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Assessment of Left Ventricular Outflow Gradient

Hypertrophic Cardiomyopathy Versus Aortic Valvular Stenosis

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Objectives This study examined the relationship between peak-to-peak (common invasive measurement), peak instantaneous (common Doppler measurement), and mean pressure gradients in patients with hypertrophic cardiomyopathy (HCM) and aortic stenosis (AS).

Background In patients with AS, the peak-to-peak gradient and peak instantaneous gradient are discrepant, and the mean gradient best represents obstruction severity. The pathophysiology of outflow obstruction differs in HCM, with the maximum gradient occurring in late systole, thus the optimal method for quantifying gradient severity in HCM remains undefined.

Methods Fifty patients with HCM and 50 patients with AS underwent gradient characterization at cardiac catheterization (age 55 ± 15 years vs. 72 ± 9 years; 48% vs. 42% male, respectively). All HCM patients were studied with high-fidelity, micromanometer-tip catheters and transseptal measurement of left ventricular inflow and central aortic pressures. In AS, simultaneous left ventricular and central aortic pressures were recorded.

Results The peak instantaneous gradient was linearly correlated with peak-to-peak gradient in HCM ($R^2 = 0.98$, $p < 0.0001$), with the relationship close to the line of identity. In AS, more scatter and further deviation from the line of identity occurred when comparing the peak instantaneous gradient to the peak-to-peak gradient ($R^2 = 0.70$, $p < 0.0001$). Both peak-to-peak and peak instantaneous gradients were consistently higher than the mean gradient in HCM, with wide 95% confidence limits of agreement (26.7 ± 46.5 mm Hg and 16.4 ± 47.2 mm Hg, respectively).

Conclusions In HCM, peak instantaneous and peak-to-peak gradient demonstrate excellent correlation. Consequently, both peak instantaneous and peak-to-peak gradients can be used to classify obstruction severity in HCM. By contrast, the mean gradient should direct clinical management in AS. (J Am Coll Cardiol Intv 2012;5:675–81) © 2012 by the American College of Cardiology Foundation

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Hypertrophic cardiomyopathy (HCM) and aortic valve stenosis (AS) are conditions characterized by left-sided hemodynamic gradients. In HCM, myocardial hypertrophy with abnormalities of the mitral valve apparatus leads to a dynamic subvalvular left ventricular outflow tract (LVOT) gradient in most patients (1–4). Determining the magnitude of the LVOT gradient is paramount in patient management, as it is innately tied to clinical symptoms and prognosis (5–14). By contrast, the gradient of AS is fixed and develops secondary to obstruction at the valvular level. The gradient in aortic stenosis carries therapeutic and prognostic implications as well, with severe aortic stenosis defined by an aortic valve mean gradient exceeding 40 mm Hg (15–21).

Doppler echocardiography and cardiac catheterization are the current methods for measuring the left ventricular outflow gradient in both HCM and AS. Doppler echocardiography commonly reports a peak instantaneous gradient utilizing the peak Doppler velocity with application of the modified Bernoulli equation (22). By contrast, the peak-to-peak gradient is the conventional method reported from cardiac catheterization. In AS, the peak instantaneous gradient is always higher than the peak-to-peak gradient and it is the mean gradient that is recommended to be used by both noninvasive and invasive methods (15).

Abbreviations and Acronyms

AS = aortic valve stenosis

HCM = hypertrophic cardiomyopathy

LV = left ventricular

LVOT = left ventricular outflow tract

In contrast to AS, a generally accepted standard measure of the gradient in HCM does not exist. Studies using Doppler echocardiography have used the peak instantaneous gradient, whereas studies from the catheterization laboratory use the peak-to-peak gradient. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with HCM have recommended using either parameter (23), but there has not been a study comparing them directly. Thus, the purpose of this study is to assess the relationship between peak-to-peak, peak instantaneous, and mean gradient measurements in populations of HCM, comparing these relationships to the known discrepancies that occur in patients with AS.

