Morphological Determinants of Obstructive Hypertrophic Cardiomyopathy Obtained Using Echocardiography

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Summary
The morphological determinants of left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy (HCM) are not completely understood. We aimed to identify the anatomical risks of the obstruction using echocardiography.

Fifty patients with untreated HCM were classified into two groups: those with LVOT pressure gradient (LVOTPG) ≥ 30 mmHg (obstructive HCM [HOCM] group) and those with LVOTPG < 30 mmHg (HNCM group). The echocardiographic morphological variables were analyzed to determine whether they were predictive of LVOT obstruction. Systolic anterior motions of the mitral valve were observed in 100% of patients in the HOCM group but only in 58% in the HNCM group. There were no significant differences in wall thickness, end-systolic LV dimension (LVDs), or LVOT diameter between the two groups. However, HOCM subjects had a shorter distance from papillary muscles to the inter-ventricular septum (5.97 ± 2.3 versus 9.20 ± 1.9 mm, respectively, \( P < 0.0001 \)) and a longer anterior mitral leaflet (AML) length (24.7 ± 5.8 versus 20.1 ± 5.4 mm, respectively, \( P < 0.01 \)) compared to the HNCM group. The AML length/LVDs ratio was significantly higher in the HOCM group compared to the HNCM group (1.02 ± 0.34 versus 0.78 ± 0.26, \( P < 0.01 \)), and an LVOT obstruction was predicted with an area under the curve of 0.71 (\( P < 0.05 \)). Multiple linear regression revealed that only the AML length/LVDs ratio was independently associated with LVOTPG (\( P < 0.01 \)).

The AML length/LVDs ratio has a significant predictive value for LVOT obstruction and a strong relationship with LVOTPGs. The AML length/LVDs ratio determines the anatomical risk of LVOT obstruction in HCM.

Key words: Left ventricle outflow tract obstruction, Mitral valve complex, Mitral leaflet length

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, with variable clinical expression ranging from asymptomatic status to progressive heart failure or sudden death.\(^1\)\(^-\)\(^3\) Left ventricular outflow tract (LVOT) obstruction at rest is used as a predictor of the risk of sudden cardiac death.\(^4\)\(^-\)\(^6\) Previous studies have shown a number of anatomical features, such as systolic anterior motion (SAM) of the mitral valve leaflets,\(^7\)\(^-\)\(^9\) narrowing of the LVOT,\(^10\) septal hypertrophy,\(^11\) and abnormalities of the mitral apparatus (e.g., papillary muscles, leaflets, chords, and annulus),\(^12\)\(^-\)\(^14\) which contribute to LVOT obstruction. The predictive accuracies of these factors for LVOT obstruction however remain controversial. Indeed, not all HCM patients with SAM have significant LVOT obstruction.\(^15\) A previous study using cardiovascular magnetic resonance imaging (MRI) demonstrated that the LVOT diameter did not differ between HCM patients and normal subjects.\(^16\) Septal reduction strategies, such as alcohol septal ablation and surgical myectomy, have developed into highly effective therapies to relieve LVOT obstruction and intractable symptoms; however, some obstructive HCM (HOCM) patients have a residual LVOT gradient even after septal reduction strategies.\(^17\) Moreover, SAM-related LVOT obstruction can occur in patients without septal hypertrophy.\(^18\) Conversely, two-third of patients with significant septal hypertrophy have no LVOT obstruction.\(^19\) Thus, the most powerful anatomical predictor of LVOT obstruction is unclear. Therefore, we aimed to identify the anatomical risk of LVOT obstruction in HCM using echocardiography.

Methods

Study population: This was a retrospective observational study using data extracted from our prospectively collected database. The institutional review board (IRB) approved this study, and informed consent was waived based on the retrospective nature of this study (IRB no.: 1757).

