Evaluation of left ventricular dyssynchrony using combined pulsed wave and tissue Doppler imaging

Xuedong Shen[1], Wilbert S. Aronow[2], Kishlay Anand[1], Chandra K. Nair[1], Mark J. Holmberg[1], Tom Hee[1], Stephanie Maciejewski[1], Dennis J. Esterbrooks[1]

[1]Cardiac Center of Creighton, University School of Medicine, Omaha, USA
[2]Cardiology Division, New York Medical College, Valhalla, USA

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Corresponding author:
Wilbert S. Aronow, MD, FACC, FAHA
Cardiology Division
New York Medical College
Macy Pavilion, Room 138
Valhalla, NY 10595, USA
Phone: 914 493 5311
Fax: 914 235 6274
E-mail: wsaronow@aol.com

Abstract

Introduction: The combination of pulsed wave (PW) and tissue Doppler imaging (TDI) has been proposed as a new method to assess left ventricular (LV) mechanical dyssynchrony (LVMD), but results have not been validated. We investigated the correlation of a combination of PW and TDI with a positive response to cardiac resynchronization therapy (CRT).

Material and methods: We studied 108 consecutive patients who received CRT. Patients with atrial fibrillation were excluded. The time difference (T_{PW-TDI}) between onset of QRS to the end of LV ejection by PW (T_{PW}) and onset of QRS to the end of the systolic wave in LV basal segments with greatest delay by TDI (T_{TDI}) was measured before CRT and during short-term and long-term follow-up.

Results: The T_{PW-TDI} interval before CRT was 74 ±48 ms. Intra-observer variabilities for T_{PW} and T_{TDI} were 1.5 ±0.24% and 1 ±0.17%. Inter-observer variabilities for T_{PW} and T_{TDI} were 1 ±0.36% and 1 ±0.64%, respectively. T_{PW-TDI} > 50 ms was defined as the cutoff value for diagnosis of LVMD by receiver operating curve (ROC) analysis. During follow-up of 15 ±11 months, the sensitivity and specificity of TP_{PW-TDI} to predict a positive response to CRT were 98% and 82%, respectively. The area under the ROC curve was 0.92. There was a significant agreement between LVMD determined by T_{PW-TDI} and the positive response to CRT (κ = 0.80).

Conclusions: Left vertricular dyssynchrony detected by the method combining PW and TDI demonstrated a high reproducibility, sensitivity, specificity and agreement with a positive response to CRT.

Key words: cardiac resynchronization therapy, left ventricular mechanical dyssynchrony.

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with New York Heart Association (NYHA) class III or IV heart failure, reduced left ventricular ejection fraction (LVEF), and widened QRS duration by electrocardiogram (ECG) [1, 2]. Left ventricular mechanical dyssynchrony (LVMD) has emerged as a therapeutic target in heart failure patients with NYHA class III or IV and substantial left ventricular dysfunction [3-5]. Tissue Doppler imaging (TDI) is one of numerous methods to assess LVMD. Currently, there is no agreement as to which methods are superior to others to assess LVMD [6]. Tissue Doppler imaging assesses the absolute and relative left ventricular wall velocity and thereby quantifies the time

delay between opposing segments of the left ventricle, but results are inconsistent [7]. Left ventricular mechanical dyssynchrony determined by a method using combined pulsed wave (PW) and TDI is a novel method and has been recently reported [8, 9].

The aim of the current study was to evaluate the reproducibility, sensitivity, specificity, and positive and negative predictive values of this combined method in predicting a positive response to CRT.

Material and methods

We retrospectively evaluated 108 consecutive patients who received CRT (78 men and 30 women, mean age 70 ±10 years) at The Cardiac Center of Creighton University School of Medicine. The criteria for bi-ventricular pacemaker implantation were the American College of Cardiology/American Heart Association 2005 guidelines [10]: 1) left ventricular ejection fraction (LVEF) $\leq$ 35%, 2) NYHA class III-IV, 3) QRS duration (QRSD) $\geq$ 120 ms, and 4) optimal pharmaceutical regimen established prior to CRT. QRSD in all patients was measured from the surface ECGs using the widest QRS complex in leads II, V1 and V6 on the surface ECG. Patients with atrial fibrillation were excluded. There were 69 patients (64%) with ischemic cardiomyopathy (33 patients with previous myocardial infarction and 36 patients with angiographic severe coronary artery disease without myocardial infarction) and 39 patients with non-ischemic cardiomyopathy. All 108 patients underwent coronary angiography before CRT.