Methods

HCM population. Between September 2005 and October 2009, 50 patients with HCM were evaluated at the Mayo Clinic in Rochester, Minnesota, who met the following criteria: 1) absence of aortic valvular disease; 2) cardiac catheterization with high-fidelity, micromanometer-tip catheters (Millar Instruments, Houston, Texas) for simultaneous measurement of left ventricular (LV) and central aortic pressures; 3) transseptal catheterization to avoid catheter entrapment of the LV pressure (24); 4) sinus rhythm; and 5) informed consent. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic etiologies (25,26) and verified via 2-dimensional transthoracic Doppler echocardiography. Measurements of septal thickness and septal morphology were performed as previously described (27).

AS population. During the same time frame as the HCM study, 50 consecutive cases of patients with AS were selected who met the following criteria: 1) native aortic valve; 2) absence of constrictive/restrictive physiology; 3) cardiac catheterization with simultaneous measures of LV and central aortic pressures; 4) sinus rhythm; and 5) informed consent.

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. Central aortic pressure was obtained from retrograde femoral artery access with 6- or 7-F catheters. In patients with AS, simultaneous LV and aortic pressures were recorded via retrograde crossing of the aortic valve or a transseptal antegrade approach. In all patients with HCM, 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. High-fidelity, micromanometer-tip catheters (Millar Instruments) were used in HCM patients as previously described, with simultaneous assessment of LV and aortic pressures (28).

All LV pressure measurements were taken in conjunction with cineangiography to avoid catheter entrapment and associated erroneous pressure readings (29). In patients undergoing pharmacological evaluation or septal ablation, baseline invasive data were acquired before septal alcohol ablation or administration of cardiotropic medications.

Three methods to measure gradient (LVOT in the HCM subset, transvalvular in the AS population) were used in all patients. The largest spontaneous resting gradient in sinus rhythm was evaluated for all patients, and all measurements were made from the same beat. *Peak-to-peak gradient* was the difference between the peak LV systolic pressure and the peak central aortic pressure. *Peak instantaneous gradient* was the maximum gradient present when simultaneous central aortic pressure was subtracted from LV systolic pressure. *Mean gradient* was the integral difference between LV systolic pressure and central aortic pressure over the entire systolic ejection period.

Data analysis. LVOT obstruction in HCM was defined as a resting LVOT gradient of ≥30 mm Hg, with severe obstruction defined as ≥50 mm Hg (10). Continuous variables were expressed as mean ± SD. Correlation of continuous variables was examined with simple linear regres-

Table 1. Baseline Characteristics

Variable	HCM	AS	p Value
Age, yrs	55 ± 15	72 ± 9	<0.0001
Male	24 (48)	21 (42)	0.40
Body mass index, kg/m^2	33.6 ± 7.8	30.2 ± 5.4	0.01
NYHA functional class III or IV	45 (90)	19 (38)	<0.0001
Pre-syncope or syncope	21 (42)	9 (18)	0.02
History of hypertension	32 (64)	38 (76)	0.30
LDL cholesterol, mg/dl	104 ± 44	97 ± 42	0.40
History of smoking	26 (52)	32 (64)	0.20
History of atrial fibrillation	3 (6)	13 (26)	0.01
Permanent pacemaker	10 (20)	8 (16)	0.80
Internal cardioverter-defibrillator	8 (16)	1 (2)	0.03
Family history of HCM	12 (24)	—	—
Family history of SCD	3 (6)	—	—
Prior septal reduction	3 (6)	—	—
Etiology of valvular disease			
Calcific	—	38 (76)	—
Rheumatic	—	4 (8)	—
Radiation-induced	—	4 (8)	—
Bicuspid	—	4 (8)	—
Echocardiographic findings			
Left ventricular ejection fraction, %	69 ± 8	57 ± 17	<0.0001
Mitral regurgitation, moderate or greater	11 (22)	4 (8)	0.09
Maximum ventricular wall thickness, mm	20.9 ± 5.1	12.5 ± 2.6	<0.0001
Basal septal hypertrophy, %	33 (66)	—	
Aortic valve area by TVI, cm^2	—	1.02 ± 0.21	—
Corrected aortic valve MIG, mm Hg	—	54 ± 16	—
Mean AS gradient, mm Hg	—	33 ± 10	—
Medications			
Beta-receptor antagonist	42 (84)	30 (60)	0.01
Calcium-channel blocker	24 (48)	5 (10)	<0.0001
ACE inhibitor or ARB	14 (28)	28 (56)	0.008
Disopyramide	6 (12)	0 (0)	0.03
Amiodarone	1 (2)	4 (8)	0.40

