Original article

Novel dyssynchrony evaluation by M-mode imaging in left bundle branch block and the application to predict responses for cardiac resynchronization therapy

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ABSTRACT

Background: To determine an appropriate M-mode method in assessing left ventricular (LV) dyssynchrony in left bundle branch block (LBBB), and to assess feasibility of the method to predict cardiac resynchronization therapy (CRT) responses.

Methods and results: Fifty-one patients with LBBB were enrolled. Among them 31 patients underwent CRT. In addition to original septal to posterior wall motion delay (SPWMD), first peak-SPWMD was proposed as time of difference between the first septal displacement and the maximum displacement of the posterior. If an early septal point was not present, anatomical M-mode was used to visualize an early septal displacement spreading scan-area until inferoseptal wall. CRT responders were defined as LV end-systolic volume reduction (>15%) at 6 months after CRT. Twenty patients (65%) were identified as CRT responders. First peak-SPWMD in responders was significantly higher than those in nonresponders, although SPWMD did not differ between groups. Strong predicting ability of first peak-SPWMD was revealed (first peak-SPWMD: 80/90/83%; SPWMD: 35/100/58%), and area under the curve in receiver operating characteristic analysis of first peak-SPWMD (0.88) was significantly higher than that of SPWMD (0.61) (p < 0.05).

Conclusion: In patients with LBBB, time differences between early septal and delayed displacement of posterolateral wall on M-mode images were the appropriate dyssynchrony parameter, and could improve the predictive ability for CRT responses.

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Introduction

In previous studies, presence of mechanical left ventricular (LV) dyssynchrony has been focused on as the key factor to affect responses for cardiac resynchronization therapy (CRT) [1–4]. However, multi-center studies showed negative results with the utility of Doppler echocardiographic parameters in identifying CRT responders [5,6]. Among various Doppler echocardiographic methods, M-mode imaging is a classic method in assessing LV dyssynchrony. Septal to posterior wall motion delay (SPWMD) is a typical dyssynchrony parameter obtained from M-mode imaging [1]. In addition to tissue Doppler parameters, the utility of SPWMD has been controversial [5–8]. However, M-mode imaging is clinically attractive, because it is a fundamental function in any echocardiographic system and allows easy and quick online analysis. In addition, although the available scanning area of M-mode imaging is limited, septum and posterolateral wall motion are just targets of modifications by pacing in patients with left bundle branch block (LBBB), who are the most common candidates for CRT. The latest guidelines update clearly state the superiorities of CRT effects in LBBB as compared to non-LBBB type electrical disturbances [9,10]. However, even in LBBB, a number of candidates for CRT may be non-responders, therefore, improvements in echocardiographic methods still have clinical implications in prediction of CRT responders [11]. Recently, we reevaluated the utility of tissue Doppler parameters, and revealed modified tissue Doppler parameters based on the pathophysiology of LV dyssynchrony as the target of CRT to improve
ability in predicting responders to CRT [12]. As well as the novel concept of tissue Doppler echocardiography, we hypothesized the ability of M-mode imaging to predict CRT responses also may be improved in patients with LBBB if a novel concept of SPWMD was established based on the electrical–mechanical sequences in LBBB. The aims of this study were (1) to reveal the variability of LV M-mode images in LBBB, (2) to propose an appropriate novel M-mode method in assessing LV dyssynchrony based on the electrical–mechanical sequences in LBBB, and (3) to assess the reliability and feasibility of our method to predict CRT responses.

Methods

Fifty-one patients with systolic dysfunction and LBBB and 20 healthy controls were enrolled (Table 1). Among patients with LBBB, 31 (21 men, 61 ± 17 years) underwent CRT. Patients were selected prospectively. Although three patients were excluded because of inadequate imaging qualities of speckle tracking method, no patients were excluded because of inadequate L-mode images. Patients with atrial fibrillation, severe mitral valve and aortic valve regurgitation or stenosis, and inadequate imaging qualities were excluded. The project was approved by the local research ethics committee of University of Tsukuba Hospital, and the patients gave their written informed consent.