After informed written consent was obtained, all 108 patients underwent implantation of a bi-ventricular pacer in the cardiac electrophysiology laboratory. The left ventricular lead was positioned into the lateral left ventricular vein. The right ventricular defibrillation lead was actively fixated into the RV apex. The atrial pacing lead was fixated into the high lateral right atrium. All patients had successful implantation of the left ventricular lead in the lateral left ventricular vein.

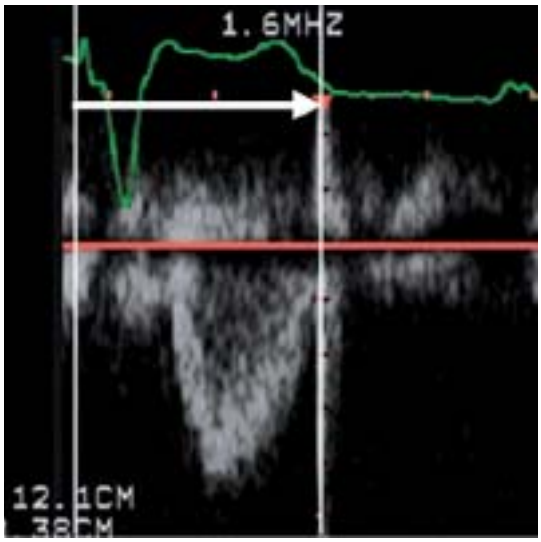

Figure 1. The time from onset of the QRS wave to the end of left ventricular ejection assessed by pulsed wave Doppler

Conventional transthoracic echocardiography was performed with a Philips Sonos 7500 echocardiographic system and s3 transducer. Baseline echocardiographic data before CRT and follow-up echocardiography after CRT were reviewed for all patients. End-systolic and end-diastolic left ventricular volumes were measured in the apical view from the videotape or Philips EnConcert digital system according to the standard recommended by the American Society of Echocardiography [11]. The LVEF was calculated from the apical four-chamber view of the left ventricle using Simpson's rule. A positive response to CRT was defined as the left ventricular end-systolic volume decreasing $\geq$ 15% after CRT [12].

Left ventricular ejection was evaluated by PW at the level of the LV outflow tract from the apical five-chamber view. Left ventricular wall motion was assessed by TDI from the four-chamber view. The following two time intervals were measured for evaluation of LVMD: measurement 1 – the onset of Q wave to the end of left ventricular ejection assessed by PW (T_{PW}) (Figure 1); and measurement 2 – the onset of Q wave to the end of the systolic wave in the basal lateral and septal segments with the greatest contraction delay assessed by TDI (T_{TDI}) (Figure 2) [8, 9].

Each measurement was taken from the average of three continuous cardiac cycles. The time difference (T_{PW-TDI}) between T_{PW} and T_{TDI} was used for evaluation of LVMD.

All measurements were analyzed by one observer with clinical and echocardiographic experience. To test intra- and inter-observer variability, T_{PW} and T_{TDI} in 20 randomly selected patients were measured again by observers A and B, who were blinded to the previous analysis. The one observer who made all measurements was not one of the two observers used for variability assessment.

Continuous variables were presented as the mean ±1 standard deviation (SD) and were compared using the analysis of variance (one way ANOVA). Categorical data were assessed with the χ^2 test or Fisher's exact test if the cell sizes were < 5. The receiver operating characteristic (ROC) curve and accuracy matrix analysis were used for evaluation of the cutoff value of T_{PW-TDI} for the diagnosis of LVMD and agreement between LVMD derived by Doppler echocardiography and a positive response to CRT. The mean percentage error (difference/mean), intra-class and inter-class

