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Quantitative Differentiation of Left Atrial Performance in Hypertrophic Cardiomyopathy

Comparison Between Nonobstruction and Occult Obstruction With 4-dimensional Volume-strain

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Objective: The objective of this study was to describe the different components of left atrial (LA) dysfunction predictors in non-obstructive and occult obstructive hypertrophy cardiomyopathy (HCM) patients especially with preserved left ventricular (LV) ejection fraction, particularly using LA 4-dimensional (D) longitudinal and circumferential strains.

Methods: Twenty-eight nonobstructive HCM patients and 30 occult obstructive HCM patients according to LV outflow tract gradient at rest and after exercise were prospectively enrolled. 4D echocardiographic evaluation was performed in 58 HCM patients, both nonobstructive and occult obstructive, and 38 control subjects. LA reservoir, conduit, contractile functions were performed by 4D volume-strain with volumes and longitudinal, circumferential strains.

Results: Optimal correlation coefficients obtained between LV 4D mass (index) and LA 4D longitudinal/circumferential strain ($r = -0.860$ to 0.518, all $P < 0.001$). Both nonobstructive and occult obstructive HCM patients had increased volumes and significantly decreased longitudinal, circumferential strain values with lower reservoir, conduit, contractile functions than the controls (all $P < 0.001$). Occult obstructive HCM patients presented incremented volumes compared with nonobstructive ones ($P < 0.001$ to 0.003). Lower conduit function and higher contractile function indicated with lower reservoir function revealed by circumferential strain in occult obstructive HCM patients than nonobstructive ones ($P < 0.001$ to 0.017). Interclass correlation coefficients of intraobserver and interobserver in the LV and LA 4D value evaluations were > 0.75 and > 0.85, respectively.

Conclusions: LA volumes were significantly increased and LA reservoir, conduit, and contractile functions were significantly impaired in HCM patients. Furthermore, different performances of LA functional analyses in nonobstruction and occult obstruction patients with 4D volume-strain echocardiography may facilitate the recognition of subtle LA dysfunctional differentiation in HCM patients.

Key Words: hypertrophic cardiomyopathy, preserved ejection fraction, left atrial function, 4-dimensional, volume-strain

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease with heterogenous clinical presentation and natural history.[1] It is first recognized as a disease of obstruction to left ventricular (LV) outflow tract, the nonobstructive subset of patients designed as incapable of developing mechanical impedance to outflow at rest or with physiological exercise. The HCM prognosis is particularly the common inherited and is still a matter of debate.[2–4] Patients with nonobstructive HCM are thought to be at relatively low risk as compared with obstructive HCM.[5] LV outflow tract obstruction results in reduced exercise capacity with a varied phenotypic expression ranging from asymptomatic to symptomatic LV systolic dysfunction. These pathophysiological mechanisms can convert these patients from symptomatic to congestive heart failure but preserved ejection fraction.

As we know, patients with occult obstruction who show LV hypertrophy and systolic dysfunction with lower ventricular volume frequently have more risk factors of LV diastolic dysfunction. LV diastolic dysfunction includes altered LV relaxation and reduced compliance with raised LV filling pressure. The filling pressure rising in LV leads to an increase of left atrial (LA) pressure. LV dysfunction inherent to HCM results in pressure overload of the LA and consecutively in its dilatation.[6,7] LA volume index is considered superior as an estimate of LA size and is suggested by initial studies to be of prognostic value for general risk stratification in patients with HCM.[8,9] LA remodeling has been shown to be an independent risk factor for cardiac events such as heart failure. The interplay between LA and LV functions throughout the cardiac cycle (LA-LV coupling) is crucial in different pathophysiological conditions.[10]

LA strain has been proposed as an alternative approach for LV filling pressure and LA dysfunction assessment. In the context of HCM, reduced 3-dimensional (D) atrial strain has been demonstrated to differentiate between patients with LV diastolic dysfunction from those who already suffer from heart failure with preserved ejection fraction.[11] Other results show that the strongest echocardiagraphic predictor of LA reservoir,

conduit, and contractile dysfunction were determined by deformation values, whereas LA strain positively correlated with LA function, underlining the importance of LA-LV coupling.[12,13] It is still unknown whether longitudinal strain combined with circumferential strain offers by LA 4D echocardiography could more sensitively and specifically detect LA dysfunction in patients with occult obstructive HCM at rest. The particular aim of this study was to use the latest developed 4D technique to comprehensively investigate LA volumetric and functional characteristic differentiation from occult obstructive HCM to nonobstructive HCM, and to analyze LA dysfunction predictors of different components in patients with preserved left ventricular ejection fraction (LVEF).

METHODS

Study Population

Fifty-eight HCM patients without previously established arterial hypertension (blood pressure of <140/90 mm Hg or no antihypertensive drugs currently in use) were prospectively included in 2019. The enrolled patients were divided into non-obstructive and occult obstructive groups according to LV outflow tract gradient at rest (18 ± 9 vs. 19 ± 11 mm Hg) and after exercise (23 ± 7 vs. 54 ± 12 mm Hg) analyzed by echocardiography. They were compared with a normotensive control group of 38 age-matched controls without LV hypertrophy, arterial hypertension, and any history of cardiovascular disease recruited within the hospital staff in randomly. Exclusion criteria were: primary and secondary arterial hypertension, pulmonary arterial hypertension, evidence or history of atrial arrhythmia, LVEF of <52% (determined using the biplane Simpson), known coronary artery disease, moderate or severe valvular disease at rest, acute or chronic renal disease. The research protocol was approved by the regional ethics committee of Nanjing First Hospital, and all included patients provided written informed consent.

