Left Ventricular Outflow Tract Gradient Variability in Hypertrophic Cardiomyopathy

Address for correspondence:
Rick A. Nishimura, MD
Gonda 05–368
200 First St. SW
Rochester, MN 55905
rnishimura@mayo.edu

Jeffrey B. Geske, MD; Paul Sorajja, MD; Steve R. Ommen, MD; Rick A. Nishimura, MD
Division of Internal Medicine, (Geske), Division of Cardiology (Sorajja, Ommen, Nishimura), Mayo Clinic College of Medicine, Rochester, Minnesota

ABSTRACT

Background: The presence and magnitude of left ventricular outflow tract (LVOT) obstruction directs the management algorithm in symptomatic patients with hypertrophic cardiomyopathy (HCM). Although it is well known that the degree of LVOT obstruction is dynamic and dependent upon ventricular load and contractility, the magnitude and potential impact of the day-to-day variability seen in practice has not been well appreciated.
Hypotheses: We hypothesized that LVOT gradient variability in HCM has an impact on clinical decision-making.
Methods: A total of 100 HCM patients (mean age, 58 ± 13 years; 47% male) underwent comprehensive 2-dimensional Doppler transthoracic echocardiography and cardiac catheterization with transseptal measurement of left-sided pressures. All studies were performed within 48 hours of one another.
Results: The correlation of LVOT gradients from both methods performed at different times had a wide scatter with the 95% confidence limits of agreement being ±84 mm Hg. For classifying patients as having severe LVOT obstruction on the basis of either method (<30 vs ≥30 mm Hg), discrepant results occurred in 21% of patients. To confirm the accuracy of Doppler measurements, 15 studies were performed with simultaneous measurement of LVOT gradient, which revealed a very strong correlation ($r = 0.98, p < 0.0001$) with 95% confidence limits of agreement ±12 mm Hg.
Conclusions: In patients with HCM, LVOT gradient measurements are routinely obtained to characterize the severity of obstruction. However, these data demonstrate the marked variability of the LVOT obstruction, which must be considered when determining appropriate therapy in symptomatic patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is a disease state characterized by disproportionate hypertrophy of the myocardium with left ventricular outflow tract (LVOT) obstruction present in the majority of patients.[1–4] Characterization of the severity of LVOT obstruction is clinically relevant because it is a major cause of symptoms and a predictor of prognosis.[5–13] In the management algorithm of HCM patients, the presence of severe LVOT obstruction leads to consideration of surgical or percutaneous septal reduction therapy in those with drug-refractory symptoms.[10]

Left ventricular outflow tract obstruction in HCM is greatly dependent upon ventricular load and the contractile state, and thus its severity is potentially highly variable.[4] However the magnitude of the variability of the obstruction has not been well appreciated by many clinicians. Accordingly, the objective of this study was to examine the clinical variability of the LVOT gradient in patients with HCM.

Methods

Study Population

This study was approved by the Mayo Foundation institutional review board. Between January 2000 and June 2007, 1656 patients with HCM were evaluated at the Mayo Clinic in Rochester, MN. Patients with HCM were enrolled in this study with the following criteria: (1) normal sinus rhythm; (2) technically adequate Doppler echocardiographic assessment of LVOT obstruction; (3) absence of aortic valvular disease; (4) cardiac catheterization for LVOT gradient assessment within 48 hours of Doppler echocardiography; (5) transseptal catheterization to avoid catheter entrapment;[14] and (6) informed consent. Of the 100 patients enrolled, reasons for cardiac catheterization were percutaneous septal alcohol ablation in 60 patients and further characterization of the LVOT gradient in the remaining 40 patients. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic etiologies.[15,16] All patients provided informed consent for review of their medical record in accordance with Minnesota law.

Echocardiography

Each of the 100 patients underwent comprehensive 2-dimensional and Doppler transthoracic echocardiography. Measurement of the resting LVOT gradient was performed by continuous-wave Doppler interrogation of the LVOT from an apical window and calculated using the modified Bernoulli equation (ie, gradient $= 4v^2$ where $v =$ peak LVOT velocity). A total of 15 patients underwent Doppler studies simultaneously with cardiac catheterization and nonsimultaneously within 48 hours of catheterization. All Doppler signals were recorded with sweep speed of

Received: January 6, 2009
Accepted with revision: February 7, 2009

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594

100 mm/s, and all data were averaged from 3 to 5 end-expiratory cycles (Figure 1).

