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An initial study on left ventricular diastolic function in patients with hypertrophy cardiomyopathy using single-beat, real-time, three-dimensional echocardiography

Bei Zhao, Juan Li, Yong Xu, Hong-Wei Zhu, Guang Zhi

Department of Cardiology, Chinese PLA General Hospital, 28 Fuxing Road, 100853 Beijing, China

Abstract

Objectives To assess the regional diastolic function in patients with hypertrophic cardiomyopathy (HCM) by using single-beat, real-time, three-dimensional echocardiography (RT-3DE). **Methods** Sixty-five patients with HCM in sinus rhythm together with fifty age- and gender-matched normal controls were studied by two dimensional echocardiography (2DE) and RT-3DE. The parameters analyzed by RT-3DE included: left ventricular (LV) volumes, left ventricular ejection fraction (LVEF), end diastolic sphericity index (EDSI), diastolic dyssynchrony index (DDI), dispersion end diastole (DISPED), and normalized 17 segmental volume-time curves. **Results** Evaluated by RT-3DE, LVEF was slightly lower compared with 2DE (63.2 ± 6.8% *vs.* 59.1 ± 6.4%, $P < 0.0001$). Normal subjects had relatively uniform volumetric curves for all LV segments. In HCM patients, the segmental volumetric curves were dyssynchronous. Increased DDI and DISPED in end diastole were observed in patients with HCM (9.95 ± 3.75, 41.76 ± 17.19, $P < 0.0001$), and not all abnormal volumetric segments occurred in the hypertrophic regions. **Conclusions** Patients with HCM have presented regional diastolic dyssynchrony in the diastole phase, and this preclinical lesion can be recognized by single-beat RT-3DE.

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1 Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiac disorders and is characterized by asymmetric left ventricular (LV) hypertrophy and, at the histological level, by myocyte hypertrophy, disarray, and fibrosis.[1] Sarcomere mutations in HCM led to the impairment of LV relaxation and significant changes in calcium signaling, which may predate the occurrence of hypertrophy.[2] Diastolic dysfunction has been shown to be an early clinical feature of HCM in both genetically engineered animal models with HCM-causing mutations and human patients.[3] With the development of non-invasive diagnostic methods, such as echocardiography and cardiac magnetic resonance (CMR), more asymptomatic patients have been identified. Real-time three-dimensional echocardiography (RT-3DE) is a novel imaging technique that can provide a more accurate assessment of complex cardiac anatomy and sophisticated functional mechanisms when compared to conventional two dimensional echocardiography (2DE).[4,5] Currently, single-beat RT-3DE is available to acquire full-volume images avoiding the stitch artifact generated by previous RT-3DE.[6] Combined with special software, it offers more exact and detailed quantitative information regarding mechanical dyssynchrony. However, the relationship between hypertrophy and regional myocardial functional properties, as well as the effects on LV diastolic abnormalities in patients with HCM, have remained unclear.[7] The aim of this study was to evaluate LV diastolic function and dyssynchrony with RT-3DE compared to 2DE and to examine the relationship between the location of hypertrophy and regional diastolic dyssynchrony.

2 Methods

2.1 Study population

Sixty-five consecutive adult patients (mean age 50.1 ± 11.5 years, 47 men) in sinus rhythm with HCM, who were diagnosed clinically by echocardiography between December 2008 and February 2010, were recruited at the General PLA 301 hospital china. The diagnostic criteria used for HCM were consistent with the definition and classification of cardiomyopathies.[8] All patients had no systemic hypertension, aortic stenosis, amyloidosis, or other diseases that may cause LV hypertrophy. Uniform morphologic criteria for

Correspondence to: Guang Zhi, MD, Professor, Department of Cardiology, Chinese PLA General Hospital, 28 Fuxing Rd., Beijing 100853, China. E-mail: zhiguang301@sina.cn

Telephone: +86-10-55499350 **Fax:** +86-10-55499209

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HCM were in agreement with previous Maron's criteria.[9] Fifty age-matched subjects without a family history of HCM and normal clinical and echocardiographic findings were enrolled. All patients were selected independent of the image quality of their acoustic window. Written informed consent to participate was obtained from all patients.

