Spontaneous Variability of Left Ventricular Outflow Tract Gradient in Hypertrophic Obstructive Cardiomyopathy

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Background—Improvement in the left ventricular outflow tract (LVOT) gradient has been used as a means of assessing response to therapy in patients with hypertrophic obstructive cardiomyopathy (HOCM). To our knowledge, no data exist regarding the spontaneous day-to-day variability of the LVOT gradient in patients with HOCM. Defining the magnitude of such variability is critical to properly understand how much improvement in LVOT gradient must be present to invoke a therapeutic response.

Methods and Results—We studied the spontaneous variation in the continuous-wave, Doppler-derived pressure gradient on 5 consecutive days in 12 HOCM patients and 5 aortic stenosis control subjects. While in some patients the day-to-day variability in resting gradient was small, in others it varied markedly. The 95% confidence interval for attributing a change in LVOT gradient to factors other than random variation is ±32 mm Hg for resting gradient and ±50 mm Hg for provoked gradient. The mean coefficient of variation for gradient across 5 days for the group was 0.52±0.33 for resting gradient and 0.46±0.16 for provoked gradient. The day-to-day variability in pressure gradient could not be explained by changes in heart rate, blood pressure, or left ventricular end-diastolic dimension, each of which had a coefficient of variation <.11. Moreover, technical factors related to the performance or interpretation of the studies did not account for it because the coefficient of variation for gradient in aortic stenosis was <10% and interobserver and intraobserver agreement was excellent (r=.96 and .98, respectively).

Conclusions—The LVOT pressure gradient varies considerably from day to day in stable patients with HOCM. A single measurement of pressure gradient is not adequate to define the severity of dynamic LVOT obstruction in HOCM. (Circulation. 1998;97:461-466.)

Key Words: cardiomyopathy ■ echocardiography ■ hypertrophy ■ hemodynamics ■ pressure

Hypertrophic cardiomyopathy is a complex disorder characterized by a broad spectrum of morphological, functional, and genetic abnormalities. The phenotypic expression of this disorder is variable and includes asymmetric septal hypertrophy, concentric hypertrophy, and apical hypertrophy with or without an LVOT gradient. Clinical presentation is also diverse, ranging from absence of symptoms to sudden cardiac death. In clinical practice, measurement of the LVOT gradient is often used to evaluate the severity of disease, the presence or absence of LVOT obstruction, and the efficacy of treatment.

Because of its dynamic nature, the LVOT pressure gradient can vary markedly with changes in preload, contractility, and afterload. Paz et al reported that ingestion of a small amount of ethanol caused a 63% increase in the mean LVOT pressure gradient and a fall in mean systolic blood pressure. In a double-blind, placebo-controlled, crossover study of dual-chamber pacing for HOCM, Nishimura et al reported a high degree of variability between LVOT gradients obtained at baseline and 3 months later in patients randomized to nonpacing therapy. As the authors pointed out in the paper, this difference could either be due to a placebo effect or to intrinsic variability of the dynamic obstruction present in HOCM. Since loading conditions and contractility fluctuate according to volume status, autonomic system activity, diurnal changes in neurohormonal status, and daily activity, the LVOT pressure gradient may exhibit considerable temporal variability.

To our knowledge, no data exist regarding the day-to-day variability of the LVOT gradient in patients with HOCM. Defining the magnitude of such variability is important, particularly if improvement in LVOT gradient is used to judge the efficacy of pacemaker or drug therapy for this disorder. Therefore we performed this study to prospectively examine the spontaneous day-to-day variability of rest and provoked LVOT pressure gradient in stable patients with HOCM.

Methods

Study Patients

The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and the Veterans Affairs Medical Center at Dallas. All patients gave written informed consent. The diagnosis of HOCM was confirmed in all patients by a previous echocardiogram demonstrating a hypertrophied nondilated ventricle in the absence of a secondary cause, along with a resting or provoked pressure gradient across the LVOT. Patients were ineligible...
bile for the study if they had atrial fibrillation, an indwelling pacemaker, or an unstable medical condition that could result in alteration of the loading conditions. Patients with concomitant valvular heart disease of aortic stenosis, aortic regurgitation, or mitral stenosis, as well as those with mitral regurgitation thought to be caused by a primary valvular abnormality, were also excluded from the study. A control group of five patients with varying severity of aortic stenosis was also studied.

