

# Assessment of Left Ventricular Function by Analysis of Volume-Time Curves of 16 Segments with Real-Time Three Dimensional Echocardiography: Left Ventricular Asynchrony as a Clinical Parameter for Patients with Heart Failure

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## ABSTRACT

**Background and Objectives :** Recent technical developments with high-resolution real-time 3-dimensional echocardiography (RT3DE) have facilitated the acquisition of high quality images and the analysis of segmental volume-time curves (VTCs). The purposes of this study were to assess left ventricular (LV) asynchrony with using the VTCs of 16 segments by RT3DE and to compare this with tissue Doppler imaging (TDI) as a clinical parameter. **Subjects and Methods :** Twenty-three heart failure (HF) patients (LVEF:  $25 \pm 6\%$ , age:  $60 \pm 13$  years) and 16 normal controls underwent TDI and RT3DE at baseline and 1-year. The standard deviation ( $SD_3$ ) of the end systolic time to reach the minimal systolic volume for the 16 segments on VTCs was obtained by RT3DE. The standard deviation ( $SD_2$ ) of the electromechanical coupling time for the 8 segments was measured using TDI. **Results :**  $SD_3$  was markedly higher in the HF patients than that in the controls ( $7.7 \pm 2.5$  vs  $1.5 \pm 1.0\%$ , respectively,  $p < 0.01$ ) and it increased as the LVEF decreased ( $r = -0.85$ ,  $p < 0.01$ ).  $SD_2$  was also significantly higher in the HF patients ( $27.0 \pm 8.6$  vs  $12.6 \pm 5.0$  msec, respectively,  $p < 0.01$ ) and it had good negative correlation with the LVEF ( $r = -0.72$ ,  $p < 0.01$ ).  $SD_3$  was well correlated with  $SD_2$  ( $r = 0.66$ ,  $p < 0.01$ ). At 1-year, the HF patients with an increased LVEF showed a decreased  $SD_3$  (7/13). In contrast, the patients with a decreased LVEF had an increased  $SD_3$  (3/13). **Conclusion :** The analysis of VTCs for the 16 LV segments with using RT3DE from a single acoustic window may be a useful clinical parameter for evaluating the LV function, including LV asynchrony, the LV volume and the LVEF. (Korean Circulation J 2006;36:669-675)

**KEY WORDS :** Heart failure ; Echocardiography.

## Introduction

Heart failure is one of the most significant disorders that causes hospitalization and death. Patients with left ventricular (LV) systolic dysfunction and dilation frequently have ventricular conduction delays and uncoordinated contraction, and this is referred to as ventricular asynchrony.<sup>1)</sup> LV asynchrony may contribute

to disease progression in heart failure (HF) patients. Hence, the correction of ventricular asynchrony is an attractive treatment goal, and the methods for evaluating ventricular asynchrony are of great interest for obtaining the prognosis and optimizing therapy for HF patients.<sup>2,3)</sup> QRS prolongation usually indicates impaired propagation of the electrical input, and this is frequently associated with increased morbidity and mortality of HF patients.<sup>4,5)</sup> However, the recent data has demonstrated that mechanical asynchrony is not necessarily related to electrical asynchrony.<sup>6,7)</sup>

Thus, various non-invasive echocardiographic approaches have emerged for assessing mechanical asynchrony. Tissue Doppler echocardiography has been used in many studies and it provides information on the location and the extent of mechanical LV asynchrony,

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which is impossible with using the QRS duration.<sup>8-10)</sup> Recent technical developments have permitted construction of a high-resolution real-time 3 dimensional echocardiography (RT3DE) transducer that allows acquisition of high quality images from a single acoustic window. Moreover, phase analyses of the segmental volume-time curves (VTCs), based on 3D data, illustrate the changes in regional myocardial motion and the LV contraction patterns in an exact and quantitative way.<sup>11)</sup>

Therefore, the purposes of this study were to assess LV function, including LV asynchrony in HF patients with using the VTCs of 16-segments that were the obtained by RT3DE, as a clinical parameter and to evaluate the accuracy of this technique as compared to tissue Doppler imaging (TDI).