Echocardiographic studies

Comprehensive echocardiographic examinations were performed with a Vivid 9 system (GE Vingmed Ultrasound, Horten, Norway) equipped with a multifrequency transducer and a workstation using a software package (EchoPac 6.3.6, GE Vingmed Ultrasound). The patients were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. The LV end-diastolic volume, end-systolic volume, IVSth, intraventricular septal thickness; PWth, posterior wall thickness; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; systolic diameter; ARB, angiotensin II receptor blocker; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; Enzyme; ACE inhibitor or ARB 0 19 (37) –

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=20)</th>
<th>Patients (n=51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>57 ± 10 (40–78)</td>
<td>62 ± 15 (20–84)</td>
<td>0.13</td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>32</td>
<td>0.86</td>
</tr>
<tr>
<td>IHD</td>
<td>0</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Secondly cardiomyopathy</td>
<td>0</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV</td>
<td>–</td>
<td>7/9/29/6</td>
<td>–</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>91 ± 9 (74–106)</td>
<td>163 ± 17 (134–198)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications</td>
<td>–</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>0</td>
<td>19</td>
<td>–</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>93 ± 17 (69–137)</td>
<td>200 ± 83 (70–423)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>69 ± 7 (57–83)</td>
<td>30 ± 5 (8–39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVSth (mm)</td>
<td>9.3 ± 1.0 (6.0–10.0)</td>
<td>8.6 ± 1.7 (5.0–12.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>PWTth (mm)</td>
<td>8.7 ± 0.7 (7.0–10.0)</td>
<td>8.7 ± 1.4 (5.0–11.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>33 ± 4 (27–42)</td>
<td>43 ± 10 (22–68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVdD (mm)</td>
<td>45 ± 3 (40–53)</td>
<td>64 ± 11 (42–84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVDds (mm)</td>
<td>28 ± 4 (19–37)</td>
<td>55 ± 12 (29–80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.5 ± 0.5 (0.8–3.4)</td>
<td>1.4 ± 0.9 (0.4–3.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>E/e'</td>
<td>7.9 ± 2.6 (3.9–13.0)</td>
<td>15.9 ± 7.6 (4.4–33.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPWMD (ms)</td>
<td>64 ± 23 (0–108)</td>
<td>166 ± 100 (48–382)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First peak-SPWMD (ms)</td>
<td>64 ± 23 (0–108)</td>
<td>321 ± 89 (49–417)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD (range). IHD, ischemic heart disease; NYHA, New York Heart Association; QRS, QRS time of electrocardiography; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; IVSth, intraventricular septal thickness; PWTth, posterior wall thickness; LAD, left atrial diameter; LVdD, left ventricular end-diastolic diameter; LVDds, left ventricular end-systolic diameter; E/A, ratio of peak velocities of early (E) to late (A) of transmitral flow; E/e', ratio of peak velocity of early transmitral flow (E) to early mitral annular motion (e'); SPWMD, septal to posterior wall motion delay.

* p < 0.01 vs. SPWMD.

** p < 0.05 vs. first peak-SPWMD.
Fig. 1. Differences of measurement methods between septal to posterior wall motion delay (SPWMD) and first peak-SPWMD. Standard SPWMD is measured at the shortest interval between maximum inward displacement of the interventricular septum (IVS) and posterior wall (case 1, left-side figures). In contrast, first peak-SPWMD is measured between the first peak of the IVS in early systolic phase and the maximum displacement of the posterior wall (case 1, right-side figures). If such an early IVS point is not present (case 2, left-side figures), anatomical M-mode is used to find an early IVS displacement (case 2, right-side figures).

The septal peak was defined as the point at which excursion was not less than 2.0 mm on the AMM images as well as the original M-mode images [14].