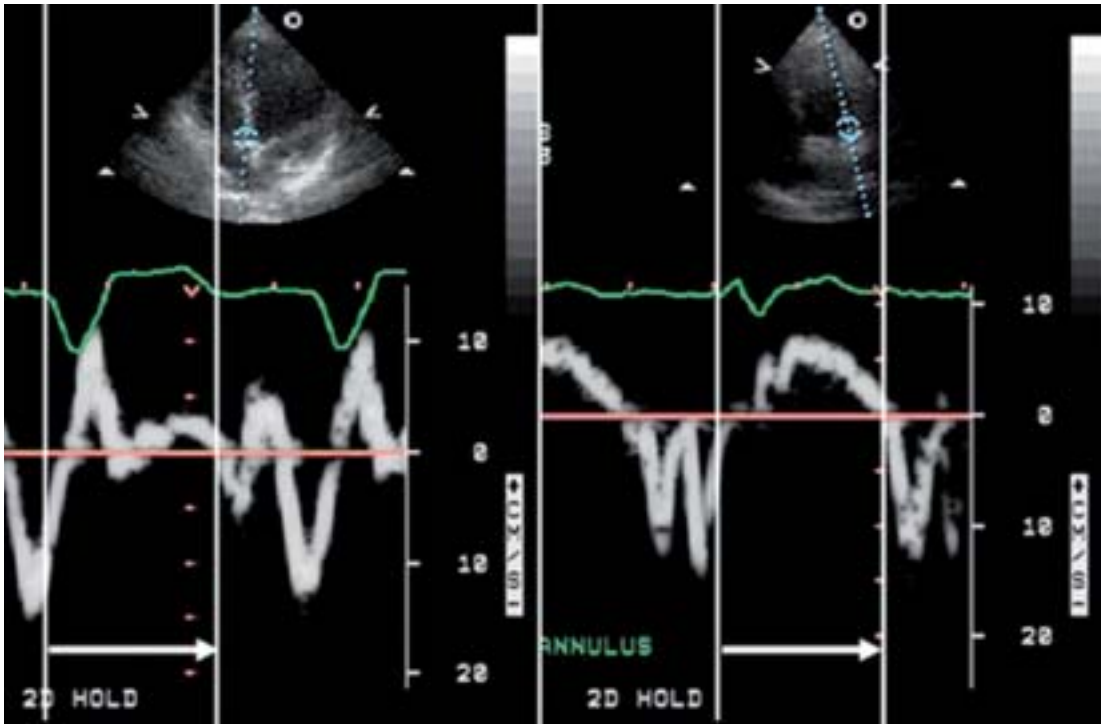

Figure 2. The time from onset of the QRS wave to the end of the systolic wave in basal segments with greatest delay (basal septal segment [left] or basal lateral wall [right] of left ventricle) assessed by TDI

regression, and Bland-Altman plot were used for evaluation of intra- and inter-observer variability. A p value of < 0.05 was considered statistically significant.

The study was approved by the Institutional Review Board of Creighton University School of Medicine.

Results

The implantation procedure was successfully performed in all 108 patients. There were no major complications after CRT implantation. The left ventricular capture threshold was 1.85 ±1.06 volts, and the mean left ventricular pacing impedance was 1,004 ±350 ohms. The QRSD at baseline and after CRT were 165 ±28 ms and 158 ±30 ms (p not significant) during follow-up of 17 ±11 months.

The patient demographics are listed in Table I. As seen in Table I, the use of β-blockers was 90% and of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was 89% in our patients. Table I also shows that 64% of the patients had coronary artery disease, 18% dilated cardiomyopathy, 14% hypertensive heart disease, and 5% valvular heart disease. In the PROSPECT Trial, 54% of the patients had coronary artery disease.

All patients underwent integrated echo-cardiographic measurements before CRT and at a mean duration of 15 ±11 months after CRT. The LVEF at baseline and after CRT were 20 ±7% and 26 ±13%, $p < 0.0001$. The $T_{PW\text{-}TDI}$ at baseline and after CRT were 74 ±48 ms and 49 ±31 ms, $p < 0.0001$. Forty-eight of 108 patients (44%) had a positive response to CRT. A positive response to CRT occurred in 23 of 69 patients (33%) with ischemic heart disease and in 25 of 39 patients (64%) with non-ischemic heart disease ($p = 0.004$). There was no significant difference in follow-up duration between