2.2 Clinical data

The baseline recorded medical history consisted of symptoms, family history, New York Heart Association functional class, blood pressure, medications at the time enrollment, and any occurrence of hypertension, diabetes, stroke, or syncope.

2.3 2DE

2DE images were acquired with a commercially available ultrasound system (Acuson SC2000; Siemens Medical Systems) equipped with a 4V1c transducer (1–4 MHz). All 2DE images were analyzed by a cardiologist who was unaware of the clinical status of the subject. Two dimensional, Doppler, and Doppler tissue imaging parameters were measured according to the guidelines of the American Society of Echocardiography.[10–12]

2.4 Real-time dimensional echocardiography (RT-3DE)

3DE images were performed with a commercially available ultrasound system (Acuson SC2000; Siemens Medical Systems) equipped with a 4Z1c transducer (2–4 MHz). The detectable depth was 15–17 cm, the scanning angle was 90 × 90° and the volume rate was > 20 frames/ s. The patients were imaged in the left lateral decubitus position while an electrocardiogram (ECG) was recorded simultaneously. The 3D data sets were analyzed offline using the Left Ventricular Analyzed System (4DLVA). The end systolic and diastolic volumes were automatically identified by the system. Endocardium in various sequences was automatically signed and manually revised. LV was automatically divided into 17 segments, and the following parameters were obtained: end diastolic sphericity index (EDSI); diastolic dyssynchrony index (DDI); dispersion end diastole (DISPED); Pre-relaxation time volume (PreRelax); Post-relaxation time volume (PostRelax); Volume-time curve displays of the 17 segmental graphs of volume (%)/time (ms, %) normalized to their individual maximum relative ratio.

DDI, as a mechanical dyssynchrony parameter, was derived from the standard deviation of the regional diastolic times reaching volume peak of the 17-segment model. Every sampling point for 17 segments was automatically located in the maximum volume by 4DLVA in the relaxation mapping. DDI were automatically acquired by the software.

2.5 Statistical analysis

Data are expressed as the mean ± SD, and variables were compared using the Chi-square test for qualitative data and the two-independent-sample design *t* test or Wilcoxon rank sum test for quantitative data. One-way ANOVA was used to compare LV function between the normal and HCM groups. Concordance between 2DE and RT-3DE was calculated using Lin's agreement. The correlations between hypertrophy and abnormal diastolic segments were determined by the Logistic regression. $P < 0.05$ was considered to be statistically significant. SAS version 9.2 was used for statistical analysis.

2.6 Repeatability and reproducibility

To assess intra-observer repeatability and inter-observer reproducibility of 3D-based indices, ten randomly chosen patients and five controls were measured a second time, after a time interval of more than one month by the same observer and, at that time, also by a second observer blinded to the measurements of the first observer. Repeatability and reproducibility coefficients, intra-class correlation coefficients (ICC) between intra-observer and inter-observer measurements were calculated as previously published.[13,14]

3 Results

Table 1 lists the clinical and 2DE characteristics of the patients with HCM and the control subjects. There was no difference between the mean age of HCM and control groups. Most HCM patients were symptomatic and had a higher incidence of dyspnea after exercising. Patients with apical HCM often were mildly symptomatic or even asymptomatic. LV maximal wall thickness and the resting left ventricular outflow tract (LVOT) gradient were significantly higher, whereas LV end-diastolic diameter was lower in patients with HCM ($P < 0.0001$). Furthermore, the early transmitral filling velocity/late transmitral filling velocity (E/A) was lower ($P < 0.01$), whereas the E-wave velocity deceleration time and the early transmitral filling velocity/early diastolic annular velocity (E/Ea) was higher in patients with HCM ($P < 0.01$).

