Impact of Left Ventricular Outflow Tract Area on Systolic Outflow Velocity in Hypertrophic Cardiomyopathy
A Real-Time Three-Dimensional Echocardiographic Study
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OBJECTIVES
The aim of this study was to use real-time three-dimensional echocardiography (3DE) to investigate the quantitative relation between minimal left ventricular (LV) outflow tract area \(A_{LVOT}\) and maximal LV outflow tract (LVOT) velocity in patients with hypertrophic obstructive cardiomyopathy (HCM).

BACKGROUND
In patients with HCM, LVOT velocity should change inversely with minimal \(A_{LVOT}\) unless LVOT obstruction reduces the pumping capacity of the ventricle.

METHODS
A total of 25 patients with HCM with systolic anterior motion (SAM) of the mitral valve leaflets underwent real-time 3DE. The smallest \(A_{LVOT}\) during systole was measured using anatomically oriented two-dimensional “C-planes” within the pyramidal 3DE volume. Maximal velocity across LVOT was evaluated by two-dimensional Doppler echocardiography (2DE). For comparison with 3DE \(A_{LVOT}\), the SAM-septal distance was determined by 2DE.

RESULTS
Real-time 3DE provided unique information about the dynamic SAM-septal relation during systole, with \(A_{LVOT}\) ranging from 0.6 to 5.2 cm\(^2\) (mean: 2.2 \pm 1.4 cm\(^2\)). Maximal velocity \(v\) correlated inversely with \(A_{LVOT}\) \(v = 496\ A_{LVOT}^{-0.80}, r = -0.95, p < 0.001\), but the exponent \((-0.80)\) was significantly different from \(-1.0\) (95% confidence interval: \(-0.67\ to \(-0.92\)), indicating a significant impact of small \(A_{LVOT}\) on the peak LVOT flow rate. By comparison, the best correlation between velocity and 2DE SAM-septal distance was significantly \((p < 0.01)\) poorer at \(-0.83\), indicating the superiority of 3DE for assessing \(A_{LVOT}\).

CONCLUSIONS
Three-dimensional echocardiography-measured \(A_{LVOT}\) provides an assessment of HCM geometry that is superior to 2DE methods. These data indicate that the peak LVOT flow rate appears to be significantly decreased by reduced \(A_{LVOT}\). Real-time 3DE is a potentially valuable clinical tool for assessing patients with HCM.

Hypertrophic cardiomyopathy (HCM) is defined as the presence of a hypertrophied, nondilated left ventricle (LV) with an absence of other diseases capable of producing significant hypertrophy. Hypertrophy of the interventricular septum (IVS), a narrowed LV outflow tract (LVOT) and, frequently, systolic anterior motion (SAM) of the mitral valve leaflets resulting in LVOT obstruction are important clinical features of HCM. Echocardiography is the noninvasive method of choice for the evaluation of morphologic and functional abnormalities (1–3). However, two-dimensional Doppler echocardiography (2DE) provides only limited quantitative parameters such as the degree of local interventricular septal thickness and distribution of hypertrophy. It may, therefore, fail to fully characterize the LVOT in HCM (4–9). Three-dimensional echocardiography (3DE) has the ability to provide unique information on the spatial geometry of a given structure (10). Recently developed real-time 3DE has overcome the limitations of technically cumbersome reconstructed 3DE (11–14), but its application in HCM has not yet been demonstrated.

When steady flow passes through an obstruction, velocity should be related to obstruction area in a precise inverse relation. However, if the obstruction is enough to actually reduce flow rate, then the relation will be “flatter” than inverse, with velocity rising less than expected with falling LVOT area. Controversy exists over the functional significance of LVOT obstruction in HCM with some work suggesting that the pressure gradient (PG) implied by high velocity in the LVOT does not significantly impact LV ejection (15,16), insisting that the most important “obstruction” occurs during diastolic filling (17). Others note a fall in midcavity LV velocity at the time of maximal LVOT velocity, implying functionally significant obstruction (18). The purpose of this study was, therefore, to establish the
superiority of real-time 3DE over standard 2DE methods in assessing LVOT geometry and then use this technique to test the hypothesis that LVOT obstruction in HCM produces a significant reduction in the peak LVOT flow rate.

METHODS

Forty consecutive patients with HCM underwent both real-time 3DE and 2DE at the Cleveland Clinic Foundation in 1998. Twenty-five patients with optimal image quality of 3DE (16 men, average age: 53 ± 18 years) were enrolled. Routine 2DE was performed for each patient followed within 10 min by real-time 3DE with unchanged hemodynamic conditions.