Table I. Patient demographics

Variable	*N* (%)
Men	78 (72)
Women	30 (28)
Age [years]	70 ±10
QRS duration [ms]	165 ±28
Coronary artery disease	69 (64)
Hypertension	15 (14)
Valvular heart disease	5 (5)
Dilated cardiomyopathy	19 (18)
β-Blocker	97 (90)
Angiotensin-converting enzyme inhibitors	64 (59)
Angiotensin receptor blockers	32 (30)
Diuretics including spironolactone or eplerenone	96 (89)
Digoxin	78 (72)

responders to CRT (16 ±11 months) and non-responders to CRT (14 ±11 months).

The intra-observer variability for T_{PW} and T_{TDI} were 1.5 ±0.24% and 1 ±0.17%, respectively. There was an excellent correlation (r = 0.98 and r = 0.99, $p < 0.001$ and $p < 0.001$) and agreements (mean difference 6.7 ±10.7 ms and 2.8 ±9.1 ms) in T_{PW} and T_{TDI} between the first and second measurements measured by one observer at different times, respectively (Figure 3). The inter-observer variability for T_{PW} and T_{TDI} were 1 ±0.36% and 1 ±0.64%, respectively. There was an excellent correlation (r = 0.89 and r = 0.86, $p < 0.001$ and $p < 0.001$) and agreements in T_{PW} and T_{TDI} (mean difference 4 ±15.5 ms and –1 ±30.4 ms) between the first and second observer, respectively (Figure 4).

The ROC analysis curve compared the relationship between our technique and the gold standard (response to CRT). The cutoff point for diagnosis of LVMD was $T_{PW\text{-}TDI}$ > 50 ms demonstrated by ROC analysis. There were 59 of 109 patients (55%) with an abnormal $T_{PW\text{-}TDI}$ at baseline according to the above criteria. There was no significant difference in LVMD detection rate between patients with ischemic heart disease (34 of 69 or 49%) and without ischemic heart disease (25 of 39 or 64%). The sensitivity, specificity, and positive and negative predictive values of $T_{PW\text{-}TDI}$ > 50 ms to predict a positive response to CRT were 98%, 82%, 81%, and 98%, respectively. The area under the ROC curve was 0.92 (Figure 5). There was a substantial agreement between LVMD determined by $T_{PW\text{-}TDI}$ and the positive response to CRT (κ = 0.80, proportion agreement 0.82, and Bias Index –0.13).

Table II shows in responders versus non-responders to CRT the mean QRSD, LVEF, and $T_{PW\text{-}TDI}$, at baseline, during short-term follow-up, and during long-term follow-up. Table II also lists levels of statistical significance.

Discussion

Tissue Doppler methods for qualitatively and quantitatively assessing intraventricular dyssynchrony are useful in selecting and monitoring patients for CRT. Using dyssynchrony indexes based on tissue velocity measurements, Yu *et al.* [13] and Bax *et al.* [14] demonstrated a high predictive value for both symptomatic improvement compared to remodeling and long-term prognosis after CRT. Aspects of acquisition and analysis that may lead to poor reproducibility have limited this technique. Poor intra- and inter-observer variability (usually > 5%) is