In total, 57 consecutive patients diagnosed with HCM between April 2009 and March 2015 at Akita University Hospital were enrolled in the present study. HCM was di-
Echocardiography: Two-dimensional (2D) transthoracic echocardiography was performed using a Philips iE33 Ultrasound Machine (Philips Medical Systems, Andover, MA, USA). The anatomical parameters analyzed are as follows: left atrial dimension, inter-ventricular septal thickness, posterior wall thickness, LV end-dias- tolic dimension, LV end-systolic dimension (LVDs), LVOT diameter, mitral annular size, anterior mitral leaflet (AML) length, and posterior mitral leaflet (PML) length. The mitral annular size was defined as an antero-posterior diameter measured in systole. The AML and PML lengths were measured in diastole in a parasternal long-axis view, with the leaflets maximally extended parallel to the anterior septum and LV-free wall (Figure 1A). The leaflet length was defined as the distance from the most distal extent of the anterior leaflet to its insertion into the posterior aortic wall and the most distal extent of the posterior leaflet into the basal LV posterior free wall. The LVOT diameter was measured 1 cm below the aortic valve on the long-axis view image at end-systole (Figure 1B). Resting LVOT
peak velocity was measured using continuous-wave Doppler echocardiography and LVOTPG was estimated using a simplified Bernoulli equation. LVEF was measured using a modified biplanar Simpson’s method.

Papillary muscle abnormalities also contribute to LVOT obstruction. We therefore evaluated papillary muscle hypertrophy, anterior apical displacement of the papillary muscles, and malformation of the papillary muscle. To obtain the maximal papillary muscle thickness, the diameter of both papillary muscles was measured at end-diastole on short-axis images. To assess the anterior apical displacement of the papillary muscles, the distances between the inter-ventricular septum and an anterior papillary muscle (or posterior papillary muscle) were measured in four-chamber view at end-systole (Figure 1C). The shorter distance between the inter-ventricular septum-anterior papillary muscle distance and the inter-ventricular septum-posterior papillary muscle distance was defined as the papillary muscle-septum distance. Malformation of the papillary muscle was defined as the presence of any of the following: papillary muscle insertion directly into the AML, papillary muscle fusion to the ventricular septum, papillary muscle fusion to the LV-free wall, double bifid papillary muscle, or accessory papillary muscle.

Experienced sonographers analyzed the echocardiographic images. Two independent echocardiologists who were blinded to the clinical data reviewed all images offsite. The inter-observer variability for all measurements was analyzed by determining the difference between two measurements made by two observers. The intra-observer variability was analyzed using two measurements taken by one observer. Inter- and intra-observer agreement for these measurements were evaluated using intra-class correlation coefficients. The following values for intra-class correlation coefficients (± 95% confidence intervals [CIs]) were obtained, which suggested good reproducibility of the echocardiographic parameters. Inter-observer variability was as follows: LVEF, 0.790 (0.614-0.892); LVDs, 0.873 (0.756-0.936); left atrial dimension, 0.837 (0.694-0.917); mitral annular size, 0.871 (0.748-0.937); AML length, 0.885 (0.778-0.942); and PML length, 0.846 (0.708-0.921). Intra-observer variability was as follows: LVEF, 0.807 (0.642-0.901); LVDs, 0.925 (0.853-0.963); left atrial dimension, 0.848 (0.713-0.923); mitral annular size, 0.830 (0.674-0.915); AML length, 0.891 (0.790-0.945); and PML length, 0.908 (0.821-0.954).

Statistical analyses: Continuous variables were expressed as means ± standard deviation. For continuous and normally distributed data, Student’s t-test was used to compare differences between groups. For data with a non-normal distribution, the Mann-Whitney U test was used. Correlations were analyzed using Pearson’s correlation coefficient. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to assess the usefulness of anatomical parameters for identifying significant LVOT obstruction (LVOTPG ≥ 30 mmHg). Stepwise multiple linear regression analyses were performed to estimate factors that influence LVOTPG. All parameters with a significance value of < 0.10 by univariate analysis were entered into the multivariate analysis. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows (ver. 16.0; SPSS Inc., Chicago, IL, USA).