Real-time 3DE. Images were obtained transthoracically by a three-dimensional echocardiographic system with a 2.5 MHz phased array transducer (Volumetrics Medical Imaging Inc., Durham, North Carolina) (11–14). Two 3DE datasets from parasternal and apical windows (14) were acquired with the patients in a left lateral decubitus position.

Conventional 2DE and Doppler echocardiography.

RATIO OF SEPTUM TO POSTERIOR WALL THICKNESS (PWT). The thickness of basal IVS and posterior wall was measured from a standard M-mode echocardiogram (19), and the ratio was calculated.

DEGREE OF SAM. After we surveyed the closest approach of the anterior mitral leaflet to the septum, the minimal mitral-septal distance was measured with 2DE, as a displacement of the anterior mitral leaflet toward the septum in systole. It was graded as mild, moderate or severe (20).

MAXIMAL VELOCITY AND PEAK PG. Continuous-wave Doppler was used to measure maximal velocity (v) across LVOT. Then PG was estimated by using the simplified Bernoulli equation, \[ \Delta p = 4v^2 \] (21).

MITRAL REGURGITATION. Mitral regurgitant (MR) volume and MR orifice area were determined by the flow convergence method (22).

Analysis of real-time 3DE images. After the real-time 3DE image acquisition, parasternal images were displayed on the screen as seen in Figure 1. To show the LVOT in three dimensions during SAM, the echocardiography

**Abbreviations and Acronyms**

- ALVOT = area of left ventricular outflow tract
- CI = confidence interval
- HCM = hypertrophic cardiomyopathy
- IVS = interventricular septum
- LV = left ventricle or left ventricular
- LVOT = left ventricular outflow tract
- MR = mitral regurgitant
- PG = pressure gradient
- PWT = posterior wall thickness
- Qmax = peak cardiac output
- SAM = systolic anterior motion of mitral valve leaflets
- v = peak velocity
- 2DE = two-dimensional echocardiography
- 3DE = three-dimensional echocardiography

Figure 1. Real-time three-dimensional echocardiographic image obtained from parasternal window at midsystolic phase in a patient with hypertrophic cardiomyopathy. The right top and bottom images are parasternal long-axis and short-axis view images from B-scans, respectively. The left two images are the two parallel C-plane images (C1 and C2) obtained from cutting planes, which are shown on the right in green lines perpendicular to the long axis of the left ventricular outflow tract (LVOT). The area of the LVOT was traced shown in red in the three short-axis planes. The smallest area was counted as the area of LVOT in this particular systolic phase. Ao = aorta; LA = left atrium; LV = left ventricle.
B-scan sector tilt was moved carefully to display the SAM clearly on the two orthogonal planes (i.e., parasternal long-axis view [right top] and parasternal short axis view [right bottom]). The cutting planes (C-scans) were tilted and crossed the SAM perpendicular to the long axis of LVOT (two green lines in right top). These short axis views of the LVOT at different levels were shown in two C-scans (left panel). Then, the areas of LVOT in three short axis views were traced (shown in red lines), and the smallest area was counted as A_{LVOT} for the particular systolic phase. The 3DE images were displayed frame by frame during systole to search for the narrowest LVOT. All measurements were performed by an experienced investigator in real-time 3DE analysis and without knowledge of the conventional 2DE Doppler measurements.

**Inter- and intraobserver variabilities.** In order to assess the effect of observational variability on the real-time 3DE measurement for area of LVOT (A_{LVOT}), the real-time 3DE images of three patients were examined. The areas of LVOT on each frame during systole were measured by two independent observers and by the same observer on a different day.

**Statistical analysis.** All data are presented as the mean value ± SD. To assess the hypothesis that three-dimensional methods provide a better assessment of LVOT geometry than two-dimensional methods, linear regression was used to examine the relation between PG and: 1) A_{LVOT} (3DE parameter); 2) mitral-septal distance; and 3) IVS/PWT. Analysis of variance was used to compare the differences in PG and in MR volume between the mild, moderate and severe SAM groups. Unpaired t testing was used to compare PG between patients with A_{LVOT} ≤2 cm^2 and those with A_{LVOT} >2 cm^2 by real-time 3DE. A p value <0.05 was considered significant.

