEDd, LVESd or LV ejection fraction between the 2 groups before or shortly after BVP (Fig 3A,B). In both groups, the LVEDd, LVESd and the LV ejection fraction also did not change significantly after BVP in the responder group (p<0.01), but did not change in the nonresponder group (Fig 3C). However, no significant difference was observed in the QRS duration before BVP (Table 1) or the % shortening of the QRS duration after BVP (responders: $27\pm11$%; nonresponders: $20\pm5$%; p=0.26) between the 2 groups.

**Intraventricular Conduction Delay in the LV Before and After BVP**

Before receiving BVP, the intraventricular conduction delay in the LV was greater in the responder group ($126\pm103$ ms) than in the nonresponder group ($36\pm20$ ms; Fig 4).

However, after BVP, it did not differ between the 2 groups (responder group, $44\pm40$ ms; nonresponder group, $44\pm19$ ms). The LV intraventricular conduction delay significantly improved in the responder group (p<0.01), but did not improve in the nonresponder group (Fig 4).

**LV Strain and Coefficient of Variation Before and After BVP**

The LV-strain significantly improved in the responder group, but deteriorated in the nonresponder group (p<0.05; Fig 5A). Improvement in the LV-strain was observed more often in the responder group (92%) than in the nonresponder group (20%; p<0.05). The CV-strain or CV-time did not differ between the 2 groups before or after BVP (Fig 5B,C).
Changes in the Measurements Variables During a Follow-up

In 6 responders, although the LV diameter and EF measured 12±6 months after undergoing BVP had improved more than at shortly after BVP, there was no significant difference (Fig 6). The improvement in the LV intraventricular conduction delay and LV-strain shortly after BVP was unchanged at the time of follow-up (Fig 6); however, those measurements did not change during the follow-up period in 2 nonresponders. No significant difference was observed in the CV-strain or CV-time in either group during the follow-up period (Fig 6).

Discussion

Major Findings

The analysis of TDI and SDI in patients undergoing BVP revealed the following findings: (1) the intraventricular conduction delay in the LV was significantly longer in responders than in nonresponders, and after BVP it improved in the responders; (2) LV-strain improved after BVP in responders, but not in the nonresponders; (3) no significant differences were found in the CV-strain and CV-time between the responders and nonresponders before or after BVP; (4) the intraventricular conduction delay and LV-strain that improved shortly after the initiation of BVP...
was maintained in responders during the follow-up period. These results indicate that a high intraventricular conduction delay in the LV and decreased strain shortly after BVP, irrespective of the dispersion of CV-strain and CV-time, may predict long-term clinical improvement in patients undergoing BVP, and that TDI and SDI are useful for evaluating ventricular synchrony and function and predicting long-term clinical improvement.

Role of TDI and SDI in Patients Undergoing BVP

BVP has become a promising new therapy for the treatment of patients with end-stage heart failure and contractile dysynchrony caused by intraventricular conduction delay.1-4,12,14 Better coordination of ventricular contractions may be responsible for the beneficial effects of BVP, and precise assessment of ventricular synchrony is crucial for evaluating and predicting the efficacy of BVP.1,4 In this regard, TDI has emerged as a technique that allows accurate assessment of the regional timing of mechanical events relative to the phase of the cardiac cycle.1-12,14 Recent studies have reported the usefulness of TDI for assessing and quantifying LV dyssynchrony. Specifically, the intraventricular conduction delay in the LV can be measured by placing 2 sample volumes at the base of the septum and lateral wall, and a delay ≥60 ms between the peak systolic velocity of the septum and the lateral wall before BVP can predict clinical improvement after BVP.10,11 In the present study, the intraventricular conduction delay in the LV was greater in the responders than the nonresponders before BVP, and a significant improvement of the delay was found only in the responders after BVP. Therefore, we hypothesize that the presence of a greater intraventricular conduction delay in the LV may predict the effectiveness of BVP and that TDI is a useful technique for assessing the intraventricular conduction delay.

Myocardial strain determined by Doppler echocardiography is a new, powerful method for quantifying regional myocardial function and is less influenced by tethering effects than TDI.1-4-16 Myocardial strain is a measure of the regional deformation, and by definition, negative strain reflects shortening whereas positive strain indicates elongation.16 In the present study, the LV-strain significantly improved in the responders, but not in the nonresponders. These findings indicate that BVP acutely improved regional LV contractility in the responders, which may be a consequence of improvement in the intraventricular conduction delay in the LV. On the other hand, CV-strain and CV-time did not differ between the responders and nonresponders before or after BVP, which indicates that the LV-strain, CV-strain or CV-time before BVP may not be useful for identifying candidates or for predicting the long-term clinical improvement in patients undergoing BVP, and that a decreased LV-strain shortly after BVP potentially may predict long-term clinical improvement.

In the present study, the LV-strain improved shortly after BVP in the responder group, and its effect continued throughout the follow-up period. However, the CV-strain and CV-time did not improve either shortly after the BVP or during the follow-up period in the responder group. A previous study demonstrated that an improvement in the LV-strain after BVP occurred unevenly in the LV14 which may be caused by ventricular pacing itself decreasing the performance of the regions close to the electrode tip by disrupting the normal electrical mechanical activation sequence.17 Therefore, positioning the ROI at or near the pacing lead might not result in improved regional LV strain. It is also well known that the position of the LV electrode also affects the response to BVP.13 Variable lead positions and the underlying etiology, together with insufficient numbers for subgroup analysis, might explain the absence of a consistent effect of BVP on regional LV strain, resulting in no improvement in the CV-strain and CV-time after BVP in the responders.

In the present study, there was also no significant difference in the LV diameter or EF between before and shortly after initiating BVP in the responders or the nonresponders, indicating that echocardiographic LV parameters cannot predict long-term clinical improvement in patients undergoing BVP. These parameters improved during the follow-up period in the responders, but without significant differences. In contrast, the LV intraventricular conduction delay and LV-strain improved shortly after initiation of BVP, and that improvement was maintained throughout the follow-up period. Studies of acute BVP have shown that the most significant improvements occur in the pulse pressure, by an average of 18%19 and in the stroke volume by 14%.20 However, the changes in the LV EF have been less pronounced, and range from 1% to 4%.19,21 Therefore, the effects of BVP on all the LV measurements, such as the LV diameter and EF, might appear later than on the regional parameters (intraventricular conduction delay and LV-strain).

Study Limitations

First, the definition of responders might be subject to the inherent inaccuracy of assessing NYHA class. However, during the follow-up period, none of the responders was rehospitalized for heart failure whereas all the nonresponders were. Therefore, our definition of the responders may be acceptable for identifying a satisfactory clinical outcome after BVP in patients with advanced heart failure.

Second, interventricular conduction delay4,12 as well as intraventricular conduction delay, has been demonstrated in patients with advanced heart failure. BVP may also improve the interventricular conduction delay, but because it was not measured in this study, no conclusions about it could be drawn.

Finally, the follow-up period after undergoing BVP was relatively short, and our sample size was relatively small. Not all variables could be measured in all the patients during the follow-up period. Therefore, future studies are needed to clarify and establish the effectiveness of TDI and SDI in patients undergoing BVP.

Conclusions

TDI and SDI are useful for evaluating ventricular synchrony and function in patients undergoing BVP. A high intraventricular conduction delay in the LV before BVP and decreased LV-strain shortly after BVP, irrespective of the dispersion of the coefficient of variation of the LV strain and time, may predict long-term clinical improvement.

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References