Echocardiography

Transthoracic echocardiographic examinations were performed at rest in the left lateral recumbent position with Vivid E95 Version 203 instrument (GE Medical Systems, Horten, Norway). The ultrasound investigation started with an optimal electrocardiogram signal with a clear definition of the QRS-complex and P-wave ensuring a consistent electrocardiogram triggering. Images were obtained using Vivid Dimension with a 2 to 4.5 MHz M5Sc 2D transducer and a 2.5 to 4 MHz 4Vc 4D transducer. Images were stored digitally and were analyzed offline using EchoPAC software (GE Healthcare, Milwaukee, WI).

2D and Doppler Assessment

Traditional 2D evaluation was performed with maintained images. LVEF was obtained by the modified biplane Simpson method. LV diastole diameter and LA systole diameter were observed and measured in long-axis view. Peak early diastolic (E) and late diastolic (A) filling velocities were assessed by the transmitral flow measured by pulsed-Doppler ultrasound. Peak mitral diastolic annular velocities (E′ and A′) were obtained in the apical 4-chamber view by pulsed tissue Doppler echocardiography, averaging septal and lateral velocities. Left ventricle filling pressure was evaluated according to E/E′.

4D Volume and Strain Assessment

Following conversion to the 4D volume transducer with an apical 4-chamber view, the LV and LA walls were

displayed clearly. Images of 3 cardiac cycles were acquired with angle (70 to 80 degrees)×(70 to 80 degrees) and 4D frame rate >40% of the heart rate. Then, as the 4D mode was entered, the patient was asked to hold their breath at the end of expiration. The imaging was maintained and real-time cardiac cycles in the form of 4D dynamic images were acquired.

Quantification of LV mass (index) was performed according to the 4D echocardiography: Entering volume 4D auto LVQ measurement mode, aligning view of apical 4-chamber, adjusting the baseline and angle on every plane at end-diastole, clearly displaying the image of the mitral annulus, wall and apex. LV border was manually traced using the point-and-click technique. The LV volume was presented end-diastole to end-systole; LVEF and LV mass were calculated with 4D algorithm automatically. LV mass index was identified by indexing LV mass to body surface area. The software provides the following standard 4D echocardiographic parameter values: LV end-diastolic volume (mL), LV end-systolic volume (mL), LVEF (%), LV end-diastolic mass (g), and LV end-diastolic mass index (g/m²) (Fig. 1).
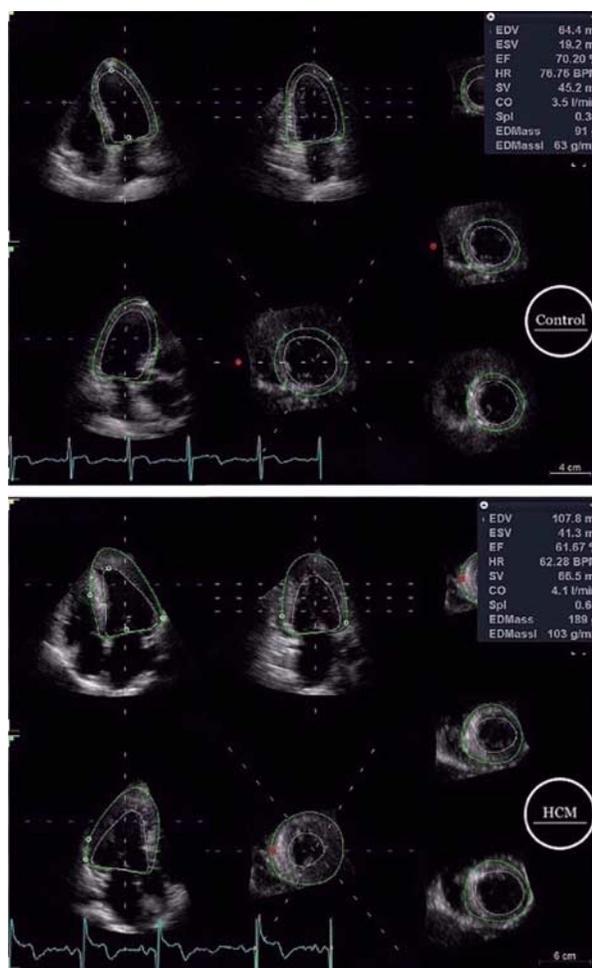
FIGURE 1. LV 4D mass (index) clarified by 4D echocardiography in controls and HCM patient. CO indicates cardiac output; EDmass, end-diastolic mass; EDmassI, end-diastolic mass index; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; SpI, sphericity index; SV, stroke volume. full color online