Study Design
Serial echocardiograms were performed on 5 consecutive days for each patient. To ensure blinded reading, the studies were labeled with a preassigned random study number instead of the patient’s name. Each study was done at approximately the same time of day by the same technician using the same instrument. Patients were asked to take their medications at the same time each day. Medication dosage was kept constant during the study period. On each day, blood pressure and heart rate were measured after 10 minutes of supine rest.

Echocardiography
Echocardiograms were performed in the partial left lateral decubitus position with the use of standard imaging planes and a commercially available instrument (Hewlett-Packard Sonos 2500 or Vingmed 800C). For each individual patient, the same echo machine and instrument settings were used for each of the five subsequent examinations to keep the imaging conditions constant between studies. Standard two dimensional echocardiography was performed with the use of a 2.5-MHz transducer. Continuous-wave Doppler examination was performed with the use of a 1.9-MHz nonimaging transducer. Examination was done from multiple imaging planes, using careful transducer angulation to isolate maximum velocity across the LVOT. Particular effort was made to isolate a spectral profile showing a relatively slow increase in velocity culminating in a delayed peak velocity in mid-systole, a characteristic waveform of HOCM patients (Fig 1). Gain and filter settings were adjusted to obtain the signal with the highest audible frequency, the maximal peak velocity, and optimal signal-to-noise ratio. These gain and filter settings were recorded and kept constant for each subsequent study on that patient. Particular care was taken to distinguish the LVOT signal from that of the mitral valve. Systolic anterior motion of the mitral valve was used to assess the presence and the severity of systolic anterior motion of the mitral valve. Systolic anterior motion was graded as follows: 0, absent; 1+, present with minimum distance between mitral valve and ventricular septum during systole >10 mm; 2+, without mitral-septal contact but with a distance <10 mm between mitral valve and septum; 3+, brief mitral-septal contact (<30% of echocardiographic systole); and 4+, prolonged mitral-septal contact (>30% of systole).

Provoked pressure gradient was obtained after giving 0.4 mg NTG sublingually. All patients tolerated NTG, except one who refused it due to a history of severe nitrate headaches and alternatively performed the Valsalva maneuver. Blood pressure was obtained before and after each minute of NTG intake. Continuous-wave Doppler examination of LVOT was repeated once the systolic blood pressure had fallen by >10 mm Hg.

Doppler recordings were reviewed independently and in random order by two blinded observers (P.G. and S.H.). The observers analyzed only those beats having a Doppler spectral signal that was judged to represent the velocities across the LVOT and for which there was sharp and unambiguous definition of the entire waveform contour. Post–ectopic beat waveforms were disregarded. The Doppler beam was assumed to be almost parallel (angle $\phi <20^\circ$) to systolic flow in the LVOT, therefore no angle correction was used in the estimation of the pressure gradient. LVOT pressure gradient was estimated utilizing the modified Bernoulli equation: $P=4V^2$, where $P$ is pressure gradient in mm Hg and $V$ is maximal flow velocity in m/s. For each study, an average of the three highest velocity beats was obtained.

Intraobserver variability was assessed by having one investigator (P.G.) read the first 12 studies on two different occasions at least 4 weeks apart. Interobserver variability was assessed by having a second investigator (S.H.) read the first 25 studies independently.