## Subjects and Methods

### Patients and controls

We performed 2D and 3D echocardiography in 28 consecutive HF patients and 17 healthy controls. Echocardiographic studies were performed at baseline and 1-year for the HF patients. The inclusion criteria were as follows: 1) heart failure of New York Heart Association (NYHA) class II or more for at least 6 months, 2) an LV ejection fraction (LVEF)  $\leq 35\%$ , as assessed by echocardiography, 3) dilated cardiomyopathy with diffuse hypokinesia, and 4) stable medication (ACE inhibitors,  $\beta$ -blockers) for  $\geq 3$  months. The patients with acute coronary syndromes or those who had undergone revascularization during the previous 6 months were excluded. The healthy controls had normal echocardiographic findings with an LVEF  $\geq 50\%$  and they did not have any symptoms of heart disease.

### Standard two dimensional echocardiographic studies

All subjects were studied in the left lateral decubitus position using an ultrasound system equipped with tissue Doppler (Sonos 7,500, Philips Medical Systems, Andover, Massachusetts) and with employing a 3-MHz

transducer. The standard two-dimensional (2D) and M-mode echocardiograms were obtained, according to the guidelines of the American Society of Echocardiography.<sup>12)</sup> Global LV function was assessed from the two-dimensional apical views by measuring the LVEF and using the modified biplane Simpson rule. The average value from 3 consecutive beats was taken for each measurement.

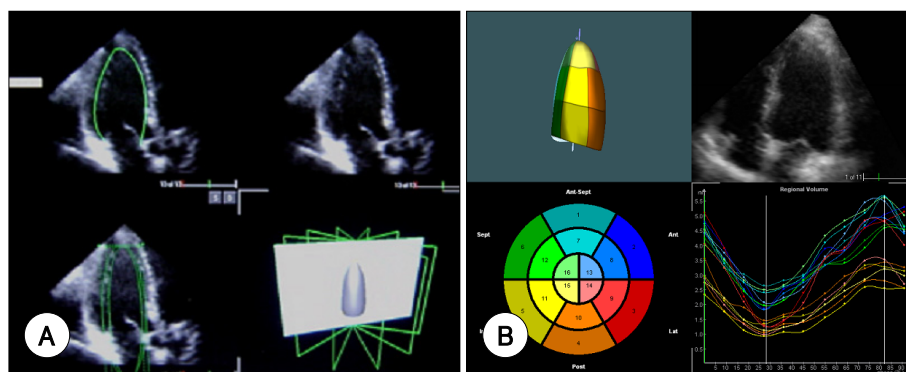
### Transthoracic RT3DE and the generation of volume-time curves

RT3DE scanning was performed using a commercially available system (Live 3D Echo, Phillips, Co.). The RT3DE images were obtained from the apical window. Images for the VTC analysis were gathered over four cardiac cycles by using a matrix array ultrasonographic transducer. To generate the VTCs of the 16 segments over a complete cardiac cycle, off-line measurements of the 3D volumes of the 16 segments were performed using 3D computer software (4D LV analysis, Tomtec GmbH, Unterschleißheim, Germany). The endocardial contours were marked in 6 slices (i.e., 30 degrees per slice) and contour tracing was performed using semi-automatic border detection following identification of the apex and mitral annulus on each slice, and a pre-configured ellipse was fitted to the endocardial borders of each frame and it was adjusted as required (Fig. 1A).

### Quantitative analysis of the volume-time curves

The LV end diastolic and end systolic volume (LVEDV and LVESV) were defined as the largest and smallest LV volumes throughout the cardiac cycle, respectively.