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AS = aortic valvular stenosis; HCM = hypertrophic cardiomyopathy; LDL = low-density lipoprotein; MIG = maximal instantaneous gradient; NYHA = New York Heart Association; SCD = sudden cardiac death; TVI = tissue velocity imaging.

sion analysis. Student *t* tests, Pearson chi-square analyses, and Fisher exact tests were used as appropriate. 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 HCM population was significantly younger than the patients with AS (55 ± 15 years vs. 72 ± 9 years, $p < 0.0001$). Sex was evenly distributed for both groups. Most patients in the HCM group (n = 45, 90%) had moderately severe or severe dyspnea (New York Heart Association functional class III or IV). Significantly fewer were severely symptomatic in the AS population (n = 19, 38%, $p < 0.0001$). Basal septal hypertrophy was noted in most HCM patients (n = 33, 66%), with the remainder demonstrating concentric hypertrophy or hypertrophy isolated to the distal septum, apex, or free wall. The most common etiology of valvular stenosis was calcific degenerative (n = 38, 76%). The groups were not different with regard to history of hypertension, measured low-density lipoprotein cholesterol, smoking history, or history of permanent pacemaker implantation.

Hemodynamic assessment. Hemodynamic variables at cardiac catheterization are outlined in Table 2. Patients with AS were significantly more hypertensive than patients with HCM at the time of cardiac catheterization, with similar diastolic blood pressure and heart rates. Representative hemodynamic tracings are shown for patients with HCM and AS (Fig. 1).

Quantitation of gradient. Peak instantaneous LVOT gradient showed a strong linear correlation with peak-to-peak gradient in patients with HCM ($y = 0.99x + 10.6$, $R^2 = 0.98$, $p < 0.0001$) (Fig. 2A), closely paralleling the line of identity. Peak instantaneous aortic valve gradient was linearly correlated with peak-to-peak gradient in patients with AS. More scatter and further deviation from the line of identity occurred in patients with AS ($y = 1.05x + 18.8$, $R^2 = 0.70$, $p < 0.0001$) (Fig. 2B), albeit in the setting of a smaller gradient range.

Peak-to-peak gradient correlated with mean gradient within the HCM population ($R^2 = 0.98$, $p < 0.0001$), but deviated from the line of identity (Fig. 3). Similarly, the peak instantaneous gradient correlated with the mean gradient in HCM patients ($R^2 = 0.98$, $p < 0.0001$) but deviated from the line of identity (Fig. 4). When compared with the mean LVOT gradient measures in HCM, both peak-to-peak and peak instantaneous values were consistently higher, with wide 95% confidence intervals of agreement (26.7 ± 46.5 mm Hg and 16.4 ± 47.2 mm Hg, respectively).

Table 2. Hemodynamic Variables at Cardiac Catheterization

Variable	HCM	AS	p Value
Aortic systolic blood pressure, mm Hg	117.5 ± 19.6	141.3 ± 30.0	<0.0001
Aortic diastolic blood pressure, mm Hg	71.0 ± 11.4	66.4 ± 11.4	0.05
Heart rate, beats/min	71 ± 13	71 ± 13	0.80
Double product, mm Hg/min	8,387 ± 2,393	10,068 ± 2,742	0.002
Peak-to-peak gradient, mm Hg	51.8 ± 51.9	27.2 ± 12.2	0.002
Peak instantaneous gradient, mm Hg	62.1 ± 52.1	47.5 ± 15.5	0.06
Mean gradient, mm Hg	35.4 ± 29.6	30.0 ± 10.2	0.20

Values are mean ± SD.