Statistical Analysis
The values for LVOT pressure gradient were plotted for all patients and were observed to follow a gaussian distribution. Mean LVOT pressure gradient for each patient was calculated from the values obtained on 5 consecutive days. This mean gradient was considered to represent the true pressure gradient. Day-to-day variation from the mean was determined by subtracting each day’s value from the mean value of all 5 days. The 95% confidence intervals for day-to-day variation were determined as 2 standard deviations from the mean difference. In addition, the coefficient of variation (standard deviation divided by the mean) for the 5 consecutive daily measurements of pressure gradient was calculated for each patient as an index of spontaneous variability. Similarly, coefficients of variation for blood

Selected Abbreviations and Acronyms

HOCM = hypertrophic obstructive cardiomyopathy
LVOT = left ventricular outflow tract
NTG = nitroglycerin

![Figure 1](image_url)

Figure 1. Top, Continuous-wave Doppler signal at rest showing a peak velocity of 2.2 m/s, corresponding to a gradient of 19 mm Hg. Bottom, After sublingual NTG, the peak velocity increases to 4.0 m/s, corresponding to a gradient of 64 mm Hg. Note the late peaking waveform, which is characteristic of HOCM.
pressure, heart rate, left ventricular end-diastolic dimension, and provoked LVOT pressure gradient were calculated. Linear regression was used to assess whether patients who have a higher mean pressure gradient across their LVOT have a greater day-to-day variability. Finally, interobserver and intraobserver variability were assessed by linear regression with Bland-Altman analysis.21

**Results**

**Patient Group**

The study population consisted of 12 patients with HOCM, ranging in age from 34 to 77 years. There were 7 men and 5 women. All patients were clinically stable and in sinus rhythm. Patients on a stable dose of cardioactive medication were included in the study. Medications for HOCM included calcium channel blockers (n=6), β-blockers (n=2), and both a calcium blocker and a β-blocker (n=2). Two patients were not taking any medication for HOCM. The dose range of β-blockers was equivalent to 50 to 150 mg of metoprolol, and the dosage range of calcium channel blockers was equivalent to 120 to 360 mg of verapamil. All patients except for one were symptomatic. Dyspnea was present in all symptomatic patients. Eight patients suffered from exertional presyncope, stable angina, and palpitations. Only 2 patients had a history of a complete syncopal event in the past. Of the 12 patients, 5 were New York Heart Association functional class 1, 6 were class 2, and 1 was class 3. All patients had asymmetric septal hypertrophy. Mean septal thickness was 1.8±0.3 cm (range, 1.4 to 2.2 cm). Systolic anterior motion of the mitral valve was present in 9 patients. The mean rest LVOT pressure gradient by continuous-wave Doppler echocardiography was 27±27 mm Hg (range, 3 to 108 mm Hg). Individual values for resting and provoked gradient in each patient are given in Table 1. The coefficients of variation for heart rate, systolic blood pressure, LV end-diastolic dimension, and rest and provoked gradients are listed in Table 2.

**Day-to-Day Variability of Resting Pressure Gradient**

The difference between each day’s resting gradient and the mean for all 5 days for each patient is illustrated in Fig 2. While in some patients, the day-to-day variability in resting gradient was small, in others it varied markedly. The 95% confidence interval for attributing a change in resting LVOT gradient to factors other than random variation was ±32 mm Hg. In individual patients, the coefficient of variation for resting gradient over the 5-day study period ranged from 0.11 to 1.18 (mean, 0.52±0.33). We found no significant correlation be-

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### TABLE 1. Daily Measurements of Resting and Provoked Gradient in HOCM

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Rest Gradient, mm Hg</th>
<th>Provoked Gradient, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>1</td>
<td>73/M</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>77/F</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>34/M</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>65/M</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>52/F*</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>72/F</td>
<td>14</td>
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<tr>
<td>8</td>
<td>71/F</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>55/M</td>
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<tr>
<td>11</td>
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<td>12</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>59/M</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*Coeff indicates coefficient of variation for the 5-day measurements.

*Patient in whom Valsalva was used for provocation.*
between the coefficient of variation of resting pressure gradient and the magnitude of the mean gradient ($r^2 = .15$, $P = .22$).

Systolic anterior motion of the mitral valve was present in 9 of the 12 HOCM patients and was generally mild to moderate. However, the large increase in resting pressure gradient seen on a single day in patients 8, 9, and 10 (Table 1) was accompanied by a corresponding increase in systolic anterior motion score from 1 to 2+ to 4+.