Deformation analysis of the LA was performed by 4D echocardiography in the apical 4-chamber view: Entering volume 4D auto LAQ measurement mode, setting landmark and adjusting the mitral valve center on every plane at end-systole, clearly displaying the image of the mitral annulus, wall and roof. The endocardial mesh was used to measure the end-systolic and end-diastolic volumes, and strain assignment on every plane. Images were acquired with the reference point set to the onset of the QRS-complex resulting in the acquisition of reservoir, conduit, and contractile function. The software provides the following standard 4D echocardiographic parameter values: left atrial minimal volume (LAVmin, mL), left atrial maximum volume (LAVmax, mL), left atrial maximum volume index (LAVmaxI, mL/m^2), left atrial volume preatrial contraction (LAVpreA, mL), left atrial emptying fraction (LAEF, %), left atrial peak circumferential strain of reservoir function (LASr, %), left atrial peak longitudinal strain of conduit function (LAScd, %), left atrial peak longitudinal strain of contractile function (LASct, %), left atrial peak circumferential strain of reservoir function (LASr-c, %), LAScd-c (peak circumferential strain of conduit function, %), and LASct-c (peak circumferential strain of contractile function, %) (Fig. 2).

All echocardiographic measurements were analyzed by 2 independent operators without the knowledge of the patients' clinical status, and adopted the average values of 3 cycles.
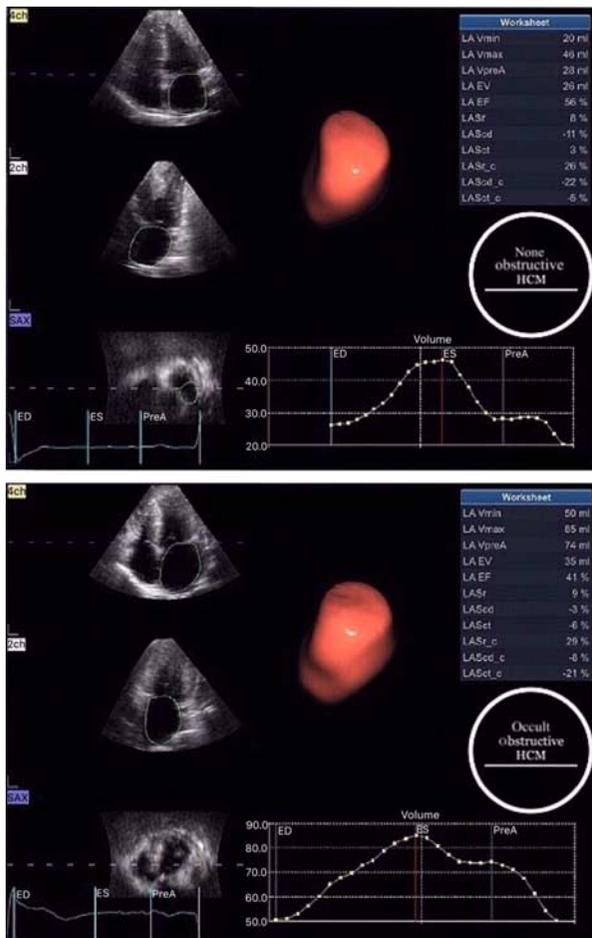
FIGURE 2. LA 4D volume-strain clarified by 4D echocardiography in nonobstructive and occult obstructive HCM patients. full color online

Statistics

Data were expressed as mean ± SE for continuous variables and as percentages for categorical variables. Statistical analysis was performed using IBM SPSS Statistics 23.0 software. Correlation between LV 4D mass (index) and LA 4D strain parameters was tested by the Pearson correlation. The Student t test had been used for comparison of groups after having verified the normal distribution of variables. Between-group differences were compared by Analysis of variance with Tukey post hoc test. P-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were plotted to examine the ability of LA 4D volume-strain to differentiate the occult obstructive HCM, nonobstructive HCM, and controls. Interclass correlation coefficient (ICC) was used for the evaluation of reproducibility.

RESULTS

Baseline Characteristics and General Data

Twenty-eight nonobstructive HCM patients, 30 occult obstructive HCM patients, and 38 controls were enrolled into the present study. Baseline characteristics and traditional echocardiography results of the control, nonobstructive HCM, and occult obstructive HCM groups are shown in Table 1. Pulsed-Doppler and tissue Doppler echocardiography presented E/A ratio, E′/A′ ratio, E/E′ ratio of LV diastolic function, and filling pressures. These parameters were impaired in nonobstructive HCM and occult obstructive HCM patients, whereas LVEF was preserved ($P < 0.05$). LA diameter in long axis was significantly greater in all HCM patients than in controls ($P < 0.001$). The patients with occult obstructive HCM were more likely to undergo moderate mitral regurgitation (MR) after exercise as compared with the control group ($P < 0.05$).

