Velocity vector imaging echocardiography and N-terminal pro- brain natriuretic peptide study of people with preclinical hypertrophic cardiomyopathy

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Research

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Abstract

Background: To investigate whether familial hypertrophic cardiomyopathy (HCM) gene mutation carriers without overt left ventricular hypertrophy have subclinical changes in left ventricular function.

Methods: We studied Eighteen HCM families with pathogenic mutations, 45 patients with overt HCM (gene positive/phenotype positive (G+/P+)), 40 patients without myocardial hypertrophy (gene positive/phenotype negative G+/P-), and 48 genotype-negative related healthy controls. Conventional echocardiography and velocity vector imaging (VVI) were

performed, and blood levels of N- terminal pro- brain natriuretic peptide (NT- pro- BNP) were analyzed.

Results: Although the global longitudinal, circumferential and radial strain was similar between the G+/P- group and the control group, the longitudinal strain of basal inferoseptum and basal anteroseptum was lower in G+/P- patients than in controls, while the basal and middle inferolateral longitudinal strains were significantly higher. Compared with the controls, G+/P+ patients had significantly lower global and segmental longitudinal and radial strains. There were no significant differences between the normal control and G+/P+ groups for global and segmental circumferential strains. The middle of the left ventricle (LV) was clockwise in G+/P+ patients (opposite to normal). The rotation angle of the mid LV rotation in the G+/P+ group were significantly higher than those in the G+/P- subjects and controls. The NT-proBNP levels were higher in G+/P+ patients than in G+/P- people and controls.

Conclusions: Sarcomere gene mutation carriers without overt left ventricular hypertrophy have subclinical segmental systolic dysfunction. Velocity vector imaging is feasible for differentiating HCM, G+/P- patients from controls.

Background

Hypertrophic cardiomyopathy (HCM) is one of the most common autosomal dominant cardiovascular diseases, and it is the primary cause of sudden death in young people and athletes. In most patients, gene mutation is the primary cause of HCM. Most mutations are sarcomere protein gene mutations encoding myocardium that exhibit autosomal dominant inheritance[1]. HCM demonstrates obvious family clustering, and the genetic probability is 50%. According to statistics, the proportion of patients with familial HCM who eventually develop HCM is 40%-100%. Early recognition of and intervention for cardiac function changes are particularly important.

Familial HCM gene mutation carriers without overt left ventricular hypertrophy (gene positive/phenotype negative G+/P-) may experience syncope and have other clinical symptoms, including abnormal electrocardiogram (ECG) repolarization, and they may develop subclinical changes in cardiac function before developing myocardial hypertrophy. Therefore, it is urgent to identify these patients via imaging methods.

Velocity vector imaging (VVI) is based on two-dimensional grayscale images that track the spatial motion of cardiovascular tissue to show echo spots. The tracking of multiple regional myocardial segments is performed simultaneously. The velocity and displacement of the regional myocardium are displayed quantitatively as a curve. VVI can be used to analyze the movement and deformation of the myocardium, and it is possible to detect fine space and time distinctions in cardiac deformation in different myocardial segments during systole and diastole[1–5]. Therefore, VVI is valuable for evaluating regional and global cardiac function.

Many studies have shown that VVI is potentially viable for assessing myocardial function[6]. N-terminal pro-brain natriuretic peptide (NT-proBNP) level may be related to cardiovascular damage, reflecting ventricular function[7]. However, there are no VVI parameters for the left ventricle (LV), globally or segmentally, in preclinical HCM. We aimed to evaluate changes in the long and short-axis function of the LV using VVI combined with NT-pro-BNP levels.

Methods

Study Population

A total of 96 unrelated HCM patients who were diagnosed in our hospital from March 2016 to April 2019 were selected for gene detection, and 45 HCM patients who were carrying sarcomere gene mutations were selected as the gene positive/phenotype positive (G+/P+) group. Gene detection and conventional echocardiography were performed on the first-degree relatives of 45 unrelated patients (i.e., parents, children, siblings of the same parent). According to the examination results, 40 patients with HCM sarcomere mutation genes but no ventricular wall hypertrophy were selected as the gene positive phenotype negative (G+/P-) group. At the same time, 48 healthy volunteers without gene mutations were selected as normal controls.

