Tissue Doppler Imaging Dyssynchrony Parameter Derived From the Myocardial Active Wall Motion Improves Prediction of Responders for Cardiac Resynchronization Therapy

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Background: The aim of this study was to propose modified tissue Doppler imaging (TDI) parameters derived from the first active wall motion and to assess them for the better prediction of cardiac resynchronization therapy (CRT) responders in comparison with original TDI parameters.

Methods and Results: In 61 patients with CRT, time from QRS onset to peak velocities by TDI (Ts), which were derived from active wall motion identified by longitudinal strain rate (LSR) value, were assessed. Time from QRS onset to the negative peak of LSR (TLRS) was also assessed. Modified standard deviation of Ts in 12 left ventricular (LV) segments (Ts-SD), that of TLRS (TLRS-SD), differences of Ts between septum and lateral wall (Ts-SL), and that of TLRS (TLRS-SL) were calculated. Original Ts-SD and Ts-SL were calculated by previously described methods. Responders were defined as patients with LV end-systolic volume reduction (>15%) at 6 months after CRT: 35 patients (57%) were identified as CRT responders. Area under the receiver-operating characteristics curve (AUC) of modified Ts-SD (0.87) was significantly higher than that of Ts-SD (0.65), Ts-SL (0.62), and TLRS-SL (0.69). AUC of modified Ts-SL was significantly higher than those of Ts-SD, and Ts-SL. AUC of TLRS-SD (0.82) also was significantly higher than that of Ts-SD.

Conclusions: Modified TDI dyssynchrony parameters derived from the first active wall motion improve the ability to predict responders to CRT. (*Circ J* 2012; **76**: 689–697)

Key Words: Cardiac resynchronization therapy; Dyssynchrony; Speckle tracking imaging; Tissue Doppler imaging

Numerous echocardiographic dyssynchrony parameters have been introduced for the selection of cardiac resynchronization therapy (CRT) responders.^{1–5} However, recent studies, including the Predictors of Response to CRT (PROSPECT) trial and Japan Cardiac Resynchronization Therapy Registry Trial (J-CRT), showed negative results for the utility of tissue Doppler imaging (TDI) in identifying CRT responders.^{6–9} Left ventricular (LV) dyssynchrony with TDI has been assessed by myocardial velocity-time curves, and almost all TDI-derived dyssynchrony parameters are defined by measurements restricted to the ejection period.^{1–5} However, myocardial velocity-time curves have multiple and various

peaks throughout the systolic phase, which confuses the selection of appropriate peaks. CRT improves cardiac performance through resynchronization of intraventricular active wall motion, not through passive wall motion.^{10,11} In contrast, the septal early active wall motion during the pre-ejection period in patients with left bundle branch block (LBBB) has been shown by a magnetic resonance imaging study to be active contraction.¹² Recently, we reported that a peak velocity derived from the first active septal wall motion was observed during the pre-ejection period in almost cases of LBBB.¹³ Therefore, the TDI parameters restricted to the ejection period regardless of active or passive wall motion, which were defined as the method of

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Table 1. Baseline Characteristics of the Study Subjects

Parameter	Controls (n=20)	Patients (n=61)	P value
Age (years)	59±7 (52–75)	61±15 (20–84)	–
Male	15 (75)	45 (74)	–
IHD	0	16 (26)	–
NYHA class III/IV	–	52/9 (85)/(15)	–
QRS duration (ms)	91±8 (80–100)	165±39 (120–291)	<0.001
LBBB/NSVD/RBBB/RVP	–	23/24/9/5 (38)/(39)/(15)/(8)	
Medications			
β-blockers	0	53 (86)	–
ACE inhibitor or ARB	0	53 (86)	–
Diuretics	0	57 (93)	–
Digoxin	0	6 (10)	–
LVEF (%)	71±10 (58–83)	27±9 (8–45)	<0.001
LVEDV (ml)	89±19 (64–137)	207±82 (87–447)	<0.001
LVESV (ml)	27±11 (12–57)	155±74 (45–386)	<0.001
Ts-SD (ms)	14±11 (4–46)	43±17 (10–81)	<0.001
Ts-SL (ms)	11±9 (0–28)	54±32 (2–126)	<0.001
Modified Ts-SD (ms)	14±6 (5–26)	62±23* (10–130)	<0.001
Modified Ts-SL (ms)	13±22 (2–33)	109±58* (4–247)	<0.001
TLSR-SD (ms)	15±5 (9–23)	78±25* (37–141)	<0.001
TLSR-SL (ms)	18±17 (3–45)	102±74* (0–328)	<0.001

Values are n (%) or mean±SD (range). *P<0.001 vs. Ts-SD, #P<0.001 vs. Ts-SL.