4D Parameter Evaluation

HCM patients in both groups had significantly higher LV end-diastolic mass and LV end-diastolic mass index than controls (all $P < 0.001$). Correlation analysis indicated significant relationship between LV 4D mass, 4D mass index, and LA 4D longitudinal (LASr: $r = -0.860$ to -0.826, $P < 0.001$, LAScd: $r = 0.747$ to 0.721, $P < 0.001$, LASct: $r = 0.761$ to 0.727, $P < 0.001$)/circumferential (LASr-c: $r = -0.782$ to -0.746, $P < 0.001$, LAScd-c: $r = 0.651$ to 0.573, $P < 0.001$, and LASct-c: $r = 0.518$ to 0.541, $P < 0.001$) strain (Fig. 3). HCM patients in 2 groups had impaired LAEF as compared with controls (all $P < 0.001$). Both nonobstructive HCM and occult obstructive HCM patients had increased LAVmin, LAVmax, LAVmaxI, LAVpreA, and significantly decreased strain values with lower LASr, LAScd, LASct, and LASr-c, LAScd-c, LASct-c than the controls (all $P < 0.001$). Occult obstructive HCM patients presented incremented LAVmin, LAVmax, LAVmaxI, and LAVpreA compared with nonobstructive HCM patients (LAVmin: $P = 0.003$; LAVmax: $P = 0.002$; LAVmaxI: $P < 0.001$; LAVpreA: $P = 0.003$). Lower LAScd-c, higher LASct-c with lower LASr-c separated occult obstructive HCM patients from nonobstructive HCM patients (LAScd-c: $P < 0.001$; LASct-c: $P = 0.004$; LASr-c: $P = 0.017$) (Table 2, Fig. 4). ROC with area under the curves were 1.000, 0.974, 0.907, 0.999, 0.839, and 0.883 for predicting the ability of 4D strains LASr, LAScd, LASct, LASr-c, LAScd-c, LASct-c to differentiate the nonobstructive HCM and controls, respectively. ROC with area under the curves were 1.000, 0.987, 0.997, 1.000, 0.975, 0.729 for predicting the ability of 4D strains LASr, LAScd, LASct, LASr-c, LAScd-c, and LASct-c to differentiate the occult obstructive HCM and controls, respectively. ROC with area under the curves were

TABLE 1. Clinical and 2-dimensional Echocardiographic Characteristics of the Study Populations

Baseline	Control (1)	Nonobstructive HCM (2)	Occult Obstructive HCM (3)	P (2 vs. 1)	P (3 vs. 1)	P (3 vs. 2)	P (ANOVA)
		n (%)					
Patient characteristics							
No. patients	38	28	30	—	—	—	—
Male sex	19 (50)	18 (64)	19 (63)	0.255	0.278	0.941	0.414
Age, mean (± SD) (y)	43 (± 8)	45 (± 8)	46 (± 7)	0.409	0.203	0.734	0.431
Heart rate, mean (± SD) (L/min)	67 (± 9)	66 (± 10)	65 (± 8)	0.748	0.345	0.621	0.673
Cardiac event risk factors							
Smoking	6 (16)	7 (25)	5 (17)	0.360	0.924	0.443	0.608
Drinking	3 (8)	3 (11)	4 (13)	0.699	0.471	0.765	0.771
Diabetes mellitus	3 (8)	3 (11)	3 (10)	0.699	0.765	0.930	0.920
LVED pressure elevated	0 (0)	10 (36)	19 (63)	< 0.001*	< 0.001*	0.036*	< 0.001†
Arterial hypertension	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
Current systolic pressure, mean (± SD) (mm Hg)	124 (± 8)	125 (± 12)	126 (± 9)	0.790	0.298	0.573	0.639
Current diastolic pressure, mean (± SD) (mm Hg)	75 (± 6)	77 (± 7)	76 (± 8)	0.365	0.826	0.589	0.695
Medications							
Diuretics	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
β-blockers	0 (0)	4 (14)	5 (17)	0.043*	0.023*	0.807	0.036†
CC blockers	0 (0)	2 (7)	2 (7)	1.000	1.000	1.000	1.000
Disopyramide	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
NYHA functional class							
I/II	—	22 (79)	21 (70)	—	—	0.296	—
III/IV	—	6 (21)	9 (30)	—	—	0.296	—
2D echocardiography parameters							
LAD_{lax} (mm)	33.08 ± 2.69	42.79 ± 3.68	43.63 ± 3.48	< 0.001*	< 0.001*	0.371	< 0.001†
$LVDD_{lax}$ (mm)	46.87 ± 3.15	45.50 ± 2.64	44.83 ± 2.23	0.026*	0.004*	0.203	0.004†
Biplane LVEF (%)	63.97 ± 2.59	62.29 ± 2.80	62.17 ± 2.97	0.014*	0.009*	0.876	0.013†
$E_{velocity}/A_{velocity}$ ratio	1.06 ± 0.32	0.91 ± 0.29	0.86 ± 0.34	0.054	0.015*	0.558	0.029†
E'_{septal}/A'_{septal} ratio	1.10 ± 0.34	0.78 ± 0.33	0.60 ± 0.17	< 0.001*	< 0.001*	0.016*	< 0.001†
$E'_{lateral}/A'_{lateral}$ ratio	1.16 ± 0.35	0.86 ± 0.45	0.70 ± 0.31	0.003*	< 0.001*	0.106	< 0.001†
$E'_{average}/A'_{average}$ ratio	1.13 ± 0.27	0.82 ± 0.36	0.65 ± 0.17	< 0.001*	< 0.001*	0.024*	< 0.001†
$E_{velocity}/E'_{average}$ ratio	7.28 ± 1.95	8.64 ± 2.28	10.73 ± 3.16	0.011*	< 0.001*	0.006*	< 0.001†
AR ≥ moderate, rest	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
AR ≥ moderate, exercise	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
MR ≥ moderate, rest	0 (0)	0 (0)	0 (0)	1.000	1.000	1.000	1.000
MR ≥ moderate, exercise	0 (0)	1 (4)	4 (13)	0.247	0.043*	0.185	0.044†

ANOVA indicates analysis of variance; AR, aortic regurgitation; CC, calcium channel; E/A, early diastolic/late diastolic filling velocities; E′/A′, early diastolic/late diastolic mitral annular velocities; HCM, hypertrophy cardiomyopathy; LAD, left atrial diameter; lax, long axis; LVDD, left ventricular diastolic diameter; LVED, left ventricular end-diastole; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association.