The diagnostic criterion of HCM is that the thickness of the left ventricular wall in one or more myocardial segments is greater than or equal to 15 mm. It was necessary to exclude myocardial hypertrophy due to athletics, metabolic diseases, congenital heart diseases and other systemic diseases. In patients with a clear family history, an unexplained left ventricular wall thickness of one or more myocardial segments ≥ 13 mm was observed[1].

All G+/P+ individuals had interventricular septum thickening, with or without other left ventricular wall thickening. Before examination, β -blockers, calcium antagonists and angiotensin-converting enzyme inhibitors were stopped for at least 24 hours. The exclusion criteria were as follows: 1) patients with ventricular wall hypertrophy caused by hypertension, coronary heart disease, diabetes mellitus, valvular disease, congenital heart disease, pulmonary heart disease, metabolic disease or other factors, as well as athletes with cardiac hypertrophy, were excluded after obtaining a medical history and performing a physical examination, ECG and echocardiography; 2) patients with HCM whose left ventricular ejection fraction was less than 50%; 3) accepted patients with HCM who underwent percutaneous septal

myocardial ablation, surgical septal myomectomy or permanent pacemaker implantation or experienced atrial fibrillation.

The inclusion criteria for the G+/P- group were as follows: 1) carrier of a sarcomere mutation gene verified by gene generation; 2) maximum left ventricular wall thickness (LVMWT) less than 13 mm detected by echocardiography. The exclusion criteria were as follows: 1) diabetes mellitus and hypertension; 2) cardiac muscle noncompaction and amyloidosis; 3) metabolic diseases and other systemic diseases; 4) significant pulmonary lesions; 5) treadmill test, coronary angiography or coronary artery computed tomography (CT) results indicating coronary heart disease, which was definitively diagnosed by imaging; 6) congenital heart disease; 7) moderate and severe valve stenosis and regurgitation detected by echocardiography.

Thirty first-degree relatives (parents, children, siblings of the same parent) of 45 unrelated patients were examined by gene testing and routine echocardiography. According to the results of the examination, 40 patients with HCM sarcomere mutation genes but no ventricular wall hypertrophy were selected as the positive gene group, and 48 healthy volunteers without gene mutations were selected as the normal control (G-/P-) group.

This cross-sectional study was conducted with the permission of the Institutional Ethics Committee. All subjects provided written informed consent.

Conventional echocardiography

For the ECG recordings, all subjects laid on their left side. Three short-axis views (mitral valve level, papillary muscle level and apical level) and three long-axis views (apical three-chamber view, apical two-chamber view and apical four-chamber view) of the LV were obtained on a Siemens S2000 ultrasound system (Axius, Siemens Medical Solutions, Malvern, PA, USA) with a 4Px probe (2.75–4.25 MHz). All images and clips were stored on the echocardiographic machine for analysis.

The interventricular septal thickness in diastole (IVSD) and left atrial diameter (LAD) were detected in the parasternal long-axis view. The LVMWT was measured in diastole in the basal, mid and apical short-axis views and in the apical long-axis view.

The left atrial volume (LAV), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured by the Simpson biplane method in the apical two-chamber and four-chamber views. The left atrial volume index (LAVI) was calculated as $LAVI = LAV / \text{body surface area (BSA)}$.

The left ventricular outflow tract pressure gradient (LVOT-PG) was measured by continuous-wave Doppler (CW), and the sampling line was placed at the stenosis of the left ventricular outflow tract. In the apical four-chamber view, E/A was measured by pulsed-wave Doppler (PW). The ejection fraction (EF) was estimated using the Simpson biplane method.

All recordings were performed by professional sonographers. All conventional echocardiography parameters were read offline.

Velocity vector imaging echocardiography

Movie clips were recorded in 3 cardiac cycles and stored, and three apical views of the LV were analyzed offline using VVI software (Axius, Siemens Medical Solutions). A line was fitted along the internal surface of the LV endocardium at end-diastole. We used a frame-by-frame image tracking mode to estimate the movement of the myocardium. The acoustic marker of the myocardium was accurately identified and automatically tracked during several consecutive frames.

The longitudinal strain, circumferential strain, and radial strain curves were measured for each LV segment using long-axis and short-axis views according to the 16-segment model of the American Society of Echocardiography [8,9]. In this model, we placed a sampling point on each segment to record the strain experienced during 3 cardiac cycles. The mean value of each measurement was calculated for further analysis.