LV wall thickness values at 17 measurement sites were determined for each patient (Figure 1). The most common form of HCM is septal hypertrophy, but it is often associated with hypertrophy of another site, such as the anterior, lateral and apical walls. The lateral and apical walls are often involved in patients with septal HCM. In apical HCM, the lateral apical wall and apex are often involved, and the degree of hypertrophy is greater compared to other sites.

We compared the measurements of left ventricular function acquired by 2DE and RT-3DE. A significant decrease in the end diastolic volume (EDV) (93.1 ± 17.5 mL in 2DE *vs.* 88.9 ± 18.2 mL in RT-3DE, $P < 0.0001$) coupled with

Table 1. Clinical and 2D echocardiographic characteristics of the study population.

Variable	Patients with HCM (n = 65)	Controls (n = 50)	P-value
Clinical characteristics			
Age (year)	50.1 ± 11.5	49.6 ± 10.2	0.52
Men, n(%)	47 (72%)	42 (70%)	0.46
Body surface area (m^2)	1.8 ± 0.2	1.7 ± 0.1	0.21
Systolic blood pressure (mmHg)	125 ± 16	122 ± 13	0.09
Heart rate (beats/minute)	65 ± 11	67 ± 10	0.59
NYHA function class Ⅲ (%)	6/65 (9.2%)	-	-
Dyspnea (%)	47/65 (72%)		
Chest pain (%)	27/65 (42%)	-	-
Syncope (%)	9/65 (14%)	-	-
Paroxysmal atrial fibrillation (%)	7/65 (11%)	-	-
β-blocker (%)	33/65 (50%)		
2D echocardigraphic characteristics			
Maximal LV wall thickness (cm)	2.2 ± 0.5*	0.9 ± 0.5	< 0.0001
LVOT obstruction, n(%) (Pressure gradient ≥ 30 mmHg)	20/65 (32%)	-	-
Resting LVOT gradient (mmHg)	26.2 ± 24.5*	5.4 ± 1.3	< 0.0001
LVEDD (cm)	4.4 ± 0.7*	4.7 ± 0.5	< 0.0001
LVESD (cm)	3.2 ± 0.8*	3.1 ± 0.5	< 0.0001
LV ejection fraction (%)	59.2 ± 9.8	60.9 ± 6.6	0.1998
E/A	1.1 ± 0.7*	1.26 ± 0.6	0.0058
DT (ms)	179.7 ± 76*	170.1 ± 44	0.0096
E/Ea	12.5 ± 4.3*	7.3 ± 2.0	<.0001

Data are expressed as the mean ± SD or as percentages. *P < 0.05 *vs*. control subjects. DT: E-wave velocity deceleration time; E/A: early transmitral filling velocity/late transmitral filling velocity; E/Ea: early transmitral filling velocity/early diastolic annular velocity; LV: left ventricular; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end systolic dimension; LVOT: left ventricular outflow tract; NYHA: New York Heart Association.