For quantitative analysis of the volume changes during the cardiac cycle, the VTCs of the 16 segments were sampled and converted into Excel data at intervals of 1.02 milliseconds (Fig. 1B). The end systolic time (EST) was defined as the time when the segmental volume reached the end systolic volume on each VTC, and the corrected EST (cEST) was obtained by adjustment according to the heart rate.



**Fig. 1.** Semi-automatic endocardial border detection using real-time three-dimensional echocardiography (A). Left ventricular case generated by quantitative analysis in 16 segments (B).

$$\text{cEST}(\%) = (\text{EST}/\text{cardiac cycle length}) \times 100$$

The degree of LV asynchrony was determined from the VTCs as the standard deviation of the cESTs (SD<sub>3</sub>) of the 16 segments.

### Tissue Doppler imaging

TDI was obtained in the pulsed-wave Doppler mode from the apical view to assess the longitudinal myocardial regional function of the septal, lateral, anterior and inferior walls. The velocity profiles were recorded with a sample volume placed in the middle of the basal and mid segments of each wall. Gain and filters were adjusted as needed to eliminate background noise and to allow for a clear tissue signal. The TDI signals were recorded at a sweep speed of 100 mm/s. At least 3 consecutive beats were stored, and the images were analyzed offline. The electromechanical coupling time was measured from the Doppler spectrum (The EMT was defined as the time interval from the onset of the QRS complex on the surface ECG to the onset of the systolic TDI wave).<sup>13)</sup> For the assessment of synchronicity, the standard deviation of the EMTs (SD<sub>2</sub>) for the 8 segments was calculated.

### Statistical analysis

Data are presented as means  $\pm$  S.Ds. Mann-Whitney testing was used to compare the SD<sub>2</sub> and SD<sub>3</sub> of the HF patients with that of the normal controls. Linear regression analysis was performed to investigate the correlations between the parametric variables. All statistical analyses were performed using SPSS software SPSS, Version 10.0, SPSS Inc., Chicago, Illinois). Statistical significance was defined at  $p < 0.05$ .

## Results

### Clinical baseline characteristics

23 HF patients and 16 normal controls were included in the analysis (Table 1). We had to exclude one normal control subject and 5 HF patients (13.3% of the total study population) due to poor image acquisition. Of the 23 HF patients, 5 (21.7%) had a history of multiple coronary artery stenoses. Five of the HF patients had a wide QRS complex ( $\geq 120$  msec) on ECG, and the remaining 18 patients had a normal QRS duration that was not significantly different from that of the controls ( $98 \pm 14$  vs  $91 \pm 14$  msec, respectively  $p = 0.18$ ). In the HF patients, the mean LVEF was  $25.0 \pm 5.6\%$  and the LV end diastolic diameter was  $65.9 \pm 7.1$  mm. The controls had normal values for these parameters, which were assessed by 2D echocardiography (Table 2).

### Transthoracic RT3DE and generation of volume-time curves

In accordance with the 2D echocardiography findings,

the LVEDV and LVESV, as measured by RT3DE, were larger in the HF patients than those in the controls. The ESTs of the 16 segments were more delayed and dispersed in the HF patients than were those of the controls (Fig. 2). The mean cEST for the 16 segments was significantly increased in the HF patients as compared to the controls ( $47.7 \pm 6.9$  vs  $37.8 \pm 9.7\%$ , respectively,  $p < 0.05$ ). The SD<sub>3</sub> was significantly larger in the HF patients than that in the controls ( $7.7 \pm 2.5$  vs  $1.5 \pm 1.0\%$ , respectively,  $p < 0.01$ , Table 3) and it increased as the LVEF decreased, and there was significant correlation ( $r = -0.85$ ,  $p < 0.01$ ). Using a SD<sub>3</sub> of  $> 5\%$  to define significant LV asynchrony, none was found in the control group; however, 14 patients (77%) in the narrow QRS group and 4 patients (80%) in the wide QRS group showed significant LV asynchrony. Using a SD<sub>3</sub> of  $> 3.5\%$  ( $+2$  SDs of the normal controls) to define significant systolic asynchrony, we identified 1 control subject (6%) and 15 (83%) patients in the na-