IHD, Ischemic heart disease; NYHA, New York Heart Association; LBBB, left bundle branch block; NSVD, nonspecific ventricular conduction delay; RBBB, right bundle branch block; RVP, right ventricular pacing; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; Ts, time from QRS onset to peak velocity during ejection period with tissue Doppler imaging; Ts-SD, standard deviation of Ts; Ts-SL, difference in Ts between septum and lateral wall; modified-Ts-SD, standard deviation of modified Ts; modified-Ts-SL, difference in modified Ts between septum and lateral wall; TLSR-SD, standard deviation of the time peak early systolic strain rate from QRS onset; TLSR-SL, time difference of peak early systolic peak strain rate from QRS on set between septum and lateral wall.

measuring in both PROSPECT⁶ and J-CRT,⁷ may not be related to intraventricular dyssynchrony of active wall motion. The methodological issues of vagueness may be associated with the poor reproducibility of TDI measurements and ability to predict LV reverse remodeling after CRT.⁶

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We hypothesized that TDI dyssynchrony parameters derived from the first active wall motion may contribute to improved performance in predicting CRT responders and performed the present comparative study to assess the ability of the modified and original TDI parameters to predict CRT responders.

Methods

We enrolled 61 consecutive patients (45 men, 16 women; mean age, 61±15 years) who underwent CRT, and 20 normal control subjects (15 men, 5 women; mean age, 59±7 years) to identify the normal range of each dyssynchrony parameters. The baseline characteristics of these patients are summarized in **Table 1**. The selection criteria for CRT were drug-refractory symptomatic heart failure despite optimal pharmacological therapy, New York Heart Association (NYHA) class III or IV heart failure, LV ejection fraction (EF) ≤35%, and QRS duration ≥120 ms in the form of LBBB, intraventricular conduction delay, right bundle branch block and right ventricular pacing.^{14–16} Patients with atrial fibrillation, or complete atrioventricular block were excluded. The intrinsic rhythm in all patients was sinus rhythm. The project was approved by the

Local Research Ethics Committee of Tsukuba University Hospital, and the patients gave their written informed consent.

Echocardiography

Echocardiographic examinations were performed with a Vivid 7 system (GE Vingmed Ultrasound, Horten, Norway) equipped with a multifrequency transducer. The LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and EF were measured using a modified Simpson's equation and the apical 4- and 2-chamber views.¹⁷ Pulsed Doppler transmitral flow and aortic ejection flow were obtained on an apical long-axis view. Timing of the onset and end of each pulsed Doppler flow image was determined on a workstation using a software package (EchoPac 6.3.6, GE Vingmed Ultrasound), and the timing of the opening and closure of the aortic valve and mitral valve was automatically displayed on an analysis image of myocardial velocity-time curves.

Color-Coded TDI

The color-coded TDI was obtained in the apical 4-chamber, 2-chamber, and long-axis views. The image sector was set as narrow as possible, which resulted in a frame rate greater than 100 frames/s, and a cine-loop of 3 consecutive beats were stored for later offline analysis on a workstation. Myocardial Doppler velocity curves were reconstituted offline. The region of interest (ROI) was adjusted to a 5×5-mm area with a circular shape that would not disappear with myocardium thickening. The ROI was placed in the 6 basal and 6 mid-LV segments, including the anteroseptal, inferoseptal, inferior, posterior, lateral, anterior wall segments, to be as parallel as possible to the cen-

Figure 1. Myocardial velocity-time curves (**Upper**) and longitudinal strain rate-time curves (**Middle** and **Lower**) with speckle tracking imaging for measurement of peak velocity (Ts), modified Ts and peak longitudinal strain rate (TLRSR). Basal and mid-septal wall motions are shown as yellow and blue; basal and mid-lateral motions are shown as red and green, respectively. The peak positive velocity component in which the corresponding longitudinal strain rate value is negative as active wall motion (downward solid and dotted arrows) and the component with positive strain rate as passive wall motion (upward solid and dotted arrows). Note the differences in the time from QRS onset to Ts, shown as solid line with double arrowheads, and the modified Ts of the septal wall, shown as dotted line with double arrowheads. Time from QRS onset to the negative TLRSR (downward solid and dotted arrows) is shown as dotted line with double arrowheads (**Lower**). MVC, mitral valve closing; AVO, aortic valve opening; AVC, aortic valve closing; ECG, electrocardiogram.