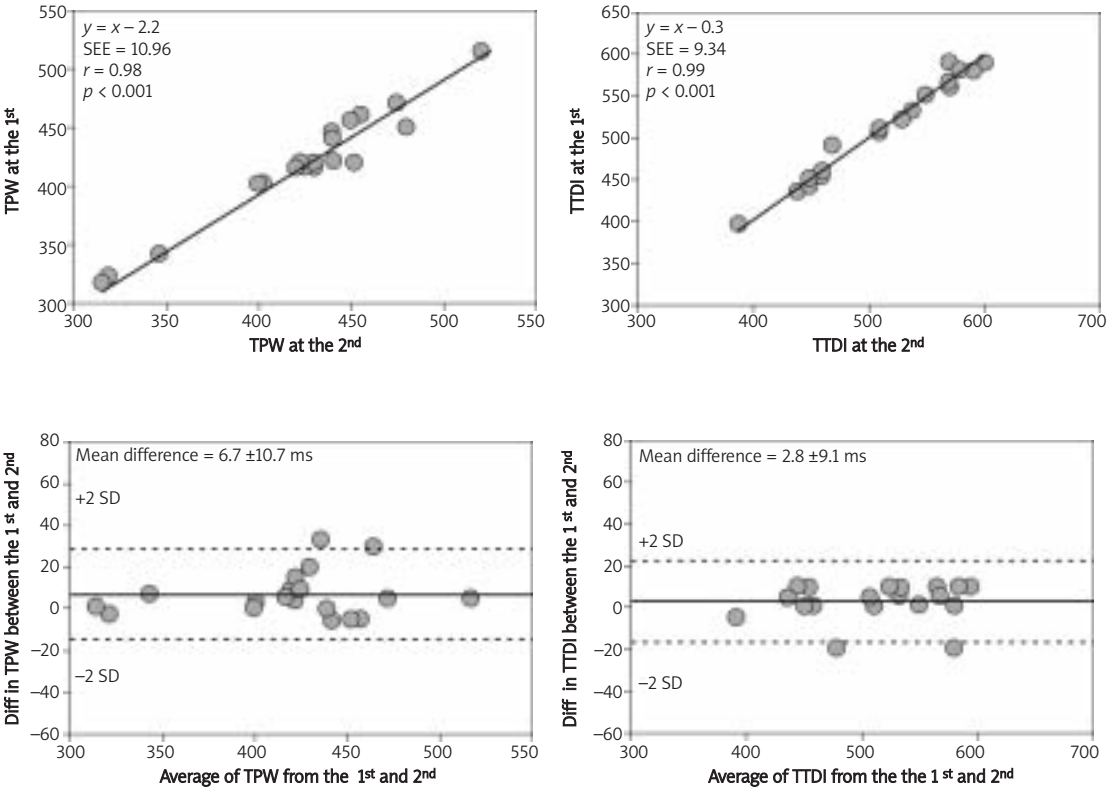

Figure 3. Intra-observer variabilities for T_{PW} and T_{TDI}. There was excellent correlation between the first and second measurements (r = 0.98 [top left] and 0.99 [top right], $p < 0.001$ in both). The mean difference (Diff) between first and second measurements was 6.7 ±10.7 ms (bottom left) and 2.8 ±9.1 ms (bottom right)