*$P < 0.05$ versus nonobstructive HCM, occult obstructive HCM, and control groups with t test.

†$P < 0.05$, ANOVA.

0.686, 0.623, 0.528, 0.672, 0.834, and 0.280 for predicting the ability of 4D strains LASr, LAScd, LASct, LASr-c, LAScd-c, LASct-c to differentiate the occult obstructive HCM and non-obstructive HCM, respectively (Fig. 5).

Interobserver and Intraobserver Variability

The assessment of intraobserver and interobserver variability in the 4D echocardiography data documented good ICCs. ICCs of intraobserver and interobserver of LV 4D mass and mass index were > 0.75. ICCs of intraobserver and interobserver of LA 4D longitudinal (LASr, LAScd, LASct) and circumferential (LASr-c, LAScd-c, LASct-c) strain values were > 0.85.

DISCUSSION

The main findings of the current study can be summarized as follows: (1) both nonobstructive and occult obstructive HCM patients had significant reduction of LA reservoir, conduit, and contractile functions according to LA 4D longitudinal and circumferential strains, and increased LA stiffness with decreased LAEF had been revealed; (2) strain outcomes were significantly worse in occult obstructive HCM patients who had more decreased conduit functions and passively slightly increased contractile function with higher LV filling pressure and LA stiffness than nonobstructive ones.

Various echocardiographic modalities for HCM assessment have been used, including conventional and novel echocardiographic methods.[10,12,14–16] In this evaluation, both nonobstructive and occult obstructive HCM patients presented impaired LV diastolic function and increased LV filling pressures measuring by E/A ratio, E′/A′ ratio, E/E′ ratio, and LV end-diastolic pressure with higher LA stiffness. Elevated LV filling pressures related to LV diastolic dysfunction have been
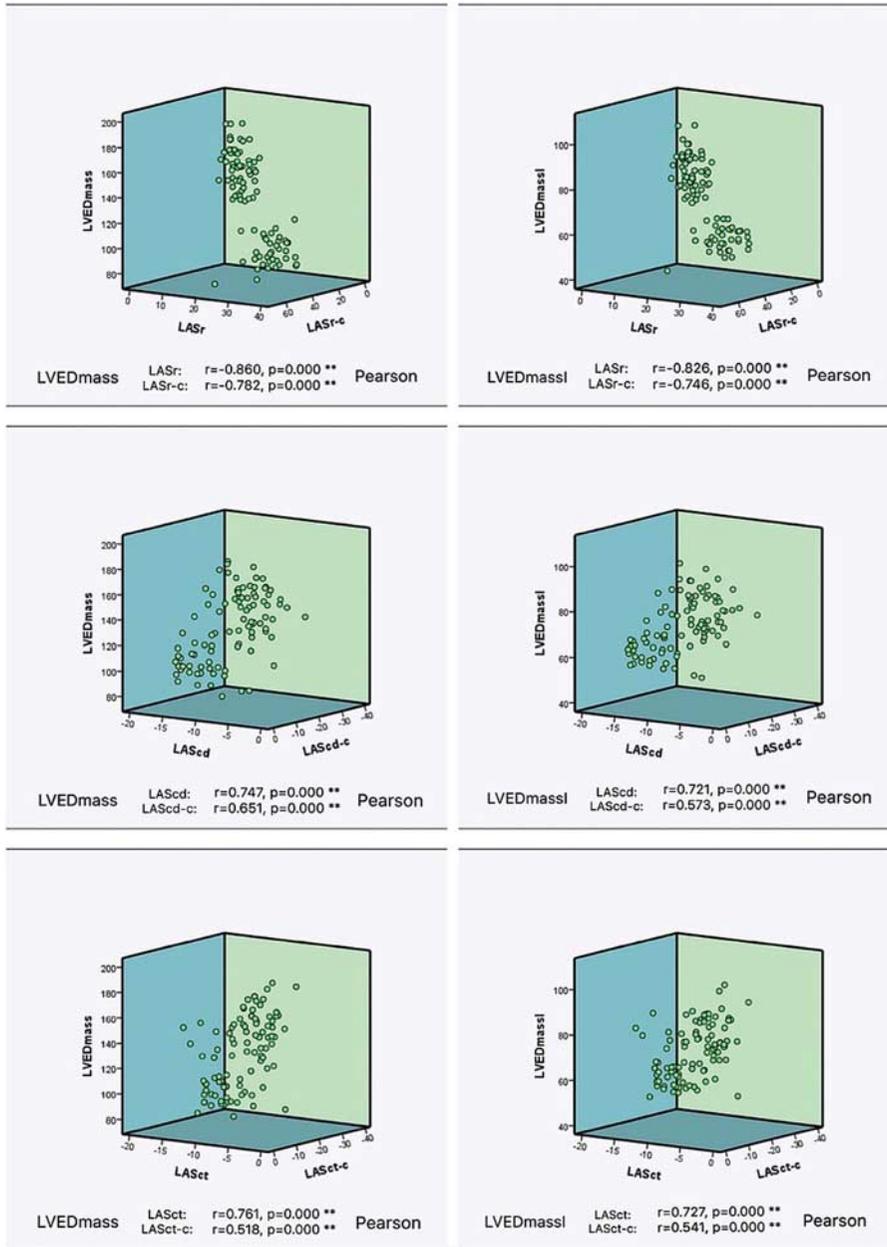
FIGURE 3. Significant correlation relationship clarified between LVEDmass/LVEDmassI and LA longitudinal/circumferential strain parameters with 4D echocardiographic evaluation. LVEDmass indicates left ventricular end-diastolic mass; LVEDmass(I), left ventricular end-diastolic mass (index). **$P < 0.001$. full color online