tral ultrasound beam.¹⁸

Speckle Tracking Imaging (STI)

To identify whether color-coded TDI-derived myocardial velocities were derived from active or passive wall motion, corresponding strain rate values were assessed with STI, because strain rates based on STI are more accurate than those based on TDI measurements.¹⁹ STI was performed as soon as possible after TDI scanning. All images were recorded with a frame rate of at least 30 frames/s, and cine loops of 3 consecutive beats were stored for offline analysis on the workstation.²⁰ Longitudinal STI was assessed on the workstation as follows: from an end-systolic frame, a ROI was traced on the endocardial cavity interface by a point-and-click approach. The ROI was automatically selected to approximate the myocardium between the endocardium and epicardium. Further adjustment of the ROI was performed to ensure that all of the myocardial regions were included.²¹ Next, the software captured the myocardium, automatically tracked its motion and thickening on subsequent frames. Finally, the myocardium in each apical view was divided into 6 segments.²² Longitudinal strain rate (LSR) values of the 6 basal and 6 mid-LV segments, including antero-septal, inferoseptal, inferior, posterior, lateral, anterior wall segments, were calculated, as well as the color-coded TDI.

Definition of Active and Passive Wall Motions

We carefully compared the myocardial velocity-time curve from TDI with the LSR-time curve from STI because the cardiac cycle used to assess TDI was different from that used to assess STI. We defined the peak positive velocity component in which the corresponding LSR value was negative as “active wall motion” and the component with positive strain rate as “passive wall motion” during the pre-ejection and ejection periods (Figure 1).²³

Assessment of Intraventricular Dyssynchrony

Intraventricular dyssynchrony was assessed by 3 methods. First, the time to the maximum peak myocardial velocity from QRS onset during the ejection period (Ts) was assessed as in previous studies.^{1–4} Second, modified Ts was assessed as the time to a peak on the velocity curve derived from the first active wall motion not restricted to the ejection period, which was identified by the STI-derived LSR value regardless of the magnitude of velocity (Figure 1). Finally, the time from QRS onset to the negative peak of LSR (TLRS) was measured in each segment.

We calculated the standard deviation of Ts in 12 LV segments (Ts-SD) according to the previous method.^{1–4} The standard deviation of the modified Ts in 12 LV segments (modified Ts-SD) and that of TLRS in 12 segments (TLRS-SD) were also calculated in the same manner. In the case of optimal images not being obtained in all segments, the standard deviation was calculated with data from the remaining segments. In addition, the differences in Ts between the basal septal and lateral wall (Ts-SL), that of modified Ts (modified Ts-SL), and that of TLRS (TLRS-SL) were calculated.⁵ Original Ts-SD >34.4 ms and original Ts-SL >65 ms were used as the cutoff values in predicting CRT responders based on the previous studies.^{4,5}

CRT Procedure

CRT devices were implanted transvenously in all 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 because of unusual anatomy preventing access to the coronary sinus or 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. Patients were defined as responders if there was a reduction of LVESV (Δ LVESV) >15% at the 6-month examination after CRT as previously described.¹⁶

Reproducibility

We randomly selected 30 patients for the assessments of the intra- and interobserver variabilities of the Ts-SD, Ts-SL, modified Ts-SD, modified Ts-SL, TLRS-SD, and TLRS-SL measurements. Intra- and interobserver variabilities were assessed by linear regression analysis with the Bland-Altman method. In addition, we investigated intra- and interobserver agreement of the diagnosis of dyssynchrony with Cohen's κ coefficients. Interobserver variabilities and agreement was independently assessed by 2 observers (F.S., S.Y.).

Statistical Analysis

Results are expressed as number (%) or the mean $\pm$ 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 2 parameters. Receiver-operating characteristics (ROC) analysis was used to determine the optimal cutoff value of the modified Ts-SD, modified Ts-SL, TLRS-SD, and TLRS-SL for prediction of CRT responders. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity. The area under the ROC curve (AUC) was used to quantify the ability to predict responders to CRT. 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, UK).

