Variability of Left Ventricular Outflow Tract Gradient During Cardiac Catheterization in Patients With Hypertrophic Cardiomyopathy

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Objectives This study characterizes left ventricular outflow tract (LVOT) gradient variability in patients with hypertrophic cardiomyopathy (HCM) during cardiac catheterization.

Background Management of HCM is directed by the presence and magnitude of LVOT obstruction. The magnitude and clinical impact of spontaneous variability during a single cardiac catheterization has not been described.

Methods Fifty symptomatic patients with HCM (mean age 55 ± 15 years; 48% men) underwent cardiac catheterization with high-fidelity, micromanometer-tip catheters and transseptal measurement of left ventricular pressures. Obstruction was defined as resting LVOT gradient ≥30 mm Hg and severe obstruction as ≥50 mm Hg. Variability in LVOT gradient was calculated as the difference of the largest and smallest LVOT gradients in the absence of provocative maneuvers or interventions.

Results The largest LVOT gradient was 54.6 ± 56.4 mm Hg. The spontaneous variability in LVOT gradient was 49.0 ± 53.1 mm Hg (range 0 to 210.8 mm Hg, median 15 mm Hg). Discrepant classification of resting LVOT gradient severity was possible in 25 patients (50%). Twenty patients (40%) with severe obstruction could have been misclassified with regard to obstruction severity.

Conclusions In patients with HCM, the LVOT gradient fluctuates significantly during a single hemodynamic assessment. Spontaneous variability could lead to misclassification of obstruction severity in one-half of studied patients. The dynamic nature of LVOT obstruction must be considered when assessing resting hemodynamics or the success of a given intervention during cardiac catheterization. (J Am Coll Cardiol Intv 2011;4:704–9) © 2011 by the American College of Cardiology Foundation
Hypertrophic cardiomyopathy (HCM) is a genetically and phenotypically diverse disease characterized by prominent myocardial hypertrophy and accompanying LVOT obstruction in most patients (1–4). The physiology underlying left ventricular outflow tract (LVOT) hemodynamics in HCM is complex and dependent on a myriad of clinical factors (4–8). Thus, LVOT obstruction severity has the potential for substantial variation and, indeed, has been shown to fluctuate significantly over the course of days (4,9).

Ascertaining the magnitude of LVOT obstruction is of clinical utility, as the degree of obstruction is inherent to symptom etiology and serves as a prognostic indicator (10–19). In patients refractory to pharmacotherapy, consideration of septal reduction therapy is guided by the presence of severe LVOT obstruction (15). Furthermore, determination of successful septal reduction is often assessed by quantification of post-procedural LVOT gradient (12,20–25). However, the magnitude of spontaneous gradient variability during a single cardiac catheterization study has not been described, which may complicate accurate assessment of gradient. Therefore, this study was performed to examine the spontaneous variability of LVOT gradient in patients with HCM undergoing cardiac catheterization.

Methods

Study population. Between January 2006 and July 2009, 50 patients with HCM were evaluated at the Mayo Clinic in Rochester, Minnesota. Those patients met the following criteria: 1) absence of aortic valvular disease; 2) cardiac catheterization with high-fidelity, micromanometer-tip catheters (Millar Instruments, Houston, Texas) for LVOT gradient assessment; 3) transseptal catheterization to avoid catheter entrapment (26); 4) transthoracic echocardiography imaging including LVOT characterization before cardiac catheterization; 5) normal sinus rhythm; and 6) informed consent provided. Reasons for cardiac catheterization were percutaneous septal alcohol ablation in 14 patients and further characterization of the LVOT gradient in the remaining 36 patients. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic etiologies (27,28) and had been verified via 2-dimensional Doppler transthoracic echocardiography. Measurements of septal thickness and septal morphology were performed as previously described (29). This study was approved by the Mayo Clinic Institutional Review Board. All patients provided informed consent for review of their medical record in accordance with Minnesota law.