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 French catheters. Left ventricular pressure measurements were taken in conjunction with cineangiography to avoid catheter entrapment and associated erroneous pressure readings (Figure 1).[17] Central aortic pressure was obtained from retrograde femoral artery access with 6 or 7 French catheters. High-fidelity, micromanometer-tip catheters (Millar Instruments, Houston, TX) were utilized in 55 patients as previously described.[18] Invasive data was acquired prior to septal alcohol ablation or administration of cardiotropic medications. All measurements were recorded from end-expiratory cycles. Left ventricular outflow tract gradient at cardiac catheterization was calculated as peak left ventricular systolic pressure minus the peak central aortic pressure.

Simultaneous Echocardiography and Cardiac Catheterization

A total of 15 patients underwent prospective, simultaneous Doppler echocardiography and cardiac catheterization measurements of LVOT gradient. Same beat analysis of both Doppler and catheterization hemodynamics was performed (Figure 2).

Data Analysis

Severe LVOT obstruction was defined as a resting LVOT gradient of ≥30 mm Hg.[10] Continuous variables are expressed as mean ± SD. Correlation of continuous variables was examined with simple linear regression analysis. Paired 2-sample Student *t* tests were utilized as appropriate. Bland-Altman analyses with 95% confidence limits of agreement were used to compare LVOT gradients obtained using echocardiography and cardiac catheterization.[19] 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 58 ± 13 years. The majority of patients (n = 82, 82%) had moderately-severe or severe dyspnea (New York Heart Association class III or IV). Moderate or severe mitral regurgitation was present in 20 patients. A total of 23 patients had either a history of atrial fibrillation (n = 15) or permanent pacing (n = 14), but were in normal sinus rhythm during the hemodynamic studies.

Table 1. Baseline Characteristics

Variable	Value
Age (y)	58 ± 13
Male gender, no. (%)	47 (47)
NYHA class III or IV, no. (%)	82 (82)
Prior septal myectomy, no. (%)	2 (2)
Presyncope or syncope, no. (%)	51 (51)
History of atrial fibrillation, no. (%)	15 (15)
History of diabetes, no. (%)	13 (13)
Family history of HCM, no. (%)	20 (20)
Family history of SCD, no. (%)	11 (11)
Mitral regurgitation, moderate or severe, no. (%)	20 (20)
Maximum ventricular wall thickness (mm)	20.0 ± 5.6
End-diastolic diameter (mm)	45.7 ± 5.9
Left atrial volume index (cc/m²)	47 ± 17
Left ventricular ejection fraction (%)	72 ± 6
Permanent pacemaker, no. (%)	14 (14)
Internal cardioverter-defibrillator, no. (%)	7 (7)
Medications, no. (%)	
β-Receptor antagonist	88 (88)
Calcium channel blocker	52 (52)
ACE-inhibitor or ARB	24 (24)
Disopyramide	10 (10)
Amiodarone	6 (6)
Time between echo and cath (d)	1.0 ± 0.9

Continuous variables expressed as mean ± SD. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; SCD, sudden cardiac death; SD, standard deviation.

Mean time to catheterization was 1.0 ± 0.9 days with all catheterizations performed within 2 days of echocardiography. There were no significant differences in blood pressure at the time of echocardiography and at the time of invasive cardiac catheterization (Table 2).

LVOT Gradient Comparison

The resting LVOT gradient at echocardiography correlated with the LVOT gradient observed at cardiac catheterization ($r = 0.59, p < 0.0001$; Figure 3A). The catheter-derived