Definition of complete LBBB

Complete LBBB patients were selected by QRS duration greater than or equal to 120 ms. In addition, broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex [17].

Definition of dyssynchrony

A cut-off value of dyssynchrony was defined as \( a + 2 \sigma \) value of control subjects in each SPWMD, first peak-SPWMD, and Td. If presence of LV dyssynchrony was determined based on the Td by STE, the sensitivity, specificity, and accuracy to detect presence of dyssynchrony were evaluated in each assessment by SPWMD and first peak-SPWMD.

CRT procedure

CRT devices were implanted transvenously in 31 patients. After performing retrograde coronary venography, we selected a lateral or posterolateral vein as the target branch of the coronary sinus to stimulate the latest activation site identified by STI. If attempts to access these veins were impossible due to an unusual anatomy preventing access to the coronary sinus or which resulted in poor sensing, phrenic nerve stimulation, or pacing failure, the middle cardiac vein was considered as an alternative branch.

Definition of CRT responders

Serial echocardiographic examinations were performed before and 6 months after CRT. The patients were defined as responders with reduction of LVESV >15% at 6-month examinations after CRT as previously reported [5,6,18].

Reproducibility

Twenty patients who underwent CRT were selected at random for the assessments of the intra- and inter-observer variabilities of SPWMD, and first peak-SPWMD measurements. Intra- and inter-observer variabilities were assessed by linear regression analysis with the Bland–Altman method. In addition, we investigated intra- and inter-observer agreement of the diagnosis of dyssynchrony with Cohen’s \( \kappa \) coefficients. Inter-observer variability and agreement were independently assessed by 2 observers (F.S., S.N.).
Statistical analysis

Results are expressed as number (%) or mean ± SD. Comparisons between groups were performed with Student's t-test for continuous variables and the chi-square test for categorical variables. Correlation analysis was used to assess relationship between two parameters. The area under the receiver–operating characteristics (ROC) curve (AUC) was used to quantify the ability to predict the responders to CRT. In addition, ROC analysis was used to determine the best optimal cut-off value for prediction of CRT responders. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity. A p-value less than 0.05 was considered to indicate statistical significance. These analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). In addition, comparisons of AUC among dyssynchrony parameters were performed with Analyse-it (Analyse-it Software, Ltd., Leeds, UK).

Results

Comparisons of clinical characteristics and echocardiographic parameters between control subjects and patients with LBBB are summarized in Table 1. In patients with LBBB, first peak-SPWMD was higher than SPWMD.

IVS M-mode images

IVS M-mode images in patients with LBBB were classified into 10 patterns (Fig. 2). Flat IVS pattern (J pattern), which was not available for SPWMD measurements, was observed in 6 cases. In 9 cases with D pattern, 12 cases with E pattern, and 1 case with F pattern, who had the maximum displacement of IVS behind the early smaller displacement, measurement points for first peak-SPWMD were moved to the earliest point. Since no case with H pattern was present in original M-mode images, AMM was applied for 20 patients with G, I, and J patterns. An early IVS displacement was newly visualized in 11 patients; 4 cases with G pattern were changed into F pattern, in 4 cases with I pattern 2 cases was changed into B pattern, and change into D and H pattern in 1 case each, and in 4 cases with J pattern 3 cases were changed into B pattern and C pattern in 1 case. In the remaining 2 cases with J pattern, AMM also could not visualize an early systolic displacement point of IVS; IVS pattern was not changed in one case and another case was changed into I pattern, who were not available for first peak-SPWMD method. Finally, measurable rate of first peak-SPWMD was increased to 49 cases (96%).

Comparison with speckle tracking echocardiography

Agreement rate of the earliest segments between STE and first peak-SPWMD, and SPWMD were 98% and 27% (p < 0.001), and those of the latest segments were 90% and 16% (p < 0.001). Additionally, a strong correlation was observed between first peak-SPWMD and Td compared to SPWMD (first peak-SPWMD: $r^2 = 0.83$, p < 0.001; SPWMD: $r^2 = 0.28$, p < 0.001).