Invasive hemodynamic study. All invasive studies were performed in a fasting state with conscious sedation. Cardioactive medications were continued the day of the procedure. Femoral venous access was used to gain access to the right heart, and left heart pressure measurements were performed via transseptal puncture using 7- or 8-F catheters. Left ventricular pressure measurements were taken in conjunction with cineangio graphic to avoid catheter entrapment and associated erroneous pressure readings (30). Central aortic pressure was obtained from retrograde femoral artery access with 6- or 7-F catheters. High-fidelity, micromanometer-tip catheters (Millar Instruments) were used in all patients as previously described (31).

Baseline invasive data were acquired before septal alcohol ablation or administration of cardiotropic medications. The LVOT gradient was calculated as the difference between the peak left ventricular systolic pressure and the peak central aortic pressure. The largest and smallest resting LVOT gradients during sinus rhythm for the study were recorded, and spontaneous LVOT gradient variability was defined as the difference between these values. For all studies, the gradient after a premature ventricular contraction (PVC) was also recorded.

Data analysis. LVOT obstruction was defined as a resting LVOT gradient of ≥30 mm Hg, with severe obstruction defined as ≥50 mm Hg (15). Continuous variables were expressed as mean ± SD. Correlation of continuous variables was examined via the Spearman rank correlation coefficient given a nonparametric distribution of covariates. The Wilcoxon signed-rank test was used to assess the relationship between LVOT gradient variability and categorical variables. Statistical significance was set a priori at p < 0.05.

Results

Baseline characteristics. Clinical characteristics of the study population are listed in Table 1. The mean age of the population was 55 ± 15 years. Most patients (n = 45, 90%) had moderately severe or severe dyspnea (New York Heart Association class III or IV). Basal septal hypertrophy was noted in most patients (n = 33, 66%). Moderate mitral regurgitation was present in 11 patients (22%); no patients had mitral regurgitation of higher severity.

LVOT gradient characterization. Hemodynamic findings at cardiac catheterization are shown in Table 2. The largest resting LVOT gradient was 54.6 ± 56.4 mm Hg, with 28 patients (56%) found to have a gradient >30 mm Hg. Post-PVC LVOT gradient was 73.8 ± 61.6 mm Hg for the entire population.

The spontaneous LVOT gradient variability was 49.0 ± 53.1 mm Hg (range 0 to 210.8 mm Hg, median 15 mm Hg). Figures 1 and 2 show hemodynamic tracings from individual patients with marked spontaneous LVOT variability. Largest and smallest LVOT gradients during sinus rhythm...
A severe resting LVOT gradient was found in 21 patients (42%), with LVOT gradient 109.7 ± 50 mm Hg in this subgroup. Twenty patients (95% of those with severe obstruction) had the potential for discrepant severity classification, given a smallest LVOT gradient measure of <50 mm Hg.

Discussion

This study analyzed spontaneous LVOT gradient variability in symptomatic patients with HCM during a single cardiac catheterization with high-fidelity, micromanometer-tip catheters performed for either diagnostic hemodynamic evaluation or percutaneous septal ablation. The largest resting LVOT gradient was found to be 54.6 ± 56.4 mm Hg with LVOT gradient variability 49.0 ± 53.1 mm Hg over a short period (on average <8 min). One-half of the study population (50%) had fluctuation in their LVOT gradient measurement to a degree that their classification as severe versus nonsevere obstruction varied during a single study.

Defining the nature and degree of LVOT obstruction is a fundamental aspect of prognostic and therapeutic decision making in patients with HCM (14–16,18). It has been well demonstrated and clinically accepted that the presence of obstruction is associated with increased cardiac morbidity and mortality (32). On this basis, pharmacotherapy in HCM has predominantly focused on alleviation of obstructive physiology. When severe obstruction is present and refractory to medical management, septal reduction is warranted, either via surgical myectomy or percutaneous alcohol ablation (10–13,17). Obstruction has been defined as an LVOT gradient in excess of 30 mm Hg (15). Septal reduction therapy is usually performed for severely symptomatic patients with severe obstruction >50 mm Hg. Measures of LVOT gradient are most often obtained from a single study in clinical practice, commonly via echocardiographic or cardiac catheterization assessment. Although studies have demonstrated significant fluctuations in LVOT gradient over the course of days (4,9), before the present study, the degree of fluctuation within a single hemodynamic study has not been elucidated.