Results

CRT devices were implanted successfully in all patients, and the LV lead was placed in the lateral branch or posterolateral branch in all patients. Appropriate images for analysis could be obtained in almost all segments; however, TDI images in 7 mid-anterior, 3 basal-anterior, and 1 mid-lateral wall segments were inappropriate for assessing tissue velocities. In addition, inappropriate B-mode images for LSR analysis were present in 9 mid-anterior, 3 basal-anterior, 2 mid-lateral, 1 mid-inferior, and 1 mid-posterior wall segments. Finally, Ts-SD was calculated from 11 segments in 4 patients, 10 segments in 2 patients, and 9 segments in 1 patient. Modified Ts-SD and TLRS-SD were calculated from 11 segments in 7 patients, 10 segments in 4 patients, and 9 segments in 1 patient. Ts-SL, modified Ts-SL, and TLRS-SL could be calculated in all patients.

Analysis of Time-Velocity Curve

The total number of peak velocities in LV basal segments during systole was 152 (2.5/patient) in the antero-septal, 147 (2.4/patient) in the inferoseptal, 139 (2.3/patient) in the inferior, 140 (2.3/patient) in the posterior, 134 (2.2/patient) in the lateral, and 129 (2.2/patient) in the anterior wall, respectively. The

Figure 2. Origin of peak velocities during pre-ejection (Upper) and ejection (Lower) periods. AS, anteroseptal wall; IS, inferoseptal wall; I, inferior wall; P, posterior wall; L, lateral wall; A, anterior wall.

Figure 3. Comparison of the differences between the time from QRS onset to peak velocity (Ts), modified Ts, and peak longitudinal strain rate (TLSR) in each segment. AS, anteroseptal wall; IS, inferoseptal wall; I, inferior wall; P, posterior wall; L, lateral wall; A, anterior wall. * $P < 0.01$ vs. modified Ts and TLSR in the same segment; # $P < 0.01$ vs. modified Ts in AS, IS, and I; † $P < 0.05$ vs. TLSR in AS, IS, and I.

number of peak velocities in the anteroseptal wall was significantly more than that in the anterior wall ($P = 0.02$) or the lateral wall ($P = 0.01$).

The majority of the peaks derived from the first active wall motion in the anteroseptal, inferoseptal and inferior wall were

observed during the pre-ejection period (Figure 2). In contrast, the majority of those in posterior, lateral, and anterior wall were observed during the ejection period. During the ejection period, the prevalence of peak velocities derived from the second active wall motion was the most frequent in the antero-

Table 2. Comparison of Dyssynchrony Parameters Between Responders and Nonresponders at Baseline and 6-Months After Cardiac Resynchronization Therapy

	Responders (n=35)		Nonresponders (n=26)	
	Baseline	6 months	Baseline	6 months
Age (years)	64±14 [§]	—	57±15	—
Male	25 (71)	—	20 (77)	—
NYHA class III	32 (91)	—	20 (77)	—
IHD	8 (13)	—	8 (13)	—
QRS duration (ms)	168±40 [¶]	160±29	162±39	173±33
LBBB	15 (43)	—	8 (31)	—
LVEDV (ml)	202±76* (87–437)	147±62	214±90 (88–447)	227±92*
LVESV (ml)	152±69* (45–379)	92±49	159±81 (59–386)	174±78*
LVEF (%)	26±6 (8–41)	39±12 ^{†,‡}	28±7 (14–34)	25±7
Wall thickness (mm)	8.6±2.0 (4–13)	9.0±2.3	8.2±1.8 (5–13)	8.7±1.2
Ts-SD (ms)	47±16 ^{¶,§} (15–81)	35±16 (0–71)	37±16 (0–64)	43±12 [¶] (18–62)
Ts-SL (ms)	60±33 [¶] (9–125)	49±30 (15–153)	46±29 (2–108)	53±32 (3–112)
Modified Ts-SD (ms)	73±19* [¶] (28–130)	37±15 (22–71)	47±18 (10–73)	40±14 (18–62)
Modified Ts-SL (ms)	137±50* [¶] (26–247)	50±36 (12–247)	71±47 (4–182)	52±26 (12–94)
TLSR-SD (ms)	89±24* [¶] (52–142)	51±16 (24–86)	64±17 (37–113)	60±18 [¶] (18–86)
TLSR-SL (ms)	130±81* [¶] (0–328)	39±32 (0–131)	64±40 (0–144)	58±31 [¶] (0–128)

Values are mean ± SD (range). *P<0.001, †P<0.05 vs. responders at 6 months; ‡P<0.001, §P<0.05 vs. nonresponders at baseline.