The detection rate of dyssynchrony

A cut-off value of Td in defining LV dyssynchrony was 90 ms. In contrast, both cut-off values of SPWMD and first peak-SPWMD were 110 ms. Based on the cut-off values, presence of LV dyssynchrony in patients with LBBB was determined in 29 cases (57%) by SPWMD, 46 cases (90%) by first peak-SPWMD, and 48 cases (94%) by Td.

Abilities to predict CRT responders

Comparisons of echocardiographic and dyssynchrony parameters between CRT responders and nonresponders are summarized in Table 2. Among 31 patients with CRT, 20 patients (65%) were
The ROC curves of SPWMD, first peak-SPWMD, and Td are shown in Fig. 3. Strong predicting ability of not only Td but also first peak-SPWMD was revealed (first peak-SPWMD cut-off value 345 ms: sensitivity 35%, specificity 100%, accuracy 58%; Td cut-off 198 ms: sensitivity 35%, specificity 100%, accuracy 58%). The AUC of Td and first peak-SPWMD was significantly higher than that of SPWMD (p = 0.021, respectively). The usefulness of first peak-SPWMD was confirmed by the data of 26 patients with early IVS displacement, where 4 patients with early IVS displacement and first peak-SPWMD were nonresponders. Among them, first peak-SPWMD could predict 4 patients to be nonresponders if a cut-off value 345 ms based on the ROC analysis was used. In contrast, among 12 patients who were predicted to be nonresponders by SPWMD, 8 patients were responders, in whom 7 patients were predicted to be responders by first peak-SPWMD. In addition, among 5 excluded patients in SPWMD measurements, CRT responses in 3 patients could be accurately predicted by first peak-SPWMD, and in only one patient first peak-SPWMD was not available. Note that 4 patients with early IVS displacement and first peak-SPWMD >345 ms were nonresponders. Among them, 3 patients were diagnosed as having cardiac sarcoidosis, and another patient had muscle dystrophy-related cardiomyopathy.

Reproducibility

Intra- and inter-observer variabilities with the Bland–Altman method are summarized in Table 3. There was no significant proportional bias in each parameter. The 95% confidence interval of first peak-SPWMD was narrower compared to those of SPWMD. The coefficients of first peak-SPWMD was higher than that of SPWMD.

Discussion

The major findings in this study were as follows: various IVS image patterns were observed in patients with LBBB, however,
SPWMD based on the original definition could not assess the presence of LV dyssynchrony. Second, a novel LV dyssynchrony definition using early septal displacement could increase the diagnostic ability of LV dyssynchrony in the same way as the STE method. In addition, AMM was a useful option to visualize an early septal displacement, which could not be identified on the standard M-mode images. Finally, the modified method of SPWMD measurements could improve the ability to predict CRT responses.

The septal motion in LBBB depends on electrical propagation and pressure interaction between both ventricles [19]. However, based on electrical propagation pattern in LBBB, septal contraction ought to be generated first, or at least generated faster than LV free wall contraction [20–22]. Then, we focused on the presence of early septal displacement in LBBB. The early displacement of IVS may be corresponding to so-called septal flash motion, which can be visualized in B mode images. In addition the septal flash has been reported as a key motion to predict CRT responses [23,14]. However, the detection rate by eyeball evaluation is low. In addition, as the present study confirmed, standard M-mode imaging has limitations to visualize septal flash, despite the higher temporal resolution. The main reason is the limited scan area of M-mode beam on the LV short-axis images [7,8]. In particular, inferoseptal area cannot be scanned by M-mode beam, although the present study confirmed early septal motion was present in the inferoseptal wall area as well as anteroseptal wall area using STE. The limitation of M-mode method was the main reason of low ability of SPWMD in assessing accurate LV dyssynchrony in patients with LBBB.

