IDENTIFYING ADVERSE REMODELING IN HYPERTROPHIC CARDIOMYOPATHY PHENOTYPES ROLE OF LEFT ATRIAL PARAMETERS

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Objective: Documenting adverse remodeling in absence of left ventricular outflow tract (LVOT) obstruction and mitral regurgitation in a classical hypertrophic cardiomyopathy (HCMP) phenotype is difficult. Changes in the left atrium (LA) are a consequence of progressive left ventricular (LV) fibrosis and have been shown to progress in a linear fashion. Therefore, studying LA changes for identifying adverse remodeling in HCMP patients is important.

Materials and Methods: This was a prospective study which included HCMP patients and age- and gender-matched controls. Various echocardiographic parameters of adverse cardiac remodeling were investigated.

Results: A total of 160 patients with HCMP and 75 age- and sex-matched controls were analyzed over a 5-year period. HCMP patients had an enlarged LA, greater segmental thickness, and mildly increased LV filling pressure. Patients with maximum LA volume >40 mL and global LA strain <21.5% showed greater maximum segmental thickness and increased ratio of pulse wave Doppler derived mitral E wave and tissue Doppler derived annular e wave with reduced LA strain and LV strain, LA emptying fraction, and strain-derived LV ejection fraction. In both groups, significant difference was not observed in age, sex, HCMP phenotype, presence or absence of LVOT obstruction, LV volume, and mitral Doppler ratio of pulse wave Doppler derived mitral E and A waves.

Conclusion: Monitoring HCMP in asymptomatic patients is challenging. Assessment of adverse cardiac remodeling in classical HCMP phenotype is feasible using global LA strain and maximum LA volume. Global LA strain identifies early changes and maximum LA volume late changes of cardiac remodeling and therefore provide an early indication of disease progression in asymptomatic HCMP patients.

Key words Hypertrophic cardiomyopathy · Left atrial strain · Adverse remodeling.
tricle and increased filling pressure. Studying these changes to document adverse remodeling in a classical HCMP phenotype is important.

Aims and objectives
In the present study, maximum left atrial (LA) volume and global LA strain were estimated in HCMP patients and compared with age- and sex-matched controls.

To correlate these two parameters and establish adverse remodeling with other variables such as HCMP phenotype, LVOT obstruction, LV filling pressure, maximum segmental thickness, global LV strain, and LVEF.

MATERIALS AND METHODS

Study population
The study subjects consisted of consecutive patients who had been referred to our echocardiography laboratory and met the diagnostic criteria for HCMP [two-dimensional echocardiographic evidence of a hypertrophied (diastolic wall thickness >15 mm), a nondilated LV in absence of conditions capable of inducing that magnitude of hypertrophy] were prospectively screened [1].

Patients with a poor acoustic window and who were technically unsuitable for Speckle Tracking analysis and those with non-sinus rhythm were excluded.

The final study population consisted of 160 patients. The control group consisted of 75 age- and sex-matched healthy volunteers who had no evidence of heart disease based on physical examination, 12-lead electrocardiogram (ECG), and echocardiography. All subjects provided informed consent to participate in the study (approval number M1029). The following clinical data were collected: age, sex, history of hypertension, diabetes mellitus (requiring medical therapy), family history of HCMP, and sudden cardiac death. Clinical status was defined according to the New York Heart Association classification.

Echocardiography study
Two commercially available ultrasound machines (Philips Affinity 50 and Epiq CVX; Philips Medical Systems, Amsterdam, Netherlands) equipped with an S-4 probe were used for all echocardiographic examinations. Standard ECG gated echocardiographic views were obtained using second-harmonic imaging with frequency, depth, and sector width adjusted for frame-rate optimization (between 60–100 fps). Image settings and frame rates were kept similar for LV apical four-chamber, two-chamber, and long-axis views [2].

For LA measurements (maximum volume, emptying fraction, and deformation analysis), a conventional apical four-chamber view was recorded with focus on the LA cavity optimization and wall definition excluding LA appendage and the confluence of the pulmonary veins. Maximum LA volume was measured at end-systole using area-length method. LV volumes and LVEF were calculated using Simpson’s biplane method. Peak early diastolic mitral annular velocity (e’) was obtained using tissue Doppler imaging from the apical four-chamber view using both the septal and the lateral sites. The average’ value was used to calculate the ratio of early diastolic transmitral flow velocity (E) to e’. LVOT resting gradient was measured using continuous-wave Doppler from the apical 5-chamber view. LVOT obstruction was defined as a peak gradient >30 mm Hg at rest [3].