considered to be the main underlying mechanism of LA dysfunction in patients with HCM. Otherwise, our observation indicated significant grade MR after exercise in occult HCM as compared with non-HCM and controls as a consequence of LA dysfunction. Enlargement of LA occurs frequently in patients with HCM, LV outflow tract obstruction, reflecting significant LV diastolic dysfunction, presence of more than moderate MR, and intrinsic atrial myopathy.[17] But Henein et al[7] showed that irrespective of LA morphology, LA volume overload because of MR had a less negative effect on intrinsic LA function than pressure overload because of increased LV filling pressure.

Determination of LA 4D volume is preferred over measurement of linear dimensions and area because the volumetric calculation allows for more accurate assessment of the asymmetric geometry of the chamber and has been shown to have stronger association with disease progression than linear models.[9,18] The developed tools of automated analysis of 4D strain echocardiography may provide useful quantitative and objective parameters to assist the clinical expert in the diagnosis of LA function, according to the better conformance and geometric assumption demonstrate advantages with a higher temporal spatial and resolution, which may provide valuable analysis of prompt events such as relaxation phase and isovolumic contraction. This study used 4D echocardiographic volume-strain to measure LA volumes and strains in HCM patients. We tried to clarify

TABLE 2. Four-dimensional Echocardiographic Parameters With Functional Evaluation of the Study Populations

Parameters	Mean ± SD			P (2 vs. 1)	P (3 vs. 1)	P (3 vs. 2)	P (ANOVA)
	Control (1)	Nonobstructive HCM (2)	Occult Obstructive HCM (3)				
LV 4D echocardiography parameters							
LVEDV (mL)	84.08 ± 16.29	76.86 ± 10.37	75.27 ± 8.03	0.044*	0.005*	0.515	0.010†
LVESV (mL)	34.13 ± 9.88	31.18 ± 6.39	31.30 ± 5.48	0.125	0.107	0.919	0.158
LVEF (%)	60.34 ± 5.83	59.32 ± 4.20	57.77 ± 4.52	0.434	0.051	0.181	0.113
LVEDmass (g)	102.16 ± 11.06	153.96 ± 16.78	158.90 ± 14.88	< 0.001*	< 0.001*	0.240	< 0.001†
LVEDmassI (g/m²)	57.82 ± 4.84	84.14 ± 9.18	82.87 ± 6.42	< 0.001*	< 0.001*	0.540	< 0.001†
LA 4D echocardiography parameters							
LAVmin (mL)	17.55 ± 4.37	39.79 ± 7.99	48.33 ± 12.11	< 0.001*	< 0.001*	0.003*	< 0.001†
LAVmax (mL)	41.45 ± 8.09	72.32 ± 12.61	83.30 ± 13.45	< 0.001*	< 0.001*	0.002*	< 0.001†
LAVmaxI (mL/m²)	24.34 ± 5.01	39.89 ± 6.88	43.68 ± 7.06	< 0.001*	< 0.001*	< 0.001*	< 0.001†
LAVpreA (mL)	28.21 ± 7.44	54.89 ± 12.48	65.80 ± 14.03	< 0.001*	< 0.001*	0.003*	< 0.001†
LAEF (%)	57.87 ± 4.64	45.02 ± 6.23	42.28 ± 7.76	< 0.001*	< 0.001*	0.145	< 0.001†
LASr (%)	28.76 ± 3.55	13.54 ± 3.20	11.53 ± 4.26	< 0.001*	< 0.001*	0.135	< 0.001†
LAScd (%)	−16.34 ± 2.98	−7.25 ± 3.45	−5.87 ± 3.09	< 0.001*	< 0.001*	0.113	< 0.001†
LASct (%)	−12.42 ± 2.65	−6.36 ± 3.51	−6.40 ± 2.82	< 0.001*	< 0.001*	0.959	< 0.001†
LASr-c (%)	38.18 ± 8.04	22.96 ± 4.58	20.73 ± 4.13	< 0.001*	< 0.001*	0.017*	< 0.001†
LAScd-c (%)	−19.92 ± 4.97	−13.64 ± 3.97	−7.60 ± 4.22	< 0.001*	< 0.001*	< 0.001*	< 0.001†
LASct-c (%)	−18.29 ± 6.53	−9.32 ± 4.41	−12.83 ± 4.41	< 0.001*	< 0.001*	0.004*	< 0.001†