The global longitudinal strain (GLS), circumferential strain (GCS), and radial strain (GRS) were obtained by averaging all the segment strain values.

The displacement angle of the left ventricle was defined as the left ventricular rotation, with the clockwise direction rotation being positive and the counterclockwise direction rotation being negative. The Peak basilar rotation angle (PBr), the Peak mid rotation angle (PMr) and the peak apex rotation angle (PAr) were measured. The peak left ventricular twist (Ptw) angle was the pure difference in left ventricular rotation angle between the apex and the base, $Ptw = PBr - PAr$.

NT-pro-BNP Test

Fasting blood samples were collected from each patient within 24 hours after enrollment. Blood sampling was standardized without tourniquet and immediately centrifuged twice. NT-pro-BNP was analyzed on a Modular E 170 (Roche Diagnostics, Mannheim, Germany).

Interobserver and Intraobserver Variability

To assess the interobserver variability, which was expressed as the coefficient of variation (CV), 2 independent investigators who were blinded to each other's results analyzed 30 randomly selected VVI movie clips. For intraobserver variability, 30 VVI movie clips were analyzed 3 times within an interval of 2 weeks by one investigator who was blinded to the previous results.

Data and Statistical analysis

All measurement data are expressed as the mean $\pm$ standard deviation (SD) and were analyzed using the SPSS 17.0 statistical software package (IBM Corp., Chicago, IL, USA). Significant differences between the two groups were analyzed by one-way ANOVA, and comparisons between the two groups were conducted

using independent sample t tests. Pearson's correlation analysis was used if the independent variables and dependent variables were normally distributed. The plasma concentration of NT-pro-BNP was logarithmically converted to log NT-pro-BNP, and the normal distribution was analyzed by analysis of variance. $P < 0.05$ and $P < 0.01$ indicated significant differences. Correlations between VVI parameters and NT-pro-BNP levels were analyzed by linear regression.

Results

Clinical characteristics

There were no significant differences in age, sex, BSA, heart rate, or blood pressure among the 3 groups (Table 1).

Conventional echo parameters

The IVSD, LVMWT, LAD, LAVI, and LVOT-PG of the HCM patients were significantly higher than those of the patients in the G+/P- group and the control subjects. Meanwhile, G+/P+ patients had a significantly lower E/A. However, none of the conventional echo parameters were significantly different between the G+/P- group and the control group. In addition, there were no significant differences in LVEDV, LVESV or EF among the three groups (Table 1).

Regional longitudinal peak systolic strain

The longitudinal peak systolic strain of the basal inferoseptum and basal anteroseptum in the G+/P- group was significantly lower than that in the control group ($P < 0.05$). The longitudinal peak systolic strain of the basal and middle segments of the inferolateral in the G+/P- group was significantly higher than that in the control group ($P < 0.05$). The peak longitudinal strain of each segment in the G+/P+ group was significantly lower than that in the control group, especially in the basal and middle segments of the inferoseptum, anterior wall and anteroseptum ($P < 0.01$). The longitudinal peak systolic strain of each left ventricular wall segment in the G+/P+ group was significantly lower than that in the G+/P- group ($P < 0.01$).

In the G+/P- group, the longitudinal peak systolic strain of the basal inferoseptum and basal anteroseptum was significantly lower than that of other ventricular wall segments ($P < 0.05$). In the G+/P+ group, the longitudinal peak systolic strain of the basal and middle segments of the inferoseptum, anterior wall and anteroseptum was significantly lower than that of the corresponding segments of the left ventricular wall ($P < 0.05$) (Table 2) (Figure 1) (Figure 2).

Regional circumferential peak systolic strain

There were no significant differences among the normal control, G+/P- and G+/P+ groups for GCS values at all levels. The circumferential systolic strain increased from base to apex in the three groups ($P < 0.01$) (Table 3) (Figure 1) (Figure 2).

Regional radial peak systolic strain

In the G+/P- group, the peak radial strain at all levels no significant differences compared with the control group ($P < 0.05$). The peak radial strain of each segment in the G+/P+ group was significantly lower than those in the control and G+/P- groups ($P < 0.05$).

