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RESEARCH ARTICLE

Incremental value of contrast echocardiography in the diagnosis of left ventricular noncompaction

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Abstract **Contrast echocardiography with left ventricular opacification (LVO) improves the definition of endocardium in two-dimensional echocardiography (2DE). This study was aimed to determine whether LVO offered added diagnostic value in noncompaction of left ventricular myocardium (NCVM). A total of 85 patients (40 ± 20 years, 54 males) with suspected NCVM were subjected to transthoracic 2DE and LVO, and 40 healthy volunteers were examined with 2DE and assigned as control subjects. The location of NCVM, the thickness ratio of noncompacted to compacted myocardium (NCR), and the cavity size and ejection fraction of LV were quantified. Results revealed that NCVM was mainly located in the LV medium (53.2%), apical (46.2%) segments, and lateral wall (39.8%). The NCR obtained through LVO was greater than that detected through 2DE (4.2 ± 1.3 vs. 3.3 ± 1.2, $P < 0.001$), and higher inter-correlations and less intra- and inter-observer variabilities were determined in the former than in the latter. The NCVM detection rates were also increased from 63.5% via 2DE to 83.5% via LVO and 89.4% via 2DE combined with LVO (2DE + LVO) ($P = 0.0004$). The LV cavity size was greater and the LV ejection fraction (LVEF) was lower in the NCVM patients than in the control group ($P < 0.01$). In the NCVM group, the LV cavity size was higher and the LVEF was lower in LVO than in 2DE ($P < 0.01$). In conclusion, contrast echocardiography contributes significant sensitivity and reproducibility to routine transthoracic echocardiography in NCVM diagnosis. Therefore, this technique should be clinically performed to diagnose suspected NCVM.**

Keywords echocardiography; left ventricular noncompaction cardiomyopathy; echo contrast media

Introduction

Noncompaction of the ventricular myocardium (NCVM) is a genetically inherited form of cardiomyopathy. This condition is characterized by two layers of myocardium, namely, compaction and noncompaction layers, prominent trabeculations, and adjacent deep intertrabecular recesses that communicate with the left ventricular (LV) cavity. NCVM is also manifested by various clinical features, including asymptomatic to heart failure, thromboembolism, arrhythmias, and sudden cardiac death [1]. NCVM affects 0.01%–0.26% of adults referred for echocardiography, but the prevalence of isolated NCVM in adult population remains unclear [2].

With advanced cardiac imaging modality, increased clinical awareness, and improved family screening methods, the detection rate of NCVM has increased. Robust and timely diagnosis of NCVM plays an important role in early medical treatment and cardiogenetic screening of first-degree relatives.

Although cardiac magnetic resonance imaging (cMRI) is considered a gold standard of NCVM diagnosis, conventional transthoracic echocardiography (TTE) remains the first line of modality. In clinical practice, NCVM is likely under diagnosed through two-dimensional echocardiography (2DE) because of diverse pathological features, insufficient imaging diagnostic experiences, unfamiliarity with this disease, and suboptimal echo imaging quality [3]. Contrast echo with left ventricular

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opacification (LVO) can significantly improve the definition of the left ventricular endocardium; as such, this technique is recommended by the American Society of Echocardiography (ASE) when suboptimal imaging is achieved and thus has been widely used in echo laboratories and clinical settings [4,5]. The application of contrast echo in NCVM diagnosis has been reported largely in case studies. In our study, the diagnostic value of LVO performances in NCVM patients was prospectively evaluated by comparing this technique with conventional transthoracic 2DE. This study demonstrated the relevant contributions of LVO in NCVM diagnosis.

Materials and methods

Study subjects

(1) In the NCVM group, 85 patients (mean age = 40 ± 20 years, 54 males) with suspected NCVM diagnosed through 2DE were recruited from March 2011 to February 2013 in our department at Ultrasound Medical Imaging Union Hospital, Tongji Medical College of HUST. (2) In the normal group, 40 age-matched healthy volunteers (mean age = 40 ± 23 years, 20 males) were recruited as controls. These volunteers were investigated in terms of their medical history, physical examination, and electrocardiogram and 2DE findings. Cardiovascular diseases were excluded. This study was approved by the institutional research ethical committee. Informed consents were obtained from each participant.