ANOVA indicates analysis of variance; HCM, hypertrophy cardiomyopathy; LA, left atrium; LAEF, left atrial emptying fraction; LAScd, left atrial peak longitudinal strain of conduit function; LAScd-c, left atrial peak circumferential strain of conduit function; LASct, left atrial peak longitudinal strain of contractile function; LASct-c, left atrial peak circumferential strain of contractile function; LASr, left atrial peak longitudinal strain of reservoir function; LASr-c, left atrial peak circumferential strain of reservoir function; LAVmax, left atrial maximum volume; LAVmax(I), left atrial maximum volume (index); LAVmin, left atrial minimal volume; LAVpreA, left atrial volume preatrial contraction; LV, left ventricle; LVEDmass, left ventricular end-diastolic mass; LVEDmass(I), left ventricular end-diastolic mass (index); LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

*$P < 0.05$ versus nonobstructive HCM, occult obstructive HCM, and control groups with t test.

†$P < 0.05$, ANOVA.

occult obstruction from nonobstruction at rest and to assess the functional value changes in these measurements.

Volumetric evaluation of LA phasic function is derived from measurements of maximum, minimum, and volume immediately before atrial contraction. LA strain has an important role in predicting LV filling pressures and LA dysfunction based on volume and deformation assessment. Furthermore, it allows detailed analysis of systolic and diastolic functions: including LA reservoir, conduit, contractile assessments during LV systole, early diastole, and late diastole phases. Increased LA volumes and impaired LA myocardial deformations are well-known predictors of adverse outcomes as other studies have shown.[19,20] As we know, LA increased volumes are important predictors of adverse cardiac events and impaired LA functions are presumed to be due to LV diastolic dysfunction as a result of LV hypertrophy.[21] Therefore, we excluded LV remodeling and hypertrophy in patients with primary and secondary arterial hypertension. Moreover, some authors suggested that the strongest echocardiagraphic predictors of LA dysfunction, other than LA volume, were LV mass and LA strain values. To avoid the interference of ventricular mass to atrial strain parameters, no significant difference of mass and mass index was seen in both HCM groups.

Last, the novel LA 4D volume-strain parameters showed significant incremental LA volumes and obviously impaired LA strains in both nonobstructive and occult obstructive HCM groups. These outcomes were in accordance with other studies using speckle-tracking-derived atrial assessment. However, 2D and 3D echocardiographic methods for the calculation of chamber volumes and speckle-tracking-derived strains rely on geometric assumptions that are known to be inaccurate; their accuracy is impaired further by out-of-plane motion. In previous studies, speckle tracking echocardiography derived LA deformation indices do not truly reflect LA intrinsic function as they are difficult to separate from the influence of corresponding LV deformation indices, particularly in the case of LV dysfunction.[22] So, to further the study in patients with preserved LVEF by novel 4D echocardiographic technique is worth exploring. In clinics, the notion has been challenged that occult obstructive HCM is not a benign condition and carries a worse prognosis than nonobstructive HCM, associated with a high-risk profile or the necessity of major treatment options. Apart from differences related to imaging techniques, our studies warranted to explore whether reduced LA 4D strains, especially reservoir, conduit, and contractile functional performance diversities, may affect the clinical therapy or the overall prognosis in HCM patients with occult obstruction.

It is possible that there were differences in presenting features between both HCM groups. From this evaluation, LA volumes and strains were found to be more affected in patients with occult obstruction. Occult obstructive HCM patients presented incremented LA volumes and impaired reservoir function in circumferential shortening assessment compared with nonobstructive ones. There was more reduced contractile function compared with conduit function in nonobstructive HCM and more reduced conduit function compared with contractile function in occult obstructive HCM presented by circumferential shortening evaluation. Notably, longitudinal strain measures the shortening along the long axis of the chamber, whereas circumferential strain measures contraction along the circumference in a short axis.[23] As we know, atrial myocardium consists of 2 layers, with longitudinal and

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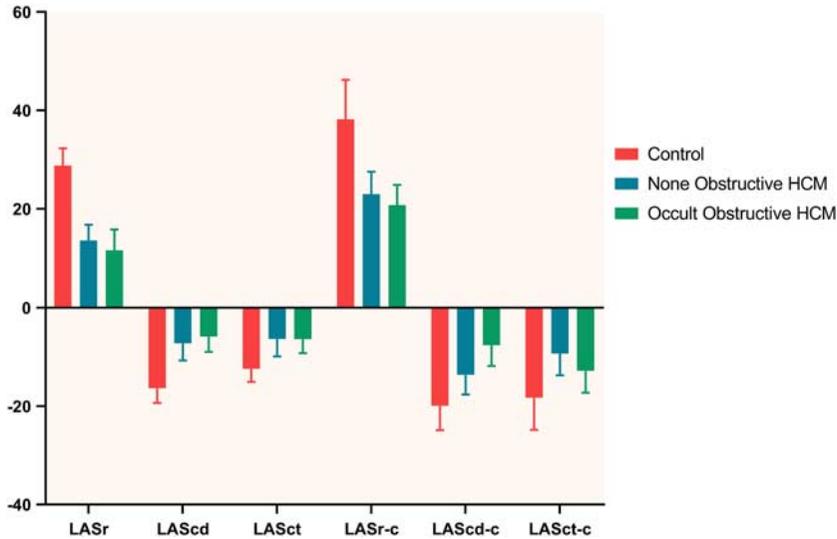
FIGURE 4. LA 4D volumes and strain values comparing between nonobstructive HCM, occult obstructive HCM, and control group. Higher volumes and lower values of longitudinal and circumferential strains in both HCM groups than the control group, more higher volumes and more lower values of longitudinal and circumferential strains in occult obstructive HCM than nonobstructive HCM. full color online