The novel finding in the present study was usefulness of AMM to visualize early displacements of IVS. In a half of the cases without early septal displacement, the septal displacement could be newly

**Fig. 4.** Receiver-operating characteristics curves for prediction of cardiac resynchronization therapy responders. SPWMD, septal to posterior wall motion delay; Td, time difference; AUC, area under the curve.

**Fig. 5.** Utility of first peak-septal to posterior wall motion delay (SPWMD) in predicting cardiac resynchronization therapy (CRT) responders. R, responder; NR, nonresponder. * means only one case who was excluded from first peak-SPWMD analysis. NR and number within open circle means nonresponders with secondary cardiomyopathy, who were predicted to be CRT responders by first peak-SPWMD.

<table>
<thead>
<tr>
<th>Table 3 Intra- and inter-observer variabilities and agreement.</th>
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<tbody>
<tr>
<td><strong>Intra-observer</strong></td>
</tr>
<tr>
<td>Bias (95%CI)</td>
</tr>
<tr>
<td>SPWMD</td>
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<tr>
<td>First peak-SPWMD</td>
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</table>

SPWMD, septal to posterior wall motion delay.
visualized if the scan area was spread at inferoseptal area using AMM. Since AMM images were reconstructed based on the B mode images, the deterioration of image quality and temporal resolution are a concern [24]. However, the high agreements with the earliest contraction segments by STE guaranteed the reliability of AMM in assessing early displacement of IVS.

Our novel concept for LV dyssynchrony assessments by M-mode imaging also contributes to improving the reproducibility of SPWMD measurements. In previous studies, the poor reproducibility was the major limitation to evaluate LV dyssynchrony using echocardiography [5]. The reason for our results is as follows; based on the dyssynchrony sequence in LBBB, we proposed the clear definition that the first displacement of IVS was the appropriate point independent of magnitude of septal displacement unlike original SPWMD definition because septal wall contraction was faster than free wall [20–22]. The better reproducibility provides feasibility in assessing LV dyssynchrony in the clinical setting.

The first-peak SPWMD improved ability to identify CRT responses compared to original SPWMD and showed higher accuracy in no way inferior to STE. In the guidelines, class I indication of CRT has been provided only in patients with LBBB [7]. However, a number of patients with CRT and LBBB may be nonresponders, but in contrast super responders were present. The present study showed the strong relation between presence of early septal displacement and CRT responses, as the presence of septal mass flash motion has been an important feature to predict CRT responses [23,14]. The results were reasonable since the dyssynchrony between septum and posterolateral wall is the just target of CRT [25,26]. In addition, as discussed above, our novel concept of SPWMD measurements with AMM and better reproducibility contributed to an improvement in the accuracy to predict CRT responses in patients with LBBB. However, 4 patients with secondary cardiomyopathy were nonresponders despite significant dyssynchrony between septum and posterolateral wall. Previous studies reported, various factors including ischemic etiology of LV dysfunction, presence of massive myocardial fibrosis at the pacing sites, inappropriate pacing lead positions, mitral regurgitation etc. affect the CRT effect [27–32]. Therefore, these factors should be taken into account to predict CRT responses in addition to LV dyssynchrony.

Limitations

IVS displacement may be small in patients with severe LV dysfunction. This may be a limitation of M-mode imaging, in particular, AMM with less spatial temporal resolutions.

The study population was small. Future multi-center studies consisting of a larger number of patients are required to confirm the clinical usefulness of our modified M-mode parameter. In addition, further studies will be necessary to evaluate our concept for cases with nonspecific conduction disturbance and right bundle branch block.

Conclusions

In patients with LBBB, time differences between early septal displacement and delayed displacement of posterolateral wall on M-mode images were the appropriate dyssynchrony parameter, and could improve predicting accuracy for CRT responses. In addition, although various motion patterns of IVS in M-mode imaging were observed, omni-directional reconstruction of M-mode images was useful to visualize an early septal displacement, and contributed to improve the clinical feasibility of the dyssynchrony assessments.

References