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594

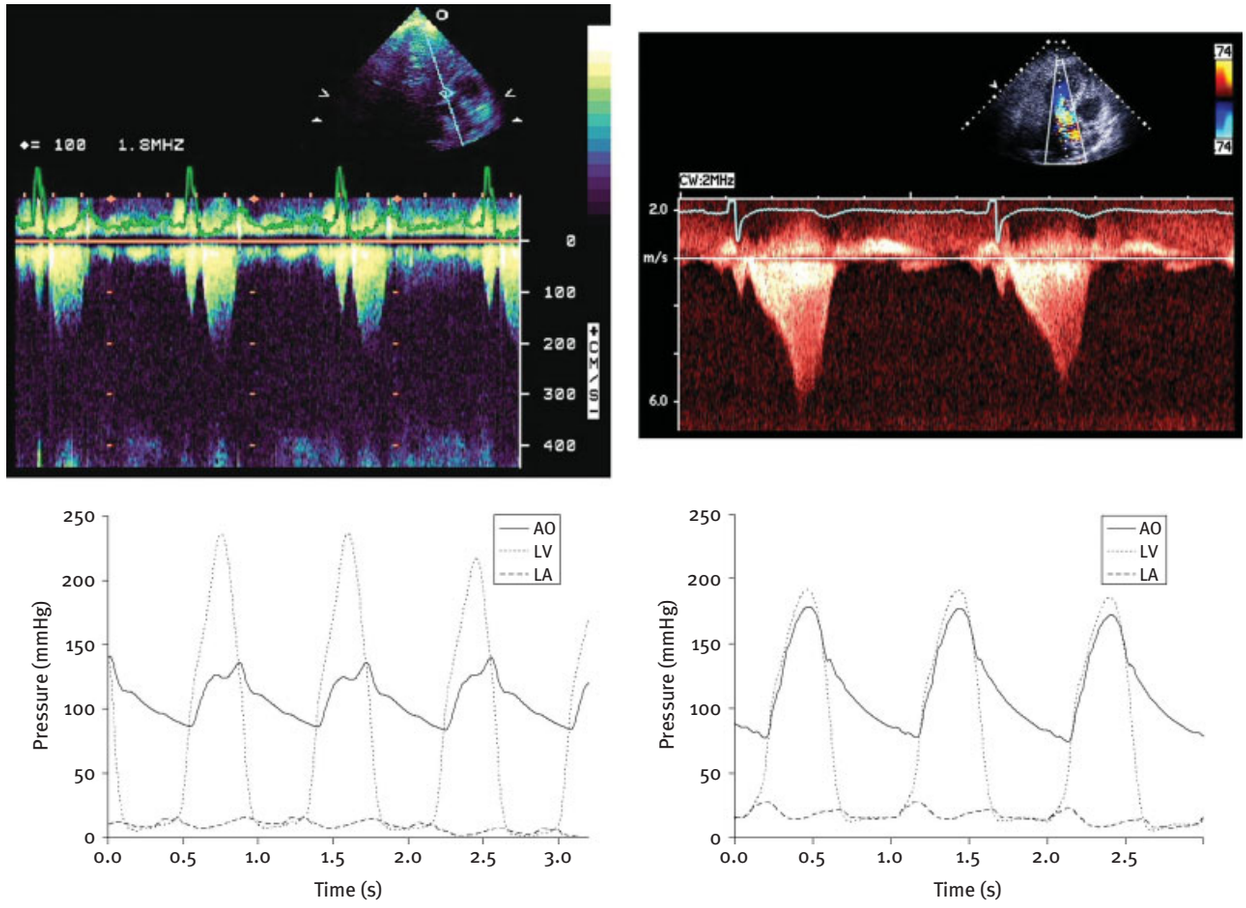

Figure 1. Hemodynamic recordings. (Upper left) Doppler echocardiographic analysis of LVOT gradient in a patient with hypertrophic cardiomyopathy; estimated gradient 21 mm Hg. (Lower left) Corresponding pressure tracing of the LV, AO, and LA performed 2 days later; gradient of 100 mm Hg. (Upper right) Doppler echocardiographic analysis of LVOT gradient in a patient with hypertrophic cardiomyopathy; estimated gradient 130 mm Hg. (Lower right) Corresponding pressure tracing of the LV, AO, and LA performed 2 days later; gradient of 14 mm Hg. Abbreviations: AO, aorta; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract.

LVOT gradient was lower than that observed at echocardiography, with a mean difference of 7 ± 42 mm Hg ($p = 0.07$). There was wide scatter of the gradient between the 2 assessments with 95% confidence limits of agreement ±84 mm Hg (Figure 3B). Discrepancy in defining severe LVOT obstruction by either echocardiography or cardiac catheterization occurred in 21% of patients (Figure 1). Severe LVOT obstruction was found at Doppler echocardiography, but not cardiac catheterization in 15% (n = 15), while severe LVOT obstruction was evident at cardiac catheterization, but not Doppler echocardiography in 6% (n = 6).

Simultaneous Doppler-Catheterization Correlation

There was a strong positive correlation of the LVOT gradient obtained via simultaneous Doppler echocardiography and cardiac catheterization ($r = 0.98$, $p < 0.0001$; Figure 3C). In this analysis, the 95% confidence limits of agreement were ±12 mm Hg (Figure 3D).