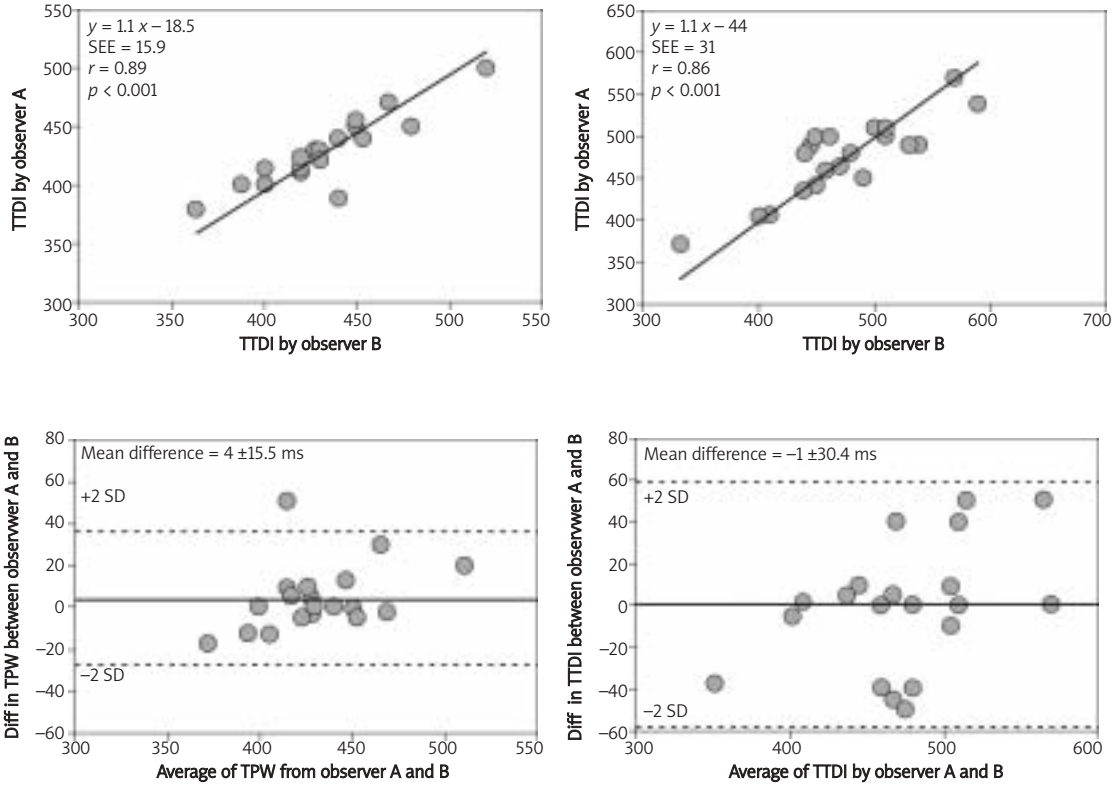

Figure 4. Inter-observer variabilities for T_{PW} and T_{TDI}. There was excellent correlation between two observers (r = 0.89 [top left] and 0.86 [top right], $p < 0.001$ in both). The mean difference (Diff) between observers A and B was 4 ±15.5 ms (bottom left) and –1 ±30.4 ms (bottom right), respectively

the main limitation in evaluation of LVMD determined by TDI only, and the issue was often evaded by authors [15, 16]. Jansen *et al.* [17] studied 69 patients by TDI before and after CRT. The intra-observer and inter-observer variability for measurements of the time interval from the Q wave to the systolic peak velocity were 5.3 ±3.4% and 7.1 ±6.6%, respectively. These results are not satisfactory for clinical use in prediction of a positive response to CRT before biventricular pacemaker implantation. Moreover, the recently finished Predictors of Response to CRT (PROSPECT) trial found that the ability of the 12 echocardiographic parameters to predict clinical composite score response varied widely, with sensitivity ranging from 6% to 74% and specificity from 31% to 93% [18]. The investigators pointed out that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines [18]. The intra- and inter-observer variability in the present study was improved compared to the study by Jansen *et al.* [17].

We agree with the data reported in the PROSPECT trial using the 12 echocardiographic parameters studied [18]. However, the PROSPECT trial did not investigate the method used by Perez de Isla *et al.* [9]. Our study using this method showed an area under the ROC curve of 0.92 (Figure 5) compared to 0.62 for the PROSPECT trial. Our intra-observer variability and inter-observer variability were also better than the values reported in the PROSPECT trial. A major limitation of our

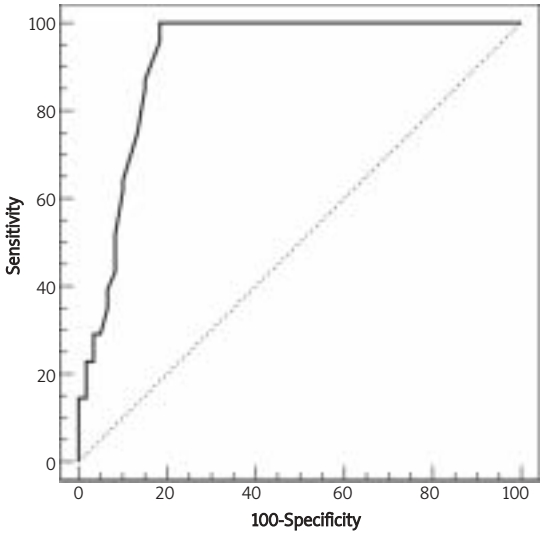

Figure 5. When a positive response to CRT was defined as left ventricular systolic volume reduction ≥ 15% after CRT, the area under the ROC curve was 0.92

Table II. QRS duration, T_{PW-TDI}, and left ventricular ejection fraction (LVEF) at baseline and during short-term and long-term follow-up