In the normal control group, G+/P- group and G+/P+ group, there were significant differences in peak systolic strain among different segments of the same ventricular wall; the strain was greater in the papillary muscle level than in the apical and mitral valve level ($P < 0.05$). In the G+/P+ group, the peak radial strain of the anteroseptum, anterior wall and Inferoseptum was significantly lower than that of the other ventricular wall segments ($P < 0.05$) (Table 4) (Figure 1) (Figure 2).

Global longitudinal, circumferential and radial strain

There was no significant difference in systolic longitudinal, circumferential, or radial strain between the G+/P- group and the control group ($P > 0.05$). The systolic GLS of the G+/P+ group was lower than that of the control group and the G+/P- group, and the difference was very significant ($P < 0.01$). The systolic GRS of the G+/P+ group was lower than that of the control group and the G+/P- group, and the difference was significant ($P < 0.05$). The systolic GCS of the G+/P+ group was not significantly different from that of the control group or the G+/P- group ($P > 0.05$) (Table 5) (Figure 3).

Left ventricular rotation parameters and NT-pro-BNP level

In the control, G+/P- and G+/P+ groups, the pattern of cardiac rotation and torsion was the same: the apical part rotated counterclockwise, and the basal part rotated clockwise. However, the rotation of the midventricle was clockwise in G+/P+ group which was different from the control and G+/P- group. In the control and G+/P- groups, the rotation of the midventricle followed the apex. whereas, in G+/P+ groups, the midventricle rotated in the same direction as the base.

The rotation angle of the middle of the LV of the G+/P+ group was significantly higher than those of the normal group and the G+/P- group ($P < 0.05$). However, there were no significant differences in the rotation angle of the base, middle or apex of the LV and the global torsion angle of the LV between the G+/P- group and the control group ($P > 0.05$) (Figure 3).

NT-pro-BNP levels were significantly higher in HCM patients compared with the control group and G+/P- group. There no detectable differences in G+/P- individuals compared with healthy controls (Table 5).

Correlation analysis results

In the HCM patients, GLS and GRS were significantly correlated with IVSD ($r=0.545, P=0.003$; $r=0.37, P=0.031$; respectively). There was no significant correlation between GCS and IVSD. NT-proBNP was significantly correlated with GLS and IVSD ($r=0.566, P=0.003$; $r=0.545, P=0.004$; respectively), but no significant associations with GRS (Figure 4).

Repeatability test

The interobserver correlation coefficients for GLS estimates of 4-, 2- and 3-chamber views were 0.45 ($P = 0.039$), 0.52 ($P = 0.043$), and 0.48 ($P = 0.027$), respectively. The interobserver correlation coefficients for GRS estimates of 4-, 2- and 3-chamber views were 0.43 ($P = 0.041$), 0.46 ($P = 0.048$), and 0.51 ($P = 0.029$), respectively. The interobserver correlation coefficients for GCS estimates at the level of the mitral valve, papillary muscle, and apex were 0.68 ($P=0.002$), 0.71 ($P = 0.001$), and 0.62 ($P = 0.004$), respectively.

The intraobserver correlation coefficients for GLS dependency estimates of 4-, 2- and 3-chamber views were 0.35 ($P = 0.183$), 0.32 ($P = 0.126$), and 0.21 ($P = 0.38$), respectively. The intraobserver correlation coefficients for GRS dependency estimates of 4-, 2- and 3-chamber views were 0.33 ($P = 0.187$), 0.36 ($P = 0.133$), and 0.19 ($P = 0.43$), respectively. The intraobserver correlation coefficients for GCS dependency estimates at the level of the mitral valve, papillary muscle, and apex were 0.71 ($P = 0.003$), 0.59 ($P = 0.019$), and 0.64 ($P = 0.047$), respectively.

Discussion

In recent years, studies have shown that the primary cause of familial HCM is mutations in the genes encoding sarcomere proteins and other modification genes. Most of the mutations are in genes encoding sarcomere proteins, and point mutations of the β -myosin heavy chain gene (MYH7), myosin binding protein C (MYBPC3), troponin T (TNNT2) and troponin I (TNNI3) are relatively common [10–14]. Abnormal genetic regulation can lead to the disordered arrangement of myocardial cells and abnormal thickening of the myocardium [15–17] and can change calcium sensitivity and muscle fiber tension, thus affecting myocardial contractile and diastolic function.