Conventional transthoracic 2DE

The patients and volunteers were subjected to 2DE by using a Philips iE33 echo machine (Philips Medical Systems, Best, The Netherlands) equipped with S5–1 (1–5 MHz) and S8–3 (3–8 MHz) probes and a left ventricle opacification (LVO) model for contrast modality. The patients were scanned in the left lateral decubitus with normal breathing, and a chest lead electrocardiogram was connected simultaneously. Echo image loops were recorded in three continuous cardiac cycles in the parasternal left ventricle (LV) long-axis view, parasternal LV short-axis views (basal, medial, and apical levels), and apical views (two, three, four, and five chamber views). Left ventricular end-diastolic diameter (LVEDD), volume (LVEDV), end-systolic diameter (LVESD), and volume (LVESV) were measured using M-mode echo in the parasternal LV long-axis view. LV ejection fraction (LVEF) was calculated by using Biplane Simpson's method. The ratios of the early (E) to late (A) ventricular filling velocities from mitral inflow (E/A ratio) were recorded through a pulsed wave Doppler to assess LV diastolic functions.

An AHA/ACC 16-segment model was used to identify the location of NCVM [6]. NCVM segments were detected by using a two-layered (compacted and noncompacted layers) myocardial structure, where the end-systolic thickness ratio of noncompacted to compacted myocardium (NCR) was > 2 for prominent trabeculations with a color Doppler flow in deep perfused intertrabecular recesses [7–10]. The segments with the most typical noncompaction image were selected for NCR measurement. These parameters were determined for three cardiac cycles, and mean values were recorded for data analysis.

LVO and its reproducibility assessment

All of the patients were subjected to LVO. No patients in the NCVM group were allergic to the components of SonoVue (Bracco Diagnostics Inc., Milan, Italy) and other contraindications [11]. The echocardiography system was set up with an intermediate mechanical index maintained at around 0.3–0.5 to obtain a LVO image. Wall motion was observed through real-time imaging during a slow bolus injection of a contrast agent via the left antecubital vein at a rate of 1 ml/min with a total volume of 1.0–1.5 ml. Subsequently, a slow saline flush (5 ml) was also provided for 10 s to optimize cavity opacification [5]. Repeat boluses were administered with at least 2 min of interval if necessary [12]. The 2DE views and measurements were repeated in a LVO mode, and gain and compression settings were optimized to minimize far-field attenuation [4].

The location of NCVM was independently assessed through 2DE, LVO, and 2DE and LVO combination. NCR was calculated through 2DE and LVO, and then independently analyzed by two experienced echo-cardiologists for inter-observer reproducibility. Intra-observer analysis was performed by using the recorded images 4 weeks after the initial reading was conducted.

Statistical analysis

Data were statistically analyzed using SPSS 20, Prism 5.0, and MedCalc 16.2. Continuous variables were expressed as mean ± standard deviations. 2DE data from NCVM and normal groups were compared through one-way ANOVA. Echo data obtained through 2DE and LVO were compared via paired *t*-test. The incidences of NCVM among different imaging modalities were compared through chi-square test. The intra- and inter-observer reproducibility of NCR was assessed by using Bland–Altman plot, with a coefficient of variation, Pearson's correlation, and intra-class correlation coefficient (ICC). The coefficient of variation was defined as the standard deviation of differences between two readings in the percentage of the mean. P values < 0.05 were considered statistically significant.

Results

LV chamber size and function

The LV cavity size (LVEDD, LVEDV, LVESD, and LVESV) was larger and the LVEF and E/A ratio were lower in the NCVM group with 2DE than in the normal group ($P < 0.05$). The LV cavity size (LVEDD, LVEDV, LVESD, and LVESV) was also larger and the LVEF was lower in the NCVM group with LVO than in the NCVM group with 2DE ($P < 0.05$; Table 1).