Both two-dimensional and Doppler loops were digitally stored as 3–5 consecutive cycles recorded during end-expiratory apnea. Data were analyzed offline using commercially available software Package (Q Lab PC version, Philips Medical Systems) by two observers experienced in two-dimensional strain quantification.

Global LV strain analysis was performed in apical views using cardiac motion tracking tool. Strain-based LVEF was derived using the formula: EF=−4.35×(global LV strain+3.9) [4]. Peak LA reservoir strain was analyzed using RR gated ECG in unzoomed focus apical view of LA [5]. HCMP phenotypes were divided into septal involvement group consisting of reverse curvature, neutral, and sigmoid, and the non-septal involvement group consisted of apical and apical with mid-segment involvement.

Statistical analysis
The clinical and echocardiographic parameters of HCMP patients and age- and sex-matched controls were reported. Continuous variables are expressed as means±standard deviations and categorical variables as proportions. Continuous variables were compared between HCMP patients and young healthy control subjects using Student’s t-test. Categorical variables were compared using the χ² test or Fisher’s exact test, as appropriate. Between-group differences based on HCMP phenotype were compared using one-way analysis of variance followed by the Bonferroni post-hoc test. In addition, the characteristics of HCMP patients were evaluated using two group comparison based on the median values of maximum LA volume and global LA strain. Covariates reaching a p-value <0.05 in univariate analyses were included in the multivariate binary logistic regression analyses. For all analyses, a two-tailed p-value <0.05 was considered to indicate a statistically significant difference. The Spearman correlation coefficient was used for correlative analysis between each variable. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).
Table 1. Patient characteristics in the different group

|                      | Age- and sex-matched controls (n=75) | HCMP patients (n=160) | HCMP phenotypes | Sepal involvement group (n=80) | Non-septal involvement group (n=80) |
|----------------------|--------------------------------------|-----------------------|-----------------|--------------------------|----------------------------------|
| Age, years           | 54±14                                | 54±14                 | 54 ±16          | 54±13                   |                                  |
| Male                 | 42 (56)                              | 106 (66)             | 50 (62)        | 56 (70)                 |                                  |
| Female               | 33                                   | 54                    | 30             | 24                      |                                  |
| Asymptomatic         | N/A                                  | 51 (32)              | 21 (26)       | 30 (37)                 |                                  |
| Symptomatic class II/III | N/A                            | 56 (35)              | 32 (40)       | 24 (30)                 |                                  |
| Symptomatic class IV | N/A                                  | 53 (37)              | 27 (33)       | 26 (32)                 |                                  |
| LVEDV                | 85±11                                | 89±25                | 88±26          | 90±24                   |                                  |
| LVESV                | 34±6                                 | 37±11                | 37±13          | 39±11                   |                                  |
| LVEF (Simpson's biplane method) | 58±4                                | 58±4                 | 58±5          | 57±4                    |                                  |
| Maximum LA volume    | 18±8                                 | 34±8*                | 50±14          | 49±17                   |                                  |
| LA emptying fraction | 60±7                                 | 52±8*                | 52±11          | 52±11                   |                                  |
| Global LA strain     | 34±7                                 | 18±8*                | 16±6          | 20±9†                   |                                  |
| Maximum segmental thickness | 10±2                              | 26±6*                | 29±6          | 23±5†                   |                                  |
| Global LV longitudinal strain | -10±2                             | -11±4*               | -11±5         | -11±5                   |                                  |
| GLS-derived LVEF     | 66±14                                | 32±20*               | 32±18          | 31±20                   |                                  |
| E/A ratio            | 1.5±0.5                              | 1.1±0.6              | 1.0±0.6        | 1.1±0.6                 |                                  |
| E/e’ ratio           | 10±2                                 | 15±6*                | 15±5          | 15±3                    |                                  |
| LVOT gradient        | -                                    | 55±28                | 55±28          | -                       |                                  |

Data are presented as the mean±standard deviation or n (%). *p<0.05 based on paired t-test (HCMP group vs. age- and sex-matched control group), †p<0.05 based on analysis of variance. HCMP: hypertrophic cardiomyopathy; LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, LA: left atrium, GLS: global longitudinal strain, LVOT: left ventricular outflow tract, LV: left ventricle, E/e’: pulse wave Doppler derived mitral E wave and tissue Doppler derived annular e wave, E/A: pulse wave Doppler derived mitral E and A waves.