Abbreviations as in Table 1.

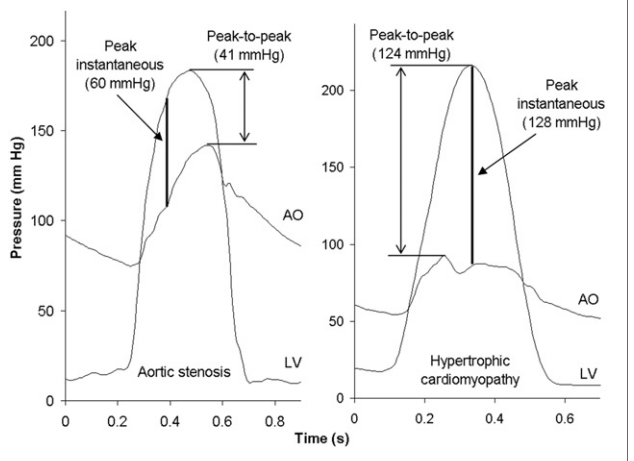

Figure 1. Gradient Measurement at Cardiac Catheterization

Continuous high-fidelity left ventricular (LV) and aortic (Ao) hemodynamic tracings were used for evaluation of patients with aortic stenosis **(left)** and hypertrophic cardiomyopathy **(right)**. Peak instantaneous and peak-to-peak gradient measures are shown.

Discussion

This paper demonstrates that in patients with HCM, the peak-to-peak gradient closely correlates with the peak instantaneous gradient. Assessment of this relationship demonstrates a very close fit to the line of identity. The correlation of peak-to-peak gradient and peak instantaneous gradient was less robust for patients with AS, as has been previously described. Given the strong linear relationship between these measures in HCM, as well as the physiological mechanism of the gradient, Doppler-derived measurements reflecting the peak instantaneous gradient and directly measured peak-to-peak gradients at catheterization can be used interchangeably in HCM.

The LVOT gradient in HCM occurs via a unique mechanism. During ventricular systole, blood flow accelerates across the septum, leading to a drag effect on the displaced mitral valve apparatus, which "pushes" the leaflets into the LVOT (30–34). Dynamic obstruction occurs primarily in late systole as systolic anterior motion of the mitral valve occurs. Effects on gradient have been demonstrated from fluctuations in volume status, autonomic nervous activity, diurnal variation, pharmacotherapy, exercise, and physical position during assessment (4,34–37), and variability in the magnitude of gradient has been demonstrated over the course of minutes (38). Quantification of LVOT gradient remains central to the management algorithm of patients with HCM. The presence of severe obstruction portends increased cardiac morbidity and mortality (9–11,13). Medical therapy that prevents exercise-induced increases in gradient is the initial treatment in patients with documented gradients. If pharmacological therapy is unsuccessful in relieving severe obstruction, septal reduction therapy is indicated (5–8,12). The ACC/AHA guidelines for the management of patients with HCM have recommended proceeding with septal reduction therapy only if there is a resting or provoked gradient >50 mm Hg (23). It is thus important to develop a standardized approach for reporting the magnitude of the gradient in HCM.

Echocardiographic assessment of valvular gradient uses the modified Bernoulli equation, pressure = $4(\text{velocity})^2$, which is usually applied to the peak instantaneous velocity (22). Mean gradient can be determined via integration of the continuous-wave Doppler signal. By contrast, measurement at invasive catheterization conventionally reports the difference between peak left ventricular and peak aortic pressure tracings. Mean gradient can be calculated as the integrated difference between these waveforms.