Detection and distribution of NCVM

The characteristic images of NCVM on LVO are a two-layered LV myocardium and hypertrabeculation with deep intertrabecular recesses, which became expanded and filled with contrast microbubbles (Figs. 1 and 2). Among the whole 1360 LV segments in the NCVM group, more segments were adequately visualized for analysis on LVO than on 2DE (1278 vs. 1183, 93.97% vs. 86.99%, $P < 0.0001$). More noncompaction segments were detected through LVO than through 2DE (314 vs. 262, 23.09% vs. 19.26%, $P < 0.0001$). Of the 921 segments interpreted as normal on 2DE, 52 (5.65%) were non-compacted on LVO. The majority of NCVM detected through LVO was located in medium (53.18%), apical segments (46.18%), and lateral wall (39.81%). NCVM was rarely involved in the basal segment (0.64%). Despite similar diagnostic performances between 2DE and LVO in the basal lateral and mid-anterior segment, LVO revealed more NCVM segments than 2DE did in the other LV segments (Fig. 3).

Comparison and reproducibility analysis of noncompaction recesses

The NCR obtained through LVO was greater than that obtained through 2DE (Table 1). Bland–Altman analysis revealed that NCRs derived by two readings, especially through LVO, were highly consistent (Fig. 4). The intra-observer reproducibility for NCR through 2DE and LVO were also excellent, with ICCs of 0.965 and 0.988, respectively. The inter-observer reproducibility of this parameter was also good, with ICCs of 0.931 and 0.979, respectively (Table 2). The intra- and inter-observer reproducibility and consistency are summarized in Table 2 and Fig. 4, respectively. The SD observed through LVO was smaller than that observed through 2DE (inter-observer SDs were 0.8 and 1.08; intra-observer SDs were 0.26 and 0.32, respectively).

Diagnostic rate comparison of 2DE and LVO

The diagnostic rates of NCVM through 2DE, LVO, 2DE and LVO combination (2DE + LVO) were significantly different ($P < 0.05$). The highest and lowest rates were obtained through 2DE + LVO (89.4%) and 2DE (63.5%), respectively (Table 3).

Discussion

In the clinical diagnosis of NCVM, transthoracic 2DE with color flow mapping (CFM) has been widely applied as a first-line modality in clinical settings and family screening. Several imaging criteria of NCVM, including Jenni and Stollberger's echocardiographic criteria and Grothoff and Jacquier's CMR criteria [7–10], have been established. NCVM may be diagnosed in patients with dilated or hypertrophic cardiomyopathy because of abnormal wall thickening and prominent hypertrabeculation [13]. Poor echocardiographic imaging quality, diverse pathological features, insufficient awareness, and limited experiences may cause underdiagnosis or misdiagnosis of NCVM [14]. With an image point of view, routine 2DE for NCVM diagnosis exhibited several limitations, including suboptimal echo images, less sensitivity when subtle, long, and narrow intertrabecular recesses are displayed, and artifacts on color flow mapping

Table 1 Echo parameters in NCVM and normal groups

Variables	NC-2DE (n = 85)	NC-LVO (n = 85)	Normal 2DE (n = 40)	P value (NC-2DE vs. normal 2DE)	P value (NC-LVO vs. NC-2DE)
LVEDD (mm)	58.9±11.6*	65.2±7.8**	45±5.1	<0. 0001	0.002
LVEDV (ml)	121±11.5*	162±14.8**	95±14.8	0.0371	<0. 001
LVESD (mm)	43.0±3.44*	47.8±5.67**	33±4.0	0.0012	<0. 001
LVESV (ml)	74.3±3.94*	84.7±2.46**	44±4.4	<0.0001	<0. 001
LVEF (%)	40.8±13.2*	38.2±12.4**	65.6±7.1	0.0435	<0. 001
E/A ratio	0.82±0.32*	0.84 + 0.46	1.62±0.5	<0. 0001	0.225
NC ratio	3.33±1.17	4.16±1.32**	N/A	N/A	<0. 001

Significant differences compared with normal 2DE are given (*, $P<0.05$). Significant differences compared with NC-2DE are given (**, $P<0.05$). NC, noncompaction cardiomyopathy; 2DE, conventional two-dimensional echocardiography; LVO, left ventricular opacification; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities from mitral inflow; NC ratio, end-systolic thickness ratio of noncompacted to compacted myocardium.