Abbreviations see in Table 1.

Figure 4. Correlations between % change in left ventricular end-systolic volume (LVEV) at baseline and 6 months after cardiac resynchronization therapy (CRT) and dyssynchrony parameters. Light yellow zones show the accurate evaluation of CRT responders or nonresponders. Ts, time from QRS onset to peak velocity; Ts-SD, standard deviation of Ts in 12 LV segments; Ts-SL, the differences of Ts between septum and lateral wall; TLSR, time from QRS onset to the negative peak longitudinal strain rate; TLSR-SD, standard deviation of TLSR in 12 LV segments; TLSR-SL, the differences of TLSR between septum and lateral wall.

Table 3. Results of Receiver-Operating Characteristics Analysis

	Cutoff value (ms)	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
Ts-SD	34	50	79	67	0.65
Ts-SL	65	69	44	55	0.62
Modified Ts-SD	60	80	82	81	0.87 ^{*,#}
Modified Ts-SL	100	73	80	77	0.83 ^{*,#}
TLSR-SD	75	82	78	80	0.82 [*]
TLSR-SL	110	86	54	68	0.69

*P<0.05 vs. Ts-SD, *P<0.05 vs. Ts-SL, †P<0.05 vs. TLSR-SL

AUC, area under the receiver-operating characteristics curve. Other abbreviations see in Table 1.

Table 4. Intra- and Interobserver Variability and Agreement

	Bland-Altman analysis							
	Intra-observer				Interobserver			
	Bias (95%CI)	R	P value	κ coefficient	Bias (95%CI)	R	P value	κ coefficient
Ts-SD	−2.8 (−13.6 to 8.0)	–	NS	0.77	−0.2 (−18.4 to 18.0)	–	NS	0.67
Ts-SL	−1.9 (−30.3 to 26.5)	–	NS	0.79	3.2 (−26.4 to 32.8)	–	NS	0.69
modified-Ts-SD	−0.5 (−7.1 to 6.1)	–	NS	0.93	2.1 (−6.1 to 10.3)	–	NS	0.83
modified-Ts-SL	−0.5 (−14.1 to 13.1)	–	NS	0.94	0.2 (−15.0 to 15.4)	–	NS	0.85
TLSR-SD	−0.5 (−14.8 to 13.8)	–	NS	0.73	2.4 (−10.4 to 15.2)	–	NS	0.72
TLSR-SL	−1.1 (−19.9 to 17.7)	–	NS	0.78	1.6 (−17.6 to 20.8)	–	NS	0.78

R, slope of the regression line; CI, confidence interval. Other abbreviations see in Table 1.

septal and inferoseptal wall.

Comparisons and Correlations of Dyssynchrony Parameters

As summarized in **Table 1**, the dyssynchrony parameters in the control subjects were significantly smaller than those in the heart failure patients with ventricular delay. In the segments with the first active motion during the pre-ejection period, the modified Ts differed from the original Ts as shown in **Figure 1**.

Comparisons of Ts, modified Ts, and TLSR in each basal segment are shown in **Figure 3**. In the control subjects, the parameters did not differ among segments. In contrast, modified Ts and TLSR were significantly shorter than Ts in each segment, in particular, the antero-septal, inferoseptal and inferior wall, in the heart failure patients with ventricular delay (**Figure 3**). In addition, the modified Ts and TLSR in the antero-septal, inferoseptal and inferior wall were shorter than those in the posterior, lateral, and anterior wall. In contrast, significant differences were not observed in the Ts among 6 segments.

The modified Ts-SD and modified Ts-SL were significantly larger than the original Ts-SD and Ts-SL in heart failure patients with ventricular delay (**Table 1**). In addition, TLSR-SD and TLSR-SL were significantly larger than the original Ts-SD and Ts-SL in heart failure patients with ventricular delay. A strong correlation between the modified Ts-SD and modified Ts-SL was observed ($R=0.73$, $P<0.001$), but correlations between other dyssynchrony parameters were not significant.