In AS, the peak instantaneous gradient often exceeds the peak-to-peak gradient (39), and thus, the 2 measurements should not be used synonymously. By contrast, peak instantaneous gradient and peak-to-peak gradient were found to

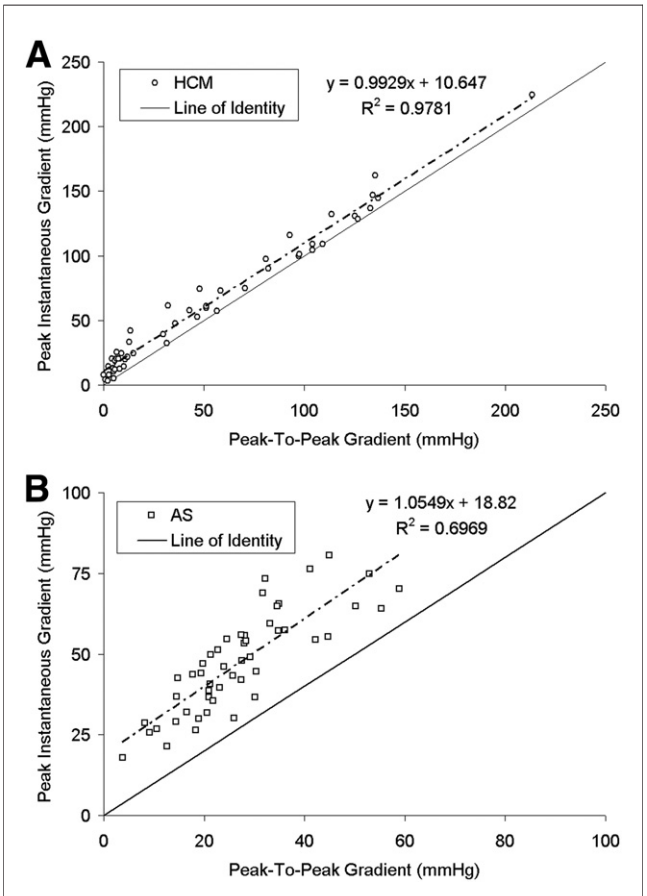

Figure 2. Peak-to-Peak Versus Peak Instantaneous Gradient

Scatterplots of peak-to-peak versus peak instantaneous gradient measures for hypertrophic cardiomyopathy (HCM) **(A)** and aortic valve stenosis (AS) **(B)** demonstrate linear correlations.

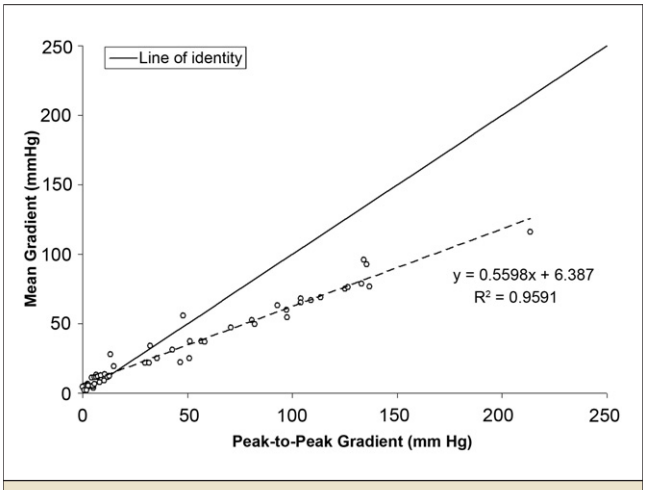

Figure 3. Peak-to-Peak Versus Mean Gradient

Scatterplots of peak-to-peak versus mean gradient measures for patients with hypertrophic cardiomyopathy.

be equivalent in HCM. The reason for this incongruity becomes apparent upon inspection of the pressure waveform morphologies (Fig. 1). In AS, a constant degree of obstruction is present from the time the aortic valve opens until the time it closes. As such, the mean gradient throughout the systolic ejection period is indicative of the severity of stenosis. By contrast, the gradient in HCM is dynamic. Obstruction is minimal in early systole, rapidly increases during the systolic ejection period, and peaks in late systole. Due to late peaking obstruction, the aortic contour has a "spike and dome" pattern, with aortic pressure changing little during mid and late systole. Thus, the true severity of the obstruction is best measured in late systole.