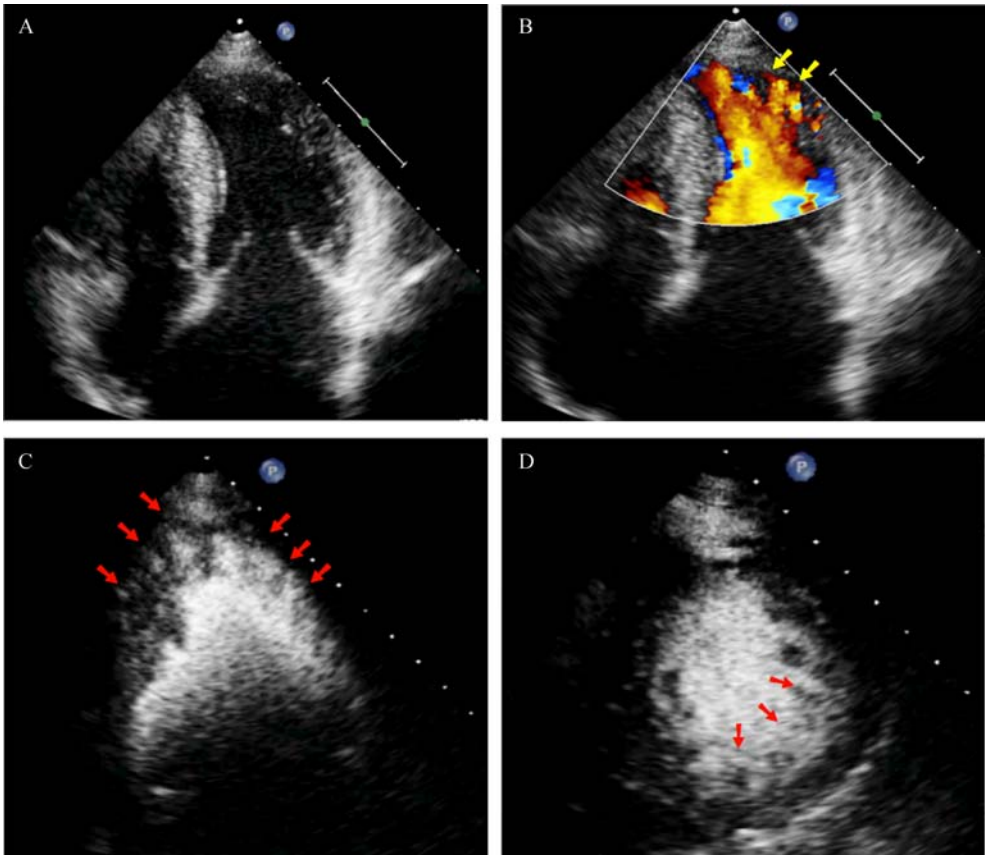

Fig. 1 2DE and LVO images in a margin case. (A) No clear NCVM lesion was detected through conventional 2DE. (B) Deeply perfused intertrabecular recesses (arrows indicated) with blood flow communicating with the LV cavity were detected. (C and D) Intertrabecular recesses were filled with contrast microbubbles in apical 2-chamber and LV short-axis views (indicated by arrows).