Chronic Response to CRT

Comparisons of the clinical characteristics and echocardiographic parameters are summarized in **Table 2**; 35 patients (57%) were defined as CRT responders. Baseline NYHA class, prevalence of ischemic etiology, QRS durations, type of conduction disturbance, LVEF, LVEDV, and LVESV did not differ between CRT responders and nonresponders. Original Ts-

SD, modified Ts-SD, modified Ts-SL, TLSR-SD, and TLSR-SL at baseline in CRT responders were significantly larger than in nonresponders.

There were no significant correlations between original Ts-SD and Ts-SL at baseline and % change in LVESV ($-15.9\pm 33.3\%$); however, significant negative correlations were observed between other parameters at baseline and % change of LVESV (**Figure 4**).

The prevalence of first active wall motion in the antero-septal and inferoseptal wall during the pre-ejection period was more frequent in CRT responders than in nonresponders (anteroseptal wall, 31 patients (89%) vs. 16 patients (62%), $P=0.004$; inferoseptal wall, 32 patients (91%) vs. 17 patients (65%), $P=0.008$).

The results from ROC analysis are summarized in **Table 3**. AUC of the modified Ts-SD was significantly higher than that of Ts-SD, Ts-SL, and TLSR-SL. AUC of the modified Ts-SL was significantly higher than that of Ts-SD, and Ts-SL. AUC of TLSR-SD also was significantly higher than that of Ts-SD, but not modified Ts-SD. As compared with the AUC of modified Ts-SL, that of TLSR-SL was lower but not statistically significant.

Reproducibility

Intra- and interobserver variabilities assessed with the Bland-Altman method are summarized in **Table 4**. There was no significant proportional bias in any parameter. The 95% confidence intervals of the modified Ts-SD and modified Ts-SL were narrower than those of other parameters. Intra- and interobserver agreements of the diagnosis of dyssynchrony with Cohen's κ coefficients are summarized in **Table 4**. The κ coefficients of the modified Ts-SD and modified Ts-SL were higher than those in other parameters.

Discussion

The major findings of the present study are as follows: (1) in most cases the first active wall motion in the septal wall where the initial contractions occurred was observed during the pre-ejection phase; and (2) the modified dyssynchrony parameters, which were measured using peak velocities identified as the first active wall motion, could predict CRT responders more accurately than the original TDI dyssynchrony parameters. However, our study did not evaluate the clinical response to CRT. Accordingly, the ability of our modified parameter in predicting the clinical effects of CRT are unknown.

TDI Parameters and Dyssynchrony of Active Wall Motion

The superiority of our modified parameters in identifying CRT responders clearly demonstrated that LV dyssynchrony analysis should be focused on the first active wall motion. CRT can resynchronize the initiation of LV contraction through electrical resynchronization of the septum and free wall. Accordingly, LV dyssynchrony assessment should be based on the intraventricular propagation of active wall motion, between the septum and the latest activated free wall that CRT can modify. Additionally, restricting the assessment phase to the ejection period is a critical factor that caused the difference in CRT responder detection between our modified parameters and the previously reported parameters, because the first peak velocity derived from initiation of active septal wall motion was observed during the pre-ejection period in more CRT responders. Miyazaki et al also emphasized the importance of the pre-ejection period in their TDI study to predict CRT responders.⁸ In early studies the weak pre-ejection motion was reported as a passive motion caused by interventricular pressure difference,^{24,25} but recent tagged magnetic resonance imaging studies showed this early active motion to be active contraction.¹² Therefore, septal flash motion is caused by multiple factors, including active contraction.²⁶ In the ejection phase, the almost peak velocities of the septal wall are derived from secondary active or passive wall motion. The present results strongly suggest that the original TDI parameters may not be related to intraventricular dyssynchrony of the first active wall motion. Accordingly our modified parameters may improve the poor ability of echocardiographic parameters to predict LV reverse remodeling after CRT, as in the results of PROSPECT⁶ and J-CRT.⁷