		Baseline	Short-term	Value of *p*	Long-term	Value of *p*
QRSD [ms]	Responders	168 ±23	150 ±25	0.03	140 ±31	0.003*
	Non-responders	162 ±30	158 ±35	NS	163 ±36	NS
	Value of *p*	NS	NS		0.04	
TPW-TDI [ms]	Responders	112 ±46	43 ±30	< 0.0001	43 ±22	< 0.0001*
	Non-responders	54 ±37	45 ±28	NS	61 ±38	NS
	Value of *p*	< 0.0001	NS		NS	
LVEF [%]	Responders	21 ±7	33 ±14	0.002	32 ±16	0.009*
	Non-responders	19 ±7	20 ±9	NS	24 ±9	NS
	Value of *p*	NS	0.002		NS	

**Compared to baseline, NS – not significant*

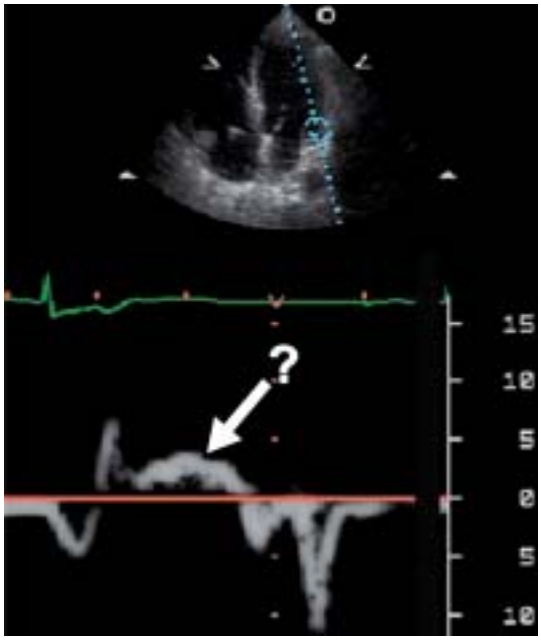

Figure 6. Wall motion velocity spectrum by tissue Doppler imaging. It is difficult to define the end point of peak velocity because of its blunt nature

study and of the PROSPECT trial is that scar tissue was not assessed because scar tissue cannot be evaluated by echocardiography.

Our study did not investigate the effect of CRT on symptoms, which are a subjective endpoint. Our positive response to CRT of 44% is low but consistent with other studies [12, 13].

Perez de Isla *et al.* [9] successfully detected LVMD by the method of combined PW and TDI in 193 heart failure patients. However, they did not perform a validation study using combined PW and TDI to predict a positive response to CRT. Our proposed study using Isla's method demonstrated that the sensitivity, specificity, and agreement were close to the method using Bax's method, but the intra- and inter-observer reproducibility improved significantly from 5-7% to 1-1.5%. The reason for the improvement is that Perez de Isla *et al.* measured the time interval from the Q wave to the end of left ventricular ejection by TDI instead of the time interval measured from the Q wave to the peak velocity because the peak velocity profile has a blunt nature and double peaks (Figure 6).

The time derived by PW represents the mean time interval of left ventricular ejection, and the time derived by TDI represents the segmental time delay of left ventricular ejection. It easily defines the end point from left ventricular flow and motion velocity spectrum by PW and TDI (Figures 1, 2), as compared to a method which defines the end point of peak systolic velocity spectrum by TDI only.

The detection rate of LVMD is lower both in Perez de Isla's *et al.* study (39 %) and our current study (55%) in patients with heart failure and a wide QRSD compared to other studies (60-75%) [13]. However, the lower LVMD detection rate did not affect the sensitivity for prediction of a positive response to CRT in our study. We found that the lower LVMD detection rate (55%) was consistent with a lower CRT response rate (44%), and the cause of a lower CRT response rate may be related to ischemic heart disease. Previous studies suggested that CRT may be less beneficial among heart failure patients with ischemic heart disease compared to non-ischemic heart disease [19-22].

Although the follow-up duration in this study was not constant for each patient after CRT, there was no significant difference in follow-up duration between responders and non-responders. Prospective studies using a large number of patients with longer follow-up times are warranted.

In conclusion, left ventricular dyssynchrony detected by the method of combined PW and TDI demonstrated a high reproducibility, sensitivity, specificity, positive and negative predictive values, and agreement with a positive response to CRT compared to single echocardiographic measurements of left ventricular dyssynchrony described previously [14, 23, 24].

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