Prior studies have reported on the maximum instantaneous gradient when using Doppler echocardiography and the peak-to-peak gradient using catheterization for both prognosis as well as criteria for treatment. Resting obstruction is present when the gradient exceeds 30 mm Hg, which does portend a poorer prognosis (10). Severe obstruction amenable to septal reduction therapy requires a gradient >50 mm Hg. However, there has not been a systematic study that correlates the peak instantaneous and peak-to-peak gradients. Our findings support the recent ACC/AHA guideline recommendations that either Doppler-derived peak instantaneous gradient or peak-to-peak gradient at cardiac catheterization can be used to accurately quantitate LVOT gradient in patients with HCM (23).

Study limitations. Significant differences exist between the baseline characteristics of the included AS and HCM patient populations. These findings are not unexpected, given the known demographic differences between these disease processes. The intent of this study was not that of a case control, but rather to characterize hemodynamic assessment of the gradient throughout these populations. Patients with HCM were significantly more symptomatic than those with AS, which prompted invasive assessment in this patient group. However, it is unlikely that functional class significantly altered quantitative assessment of gradient.

Diligent selection of high-quality measurements for gradient characterization was performed. All patients with AS had simultaneous measures of LV and aortic pressures, and all patients with HCM had transseptal studies with high-fidelity micromanometer-tipped catheters. Fastidious care was taken to avoid catheter entrapment, but this is a potential confounder in the setting of small, hyperdynamic LV cavities. We did not perform Doppler echocardiography and catheterization simultaneously; however, previous studies have shown that Doppler velocities can be accurately converted to pressure gradients across the LVOT in patients with HCM (40).

Conclusions

Peak instantaneous gradient was strongly linearly correlated with peak-to-peak gradient in HCM, paralleling the line of identity. This relationship was less robust in AS, with more scatter and further deviation from the line of identity noted. Given strong linear relationships between these 2 gradient measures as well as the pathophysiology of obstruction, Doppler-derived gradient (peak instantaneous) and peak-to-peak gradient obtained at cardiac catheterization should be the standard methodology to report the severity of obstruction in patients with HCM. This is opposed to patients with aortic stenosis, where the mean gradient is the standard for both Doppler echocardiography and cardiac catheterization.

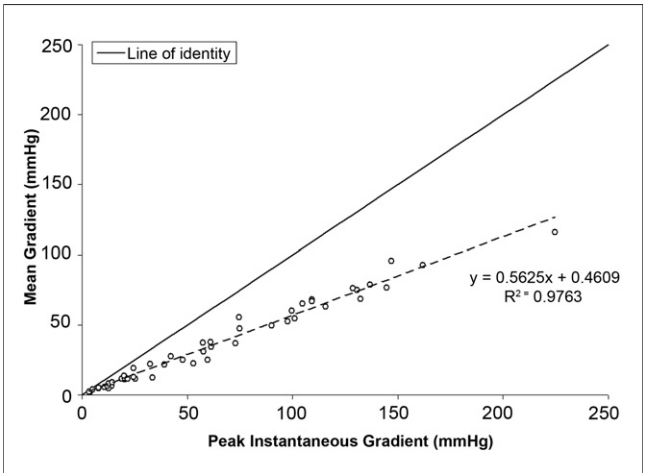

Figure 4. Peak Instantaneous Versus Mean Gradient

Scatterplots of peak instantaneous versus mean gradient measures for patients with hypertrophic cardiomyopathy.

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Key Words: aortic stenosis ■ hemodynamic assessment ■ hypertrophic cardiomyopathy ■ outflow obstruction.