In this study, subjects were analyzed from longitudinal, radial and circumferential viewpoints. The results showed that there were no significant differences in the global longitudinal, circumferential or radial strains of the systolic period of the LV between the mutation gene carriers and the control group, while the longitudinal strain of the basal inferoseptum and basal anteroseptum was significantly lower, and the longitudinal strain of the basal and mid inferolateral was significantly higher than those of the normal control group. This indicates that the regional myocardial segmental systolic function was impaired in the carriers of the HCM sarcomere gene mutation, and the impairment was limited to the inferoseptum and anteroseptum basal segment. The elevation of longitudinal strain of inferolateral remains unclear. Maybe regional myocardium experiencing higher longitudinal strain occurs as a cause of adjacent myocardial deformity (with lower strain). Germans et al.[18] found that in HCM gene mutation carriers who did not have ventricular wall hypertrophy, even if the results of conventional echocardiography and ECG were normal, cardiac magnetic resonance technology detected that 81% of HCM gene mutation carriers had a recess in the basal and intermediate segments of the interventricular septum, which may indicate early disease in the HCM gene mutation carriers that will eventually develop into HCM. At the same time, Germans et al. also found that the abnormal myocardial structure of carriers of the HCM gene involved local myocardial segments rather than all myocardial segments, and the interventricular septum

were the most obviously involved. HCM gene mutation carriers exhibit disordered arrangement and degeneration of cardiac myocytes, mild fibrosis in the intercellular matrix and increased myocardial stiffness, and the longitudinal myocardial fibers under the endocardium of these patients are more prone to interstitial fibrosis [19]. The regional radial systolic strain (the basal inferoseptum and basal anteroseptum) of the G+/P- group remained similar to that of the control group. This may be because changes in LV radial systolic function occur later than do changes in longitudinal systolic function.

Our study showed that NT-proBNP levels in HCM patients were significantly higher and correlated with myocardial deformation and interventricular septal thickness. Among genotype-negative individuals, we also found that there were no difference in NT-proBNP concentrations compared with control relatives, but their local segmental deformation parameters were different, which was different from the Doroteia Silva et al[20] who identify mutation carriers of hypertrophic cardiomyopathy by tissue Doppler imaging.

Conclusions

In conclusion, the GLS and GRS were diminished in HCM subjects, whereas a compensatory mechanism existed that tended to maintain the GCS. Although the GLS, GRS and GCS of HCM gene mutation carriers were still within the normal range, the longitudinal strain of local myocardial segments was diminished.

VVI can provide quantitative information for the early diagnosis of HCM sarcomere gene mutation carriers without myocardial hypertrophy to improve early diagnosis and identification.

Abbreviations

HCM, Hypertrophic cardiomyopathy; G+/P+, gene positive/phenotype positive; G+/P-, gene positive/phenotype negative; LAD, left atrialanteroposterior diameter; LAVI, left atrial volume index ; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVOT-PG, left ventricular outflow tract pressure gradient; EF, ejection fraction; E/A, mitral early diastolic filling ratio; IVSD, interventricular septum thickness in diastolic; LVMWT, left ventricular wall maximum thickness; BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; PBr, Peak basilar rotation angle; PMr, Peak mid rotation angle; PAr, peak apex rotation angle; Ptw, peak left ventricular twist; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; VVI, velocity vector imaging.

Declarations

Ethics approval and consent to participate

All protocols pertaining to human subjects were first approved by the Institutional Ethics Committee of Second Xiangya Hospital of Central South University. Informed consent was obtained from all of the patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declares that there no conflicts of interest.

Funding

Not applicable.

Authors' contributions

ZR,Y and QH,P analyzed and explained the patient data. QC,Z and XD,L collected the blood samples of the patients and consulted the relevant literature. Ultrasound examination were performed by LY, LY was the main contributor to the manuscripts. All authors have read and approved the final manuscript.