RESULTS

The baseline characteristics of the 160 HCMP patients and 75 age- and sex-matched control subjects are presented in Table 1. In the HCMP group, 11 subjects (7%) had hypertension and 5 subjects (3%) had diabetes mellitus. Patients in the age- and sex-matched control group had no history of hypertension or diabetes mellitus. Clinically, the HCMP population was almost equally divided with approximately 1/3rd asymptomatic, 1/3rd symptomatic class II/III, and 1/3rd symptomatic class IV. When comparing echocardiographic variables, both maximum LA volume and LA emptying fraction were significantly increased and global LA strain was significantly decreased in the HCMP group compared with controls. Among LV parameters, maximum segmental thickness was significantly increased and global LV strain and strain-derived LVEF were significantly decreased in the HCMP group compared with controls. Doppler-derived transmural flow velocities were comparable, however, the anular tissue velocity e’ was significantly lower and the E/e’ ratio was significantly higher in the HCMP group compared with controls. When the characteristics based on HCMP phenotype were compared, global LA strain and maximum segmental thickness were significantly different, however, all other variables were comparable among the two phenotypes. A significant difference in these variables was not observed between the phenotypes based on Bonferroni post-hoc analysis. Fig. 1 shows comparison of maximum LA volume and global LA strain between the HCMP phenotype and controls.

To determine significant predictors of LA remodeling and dysfunction, the characteristics of HCMP patients based on the median values of maximum LA volume and global LA strain in the HCMP group were compared (Table 2). When patients in the HCMP group were classified based on the median value of maximum LA volume, significantly more patients with >40 mL volume had higher symptomatic class, greater maximum segmental thickness, and increased E/e’ ratio with reduced LA strain and LV strain, LA emptying fraction, and LVEF derived from global LV strain.

When the HCMP group was divided based on the median value of global LA strain, patients with global LA strain <21.5% showed significantly increased LA volume, maximum segmental thickness, and E/e’ ratio with significantly reduced global LV strain, LA emptying fraction, and LVEF derived from LV global longitudinal strain (LVGLS). Significant difference was not observed in degree of symptomatic class contrary to the LA volume group.
In both groups, significant difference was not observed in age, sex, HCMP phenotype, LVOT obstruction, LV volumes, and ratio of pulse wave Doppler derived mitral E and A waves (E/A).

When multivariate linear regression analysis was performed (Table 3), maximum LA volume was associated with symptomatic class IV, maximum segmental thickness, E/e’ ratio, and GLS-derived LVEF, and global LA strain was associated with maximum segmental thickness and global LV strain.

Based on Spearman correlation analysis (Table 4), maximum LA volume and global LA strain were moderately correlated. These parameters were also moderately directly correlated with age and maximum segmental thickness and inversely correlated with global LV strain and GLS-derived LVEF but not with E/e’ ratio, LVOT obstruction, LVEF based on Simpson’s biplane method, and LA emptying fraction.

**DISCUSSION**

In the present study, the following results were observed: 1) HCMP patients had greater maximum LA volume, reduced LA emptying fraction, and decreased global LA strain compared with controls; 2) LA volume and strain did not significantly differ based on patient age, sex, and phenotype; 3) increased LA volume was significantly associated with patient’s worsening clinical status, increased LV filling pressure (increased E/e’ ratio), and maximum segmental thickness; 4) reduced global LA strain is associated with reduced global LV strain and maximum segmental thickness; 5) both LA volume and LA strain were not significantly associated with LVOT obstruction; 6) both global LA strain and maximum LA volume were moderately correlated with age and maximum segmental thickness and moderately in versely correlated with global LV strain and GLS-derived LVEF (Fig. 2).

Pathophysiological adverse remodeling in HCMP is a result of increased afterload, myocyte hypertrophy, and fibrosis. Consequently, LV hypertrophy in HCMP is a result of disturbed sarcocere energy balance leading to increased adenosine triphosphate requirement and impaired relaxation which further progresses
into apoptosis leading to myocyte loss and fibrosis. Olivotto et al. [6] described four clinical stages of HCMP. The definition of the intermediate stage of disease progression is based on a combination of several structural and functional features including LVEF in the low-normal range, moderate-to-severe diastolic function, marked atrial dilatation, moderate areas of late gadolinium enhancement, severe microvascular dysfunction, thinning of the LV walls, onset of atrial fibrillation, and spontaneous reduction or loss of LVOT obstruction [6,7].

Echocardiographic parameters, such as EF, GLS, E/A, E/e', and LVOT gradient, showed minimal change over time in HCMP patients and are difficult to obtain reliably in large subsets of HCMP patients because they have phenotypic variability.