Results

Baseline patient characteristics: The baseline characteristics of the 50 HCM patients are summarized in Table I. The mean age of the study population was 62.4 ± 15 years and 54% were men. Thirty-four patients (68%) were asymptomatic, while five patients (10%) were of New York Heart Association functional class III or IV. There were no significant differences in mean age, sex, body surface area, systolic blood pressure, heart rate, or hemoglobin level between the two groups (Table I).

Table 1: Baseline Characteristics of the Study Population

| Characteristic | HOCM group | HNCM group | P value |
|---------------|------------|------------|---------|
| Patients, n   | 17         | 33         |         |
| Age, years    | 64.2 ± 15* | 61.5 ± 15  | 0.57    |
| Men, n (%)    | 8 (47)     | 19 (58)    | 0.56    |
| Body surface area, m² | 1.54 ± 0.1  | 1.58 ± 0.2  | 0.37    |
| Systolic blood pressure, mmHg | 125 ± 22  | 122 ± 18   | 0.72    |
| Heart rate, beats/minute | 61 ± 10  | 65 ± 11    | 0.28    |
| Hemoglobin, g/dL | 12.9 ± 2.1 | 13.3 ± 1.9 | 0.48    |
| NYHA class III-IV, n (%) | 3 (18) | 2 (6) | 0.32    |
| Class I, n    | 8          | 26         |         |
| Class II, n   | 6          | 5          |         |
| Class III, n  | 3          | 1          |         |
| Class IV, n   | 0          | 1          |         |

*Continuous variables are presented as the mean ± standard deviation. HOCM indicates hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; and NYHA, New York Heart Association.
was not found between groups (17.8 ± 3.1 versus 17.1 ± 5.1 mm, HOCM group versus HNCM group; \( P = 0.63 \)). No obvious difference was noted in the septal-to-posterior wall thickness ratio between groups (1.52 ± 0.5 versus 1.52 ± 0.6, HOCM group versus HNCM group; \( P = 0.99 \)), and no significant differences in LVEF were observed (72.9 ± 8.3 versus 67.7 ± 9.1%, HOCM group versus HNCM group; \( P = 0.06 \)). Moreover, there were no significant differences in left atrial dimension, LV end-diastolic dimension, or LVDDs between groups.

**Morphological assessment of LV and mitral valve complex-related LVOT obstruction by echocardiography:** Papillary muscle morphology is summarized in Table III. In the HOCM group, the papillary muscle-septum distance was significantly shorter than in the HNCM group (5.97 ± 2.3 versus 9.20 ± 1.9 mm, respectively; \( P < 0.0001 \)). The maximal papillary muscle thickness and the prevalence of malformation of papillary muscle did not differ between the groups.

Table IV shows the anatomical parameters of the mitral valve and LVOT. SAMs were observed in 100% of patients in the HOCM group but only in 58% of patients in the HNCM group. HOCM subjects had longer AML lengths than the HNCM group (24.7 ± 5.8 versus 20.1 ± 5.4 mm, respectively; \( P < 0.01 \)). No differences in the PML length, mitral annular size, or LVOT diameter were observed between the groups. Interestingly, the AML length/LVDDs ratio (1.02 ± 0.34 versus 0.78 ± 0.26, HOCM group versus HNCM group; \( P < 0.01 \)) and PML length/LVDDs ratio (0.60 ± 0.20 versus 0.51 ± 0.15, HOCM group versus HNCM group; \( P < 0.05 \)) were significantly higher in the HOCM group compared to the