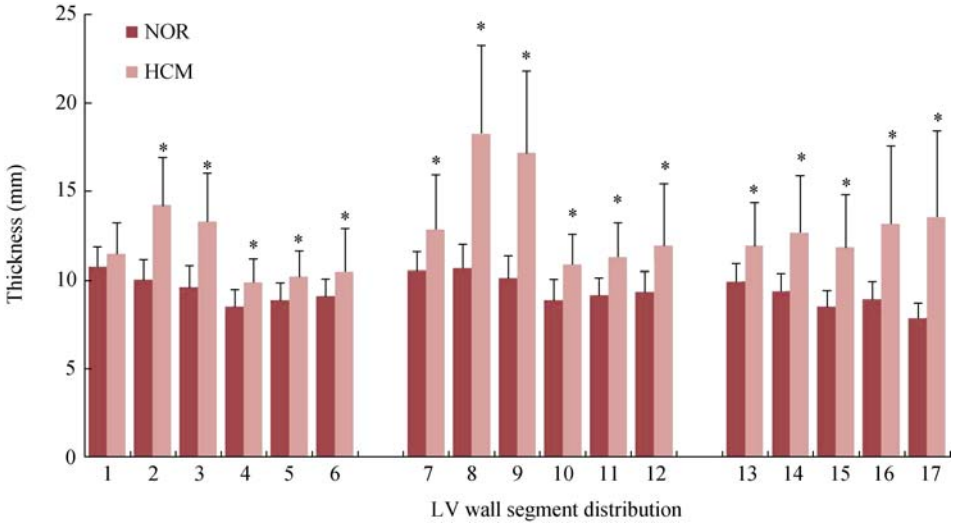


Figure 1. The comparison of wall thickness between the control and HCM group. At the basal level (from 1 to 6 segment): 1: anterior wall, 2: anterior interventricular septum, 3: posterior interventricular septum, 4: inferior wall, 5: inferior-lateral wall, 6: anterior-lateral wall; At the middle level (from 7 to 12 segment): 7: anterior wall, 8: anterior interventricular septum, 9: posterior inter-ventricular septum, 10: inferior wall, 11: inferior-lateral wall, 12: anterior-lateral wall; At the apical level (from 13 to 17 segment): 13: anterior wall, 14: septal wall, 15: inferior wall, 16: lateral wall, 17= apex. *P < 0.05 between the control and HCM; HCM: hypertrophic cardiomyopathy; LV: left ventricular; NOR: the normal control.

end systolic volume (ESV) (37.8 ± 8.9 mL in 2DE *vs.* 33.08 ± 9.9 mL in RT-3DE, $P < 0.0001$) resulted in a significant increase in the left ventricular ejection fraction (LVEF) in 2DE (63.2% ± 6.8% *vs.* 59.1% ± 6.4%, $P < 0.0001$). There was satisfactory agreement between 2DE and RT-3DE ($R^2 = 0.74$, $R^2 = 0.71$), and excellent agreement for LVEF between 2DE and RT-3DE ($R^2 = 0.81$), for determining EDV and ESV (Figure 2).

Diastolic parameters differed between the control group and HCM group. DDI in the HCM group became increasingly greater than those in the control group (8.2 ± 2.3 *vs.* 5.7 ± 1.6, $P < 0.0001$). Dispersion end diastole (DISPED) varied with DDI (29.13 ± 11.3 *vs.* 20.3 ± 6.7, $P < 0.0001$). There was no significant difference in PreRelax between the two groups, whereas PostRelax was significantly prolonged in the HCM group than those in the control group (8.4 ± 12.2 *vs.* 5.1 ± 4.9, $P = 0.0021$). This finding revealed that diastolic delay mainly contributed to the global diastolic dysfunction. EDSI was also significantly higher in the HCM group (39.07 ± 15.4 *vs.* 31.3 ± 12.0, $P < 0.0001$). This suggested that the LV longitudinal and circumferential diameters were changed in some patients with HCM (Table 2).

In the control group, the curves were smooth and regular, whereas the curves were significantly dyssynchronous in HCM (Figure 3). The Logistic regression was used to measure the matching degree between the hypertrophic segments and the segments with abnormal volumetric changes among the 17 segments (Table 3). There were significant differences in segments 1, 2, and 3 (area under the ROC curves: 74%, 84%, 79%, respectively and $P < 0.01$), meaning only the segments at the basal level had a good concordance and significant correlation between the hypertrophy of the abnormal volumetric segments.