The LA appears amore appealing target for imaging because it remains normal in size and function in early disease stages. LA remodeling may occur due to maladaptive changes in the LV or extension of the disease process into the LA [8]. Maximum LA volume has emerged as an important biomarker for adverse cardiac events in a variety of cardiovascular conditions and is an established surrogate for the severity and chronicity of LV diastolic dysfunction. In addition to size, LA function provides

| Variables | Maximum LA volume (mL) | Global LA strain (%) |
|-----------|------------------------|----------------------|
|           | <40 (n=122)             | >40 (n=113)          | <21.5 (n=117) | >21.5 (n=118) |
| Age, years | 38±15                  | 55±15                | 55±15        | 38±15        |
| Male      | 72 (59)                | 76 (67)              | 78 (66)      | 70 (60)      |
| Female    | 50 (41)                | 37 (32)              | 39 (33)      | 48 (41)      |
| Controls  | 74 (60)                | 1 (0.9)              | 0 (0)        | 75 (64)      |
| Non-septal involvement group | 26 (21) | 54 (48) | 50 (43) | 30 (25) |
| Septal involvement group | 22 (18) | 58 (52) | 67 (57) | 13 (11) |
| Asymptomatic | 16 (13) | 35 (31)* | 35 (30) | 16 (14) |
| Symptomatic class II/III | 21 (17) | 35 (31)* | 41 (35) | 15 (13) |
| Symptomatic class IV | 11 (9) | 42 (37)* | 41 (35) | 12 (10) |
| LVEDV | 87±19 | 88±24 | 89±25 | 86±17 |
| LVESV | 36±9 | 37±12 | 38±12 | 35±8 |
| LVEF (Simpson’s biplane method) | 59±3 | 58±4 | 58±5 | 58±4 |
| Maximum LA volume | - | - | 51±16 | 36±12* |
| LA emptying fraction | 58±9 | 51±12* | 51±11 | 58±10* |
| Global LA strain | 28±10 | 18±8* | - | - |
| Maximum segmental thickness | 16±7 | 26±7* | 27±6 | 15±8* |
| Global LV longitudinal strain | -17±5 | -11±4* | -11±5 | -17±4* |
| GLS-derived LVEF | 55±19 | 29±21* | 32±19 | 54±23* |
| E/A ratio | 1.3±0.4 | 1.1±0.7 | 1.1±0.5 | 1.1±0.5 |
| E/e’ ratio | 12±4 | 16±5* | 15±5 | 13±4* |
| LVOT gradient | 49±22 | 56±31 | 57±30 | 47±25 |

Data are presented as the mean±standard deviation or n (%). *p<0.05 based on chi square test. LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, LVEF: left ventricular ejection fraction, LA: left atrium, GLS: global longitudinal strain, LVOT: left ventricular outflow tract, LV: left ventricle, E/e: pulse wave Doppler derived mitral E wave and tissue Doppler derived annular e wave, E/A: pulse wave Doppler derived mitral E and A waves.
In earlier studies, LA remodeling was influenced by LVOT obstruction, presence of significant mitral regurgitation, and increased LV mass. In the present study, LA parameters were well correlated with age and maximum segmental thickness but not with degree of LVOT obstruction. LVOT obstruction is phenotype-specific and observed specifically in reverse curvature and sigmoid phenotypes. Both obstructive and non-obstructive phenotypes were compared and significant association was not found with this parameter. However, significant association with the maximum hypertrophied segment irrespective of septal or non-septal involvement was observed. The results indicate LA remodeling is not dependent on septal contour/LVOT obstruction [11,12].

Another parameter indicative of adverse remodeling is increased LV filling pressure. The E/e’ ratio has been incorporated in many studies to represent increased LV filling pressure in HCMP patients although with modest correlation with invasively determined measurements [13]. Although a modest correlation of LA volume with increased E/e’ ratio indicating deteriorated clinical status of patients was observed in the present study, a significant correlation was not found with global LA strain. Therefore, the presence of global LA strain is indicative of an advanced stage of adverse remodeling.

Measuring global LA strain and maximum LA volume is easier, reproducible, and has shown less interobserver variability than phasic volumes and strain in various studies involving normal and diseased subjects [14]. Based on this hypothesis, these parameters could be easily obtained and correlated in a large HCMP population with minimal interobserver variability.

**Conclusion**

Follow-up of HCMP in asymptomatic patients is challenging. Assessment of adverse cardiac remodeling in classical HCMP phenotype is feasible using global LA strain and maximum LA volume. Global LA strain identifies early changes and maximum LA volume identifies late changes of cardiac remodeling and therefore provide an early indication of disease progression in asymptomatic HCMP patients.

**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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