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**Table II.** Standard Echocardiographic Variables of the Study Population

| Variable                        | HOCM group     | HNCM group     | \( P \) value |
|---------------------------------|----------------|----------------|---------------|
| LVOT pressure gradient, mmHg    | 74.4 ± 46.7*   | 8.5 ± 5.9      | < 0.0001      |
| LV ejection fraction, %         | 72.9 ± 8.3     | 67.7 ± 9.1     | 0.06          |
| SV, mL                          | 62.7 ± 16      | 64.2 ± 20      | 0.80          |
| IVST, mm                        | 17.8 ± 3.1     | 17.1 ± 5.1     | 0.63          |
| PWT, mm                         | 12.3 ± 2.4     | 12.0 ± 2.5     | 0.75          |
| IVST/PWT ratio                  | 1.52 ± 0.5     | 1.49 ± 0.6     | 0.84          |
| LAD, mm                         | 44.7 ± 5.9     | 43.0 ± 7.6     | 0.43          |
| LVDD, mm                        | 44.8 ± 5.8     | 45.0 ± 5.8     | 0.58          |
| LVDs, mm                        | 25.2 ± 4.6     | 26.7 ± 5.7     | 0.33          |

*Continuous variables are presented as the mean ± standard deviation. HOCM indicates hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract; SV, stroke volume; IVST, inter-ventricular septal thickness; PWT, posterior wall thickness; LAD, left atrial dimension; LVDD, LV end-diastolic dimension; and LVDs, LV end-systolic dimension.

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**Table III.** Papillary Muscle Morphology of the Study Population

| Variable                        | HOCM group     | HNCM group     | \( P \) value |
|---------------------------------|----------------|----------------|---------------|
| Maximal papillary muscle thickness, mm | 12.0 ± 2.2*   | 12.3 ± 2.5     | 0.90          |
| Papillary muscle-septum distance, mm | 5.97 ± 2.3     | 9.20 ± 1.9     | < 0.0001      |
| Prevalence of malformation of papillary muscle, n (%) | 7 (41)          | 8 (28)         | 0.33          |

*Continuous variables are presented as the mean ± standard deviation. HOCM indicates hypertrophic obstructive cardiomyopathy; and HNCM, hypertrophic non-obstructive cardiomyopathy.

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**Table IV.** Anatomical Parameters of the Mitral Valve and LVOT

| Variable                        | HOCM group     | HNCM group     | \( P \) value |
|---------------------------------|----------------|----------------|---------------|
| Prevalence of SAM, n (%)        | 17 (100)       | 19 (58)        | < 0.01        |
| AML length, mm                  | 24.7 ± 5.8*    | 20.1 ± 5.4     | < 0.01        |
| PML length, mm                  | 14.5 ± 3.4     | 13.2 ± 4.2     | 0.32          |
| Mitral annular size, mm         | 27.0 ± 4.7     | 28.7 ± 4.0     | 0.21          |
| LVOT diameter, mm               | 16.3 ± 2.7     | 16.7 ± 2.3     | 0.59          |
| MR III or IV, n (%)             | 1 (6)          | 0 (0)          | 0.34          |
| Prevalence of MAC, n (%)         | 5 (29)         | 5 (15)         | 0.28          |
| AML length/LVDDs ratio          | 1.02 ± 0.34    | 0.78 ± 0.26    | < 0.01        |
| PML length/LVDDs ratio          | 0.60 ± 0.20    | 0.51 ± 0.15    | < 0.05        |

*Continuous variables are presented as the mean ± standard deviation. HOCM indicates hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; SAM, systolic anterior motion; AML, anterior mitral leaflet; PML, posterior mitral leaflet; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MAC, mitral annular calcification; and LVDDs, LV end-diastolic dimension.
HNCM group.

**Superior ability of the AML length/LVDs ratio to determine LVOT obstruction:** To determine the parameter with the highest predictive value for anatomical risk of LVOT obstruction, the papillary muscle-septum distance, AML length, AML length/LVDs ratio, and PML length/LVDs ratio were compared using the ROC curve analysis (Figure 2). The AML length/LVDs ratio with a cut-off value of 0.91 determined LVOT obstruction, with an AUC of 0.71 (95% CI: 0.55-0.87, \( P < 0.05 \)). The AUC was 0.69 (95% CI: 0.54-0.85, \( P < 0.05 \)) for the AML length, 0.61 (95% CI: 0.45-0.79, \( P = 0.19 \)) for papillary muscle-septum distance, and 0.64 (95% CI: 0.46-0.82, \( P = 0.11 \)) for PML length/LVDs ratio. Among these parameters, the AML length/LVDs ratio was the most powerful predictor of LVOT obstruction.