### Day-to-Day Variability of Provoked LVOT Pressure Gradient

The difference between each day’s provoked gradient and the mean for all 5 days for each patient is illustrated in Fig 3. Again, in some patients the day-to-day variability of provoked gradient was small, whereas in others it varied markedly. The 95% confidence interval for attributing a change in provoked LVOT gradient to factors other than random variation was ±50 mm Hg. In individual patients, the coefficient of variation for provoked gradient over the 5-day period ranged from 0.23 to 0.71 (mean, 0.46±0.16). We found no significant correlation between coefficient of variation of provoked gradient and the magnitude of the mean provoked gradient ($r^2 = .16$, $P = .20$).

### Control Subjects

Day-to-day values of pressure gradient across the aortic valve for the five control patients with aortic stenosis were obtained in a similar manner as that of HOCM patients. The difference between each day’s resting gradient and the mean for all 5 days is illustrated in Fig 4. The 95% confidence interval (±2 standard deviations) is ±5 mm Hg for the control group. The coefficient of variation averaged 8±5% (range, 3% to 13%).

### Observer Variability

An excellent correlation was found for rest gradient measurements between different observers ($r = .96$) and the same observer at different readings ($r = .98$). By Bland-Altman analysis, the mean difference in interobserver and intraobserver pressure gradient measurements was 0±5 mm Hg and 1±3 mm Hg, respectively. Similarly, a close correlation and strong agreement was also found for provoked gradient ($r = .99$, mean difference = ±2±5), and ($r = .95$, mean difference = 0±5) for interobserver and intraobserver variability, respectively.

### Discussion

Reduction in pressure gradient across the LVOT has been reported as objective evidence of therapeutic success in patients HOCM.8–12 To our knowledge, this is the first study to systematically address the magnitude of spontaneous day-to-day variability of pressure gradient in HOCM patients. We found the coefficient of variation for repeated measurements of resting and provoked gradient to be 0.52 and 0.46, respectively. This marked variation in LVOT gradient was not associated with a change in symptoms in most patients.

Factors that could account for such marked variability include (1) day-to-day variation in hemodynamic conditions within individual patients, (2) operator- and instrument-dependent variables, (3) differences in interpretation of studies between observers, and (4) intrinsic variability of pressure gradient. The possible effect of each of these factors on the results of this study is discussed in the following paragraphs.

Changes in heart rate and loading conditions occurring daily in patients can influence the pressure gradient.13–15 To limit the effects of these hemodynamic changes to spontaneous day-to-day variation, this study included only patients taking a stable dose of cardioactive medications. The coefficient of variation for daily changes in heart rate, systolic blood pressure, and left ventricular-end diastolic dimension was <11%, suggesting that the variability in pressure gradient observed in this study was not due to major changes in day-to-day hemodynamic conditions.

Several operator- and instrument-dependent factors may influence the serial measurements of pressure gradient. The most important of such factors is the ability of the sonographer to reproducibly align the interrogating Doppler beam parallel to the LVOT systolic flow. An unacceptably high error is induced in the estimation of pressure gradient if the angle between the interrogating ultrasound beam and the direction of blood flow is more than 20 degrees.20 To limit the influence of this variable on the daily measurements of pressure gradient,
all echocardiograms were performed by experienced sonographers who were trained to interrogate the LVOT systolic flow jet from multiple acoustic windows with careful angulation of the transducer to isolate the maximal velocity spectral profile. Aortic valve pressure gradients in a control group of aortic stenosis patients were also studied in a similar manner on 5 consecutive days to determine if the observed variability in pressure gradient found in this study was largely due to technical factors. Aortic valve pressure gradients did not change significantly between studies in individual patients with aortic stenosis, supporting the reliability and reproducibility of the continuous-wave Doppler data in this study. Gain and filter settings were also kept constant between studies for each patient. Therefore the 52% variability in pressure gradient observed in this study is not explained by variations in operator or instrument factors. Moreover, these data may underestimate the magnitude of spontaneous variability observed in clinical practice because the study was performed under a rigorous protocol optimized for repeated measurements.