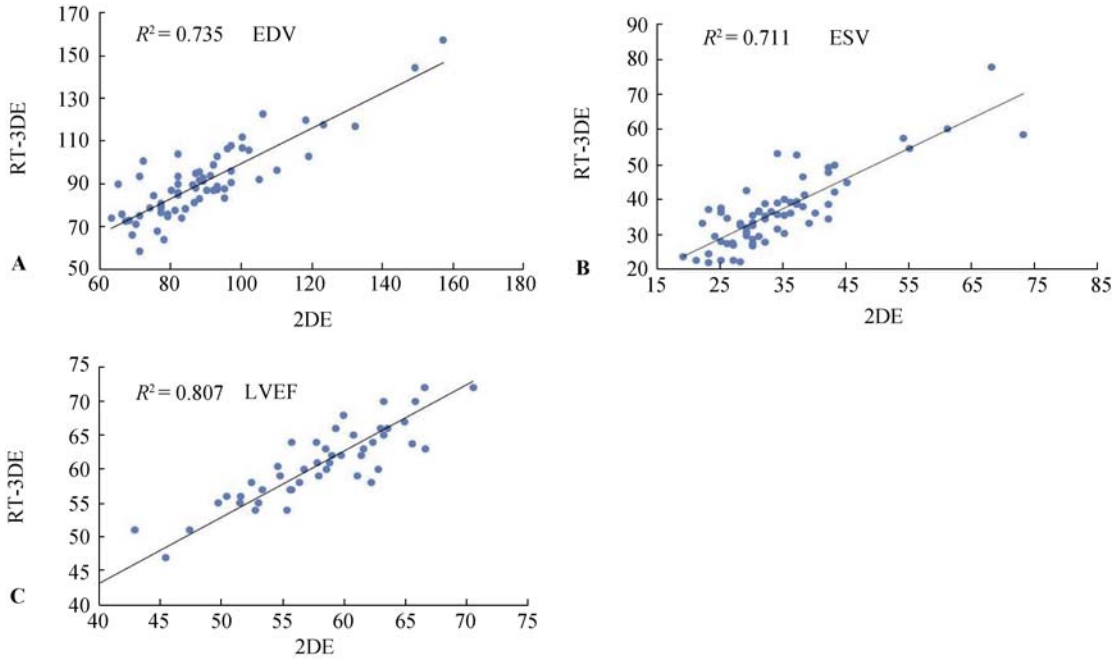
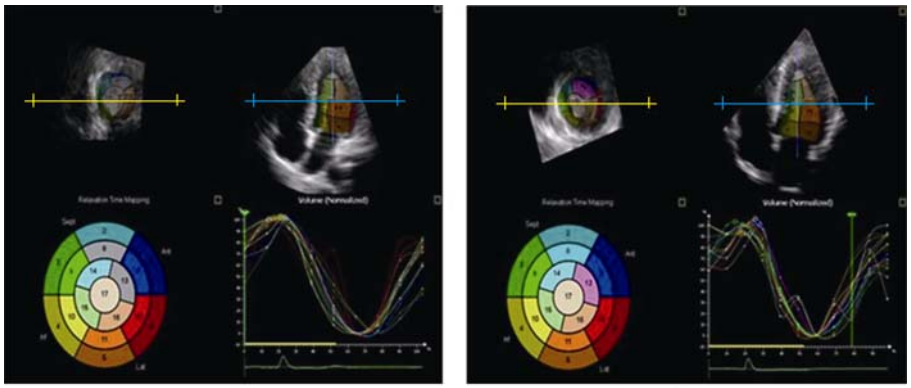


Figure 2. **Correlation in the measurements for EDV (A), ESV (B) and LVEF (C) obtained by 2DE and RT-3DE.** EDV: end diastolic volume; ESV: end systolic volume; LVEF: left ventricular ejection fraction; RT-3DE: real-time three-dimensional echocardiography; 2DE: two dimensional echocardiography.

Table 2. Comparison of RT-3DE measurements between normal and patient groups.