circumferential fibers predominantly arranged in the deep and superficial layers, respectively. The longitudinal with higher sensitivity and the circumferential with higher specificity just as we have shown. Worse circumferential strain of conduit function and passively slightly increased circumferential strain of contractile function measured by LA 4D circumferential strain should be the new predictors in patients with occult obstruction.

More declined LV diastolic function with higher LV filling pressures predicted higher cardiac risk factors and significantly worse outcomes in occult outflow tract obstruction. As a sensitive and specified index at LV early diastole, LA 4D circumferential strain suggested a progressive decline of LA conduit function with advanced stages of LV diastolic dysfunction in occult obstruction. Importantly, the LA-LV coupling pattern with LV diastolic

dysfunction and LA pump dysfunction showed to be different between nonobstructive and occult obstructive HCM patients. Taken together, these data provided a novel measurement for a more systematic evaluation with different components of LA-LV functional assessment in clinical settings according to LV hypertrophy, including different outflow tract obstruction classifications.

This study has several limitations that should be mentioned. Other potential prognostic markers, such as cardiovascular magnetic imaging with late gadolinium enhancement or myocardial biopsy with protein-derived extracellular deposition detection, were not systematically assessed. Apical-cavity and mid-cavity obstruction can coexist or absent with LV outflow tract obstruction including different obstructive gradients. Further prospective studies are needed to validate the above
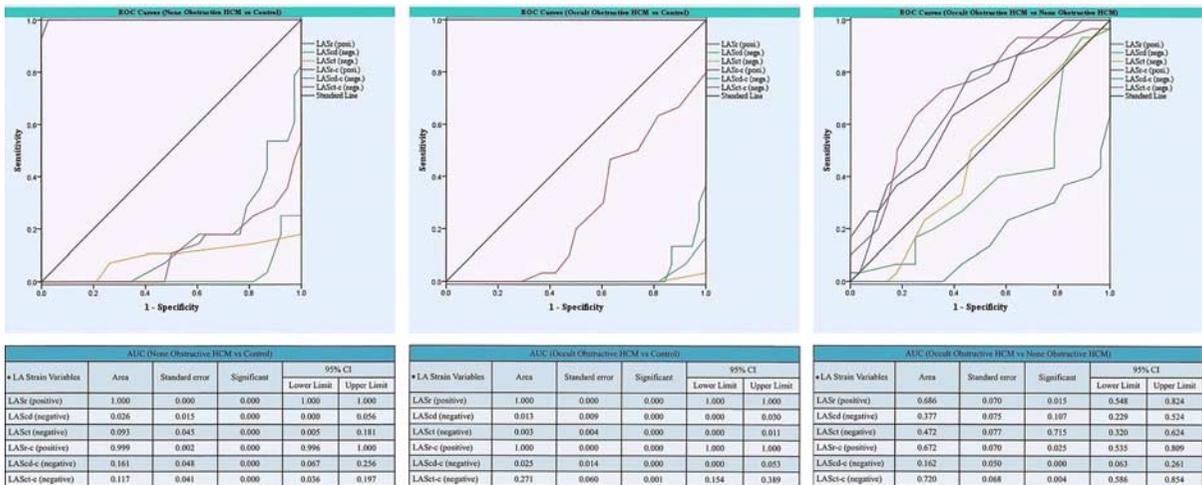
FIGURE 5. ROC curves for predicting the ability of LA 4D volume-strain to differentiate the occult obstructive HCM, nonobstructive HCM, and controls (the AUC and 95% CI outcomes for positive parameters of LASr, LASr-c shown with "n", the AUC and 95% CI outcomes for negative parameters of LAScd, LASct, LAScd-c, LASct-c shown with "1−n"). AUC indicates area under the curve; CI, confidence interval. full color online

distinction with echocardiographic evaluation data combined LV and LA functional predictors. More in-depth and detailed research works should be considered in our further study for a larger sample text.

In conclusion, HCM patients who fail to respond symptomatically to gradient obstructive at rest are considered for alternative advanced volume-strain assessment. LA 4D volume-strain is beneficial to evaluate the occult obstructive HCM from nonobstructive HCM even if without clinical exercise test. Notably, the novel offered volume-strain with longitudinal and circumferential shortening measurements might be a sensitive and specific predictor for the assessment of LA-LV phasic functional changes in patients with preserved ejection fraction with different structural HCM.

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