**Relationship between the AML length/LVDs ratio and LVOTPGs:** Figure 3 shows the relationship between LVOTPGs and the AML length/LVDs ratio in all subjects; these two factors were positively correlated \( (r = 0.466, R^2 = 0.174, P = 0.0028) \).

**Multivariate analysis of the influential factors of LVOTPGs:** We used stepwise multiple linear regression analysis to identify the influential factors of LVOTPGs among the 50 HCM patients (Table V). Variables with a significance of < 0.10 on univariate analysis were entered into the multivariate model. The candidate variables included LVEF, AML length/LVDs ratio, PML length/LVDs ratio, and papillary muscle-septum distance. The AML length/LVDs ratio was the only independent risk factor for increased LVOTPGs (coefficient = 0.430, standard error = 17.87, \( P = 0.002 \), \( R^2 = 0.185 \)).

**Discussion**

The main findings of this study are as follows: (1) the distance from the papillary muscle to the interventricular septum was significantly shorter in the HOCM group than in the HNCM group; (2) compared to the HNCM patients, the HOCM patients had a longer AML length, a larger AML length/LVDs ratio, and a larger PML length/LVDs ratio; (3) the AML length/LVDs ratio was positively correlated with LVOTPGs; (4) the AML length/LVDs ratio could determine LVOT obstruction, with a cut-off value of 0.91; and (5) in the multiple linear regression analysis, the AML length/LVDs ratio was significantly associated with LVOTPGs. Collectively, these results indicate that the AML length/LVDs ratio is an independent and powerful predictor of LVOT obstruction.

In structurally normal hearts, malformation of papillary muscle can be found in approximately 15% cases,\(^{22}\) and the maximal papillary muscle thickness is known to be ≤ 11 mm.\(^{23}\) As shown in Table III, the prevalence of both malformation of the papillary muscle and papillary muscle hypertrophy were higher in HCM patients compared to structurally normal hearts, but no differences were observed between the HOCM and the HNCM groups. However, the HOCM group had a short papillary muscle-septum distance compared to the HNCM group (5.97 ± 2.3 versus 9.20 ± 1.9 mm, respectively; \( P < 0.0001 \)). These results suggest that the distance between the inter-ventricular septum and papillary muscle is a contributing factor to LVOT obstruction. Because the papillary muscle moves close to the inter-ventricular septum during systole, a short papillary muscle-septum distance may facilitate the development of SAM, leading to LVOT obstruction. This finding is supported by a previous study, in which papillary muscle inter-position into the outflow stream by anterior displacement determined the direction of SAM.\(^{24}\)

Previous studies have demonstrated a causal relationship between septal hypertrophy and LVOT obstruction.\(^{25,26}\) However, we found no significant difference in inter-ventricular septal thickness between the HOCM and HNCM groups (Table II). The correlation between inter-ventricular septal thickness and LVOTPG was not significant in the present study \( (r = 0.034, R^2 = 0.001, P = 0.82) \). This inconsistency indicates that other mechanisms except septal hypertrophy are involved in the pathogenesis...
of LVOT obstruction in HCM with asymmetrical septal hypertrophy. Similar results in which inter-ventricular septal thickness did not differ significantly between HOCM and HNCM patients have been reported recently by other researchers.\textsuperscript{14,27,28}

HCM patients have large and long mitral leaflets compared to normal subjects.\textsuperscript{16,29,30} In this study, we demonstrated a close relationship between AML length and the development of LVOT obstruction in HCM (Figure 3). This provides evidence of a possible underlying mechanism of LVOT obstruction in HCM patients. The elongated AML could protrude into the LVOT in systole, which is subject to the large, hemodynamic force of flow that causes SAM.\textsuperscript{31} Additionally, elongation of the AML shortens the distance between the tip of the AML and the intra-ventricular septum, which easily produces a Venturi effect, leading to SAM. Conversely, the large hemodynamic force in LVOT induces fibrous degeneration and enlargement of the mitral leaflets.\textsuperscript{30} Because clinically important LVOT obstruction arises over a long period of time, this positive feedback effect could feasibly promote the development of LVOT obstruction.