	Controls ($n = 50$)	Patients with HCM ($n = 65$)	*P* value
EDSI	31.3 ± 12.0	39.07 ± 15.4*	< 0.0001
DDI	5.7 ± 1.6	8.2 ± 2.3*	< 0.0001
DISPED	20.3 ± 6.7	29.13 ± 11.3*	< 0.0001
PreRelax	3.6 ± 3.05	3.5 ± 3.9	0.2384
PostRelax	5.1 ± 4.9	8.4 ± 12.2*	0.0021

*$P < 0.05$ *vs*. control subjects. EDSI: end-diastolic sphericity index; DDI: diastolic dyssynchrony index; DISPED: dispersion end diastole; HCM: hypertrophic cardiomyopathy; PreRelax: Pre-relaxation time volume; PostRelax: post-relaxation time volume; RT-3DE: real-time three-dimensional echocardiography.



A B

Figure 3. 17-segment normalized volume-time curves in the control and hypertrophic cardiomyopathy (HCM) group. (A): volume-time curves in the control group; (B): volume-time curves in the HCM group.

Table 3. Matching the location of hypertrophy and abnormal diastolic segments.

Segment	Wald χ^2 value	*P* value	Area under the ROC curves
*1	10.7715	0.0010	0.741
*2	12.0387	0.0005	0.839
*3	18.8795	< 0.0001	0.790
4	6.0988	0.0135	0.626
5	2.4448	0.1179	0.596
6	1.8624	0.1723	0.558
7	0.4359	0.5091	0.536
8	2.8230	0.0929	0.636
9	5.3251	0.0210	0.640
10	0.0006	0.9798	0.518
11	2.6962	0.1006	0.585
12	4.3701	0.0366	0.600
13	1.7105	0.1909	0.568
14	5.7363	0.0166	0.637
15	4.3774	0.0364	0.608
16	4.5229	0.0334	0.603
17	9.8348	0.0017	0.688

*$P < 0.05$ *vs*. control subjects, area under the ROC curves > 70% represents good prediction value. ROC: receiver operating characteristic.

3.5 Repeatability and reproducibility

Intra-observer repeatability and inter-observer reproducibility analysis demonstrated good agreement between 3D indices obtained by different observers or during different visits (Table 4). These results suggested 3D indices measurements are repeatable and reproducible.

4 Discussion

HCM is linked to considerable phenotypic heterogeneity in morphologic and clinical presentations. This study revealed different septal morphologies have different clinical features and outcomes.[15] The most common pattern in HCM is asymmetrical septal hypertrophy, but the distribution of hypertrophy is variable. Other LV morphologies are seen, including concentric hypertrophy, apical hypertrophy, and hypertrophy of the LV free wall.[16] We measured the LV wall thickness in 17 segments in patients with HCM (Figure 1). As previously reported, in patients with septal HCM, the septal morphology was used to classify patients into four subgroups: neutral, apical, sigmoidal and reverse curve.[17] However, we found most types were not present independently. They were often grouped together, which resulted in more complicated LV morphologic and functional changes. In

Table 4. Repeatability and reproducibility analysis.

	ICC		Repeatability	Reproducibility
	Repeatability	Reproducibility		
EDSI	0.91	0.92	0.35	0.38
DDI	0.93	0.94	0.27	0.32
DISPED	0.93	0.93	0.33	0.49
PreRelax	0.92	0.89	0.58	0.71
PostRelax	0.91	0.90	0.65	0.69

Repeatability (the coefficient of repeatability): two standard deviations of the differences between intra-observers; reproducibility (the coefficient of reproducibility): two standard deviations of the differences between inter-observers. DDI: diastolic dyssynchrony index; DISPED: dispersion end diastole; EDSI: end diastolic sphericity index; ICC: intra-class correlation coefficient; PreRelax: Pre-relaxation time volume; PostRelax: Post-relaxation time volume.

patients with apical HCM, all apical wall segments were involved, particularly in the lateral apical wall and apex.