**Table 1.** Clinical characteristics of the study population

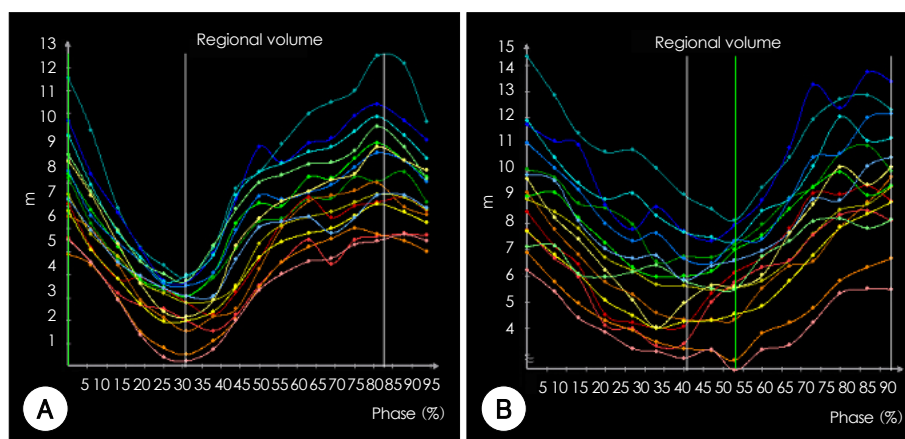
	Controls (n=16)	Patients with HF (n=23)	P
Age (years)	$37 \pm 11$	$60 \pm 13$	$< 0.05$
Men/Women	13/3	18/5	
Ischemic/Non-ischemic		5/18	
NYHA class II/III/IV		2/16/5	
Heart Rate (/min)	$68 \pm 16$	$84 \pm 16$	$< 0.05$
Normal sinus rhythm (n)	16	23	
QRS complex (ms)	$91 \pm 14$	$107 \pm 23$	$< 0.05$
QRS width $\geq 120$ (ms, n)	0	5	
Medications			
ACEI/ARB, n (%)	0	18/23 (78%)	
Diuretics, n (%)	0	21/23 (90%)	
Beta-blockers, n (%)	0	11/23 (48%)	
Digoxin, n (%)	0	3/23 (13%)	
Calcium antagonist, n (%)	0	2/23 (9%)	

Data are presented as means  $\pm$  SDs. HF: heart failure, NYHA: New York heart association, ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker

**Table 2.** Two dimensional echocardiographic and tissue Doppler imaging parameters

	Controls (n=16)	Patients with HF (n=23)	P
LVEDD (mm)	$48.4 \pm 3.3$	$65.9 \pm 7.1$	$< 0.05$
LVEDV (mL)	$87.6 \pm 10.6$	$189.1 \pm 63.4$	$< 0.05$
LVESV (mL)	$27.2 \pm 6.4$	$140.3 \pm 55.1$	$< 0.05$
LV EF 2D (%)	$61.5 \pm 4.9$	$25.0 \pm 5.6$	$< 0.05$
Mean EMT (ms)	$93.1 \pm 14.7$	$156.9 \pm 33.9$	$< 0.05$
SD <sub>2</sub> (ms)	$12.6 \pm 5.0$	$27.6 \pm 8.0$	$< 0.01$

Data are presented as means  $\pm$  SDs. HF: heart failure, LVEDD: left ventricular end diastolic dimension, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, EMT: electromechanical coupling time, SD<sub>2</sub>: the standard deviation of EMT for 8 segments



**Fig. 2.** Regional volume-time curves (VTCs) in 16 segments in a normal control subject (A) and in a patient with heart failure (B). VTCs: volume-time curves.