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References

1. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC) [J]. Eur Heart J: 2014,35(39):2733-2779.
2. Bansal M, Cho GY, Chan J, et al. Feasibility and accuracy of different techniques of two-dimensional speckle based strain and validation with harmonic phase magnetic resonance imaging[J]. 2008,21(12):1318-1325.
3. Wei Z, Su H, Zhang H, et al. Assessment of left ventricular wall motion in diabetic rats using velocity vector imaging combined with stress echocardiography[J]. Echocardiography:2008,25(6):609-616.
4. Bohs LN, Geiman BJ, Anderson ME, et al. Speckle tracking for multi-dimensional flow estimation[J]. Ultrasonics:2000,38 (14):369-375.
5. Langeland S, Dhooge J, Wouters PF, et al. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle[J]. Circulation:2005,112(14):2157-2162.

6. Pirat B, McCulloch ML, Zoghbi WA. Evaluation of global and regional right ventricular systolic function in patients with pulmonary hypertension using a novel speckle tracking method[J]. *Am J Cardiol*:2006;98(5):699-704.
7. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008;358:2107–2116.
8. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
9. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–367
10. Girolami F, Olivetto I, Passerini I, et al. A molecular screening strategy based on β -myosin heavy chain, cardiac myosin binding protein C and troponin T genes in Italian patients with hypertrophic cardiomyopathy [J]. *J Cardio Med*: 2006;7:601–607.
11. Niimura H, Patton K K, McKenna W J, et al. Sarcomere protein gene mutations in hypertrophic cardiomyopathy of the elderly[J]. *Circulation*:2002, 105(4): 446-451.
12. Watkins H, Conner D, Thierfelder L, et al. Mutations in the cardiac myosin binding protein-C gene on chromosome 11 cause familial hypertrophic cardiomyopathy[J]. *Nat Genet*:1995, 11(4):434-437.
13. Fananapazir L, Epstein N D. Prevalence of hypertrophic cardiomyopathy and limitations of screening methods[J]. *Circulation*:1995, 92(4): 700-704.
14. Maron B J, Gardin J M, Flack J M, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults[J]. *Circulation*:1995,92(4): 785-789.
15. Hulot J S, Fauconnier J, Ramanujam D, et al. Critical role for stromal interaction molecule 1 in cardiac hypertrophy [J]. *Circulation*:2011,123(7):796-805.
16. Kho C, Lee A, Jeong D, et al. Refilling Intracellular Calcium Stores[J]. *Drug Discov Today Dis Mech*:2010,7(2):145-150.
17. Kojima A, Kitagawa H, Omatsukanbe M, et al. Ca^{2+} paradox injury mediated through TRPC channels in mouse ventricular myocytes[J]. *Br J Pharmacol*:2010,161(8):1734-1750.
18. Germans T, Wilde AA, Dijkmans PA, Chai W, Kamp O, et al. Structural abnormalities of the inferoseptal left ventricular wall detected by cardiac magnetic resonance imaging in carriers of hypertrophic cardiomyopathy mutations[J]. *J Am Coll Cardiol*:2006, 48: 2518–23.
19. Spindler M, Saupe K W, Christe M E, et al. Diastolic dysfunction and altered energetics in the $\alpha\text{MHC}^{403/+}$ mouse model of familial hypertrophic cardiomyopathy[J]. *J Clin Invest*: 1998,101(8): 1775-1783.

20. Silva D, Madeira H, Almeida A, et al. Tissue Doppler imaging and plasma N-terminal probrain natriuretic peptide for the identification of hypertrophic cardiomyopathy mutation carriers. *Am J Cardiol* 2013;112:996–1004.

Tables

Table 1 Clinical characteristics and conventional echocardiographic ultrasound parameters for all groups

	Control	G+/P-	G+/P+
Number of cases	48	40	45
Age, y	39±17	42±16	48±15
Sex (male/female)	21/17	16/14	20/15
BSA, M2	1.7±0.2	1.6±0.2	1.7±0.2
Heart rate, bpm	71±18	73±14	72±16
SBP, mmHg	107±13	109±11	108±12
DBP, mmHg	74±10	73±11	75±9
Mutant gene, %			
MYH7	0	13(44%)	9(26%)
MYBPC3	0	15(50%)	22(63%)
TNNT2	0	1(3%)	3(9%)
TNNI3	0	1(3%)	1(2%)
IVSD (mm)	9.0±0.9	8.8±1.0	19.4±5.2#△
LVMWT (mm)	8.9±1.0	9.2±1.4	17.6±6.8#△
LAD (mm)	33±4	34±3	41±5#△
LAVI (ml/m ²)	21±5	22±4	31±6#△
LVEDV (ml)	72±15	73±16	75±17
LVESV (ml)	28±6	29±8	31±7
LVOT-PG (mmHg)	2.2±0.9	2.5±0.7	22±30.5#△
EF (%)	63±4	63±5	64±6
E/A	1.4±0.6	1.4±0.5	1.0±0.5*&

BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure; IVSD, interventricular septum thickness in diastolic; LVMWT, left ventricular wall maximum thickness; LAD, left atrialanteroposterior diameter; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVOT-PG, left ventricular outflow tract pressure gradient; EF ,ejection fraction; E/A, mitral early diastolic filling ratio.

* $P < 0.05$, compared with the control group.

$P < 0.01$, compared with the control group.

& $P < 0.05$, compared with the G+/P- group.

$\Delta P < 0.01$, compared with the G+/P- group.

Table 2 Comparison of left ventricular longitudinal peak systolic strain among all groups

Left ventricular wall segmentation	Control	G+/P-	G+/P+
Apical 4-chamber			
Basal anterolateral	20.31±7.15	-20.41±5.61	-13.74±2.82#△
Mid anterolateral	20.23±6.74	-20.55±6.13	-12.06±2.94#△
Apical lateral	19.35±6.94	-19.87±5.35	-11.84±2.60#△
Basal inferoseptum	21.37±7.55	-15.48±3.04*⊗	-8.12±1.34#△⊗
Mid inferoseptum	19.86±7.32	-18.65±2.72	-8.64±1.55#△⊗
Apical septum	20.14±6.76	-20.88±3.60	-11.86±1.24#△
Apical 2-chamber			
Basal anterior	23.35±7.77	-22.57±5.64	-10.54±2.07#△⊗
Mid anterior	20.26±5.52	-19.96±5.35	-9.22±1.85#△⊗
Apical anterior	20.74±6.75	-19.87±4.91	-11.80±2.46#△
Basal inferior	20.27±6.65	-20.12±5.34	-13.84±3.17#△
Mid inferior	19.38±6.83	-18.68±6.15	-12.96±2.95#△
Apical inferior	20.15±7.31	-19.73±5.80	-12.15±3.34#△
Apical 3-chamber			
Basal anteroseptum	21.23±7.82	-15.94±5.54*⊗	-9.54±2.04#△⊗
Mid anteroseptum	20.62±5.70	-20.65±4.12	-8.95±1.86#△⊗
Basal inferolateral	19.25±7.85	-22.74±6.82*	-13.61±2.74#△
Mid inferolateral	18.24±6.40	-21.12±5.94*	-12.42±1.62#△

* P < 0.05, compared with the control group.

P < 0.01, compared with the control group.

& P < 0.05, compared with the G+/P- group.

△P < 0.01, compared with the G+/P- group.

⊗P < 0.05; the same segment in the same group compared with other ventricular walls.

Table 3 Comparison of left ventricular circumferential peak systolic strain among all groups

Left ventricular wall segmentation	Control	G+/P-	G+/P+
Mitral valve level			
Anteroseptum	27.81±6.65●	27.74±6.25●	26.77±7.13●
Anterior wall	31.4±8.62●	29.34±7.63●	29.82±8.74●
Anterolateral wall	31.61±5.87●	30.97±7.86●	32.15±8.33●
Inferolateral wall	27.91±7.46	26.72±9.41	27.33±4.17
Inferior wall	25.23±5.17●	26.23±6.41●	27.41±5.80●
Inferoseptum	28.32±8.77	26.73±9.74	26.83±11.26
Papillary muscle level			
Anteroseptum	26.52±5.23●	27.41±5.74●	26.12±5.13●
Anterior wall	32.65±6.58●	31.52±6.51●	30.89±8.63●
Anterolateral wall	32.43±6.76●	32.73±7.65●	33.36±6.84●
Inferolateral wall	29.30±9.14	28.24±8.25	29.72±5.97
Inferior wall	26.75±5.95●	25.76±5.86●	27.36±5.35●
Inferoseptum	29.13±7.63	30.86±6.36	29.62±6.50
Apical level			
Anteroseptum	40.74±5.97	40.33±5.52	38.23±9.41
Anterior wall	41.85±7.94	40.64±6.84	39.12±10.24
Anterolateral wall	42.65±7.24	41.40±6.94	40.80±7.74
Inferior wall	41.87±6.25	40.29±6.04	39.82±8.51

- P < 0.01, compared with apical level.