To test the hypothesis that SAM produces functional LVOT obstruction, we noted that if peak cardiac outflow (Q_{max}) were independent of the degree of obstruction, then there should be a precisely inverse relation between peak velocity (y) and A_{LVOT} (x), y = Q_{max}/x. Similarly, because of the squared relation between maximal velocity and PG, we anticipated an approximate inverse squared relation between peak gradient and A_{LVOT}. To test this hypothesis, we fit the observed data into a general power law formula of the form y = αx^{-β} using Levinberg-Marquardt nonlinear parameter estimation. If high degrees of obstruction do reduce peak flow rate, β should be slightly <1 when y represents velocity and 2 when y represents PG. For comparison purposes, we let x represent SAM distance and repeated the nonlinear regression with y = α(x + γ)^{-β}. An additional parameter, γ, is necessary, as a SAM distance of zero cannot be entered into a general power law fit.

**RESULTS**

**2DE findings.** SAM. Of the 25 patients, there was mild SAM in nine patients, moderate SAM in nine patients and severe SAM in seven patients. The minimal mitral-septal distance was 13.1 ± 1.8 mm, 4.6 ± 2.3 mm and 0 ± 0 mm, respectively, p < 0.001.

**RATIO OF SEPTUM TO PWT.** The thickness of IVS measured by M-mode was 22 ± 5 mm (range: 12 to 34 mm); the thickness of posterior wall was 15 ± 5 mm (range: 8 to 29 mm) and the ratio of septum to PWT was 1.5 ± 0.3 (range: 0.9 to 2.5) in the 25 patients. There were three patients whose ratio was <1.3, but their PGs were significantly higher after amyl nitrite inhalation with SAM demonstrated. There were no significant differences among the three SAM grade groups for septal thickness, PWT and the ratio of IVS to PWT (Table 1).

**MAXIMAL VELOCITY AND PG.** The maximal velocity across the LVOT measured by continuous wave Doppler averaged 3.3 ± 1.7 m/s (range: 0.5 to 7.4 m/s), while PG averaged 56 ± 50 mm Hg (range: 4 to 221 mm Hg). Significant differences were seen for these indexes across the three grades of SAM (Table 1).

**Mitrail regurgitation.** Mitral regurgitant volume and MR orifice area in the severe SAM group were significantly larger than those in mild SAM group (Table 1).

**3DE findings.** The real-time 3DE system provided unique three-dimensional information about the SAM and its dynamic relation to the septum during systole allowing us to determine the smallest A_{LVOT} in three-dimensional space (Fig. 1).

The smallest A_{LVOT} during systole, determined by real-time 3DE, averaged 2.2 ± 1.4 cm^2 (range: 0.6 to 5.2 cm^2). Sixteen of 25 patients had an A_{LVOT} ≤2 cm^2. The PGs in patients with A_{LVOT} ≤2 cm^2 were significantly higher than those in patients with A_{LVOT} >2 cm^2 (80 ± 48 mm Hg vs. 13 ± 5 mm Hg, p < 0.01). All patients with A_{LVOT} ≤2 cm^2 had PG ≥50 mm Hg, while all patients with A_{LVOT} >2 cm^2 had PG <50 mm Hg (Fig. 2).

The temporal changes of A_{LVOT} were also analyzed in seven of 25 patients with HCM. The average frames in systole were 7 ± 1 frames/beat. The A_{LVOT} significantly decreased from the beginning of systole to midsystole

<table>
<thead>
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<th>Table 1. Echocardiographic Parameters in SAM Groups</th>
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<tr>
<td><strong>Mild</strong> (n = 9)</td>
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<td>IVS (mm)</td>
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<td>A_{LVOT} (cm^2)</td>
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<td>MRV (ml)</td>
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<td>MROA (cm^2)</td>
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*Comparison with mild and moderate SAM groups, p < 0.05; †Comparison with mild SAM group, p < 0.05.

A_{LVOT} = area of left ventricular outflow tract; IVS = interventricular septum thickness; MVR = mitral regurgitant volume; MROA = mitral regurgitant orifice area; PG = pressure gradient; PWT = posterior wall thickness; SAM = systolic anterior motion of mitral valve leaflets; V_{max} = maximal velocity through left ventricular outflow tract.
Figure 2. Pressure gradient (PG) across left ventricular outflow tract (LVOT) in the area of LVOT ≤2 cm² and >2 cm² groups. 3DE = three-dimensional echocardiography.

(2.5 ± 0.8 cm² vs. 1.3 ± 0.3 cm², p < 0.01) and remained similar at end-systole (1.1 ± 0.4 cm² vs. 1.3 ± 0.3 cm², p > 0.05).