**Table 3.** Real-time 3 dimensional echocardiographic parameters

	Controls (n=16)	Patients with HF (n=23)	p
LVEDV-3D (mL)	93.7 ± 13.6	190.3 ± 51.6	<0.05
LVESV-3D (mL)	35.8 ± 6.8	142.0 ± 46.0	<0.05
LV EF-3D (%)	61.7 ± 4.7	26.0 ± 6.4	<0.05
Mean cEST (%)	37.8 ± 9.7	47.7 ± 6.9	<0.05
SD <sub>3</sub> (%)	1.5 ± 1.0	7.7 ± 2.5	<0.01

Data are presented as mean ± SD. HF: heart failure, LVEDV-3D: left ventricular end diastolic volume measured by 3 dimensional echocardiography, LVESV: left ventricular end systolic volume measured by 3 dimensional echocardiography, LVEF: left ventricular ejection fraction, cEST: end systolic time corrected by heart rate, SD<sub>3</sub>: the standard deviation of cEST for 16 segments

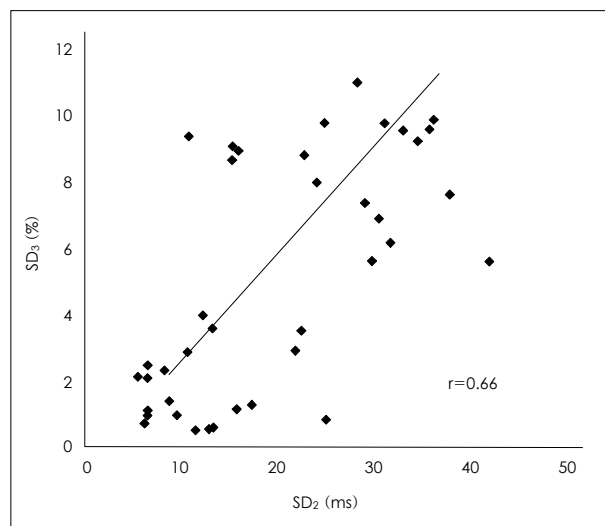
row QRS group and there were 4 patients (80%) in the wide QRS group with significant systolic asynchrony.

### Tissue Doppler imaging

The mean EMTs of 8 segments were significantly higher in the HF patients than in the controls ( $p < 0.05$ ). The SD<sub>2</sub> was also significantly greater in the HF patients than in the controls ( $27.0 \pm 8.6$  vs  $12.6 \pm 5.0$  msec, respectively,  $p < 0.01$ , Table 2). The SD<sub>2</sub> had good negative correlation with the LVEF ( $r = -0.72$ ,  $p < 0.01$ ). When a SD<sub>2</sub> of  $>27$  ms was used to define significant LV asynchrony, it was not found in the control group, but it was found in 9 (50%) patients in the narrow QRS group and in 3 (60%) patients in the wide QRS group. When a SD<sub>2</sub> of  $>22.6$  ms ( $+2$  SDs of the normal controls) was used, significant LV asynchrony was present in only 1 (6%) control subject, but it was present in 13 (72%) patients in the narrow QRS group and in 4 (80%) patients in the wide QRS group.

### Comparison between SD<sub>2</sub> and SD<sub>3</sub>

There was a good correlation between the SD<sub>2</sub> and SD<sub>3</sub> ( $r = 0.66$ ,  $p < 0.01$ , Fig. 3). For the HF patients, the



**Fig. 3.** Correlation between SD<sub>3</sub> and SD<sub>2</sub> ( $r = 0.66$ ,  $p < 0.01$ ).

longest ESTs were similarly distributed from the base to the apex except for the anterior wall. The agreement of the walls between the longest EMT and EST in each patient was about 74% (17/23), and the agreement of the segments between the two was 35% (8/23).