While 2DE is a common diagnostic tool for assessing LV volume and function, it is limited by its dependence on geometrical assumptions, leading to inaccuracies in volume quantification.[18] Recent advances in 3DE technology has enabled the acquisition of non-stitched, real-time, large volumes at high volume rates of 3D images of the heart in one cardiac cycle.[19,20] Recent studies have proved that RT-3DE is a reliable technology in clinical practice, even in those with altered ventricular morphology due to cardiomyopathy.[21] This study found that the mean EDV and LVEF in patients with HCM were lower when measured by RT-3DE compared to 2DE, which suggests 2DE may overestimate LVEF and miss the diagnosis of patients with mild systolic dysfunction. Therefore, in patients with HCM, RT-3DE could be superior to 2DE for evaluation of functional mechanisms.

Altered diastolic function is a key histological feature of HCM, and the prevalence of clinical symptoms was relatively high in HCM patients experiencing heart failure symptoms despite a normal LVEF. This confirms the importance of the complex pathophysiology of HCM. Myocardial relaxation and LV filling play a critical role in this disorder.[22] In previous studies, HCM patients with diastolic dysfunction were demonstrated by conventional Doppler echocardiography, by measuring the E/Ea ratio, deceleration time and iso-volumic relaxation time.[23] One of the greatest advantages of the current RT–3DE systems is the ability to provide 17-segment real-time volumetric images of the entire heart, which facilitates the assessment of cardiac function. Increasing evidence suggests that LV intraventricular dyssynchrony can be assessed by analyzing LV regional volumetric changes from 3DE full volume data sets.[24] It may be used to obtain a systolic dyssynchrony index (SDI), which can predict the response to cardiac resynchronization therapy (CRT).[25] Left ventricular mechanical dyssynchrony has been recognized as a therapeutic indication for CRT in heart failure patients. Several studies have demonstrated that the generation of time-volume curves representing LV volume changes over the heart cycle is feasible and accurate.[26] Therefore, DDI should be also a valuable index for the quantitative analysis of LV global diastolic function. However, whether it is any advantage to evaluate diastolic function in patients with HCM is unclear. Our data suggests an increased DDI in end diastole was more prevalent in patients with HCM, reflecting that diastolic abnormality occurs in diastole in HCM patients with HCM, who had even mild or no symptoms, and that this change can be shown using RT-3DE. It is implied that the diastolic dyssynchrony could be a cause of global diastolic dysfunction in HCM. The finding suggests the DDI in diastole could be a marker of disease severity and diastolic dysfunction in RT-3DE. PreRelax and PostRelax were two specific indeices of RT-3DE, which indicate the cause of diastolic dysfunction. Our study showed diastolic delay in some segments could mainly contribute to the global diastolic dysfunction in HCM. This delay reflected the difference of regional diastolic function between hypertrophic myocardium and non-hyertrophic myocardium.[27]

Interestingly, our study demonstrated that not all abnormal volume-time curves could occur in the hypertrophic segments. Only three segments (segments 1, 2, 3) had excellent agreement with the hypertrophic segments. These segments were at the basal level. One possible explanation for this finding is that the base was apparently less affected by thickening in these patients. Segments without marked hypertrophy still demonstrated some abnormality, implying a global mechanical change in terms of regional dyssynchrony even in the region with relatively normal thickness. In addition, the most severely affected region was the apical region, irrespective of the distribution and degree of LV hypertrophy. This finding could be correlated with the increase in longitudinal strain and decrease in circumferential strain in apical region in HCM patients.[28] Thus, this phenomenon confirmed the irregular morphologic and complicated hemodynamic changes in HCM, which can be shown by RT-3DE.

In conclusion, this study describes a new method for the fast quantification of regional LV diastolic function and dyssynchrony with RT-3DE. DDI, as a valuable index, allows for the quantification of diastolic function. An increased DDI in diastole is observed in some HCM patients, which indicates the regional dyssynchrony in diastole is probably an important determinant of preclinical diastolic dysfunction. RT-3DE provides a simple, fast, and noninvasive approach to assess LV regional diastolic function and dyssynchrony.

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