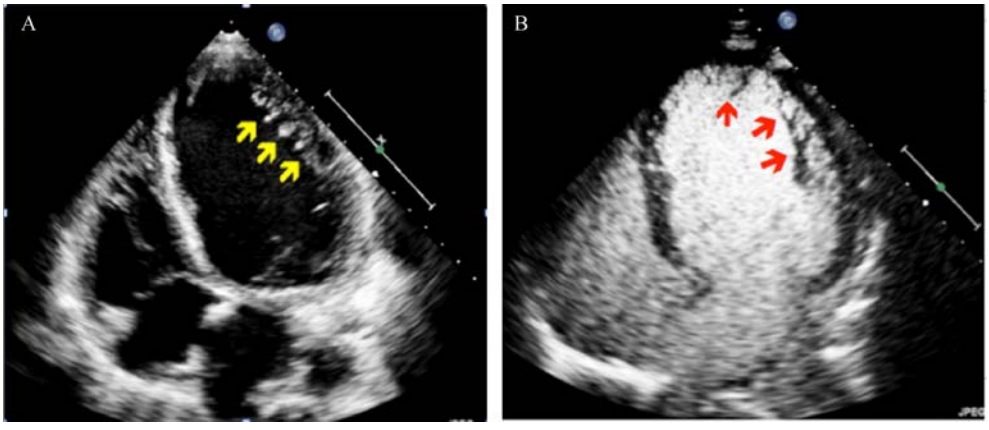

Fig. 2 Comparison of NCVM locations through 2DE and LVO. (A) Conventional 2DE revealed prominent trabeculations in NCVM in the lateral wall (arrows indicated). (B) Intertrabecular recesses were perfused with contrast agents and thus revealed NCVM in the lateral wall and apex through LVO (arrows indicated).

when velocity is set at 20 cm/s to 30 cm/s to visualize blood flow communicating between the recesses and the LV cavity. Contrast echo with LVO can significantly improve the left ventricular endocardium definition and thus has been recommended by the ASE when suboptimal imaging is obtained [4,5]. On the basis of Jenni's classic echocardiographic diagnostic criteria for NCVM, we demonstrated in a relatively large series that LVO could contribute to routine transthoracic two-dimensional echo to identify subtle noncompaction myocardium.

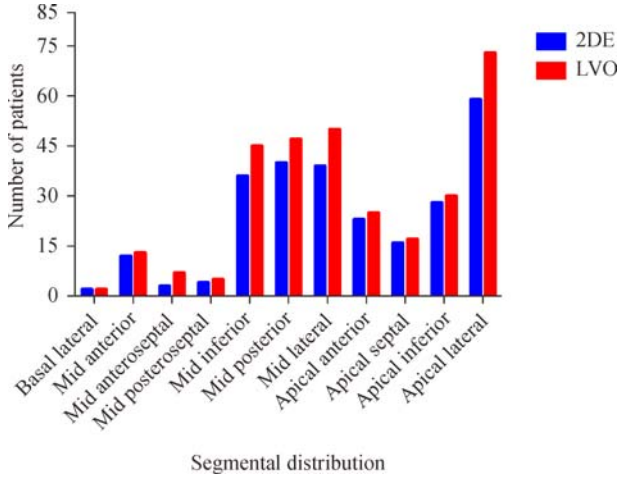

Fig. 3 Distribution of NCVM lesions on 2DE and LVO. NCVM is predominantly localized in the apical and mid-ventricular segments and lateral wall. More segments were detected through LVO than through 2DE.

Clinical applications of LVO in NCVM

Contrast-enhanced echo through LVO improves the determination of the LV endocardial border, which is recommended when suboptimal images are obtained, which is defined as the inability to detect two or more contiguous segments in apical views. Characteristic deep recesses may be identified by visualizing the contrast medium-filled intra-cavitary blood between prominent LV trabeculations when NCVM is suspected through 2DE. In this setting, an intermediate harmonic MI (0.3–0.5) and a noncompacted-to-compacted ratio ($>$ 2:1) are preferred [5,7]. LVO can also improve the accuracy of LV volume and function assessment, and the detection of apical thrombi when a foreshortened apex near-field artifact is observed through 2DE. Considering safety, researchers widely use FDA-approved SonoVue in clinical studies. In our study, no side effects were observed during or after contrast agent was administered.

Incremental value of LVO in NCVM diagnosis

LVO provides a more informative endocardial border definition than conventional 2DE does [15]. Studies on contrast-enhanced echo in NCVM are mostly based on case studies [16]. Dr. Groot-de pioneered a study by applying contrast echo in 18 patients with suspected NCVM through conventional 2DE and revealed that 16 patients suffered from NCVM [17]. Furthermore, 14% segments interpreted as normal through 2DE are diagnosed as NCVM through contrast echo [17].

In this study, long and narrow recesses were hardly detected through 2DE because of insufficient dilatation.