Maron, et al. showed that the AML length/LVOT diameter ratio has a significant relation to the LVOTPGs.\textsuperscript{40} However, we found no significant correlation between the AML length/LVOT diameter ratio and LVOTPGs in our study population ($r = 0.283$, $R^2 = 0.080$, $P = 0.06$). As shown in Figures 2, 3, the AML length/LVOTs ratio was positively correlated with LVOTPGs and exhibited a superior ability to predict LVOT obstruction. Moreover, multiple linear regression analysis demonstrated that the AML length/LVOTs ratio is a strong influential factor in LVOT obstruction in HCM. In addition to anatomical features, the composite factors of LVOT obstruction include LV contractility and LV synchronous motion. Because LVDs reflect not only morphological features but also LV contractility, the AML length/LVOTs ratio encompasses anatomical and functional factors that facilitate LVOT obstruction.

The size of LVOT influences the pathogenesis of HCM obstruction.\textsuperscript{11,12,54} However, we did not find any significant difference in the LVOT diameter between the HOCM and HNCM groups (16.3 ± 2.7 versus 16.7 ± 2.3 mm, respectively; $P = 0.59$, Table III). Moreover, the correlation between LVOT diameter and LVOTPG was not significant ($r = -0.133$, $R^2 = 0.018$, $P = 0.38$). One possible explanation for the difference between our study and previous studies is that the measurement site of LVOT diameter in the present study was distant from the mitral valve coaptation point, which comes close to the ventricular septum during SAM-related LVOT obstruction.\textsuperscript{30} Additionally, LVOT diameter does not indicate the LVOT area. In the present study, the LVOT diameter measured by 2D transthoracic echocardiography served as a substitute for LVOT size. However, information obtained from both three-dimensional transesophageal echocardiography and multidetector computed tomography has shown that LVOT shape is not round but elliptical.\textsuperscript{46,53} Thus, the 2D long-axis view does not always depict the longest span of LVOT, resulting in an underestimation of its full diameter.

**Limitations:** The present study had several limitations. First, this was a retrospective, single-center study. Moreover, the size of the study population was relatively small, particularly in terms of multiple liner regression analysis. Although the AML length/LVOTs ratio was the only independent risk factor for increased LVOTPGs, they were only evaluated in a limited study population. Further prospective studies with a larger patient population are needed to validate our findings. Second, histopathological changes in the mitral valve were not investigated. Finally, we did not perform cardiovascular MRI, which is useful for defining LVOT morphology and morphological abnormalities of the mitral valve complex. Further studies on the morphological determinants of LVOT obstruction in HCM are needed.

**Conclusions**

The anatomical risks of the LVOT obstruction in HCM patients are a large AML length/LVOTs ratio and a short papillary muscle-septum distance. Furthermore, the AML length/LVOTs ratio is an independent and powerful predictor of LVOT obstruction.

**Disclosures**

**Conflicts of interest:** The authors declare no conflict of interest.

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**Table V. Uni- and Multivariate Linear Analyses for Prediction of LVOTPG in the Enrolled HCM Patients**

| Uniivariate coefficient | Multivariate coefficient |
|-------------------------|--------------------------|
| AML length/LVOTs ratio  | 0.430  | 0.430 |
| LV ejection fraction    | 0.392  | 0.213 |
| PML length/LVOTs ratio  | 0.356  | 0.086 |
| Papillary muscle-septum distance | -0.227  | -0.161 |

HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; LVOT, left ventricular outflow tract; AML, anterior mitral leaflet; LVDs, LV end-systolic dimension; PML, posterior mitral leaflet; LVOTPG, left ventricular outflow tract pressure gradients.
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