There was excellent interobserver and intraobserver agreement for pressure gradient measurements present in this study. Therefore, we do not believe that the day-to-day variation in LVOT pressure gradient is due to interpretive differences between observers.

Given that there was minimal variation in hemodynamic conditions, technique, and observer measurements, we are left to conclude that marked day-to-day variability in gradient is largely intrinsic to hypertrophic cardiomyopathy. Moreover, since all patients were clinically stable and had only mild symptoms at the time of study, the finding of a high gradient on any given day does not necessarily correlate with severity of disease.

Clinical Implications

Widespread spontaneous fluctuations in pressure gradient from one day to another in HOCM, as reported in this study, indicate that a single measurement of pressure gradient is not adequate to describe the severity of LVOT obstruction. On the basis of our findings, we propose that the LVOT pressure gradient be assessed on at least three separate occasions and averaged in these patients. Such an approach would not be novel to clinical practice, since the diagnosis of hypertension is not made unless the patient’s blood pressure is elevated on two different measurements, or at least two separate occasions to account for the spontaneous variation in blood pressure.22,23 In addition to improving assessment of the individual patient, averaging the LVOT gradient on 3 separate days would also help to distinguish therapeutic benefit or disease progression from spontaneous variation. This is important for clinical decision making in individual patients and in clinical trials evaluating new therapies aimed at reducing the pressure gradient in HOCM.

Controversy exists as to the importance of the pressure gradient in HOCM. Traditional teaching is that the gradient represents a dynamic outflow tract obstruction that produces symptoms in a subset of patients with this disorder.4–6 Supporting this view is marked relief of symptoms after surgical myectomy in selected patients.24,25 Alternatively, the fact that the majority of left ventricular stroke volume is ejected before to the development of the gradient has led some to conclude that there is no true obstruction to left ventricular outflow and that the gradient is a result of cavity obliteration.26,27 The present study does not directly address this controversy. However, if the gradient is not important in the pathophysiology of HOCM, expensive therapies directed at relieving LVOT obstruction, such as dual chamber pacing, may not be warranted. Our data suggest that a decrease in LVOT gradient measured at a single point in time after pacing therapy may be the result of spontaneous variability and could lead to the erroneous conclusion of therapeutic efficacy. Controlled clinical trials of pacing therapy in HOCM are currently underway and should take into account the spontaneous variability of pressure gradient.

Limitations

It is difficult to accurately measure left ventricular afterload in the setting of HOCM. Noninvasive measures of afterload, such as end-systolic wall stress, use cuff systolic blood pressure as a surrogate marker for intraventricular systolic pressure.28 Such an approach would be inaccurate in HOCM since the cuff systolic pressure may not reflect the true intraventricular systolic pressure. Although we did not find a significant change in systolic blood pressure between studies in individual patients, we also cannot completely eliminate the possibility of changes in afterload between studies.

All but two of the patients in our study were already taking medications for relief of symptoms at the time of enrollment. Due to the outpatient nature of the study, and the unknown risk of drug withdrawal, patients were continued on their medical treatment. The time and dose of medication were kept constant and no new medications were added during the study. Thus the results of this study do not reflect the natural history of HOCM but rather indicate the variability of daily measurements of LVOT gradient in patients on stable medical therapy. We only studied patients in sinus rhythm. Atrial fibrillation was excluded because beat-to-beat variability in pressure gradient may confound the ability to quantify day-to-day variability.

We made no attempt to simultaneously measure the pressure gradient using catheter-based techniques. Several studies in the past have already validated continuous-wave Doppler assessment of pressure gradient against the catheter-based methods of measuring pressure differences across the LVOT in patients with HOCM.18,22

As shown in Table 1, some patients on given days did not increase their gradient with provocation. This may be due to inadequate hemodynamic change with NTG or failure to collect the Doppler data until maximal hemodynamic effect had subsided.

Conclusions

The LVOT pressure gradient varies considerably from day to day in stable patients with HOCM. A single measurement of pressure gradient is not adequate to define the severity of dynamic LVOT obstruction in HOCM.

References

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Circulation. 1998;97:461-466
doi: 10.1161/01.CIR.97.5.461

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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