LVOT obstruction is dynamic in nature and augmented by any process leading to alteration of left ventricular loading conditions or myocardial contractility. Indeed, LVOT gradient variability has been associated with fluctuations in volume status, autonomic nervous activity, diurnal variation, pharmacotherapy, exercise, general anesthesia, conscious sedation, recent cardioplegia, and even physical positioning during gradient assessment (4–8). This study demonstrates a significant degree of spontaneous LVOT gradient fluctuation during a single invasive hemodynamic evaluation or percutaneous septal ablation. The largest resting LVOT gradient was found to be 54.6 ± 56.4 mm Hg with LVOT gradient variability 49.0 ± 53.1 mm Hg over a short period (on average <8 min). One-half of the study population (50%) had fluctuation in their LVOT gradient measurement to a degree that their classification as severe versus nonsevere obstruction varied during a single study.

Table 2. Hemodynamic Variables at Cardiac Catheterization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128.0 ± 25.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71.7 ± 12.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Double product, mm Hg/min</td>
<td>8,957 ± 2,467</td>
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<tr>
<td>Largest LVOT gradient, mm Hg</td>
<td>54.6 ± 56.4</td>
</tr>
<tr>
<td>Smallest LVOT gradient, mm Hg</td>
<td>5.7 ± 17.3</td>
</tr>
<tr>
<td>Post-PVC LVOT gradient, mm Hg</td>
<td>73.8 ± 61.6</td>
</tr>
<tr>
<td>Spontaneous LVOT gradient variability, mm Hg</td>
<td>49.0 ± 53.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

LVOT = left ventricular outflow tract; PVC = premature ventricular complex.
measure, with interval measurements taken over the course of minutes.

If patients have symptoms suggestive of obstructive physiology without clear resting gradient at a single noninvasive study, this may reflect the substantial variability in resting LVOT gradient that has been demonstrated herein. Thus, it is important to perform provocative maneuvers on patients with symptoms and a low resting LVOT gradient. Indeed, our data demonstrate a significant correlation between post-PVC LVOT gradient and resting LVOT gradient variability. The magnitude of spontaneous gradient variability was not correlated with baseline echocardiographic or clinical parameters.

Study limitations. The present analysis focused on a symptomatic HCM patient population and may not be generalizable to all patients with HCM. Regardless, recognition of dynamic, clinically significant fluctuations in LVOT gradient is likely underappreciated and may have a substantial impact on diagnostic and

Figure 1. Beat-to-Beat Left Ventricular Outflow Tract Gradient Variability
Continuous high-fidelity left ventricular and aortic hemodynamic tracings demonstrate marked respiratory and beat-to-beat variability in left ventricular outflow tract gradient.

Figure 2. Spontaneous Variability in Left Ventricular Outflow Tract Gradient
Substantial spontaneous variability is noted in the left ventricular outflow tract gradient during a single cardiac catheterization. The largest LVOT gradient in this patient was 113.6 mm Hg with spontaneous complete absence of gradient during the same study.
therapeutic decision making. Meticulous care was used to avoid catheter entrapment using the left ventricular inflow pressures, but this remains a possible confounding problem in these patients with small hyperdynamic left ventricular cavities.

Conclusions

This study illustrates the spontaneous variability of LVOT gradient in patients with HCM. A single measurement of LVOT gradient may not be sufficient to determine an appropriate management approach, as 50% of studied patients had variation in the presence of obstruction during a single hemodynamic evaluation. Given the dynamic nature of LVOT gradient obstruction, resting evaluation may still underappreciate clinically significant exercise-induced LVOT obstruction. Thus, provocative maneuvers to elicit severe obstruction should be performed in all patients undergoing a hemodynamic evaluation in whom a severe obstruction is not present. The variable obstruction and labile hemodynamics in hypertrophic cardiomyopathy must be considered for diagnostic and therapeutic decision making.

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Key Words: cardiac catheterization ■ hypertrophic cardiomyopathy ■ left ventricular outflow obstruction.