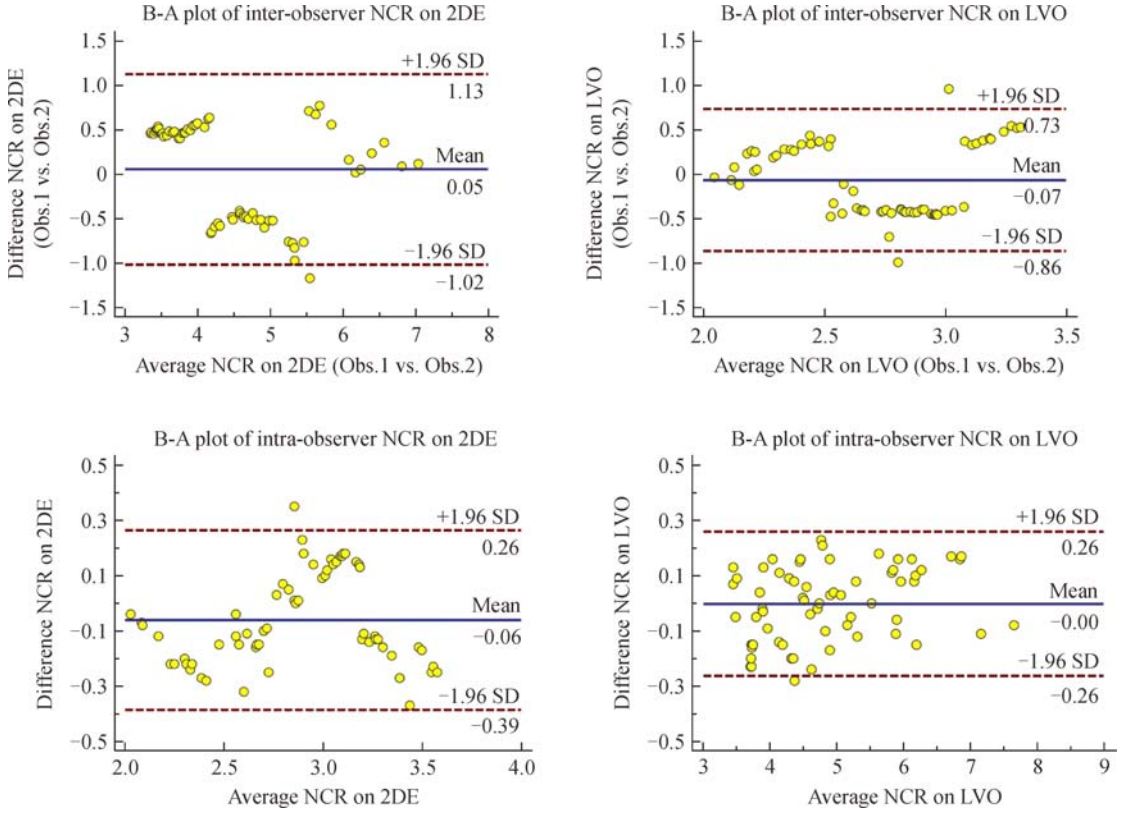

Fig. 4 Inter- and intra-observer consistency assessment of the thickness ratio of noncompacted to compacted myocardium (NCR) through Bland–Altman plots.

Table 2 Intra- and inter-observer reproducibility for NCR

	Intra-observer			Inter-observer		
	CV (%)	*R* (Pearson's)	ICC (95% CI)	CV (%)	*R* (Pearson's)	ICC (95% CI)
2DE	4.290%	0.966*	0.965 (0.944–0.979)	9.676%	0.925*	0.931 (0.891–0.958)
LVO	2.336%	0.995*	0.988 (0.981–0.993)	8.218%	0.986*	0.979 (0.966–0.993)

2DE, conventional two-dimensional echocardiography; LVO, left ventricular opacification; CV, coefficient of variation; ICC, intra-class correlation coefficient; *, $P<0.0001$.

Table 3 Comparison of the NCVM detection rates of 2DE, LVO, and 2DE + LVO

	Positive case	Negative case	Detection rate	*P*
2DE	54	31	63.5%	
LVO	71	14	83.5%	0.0127*
2DE + LVO	76	9	89.4%	<0.0001#

2DE, conventional two-dimensional echocardiography; LVO, left ventricular opacification. 2DE + LVO, 2DE and LVO combination. #, comparison among the three imaging groups. *, comparison between 2DE and LVO.