Relations between maximal velocity, PG, A LVOT and SAM distance. For both maximal velocity and PG, simple linear correlation was stronger with A LVOT obtained from real-time 3DE (r = -0.87 and -0.75, respectively) than it was with the SAM distance derived from M-mode (r = -0.79 and -0.69, respectively). Even more illustrative is the nonlinear regression analysis. As shown in Table 2, strong correlations were seen in the power law relationship between A LVOT and maximal velocity (r = -0.95, Fig. 3), with an exponent of -0.80 (95% confidence interval [CI]: -0.67 to -0.92), close to the theoretical prediction of -1.0, but it indicates a significant degree of flow reduction with increasing obstruction. In contrast, the SAM-septal distance was much less predictive of maximal velocity with r = -0.83 (despite the additional degree of freedom γ in the nonlinear equation) and an exponent of -2.36, well away from the predicted -1.0 (95% CI: -12.81 to 8.09). Similar findings were observed when peak pressure drop was used as the dependent variable. The A LVOT predicted pressure drop with r = -0.96 and an exponent of -1.46 (95% CI: -1.67 to -1.24), significantly better than the r = -0.77 and β = -3.17 (95% CI: -25.8 to 19.4) observed for SAM-septal distance.

The A LVOT by 3DE also correlated moderately well with MR volume (r = -0.73) and MR orifice area (r = -0.58) when linear correlation analysis was used. However, A LVOT and PG did not relate to the ratio of septum to PWT.

Observer variabilities. For a total of 19 A LVOT measurements, there was good agreement between the two independent observers for interobserver variability (1.4 ± 0.8 cm² vs. 1.4 ± 0.7 cm², r = 0.95, p < 0.0001, mean difference = -0.01 ± 0.23 cm²) and between the different day’s measurements for the intraobserver variability (1.4 ± 0.8 cm² vs. 1.4 ± 0.7 cm², r = 0.97, p < 0.0001, mean difference = -0.07 ± 0.19 cm²).

DISCUSSION

Previous echocardiographic studies of HCM. Initial M-mode echocardiographic studies verified that SAM of the anterior mitral valve was a typical sign of HCM (23). Conventional 2DE assists in distinguishing several patterns of LV hypertrophy, observing dynamic mitral valve motion and defining the relation between SAM and IVS. Continuous wave Doppler echocardiography provides noninvasive blood velocity and PG measurements across the LVOT, which has guided the choice of treatments such as medicine, surgery or, more recently, alcohol ablation. However, the accurate quantitative assessment of such a key parameter as the smallest A LVOT during systole, the ultimate determinant of LVOT obstruction, has been impossible with the methods mentioned above.

In previous work, 3DE reconstructions of the LVOT demonstrated the significantly smaller A LVOT in patients...
with HCM as compared with normal control subjects (24), while transesophageal acquisition of 3DE data sets provided even better image quality (25). Although both of these 3DE reconstruction methods were able to show the ALVOT dynamically, they required electrocardiogram and respiratory gating, special instruments for holding the probe and long acquisition times. Because of their sensitivity to patient movement, 3DE reconstruction applications are quite limited in the clinical setting.

Quantitative analysis of real-time 3DE. To our knowledge, this is the first study to demonstrate the relation between the smallest ALVOT and LVOT velocity and PG using real-time 3DE. In this study, LVOT and SAM structure were displayed clearly in three-dimensional space. Measurement of ALVOT is uniquely possible with real-time 3DE, as complete spatial information is available in a single heartbeat without the vagaries of reconstructing over multiple beats. The minimal ALVOT during systole observed in this study is similar to that previously reported with trans-thoracic 3DE reconstruction (24). That report also showed that the smallest ALVOT in patients with HCM (2.3 ± 1.0 cm²) was significantly smaller than that in normal control patients (5.0 ± 0.9 cm²) (24), with a highly eccentric and asymmetric shape of the LVOT and a tendency to decrease with increasing degrees of SAM. However, even in the severe SAM group, there was not complete LVOT obstruction with a small ALVOT (1.2 ± 0.5 cm²), although the PG was high (102 ± 57 mm Hg), which was similar to our observations.