Loss of efficacy of LV contraction has recently received attention in addition to LV dyssynchrony, because STI provides the magnitude of LV contraction. Iwano et al reported a novel index of LV contractility loss using STI to improve the ability to predict the effects of CRT compared with dyssynchrony parameters.²⁷ Novel findings with STI of the pathophysiological relation between LV contraction abnormalities and conduction disturbances may contribute to better understanding of the response mechanism for CRT and prediction of CRT's effects.²⁸

Comparisons and Relationship Between Parameters

A strong correlation was observed between the modified Ts-SD and modified Ts-SL. The results may be related to the uniform selection criteria of the surrogate peak velocity in our methods. Our modified parameters at baseline significantly correlated with % change in LVESV, but these results were not observed with the original TDI parameters. These facts suggest that intraventricular dyssynchrony of the initiation of active wall motion is one of the main determinants of reverse remodeling after CRT.

However, the accuracy of the modified parameters was still approximately 80%, which is not satisfactory for a clinical biomarker. Response to CRT depends on factors other than LV dyssynchrony, including LV scar burden and lead position. However, the relation of CRT response to these other factors was not assessed in the present study. Therefore, the results of this study suggest the importance of a comprehensive assessment to predict CRT effects.

Comparison Between Modified TDI Parameters and Single Use of LSR

Based on the AUC of TLSR-SD, single use TLSR-SD was superior to Ts-SD, and equivalent to modified Ts-SD. In contrast, modified Ts-SL might be superior to TLSR-SL. The differences were caused by the differences in the timing of the first peak velocity and the negative peak strain rate. Namely, a modified Ts point is chosen at the first peak of the tissue velocity curve, at which the strain rate value was negative, but not corresponding to the negative peak of time-strain rate curve.

Reproducibility

The present study showed clinically acceptable reproducibility of the measurement of our parameters. The reproducibility of Doppler echocardiographic parameter measurements has been a critical issue in identifying CRT responders.⁶ In the present study, surrogate peak velocities were selected to be combined with strain rate values to determine active or passive wall motion, independent of the magnitude of the velocities. Because velocity values by TDI may be easily changed by the position and size of the ROI, reproducibility in selecting surrogate velocities may be poor.

In addition, the reproducibility of the TLSR parameters was poorer than that of the modified TDI parameters. Therefore, we believe surrogate peak velocities combined with strain rate values may contribute to improving the reproducibility of TDI parameter measurements.

Study Limitations

The study population was relatively small and we did not evaluate the clinical response to CRT. Reverse remodeling after CRT has been used as the echocardiographic surrogate parameter, but the effect of reverse remodeling on symptomatic improvement and prognosis is controversial.^{7,29,30} Future multicenter studies with a larger number of patients are required to confirm the clinical usefulness of our modified TDI parameters. The majority of patients had nonischemic heart disease, which may have affected the results as compared with previous studies.

Because STI was used for strain rate analysis, the cardiac cycle used in assessing TDI was different from that used in assessing STI. Despite careful comparison between the myocardial velocity-time curve of TDI and the LSR-time curve of STI, the different cardiac cycles might have affected our results. In addition, the lower frame rate of STI is a limitation to determining accurate strain rate values. Thus, STI might influence the distinguishing of active and passive wall motion.

Conclusions

Modified TDI dyssynchrony parameters using peak velocities derived from the first active wall motion can more accurately predict CRT responders defined as LV reverse remodeling compared with the original TDI parameters.