Some fine recesses were easily missed through CFM, although the lowest blood flow velocity was used. The probe frequency was normally at 3–3.5 MHz for adult echo, with a resolution of 1.5–2 mm. In theory, subtle and narrow recesses with a width of < 1.5 mm are poorly imaged. In practice, the actual echo resolution and performance are further reduced because of reverberation and other interferences. However, these limitations, especially in some difficult-to-image cases, can be largely overcome by LVO. This observation is due to the improvement of LV endocardial border delineation, and the contrast agent consisted of tiny microbubbles is easily filling the atypical subtle intertrabecular recesses. The mean diameter of this small microbubbles is 2.5 μm. In a recent study on subtle noncompaction in patients with hypertrophy cardiomyopathy (HCM), LVO also helps detect subtler noncompaction segments than 2DE does; in particular, 181 and 46 segments of 647 LV segments in 40 patients with HCM are found through LVO and 2DE, respectively [15]. In our previous study, a 30-member family suffering from NCVM and hypertrophic cardiomyopathy was screened through TTE 2DE, LVO, and cMRI. Two cases with suspected antero-septal hypertrophy and three cases with suspected NCVM were overlooked when 2DE was applied, but these cases were diagnosed when contrast echo was utilized. LVO provided more details regarding NCVM segments located in the antero-septum and the apex, which were validated through cMRI. The obtained wall thickness and N/C ratio were consistent between 2DE and LVO. We demonstrated that LVO provided incremental information regarding endocardial border delineation, lesion location, and quantification; this technique also revealed consistent findings with those of cMRI [18]. Compared with real-time three-dimensional echo, contrast-enhanced real-time three-dimensional echo largely improves the LV endocardium definition and image quality grading in the NCVM group; contrast-enhanced real-time three-dimensional echo also improves the evaluation of inter-observer and intra-observer reproducibility in LV volume and function [19]. In our study, the contribution of LVO was validated, and its accuracy, detection rate, and reproducibility in NCVM diagnosis were systematically investigated. The combined diagnostic modality of LVO and 2DE yielded the highest diagnostic rate for NCVM. Although LVO demonstrated an excellent performance in detecting recesses, diagnosis may potentially be missed when images were suboptimal because of attenuation, especially in far-field attenuation [20]. This limitation could be overcome by 2DE + LVO to the highest extent among the techniques employed in this study. In our experience, applying a modest amount of contrast agents through rapid injection can minimize attenuation problems [18].

Contrast images can improve the reproducibility and accuracy of our interpretation by experienced and inexperienced image readers [21]. In our study, intra- and inter-observer reproducibility in NCVM diagnosis were improved through LVO. The size of the LV chamber was also larger when LVO was employed. Contrast agents can be used to optimize the imaging of some insufficiently dilated recesses. Consequently, blood-tissue boundary delineation is more robust. This performance also explains the relative underestimation of cardiac volumes and NCR through 2DE [22].

Study limitations

Previously published studies on the assessments of NCVM through echocardiography and cMRI modalities were largely case reports. Thuny *et al.* [23] reported their findings on 16 suspected NCVM cases by using side-by-side comparison of cMRI with conventional 2DE without LVO regarding the detection, distribution, and NCR of NCVM at end-diastole and end-systole, which confirmed that cMRI is more sensitive than other techniques. Our group previously confirmed the consistency between cMRI and 2DE with LVO in NCVM familiar study [18]. Therefore, this technique was not prospectively compared with cardiac magnetic resonance imaging in this study because of resource limitations. Nevertheless, we will perform this comparison in our future research.

Conclusions

Our study first demonstrated that LV contrast echocardiography provides greater sensitivity and reproducibility than routine echocardiography in NCVM diagnosis. Therefore, we would advocate its wider use as an important supplement to 2DE for NCVM diagnosis.

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Compliance with ethics guidelines

Xiaoxiao Zhang, Li Yuan, Linli Qiu, Yali Yang, Qing Lv, Lin Li, Jing Wang, Lin He, Li Zhang, Xinfang Wang, Mingxing Xie, and Xu Yu Jin declared that they have no conflicts of interest in connection to this research. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 [24]. Informed consent was obtained from all patients who participated in this study.

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