### Follow up data in HF patients

During a mean follow-up of  $12.5 \pm 1.0$  months, of the 23 HF patients, 4 patients died and 4 patients were missed for lack of follow-up. Among 15 patients, 13 (86.7%) were included in the VTC analysis; the other two patients (13.3%) were excluded due to sub-optimal RT3DE image acquisition. The patients who died during follow up had a slightly higher SD<sub>2</sub> and SD<sub>3</sub>, but this was without statistical significance; three of them had ischemic cardiomyopathy. As shown in Table 4, the patients with increased LVEF (7/13) during follow up showed a decreased SD<sub>3</sub>. To the contrary, the patients with a decreased LVEF (3/13) had an increased SD<sub>3</sub>.

**Table 4.** Real-time 3 dimensional echocardiographic parameters at baseline and 1-year for patients with CHF

Patients	Sex/Age (years)	Baseline					Follow up at 1 year				
		LVEDV (mL)	LVESV (mL)	LVEF (%)	EST (%)	SD <sub>3</sub> (%)	LVEDV (mL)	LVESV (mL)	LVEF (%)	EST (%)	SD <sub>3</sub> (%)
1	M/78	187.7	150.9	16.6	42.55	8.98	138.9	98.9	28.8	45.71	7.95
2	M/24	144.0	99.0	30.9	41.48	2.98	114.5	91.2	20.4	53.66	8.85
3	M/74	293.8	232.0	21.0	50.76	2.85	220.7	185.1	15.9	62.01	6.76
4	F/57	212.6	175.4	17.4	43.49	7.78	193.0	143.0	25.9	37.23	5.18
5*	M/62	177.3	115.5	34.9	47.97	3.62	118.9	71.6	40.8	46.01	8.14
6	M/70	196.4	127.8	34.9	45.60	7.55	210.4	145.6	30.6	50.78	12.35
7	M/59	141.2	97.7	30.8	44.46	9.41	110.9	58.6	37.1	43.00	5.00
8	M/61	160.9	124.0	22.7	52.61	7.18	99.9	67.6	32.3	41.72	5.75
9	M/66	174.1	125.2	28.0	52.21	9.29	91.7	43.2	53.8	35.59	5.59
10	M/41	170.1	126.8	25.4	61.18	10.1	217.6	157.4	27.5	62.63	10.48
11*	F/65	188.4	152.1	19.2	56.12	7.04	121.8	85.2	29.9	47.15	9.68
12	M/51	241.7	200.6	17.0	54.46	10.00	176.1	127.8	27.4	49.45	6.85
13	F/59	128.4	99.7	22.3	54.93	9.82	91.0	43.7	50.7	48.31	6.58

LVEDV, LVESV: left ventricular end-diastolic & end-systolic volume, LVEF: left ventricular ejection fraction, EST: end-systolic time on VTCs, SD<sub>3</sub>: the standard deviation of cEST for 16 segments. \*: patients with ischemic cardiomyopathy

from their baseline values. However, 2 patients showed an increased SD<sub>3</sub> even with an increased LVEF, and these two patients had ischemic cardiomyopathy.

## Discussion

The results of this study show that LV function can be quantified by volume-time curve analysis with using 3D analysis software.

Coordinated LV contraction depends on normal ventricular activation. When the LV is composed of regions of both early and delayed contraction, then the LV performance can be affected. Early or late shortening results in wasted work, a decrease in systolic performance, an increase in end-systolic volume and wall stress, delayed relaxation and a reduction in pumping efficiency.<sup>14)15)</sup>

In patients with HF and a wide QRS that signifies an electromechanical delay, cardiac resynchronization has been found to improve both the symptoms and quality of life, and also to reduce complications and the risk of death.<sup>16)17)</sup> However, despite careful patient selection based on QRS complex duration, some patients do not respond to CRT.<sup>18)</sup> In addition, some patients with a wide QRS complex do not exhibit LV asynchrony, whereas other patients with a narrow QRS may demonstrate LV asynchrony.<sup>19-21)</sup> Therefore, it is likely that surface ECG is not sensitive enough to detect the presence and severity of electromechanical delay that results in asynchronous contraction. In the present study, the majority of HF patients had a narrow QRS complex on their ECG and more than 50% of these patients had significant LV asynchrony. Therefore, irrespective of the QRS duration, HF patients may

have mechanical asynchrony. These results are in good agreement with those of other previous studies.<sup>19)20)</sup>