References

- Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; **105**: 438–445.
- Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BØ, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002; **40**: 723–730.
- Gorcsan J 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol* 2004; **93**: 1178–1181.
- Yu CM, Zhang Q, Fung JW, Chan HC, Chan YS, Yip GW, et al. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol* 2005; **45**: 677–684.
- Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004; **44**: 1834–1840.
- Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008; **117**: 2608–2616.
- Seo Y, Ito H, Nakatani S, Takami M, Naito S, Shiga T, et al. The role of echocardiography in predicting responders to cardiac resynchronization therapy: Results from the Japan Cardiac Resynchronization Therapy Registry Trial (J-CRT). *Circ J* 2011; **75**: 1156–1163.
- Miyazaki C, Lin G, Powell BD, Espinosa RE, Bruce CJ, Miller FA Jr, et al. Strain dyssynchrony index correlates with improvement in left ventricular volume after cardiac resynchronization therapy better than tissue velocity dyssynchrony indexes. *Circ Cardiovasc Imaging* 2008; **1**: 14–22.
- Miyazaki C, Powell BD, Bruce CJ, Espinosa RE, Redfield MM, Miller FA, et al. Comparison of echocardiographic dyssynchrony assessment by tissue velocity and strain imaging in subjects with or without systolic dysfunction and with or without left bundle-branch block. *Circulation* 2008; **117**: 2617–2625.
- Mele D, Pasanisi G, Capasso F, De Simone A, Morales MA, Poggio D, et al. Left intraventricular myocardial deformation dyssynchrony identifies responders to cardiac resynchronization therapy in patients with heart failure. *Eur Heart J* 2006; **27**: 1070–1078.
- Prinzen FW, Auricchio A. Echocardiography is not useful before cardiac resynchronization therapy if QRS duration is available. *Circ Cardiovasc Imaging* 2008; **1**: 70–78.
- Zwanenburg JJ, Götte MJ, Marcus JT, Kuijter JP, Knaapen P, Heethaar RM, et al. Propagation of onset and peak time of myocardial shortening in time of myocardial shortening in ischemic versus nonischemic cardiomyopathy: Assessment by magnetic resonance imaging myocardial tagging. *J Am Coll Cardiol* 2005; **46**: 2215–2222.
- Seo Y, Ishizu T, Sakamaki F, Yamamoto M, Machino T, Watanabe S, et al. Analysis of the origin of cardiac wall motion that constitutes myocardial velocity-time curves in patients with left bundle branch block. *J Am Soc Echocardiogr* 2009; **22**: 331–336.
- Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure: Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *N Engl J Med* 2002; **346**: 1845–1853.
- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION). *N Engl J Med* 2004; **350**: 2140–2150.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure: Cardiac Resynchronization-Heart Failure (CARE-HF). *N Engl J Med* 2005; **352**: 1539–1549.
- Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
- Pai RG, Gill KS. Amplitudes, durations, and timings of apically directed left ventricular myocardial velocities. I: Their normal pattern and coupling to ventricular filling and ejection. *J Am Soc Echocardiogr* 1998; **11**: 105–111.
- Ingul CB, Torp H, Aase SA, Berg S, Stoylen A, Slordahl SA. Automated analysis of strain rate and strain: Feasibility and clinical implications. *J Am Soc Echocardiogr* 2005; **18**: 411–418.
- Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006; **113**: 960–968.
- Kusunose K, Yamada H, Nishio S, Mizuguchi Y, Choraku M, Maeda Y, et al. Validation of longitudinal peak systolic strain by speckle tracking echocardiography with visual assessment and myocardial perfusion SPECT in patients with regional asynergy. *Circ J* 2010; **75**: 141–147.
- Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography: From technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007; **20**: 234–243.
- Mele D, Pasanisi G, Heimdal A, Cittanti C, Guardigli G, Levine RA, et al. Improved recognition of dysfunctioning myocardial segments by longitudinal strain rate versus velocity in patients with myocardial infarction. *J Am Soc Echocardiogr* 2004; **17**: 313–321.
- Little WC, Reeves RC, Arciniegas J, Katholi RE, Rogers EW. Mechanism of abnormal interventricular septal motion during delayed left ventricular activation. *Circulation* 1982; **65**: 1486–1491.
- Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block: The effect of interventricular asynchrony. *Circulation* 1989; **79**: 845–853.
- Parsai C, Bijns B, Sutherland GR, Baltabaeva A, Claus P, Marciniak M, et al. Toward understanding response to cardiac resynchronization therapy: Left ventricular dyssynchrony is only one of multiple mechanisms. *Eur Heart J* 2009; **30**: 940–949.
- Iwano H, Yamada S, Watanabe M, Mitsuyama H, Nishino H, Yokoyama S, et al. Novel strain rate index of contractility loss caused by mechanical dyssynchrony. *Circ J* 2011; **75**: 2167–2175.
- Klimusina J, De Boeck BW, Leenders GE, Faletta FF, Prinzen F, Averaimo M, et al. Redistribution of left ventricular strain by cardiac resynchronization therapy in heart failure patients. *Eur J Heart Fail* 2011; **13**: 186–194.
- Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009; **53**: 483–490.
- Cleland J, Freemantle N, Ghio S, Fruehwald F, Shankar A, Marijanowski M, et al. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response: a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. *J Am Coll Cardiol* 2008; **52**: 438–445.