Table 4 Comparison of left ventricular radial peak systolic strain among all groups

Left ventricular wall segmentation	Control	G+/P-	G+/P+
Mitral valve level			
Anteroseptum	37.91±4.72☒	36.76±4.76	26.86±7.93*&☒☐
Anterior wall	38.55±5.43☒	37.45±5.37☒	25.44±10.45*&☒☐
Anterolateral wall	37.95±7.14☒	37.19±7.42☒	32.72±7.67*&☒
Inferolateral wall	36.96±6.52☒	36.34±6.04☒	30.76±7.15*&☒
Inferior wall	37.93±9.31☒	37.67±9.16☒	31.74±10.04*&☒
Inferoseptum	36.46±8.17☒	35.37±8.27☒	25.22±11.42*&☒☐
Papillary muscle level			
Anteroseptum	43.64±8.15	41.49±8.49	33.17±10.45*&☐
Anterior wall	43.33±7.33	42.97±5.37	33.46±9.93*&☐
Anterolateral wall	43.77±7.32	43.24±7.34	37.27±7.15*&
Inferolateral wall	41.24±8.20	41.45±8.37	36.12±8.52*&
Inferior wall	43.11±8.42	42.14±8.37	37.53±7.31*&
Inferoseptum	42.42±8.52	42.79±8.46	31.16±8.23*&☐
Apical level			
Anteroseptum	36.56±4.89☒	37.26±8.37☒	26.12±11.26*&☒
Anterior wall	35.41±5.32☒	36.43±7.43☒	26.62±10.23*&☒
Anterolateral wall	34.40±7.67☒	35.45±7.04☒	28.23±8.26*&☒
Inferior wall	35.40±8.42☒	36.16±8.45☒	27.72±11.01*&☒

* P < 0.05, compared with the control group.

& P < 0.05, compared with the G+/P- group.

☒P < 0.05, compared with central section.

☐P<0.05, compared with other ventricular walls in the same level of the same group.

table 5 Comparison of left ventricular global systolic strain, rotation, torsion and NT- pro-BNP level among all groups

VVI parameters	Control	G+/P-	G+/P+
GLS	-21.64 ± 3.76	-20.56 ± 3.82	$-10.16 \pm 3.37^{\# \Delta}$
GCS	-31.78 ± 4.37	-30.94 ± 4.24	-29.92 ± 4.83
GRS	40.16 ± 5.75	39.73 ± 5.46	$34.64 \pm 4.26^{* \&}$
PBr	3.32 ± 1.75	3.45 ± 1.62	3.34 ± 1.37
PMr	-1.91 ± 1.38	-1.86 ± 1.53	$2.64 \pm 2.01^{* \&}$
PAr	-3.83 ± 2.64	-3.67 ± 2.94	-3.92 ± 2.38
Ptw	7.06 ± 3.27	6.96 ± 3.12	7.18 ± 2.66
NT-pro-BNP(log pg/mL)	1.51 ± 0.28	1.64 ± 0.27	$2.06 \pm 0.35^{* \&}$

GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; PBr, Peak basilar rotation angle; PMr, Peak mid rotation angle; PAr, peak apex rotation angle; Ptw, peak left ventricular twist; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

* P < 0.05, compared with the control group.

P < 0.01, compared with the control group.

& P < 0.05, compared with the G+/P- group.

Δ P < 0.01, compared with the G+/P group.

Figures

a

b

c

Figure 1

Longitudinal, circumferential and radial strain curve for the left ventricle in the three groups. a. radial strain curve; b. Longitudinal strain curve; c. circumferential strain curve. A. Normal control; B. G+/P-; C. G+/P+.

a

b

c

Figure 2

Longitudinal, circumferential and radial strain of 16 segments in the three groups. a. Longitudinal strain; b. circumferential strain; c. radial strain.

Figure 3

Comparison of the peak mid rotation angle of left ventricular and global systolic strain among the three groups.

Figure 4

Comparison of the peak mid rotation angle of left ventricular and global systolic strain among the three groups.