In this study, only a moderate linear correlation between the smallest ALVOT and the PG was found (r = −0.75), but this increased dramatically when the theoretically sound power function was used (r = −0.96). For a fixed flow (Qmax) situation, the maximal velocity across the LVOT (v) should be the precise inverse of ALVOT: \(v = \frac{Q_{\text{max}}}{ALVOT} \). In this case, the actual magnitude of the exponent was somewhat lower at 0.8, indicating that velocity did not rise quite as fast with decreasing ALVOT, as would be expected if flow rate were a constant (Fig. 3). The most probable explanation for this is that peak flow is reduced at increasing levels of obstruction, an issue that has been the subject of some controversy (15,16,26). In contrast, the power law relation between SAM-septal distance and maximal velocity and gradients could not even be calculated without an additional parameter (γ) to offset the zero SAM distance value commonly observed. Even with this additional degree of freedom to the model, the overall correlation was significantly worse than with ALVOT. Thus, the observed exponents did not make physiological sense. Taken at face value, they would imply increasing flow with increasing degrees of obstruction, a physically implausible situation.

Using 50 mm Hg as a dividing point, there is complete separation of the patients into two groups with ALVOT ≤2 cm² and ALVOT >2 cm² (Fig. 2). If the ALVOT is ≤2 cm², the PG can be expected to be higher than 50 mm Hg in patients with HCM, and more aggressive clinical interventions such as ablation (27,28) or myectomy (29) could be considered. The decrease of the PG has been used as a means of assessing response to therapy in patients with HCM. But the PG varies considerably from day to day even in stable patients with HCM (the variation was ± 32 mm Hg for rest PG and ± 50 mm Hg for provoked PG) (30). A single measurement of the PG was not adequate to define the severity of dynamic LVOT obstruction in HCM (30). Although serial examinations were not performed in these patients, we would expect ALVOT to show similar variability with changing loading conditions, thus requiring examination at multiple points in time. However, it may be that the analysis of the geometric relation between the anterior mitral leaflets and the IVS may provide some useful information guiding therapy and allowing refinements of surgical and ablation techniques.

Functional obstruction in HCM. From the earliest cath lab studies (31), a dynamic pressure drop across the LVOT has been considered characteristic of HCM, especially after provocative maneuvers (32). This “mantra” has been called into question by several investigators including Murgo et al. (15) and Creiley (16), who have rightly pointed out that, in patients with HCM, there is hyperdynamic ventricular emptying despite outflow tract gradients and little relation between the magnitude of these gradients and prognosis in HCM. In contrast, Sherrid et al. (33) have suggested a spiraling positive feedback loop in which obstruction is amplified by pressure against the anterior mitral leaflet. This produces further obstruction and results in a midystolic fall in velocities (and, therefore, flow) within the LV cavity at the time of maximal LVOT velocity (18). Our data differ in that they are derived from a cross-section of patients studied at a given point in time, but they are consistent with the observation that patients with the smallest ALVOT have maximal velocities that fall short of the inverse relation anticipated if LV outflows were unaffected by the obstruction. The impact is not large, as our observed exponent −0.8 came close to the −1 expected for an inverse relation, but the impact appears to be real. Adding further to the confusion is the observation that pressure recovery may occur distal to the obstruction (34). This may explain some Doppler-catheter discrepancies. In addition, LVOT flow is different from patient to patient and changes during systole even in the same patient. Nevertheless, the data of Sherrid et al. (18) along with our own suggests that the LV does indeed “feel” the obstruction, while mitral regurgitation is a confusing variable in this setting.

Study limitations. The greatest limitations for quantitative analysis of real-time 3DE are relatively low image quality and resolution, and only 25 of 40 consecutive patients had optimal images for quantitative analysis in this study. This may overstate the problem, however, as we sought to enroll only patients with the highest quality images to establish the relation between ALVOT and maximal velocity and PG; many other patients had reasonable image quality that could have been used for clinical assessment purposes. Temporal
resolution is low, 22 frames per second at the scanning depth of 12 cm in the current 3DE system as compared with M-mode (1 kHz) and 2DE systems (more than 30 Hz). It might affect the accuracy of $A_{LVOT}$ measurements. Another limitation of this study is the lack of an independent reference method for the analysis of the smallest $A_{LVOT}$, owing to the fact that no other method has been shown to accurately delineate the minimal $A_{LVOT}$ and its cardiac cyclical changes. Finally, it was impossible to obtain continuous wave Doppler recording simultaneous with 3DE images. Although the patients were all in sinus rhythm and in a stable hemodynamic state, we cannot exclude some minor degree of changes in LVOT obstruction between the times of the two examinations.

CONCLUSIONS

Real-time 3DE enables morphologic description of the LVOT and quantitative evaluation of the minimal area of LVOT in patients with HCM. The smallest area of LVOT measured by real-time 3DE revealed an excellent correlation with maximal velocity and PGs across LVOT, consistent with the physiological expectations, suggesting the potential importance of real-time 3DE for evaluating patients with HCM.

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