TDI provides a lot of information, including the location and the severity of LV asynchrony.<sup>9)10)</sup> However, the TDI indices of asynchrony also have some limitations. Apart from active contraction, the regional systolic velocities may reflect passive motion of segments due to heart motion or tethering by the adjacent segments. It is difficult to measure myocardial velocities in the apical segments of the LV. Pulsed-wave TDI does not allow simultaneous comparisons of regional timing in different segments during a single beat, though this limitation may be reduced by conducting colour-coded analysis. In addition, the longitudinal myocardial velocities are often very low in the HF patients with severely decreased LV contractility.

RT3DE allows the acquisition of high quality images from a single acoustic window. Moreover, a computerized contour tracking algorithm has been developed that it enables semi-automated data analysis with only minimal investigator involvement.<sup>22)23)</sup> RT3DE allows precise evaluation of LV volumes, even for conditions of altered load<sup>24)</sup> or distorted ventricular geometry. Phased analyses of the segmental VTCs as based on 3D data demonstrated changes in regional myocardial motion and the LV contraction patterns in an exact and quantitative way. Moreover, it provides VTCs of the 16 LV segments at one time. Previous studies have demonstrated that volume-time curves, which represent continuous LV volume changes and are determined by monitoring 16 segments throughout the cardiac cycle, allows more detailed quantitative analysis of the LV performance, and particularly in patients with asynergy.<sup>25)26)</sup>

RT3DE can accurately and quantitatively determine the dynamic LV volume changes in the whole LV chamber. Having VTCs available in routine clinical practice would provide important clinical information about patients with impaired LV function, including information about asynchronous LV contraction. It is suggested that analysis of the VTCs of the 16 LV segments can be an excellent means of assessing the global LV performance and LV asynchrony in clinical practice for each patient. However, there was a discrepancy between improvement of LV systolic function and LV asynchrony in two patients who suffered with ischemic cardiomyopathy; we should apply this parameter carefully in such patients. Several studies have recently reported using RT3DE to evaluate CRT outcomes. Krenning et al.<sup>27)</sup> and Kapetanakis et al.<sup>28)</sup> showed the possibility of using RT3DE for guiding and optimizing the CRT.<sup>27)28)</sup> Despite the numerous advantages of RT3DE for evaluating LV asynchrony, it also has some limitations. First, it is more time consuming than TDI for the offline analysis of LV volume changes. Second, LV volume analysis is dependent on image size and quality; thus, clear endocardial borders and acquiring the complete LV cavity are required. Moreover, RT3DE has lower temporal resolution than 2D echocardiography. Nonetheless, the RT3DE frame rate of 15 to 24 frames/s in our study is sufficient to generate VTCs, and the previous studies with magnetic resonance imaging and electron beam tomography have used a frame rate of 16-20 frames/s.<sup>29)30)</sup>

In this study, the agreement between the two methods was not complete. The possible causes of this discrepancy were first that there might be unrecognized segments with TDI, and especially the apical segments. Second, the LV walls were divided differently for the TDI and RT3DE studies. Finally, since RT3DE has a relatively lower temporal resolution than does 2D echocardiography, we may not have obtained the true ESTs.

There were some limitations for this study. The study population was small and only 5 patients (21%) had a wide QRS complex. Compared to the results of other studies, this study showed that more than 60% of HF patients with a narrow QRS complex had significant LV asynchrony. This may be due to the small study population, the much lower LVEF and the selection bias for patients.

In conclusion, the analysis of the volume-time curves for the 16 LV segments with using RT3DE from a single acoustic window may be a useful for evaluating LV function, including LV asynchrony, the LV volume and the LV ejection fraction, and it may provide detailed information about the 16 LV segments. However, further studies with large study populations are required to confirm the use of this methodology for assessing LV asynchrony.

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