Discussion

Characterization of the LVOT gradient is a central component of the management algorithm of patients with HCM.[9–11,13] Outflow obstruction is associated with cardiac morbidity, as well as increased mortality.[20] The goal of medical therapy in HCM is amelioration of the LVOT gradient. Septal reduction, either via myectomy or alcohol ablation, is performed when pharmacologic therapy is unsuccessful in the presence of severe obstruction.[5–8,12] The definition of severe obstruction is a LVOT gradient ≥30 mm Hg,[10] which is usually obtained from a single measurement. However, it

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594

Table 2. Hemodynamic Variables at Time of CATH and DOPP

Variable	CATH	DOPP	Difference (CATH-DOPP)	*P* Value
Systolic blood pressure (mm Hg)	127 ± 27	125 ± 23	2 ± 22	0.3
Diastolic blood pressure (mm Hg)	70 ± 12	71 ± 10	−1 ± 10	0.4
Heart rate (beats per min)	66 ± 11	64 ± 11	−2 ± 9	0.01
LVOT gradient (mm Hg)	45 ± 45	52 ± 47	−7 ± 42	0.07

Continuous variables expressed as mean ± SD. Abbreviations: CATH, cardiac catheterization; DOPP, Doppler transthoracic echocardiography; LVOT, left ventricular outflow tract; SD, standard deviation.

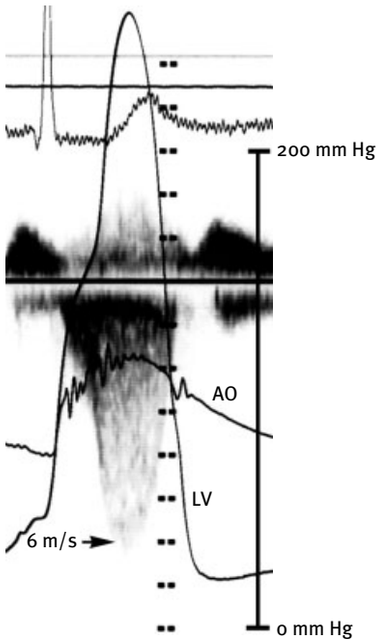

Figure 2. Simultaneous LVOT analysis. Simultaneous analysis of LVOT gradient via Doppler transthoracic echocardiography and cardiac catheterization. Doppler echocardiography revealed an estimated gradient of 144 mm Hg, cardiac catheterization revealed a gradient of 142 mm Hg. Abbreviations: AO, aortic pressure tracing; LV, left ventricular pressure tracing; LVOT, left ventricular outflow tract.

is important for the clinician to understand the large variability of dynamic obstruction when making decisions on therapy.

The pathophysiology of the dynamic outflow tract obstruction in patients with HCM is unique. The initial hypothesis was that the basal septum would project into the outflow tract during systole, causing an initial obstruction and creating a Venturi effect to "suck" the mitral valve into the outflow tract. However, subsequent studies have shown that accelerated flow around the septum produces a drag effect on an elongated and displaced mitral valve apparatus to "push" the leaflets into the outflow tract.[21,22]

The dynamic nature of LVOT obstruction results from an amalgamation of changes in ventricular loading conditions and myocardial contractility that are sensitive to fluctuations in volume status, autonomic nervous activity, diurnal variation, pharmacotherapy, exercise, and even physical positioning during gradient assessment.[4,23–26]

The recognition of the variability of LVOT outflow tract gradient in clinical practice is lacking. In the present investigation, there were very large variations in LVOT gradient over a period of less than 48 hours despite similar hemodynamic loading conditions at the time of gradient measurement. Using the cut off value of ≥30 mm Hg for defining severe LVOT obstruction, 21% of the patients had discrepant findings between the 2 studies. Moreover, the 95% confidence limits of agreement were ±84 mm Hg, far exceeding the conventional criteria for discriminating nonobstructive from obstructive physiology.[10]

We did not show spontaneous gradient variability over an extended period of time. However, Kizilbash et al[4] had previously shown a variability of over ±32 mm Hg for 12 patients with hypertrophic cardiomyopathy measured on 5 consecutive days. In addition, there was a spontaneous variability of the LVOT gradient of >40 mm Hg over 3 months observation in initial randomized pacing trials.[27]

Doppler echocardiography has been used extensively to characterize LVOT physiology.[20,28–30] Prior studies have shown an excellent correlation between Doppler and catheter-derived LVOT gradients,[31,32] similar to the findings among patients examined with simultaneous studies in the present investigation (95% confidence limits of agreement ±11 mm Hg). Thus, the large differences between the outpatient echocardiogram and invasive catheterization in this study are felt to be due to the variability of the LVOT gradient, not differences in measurement techniques. On average there was a slightly lower gradient measured by catheterization vs echocardiography, which may be related to the effect of conscious sedation on the catecholamine state of the patient. However, there were still 6 patients who had a severe gradient at catheterization, but not at Doppler echocardiography.

These findings also have important implications for assessing the clinical efficacy of therapies directed towards

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594

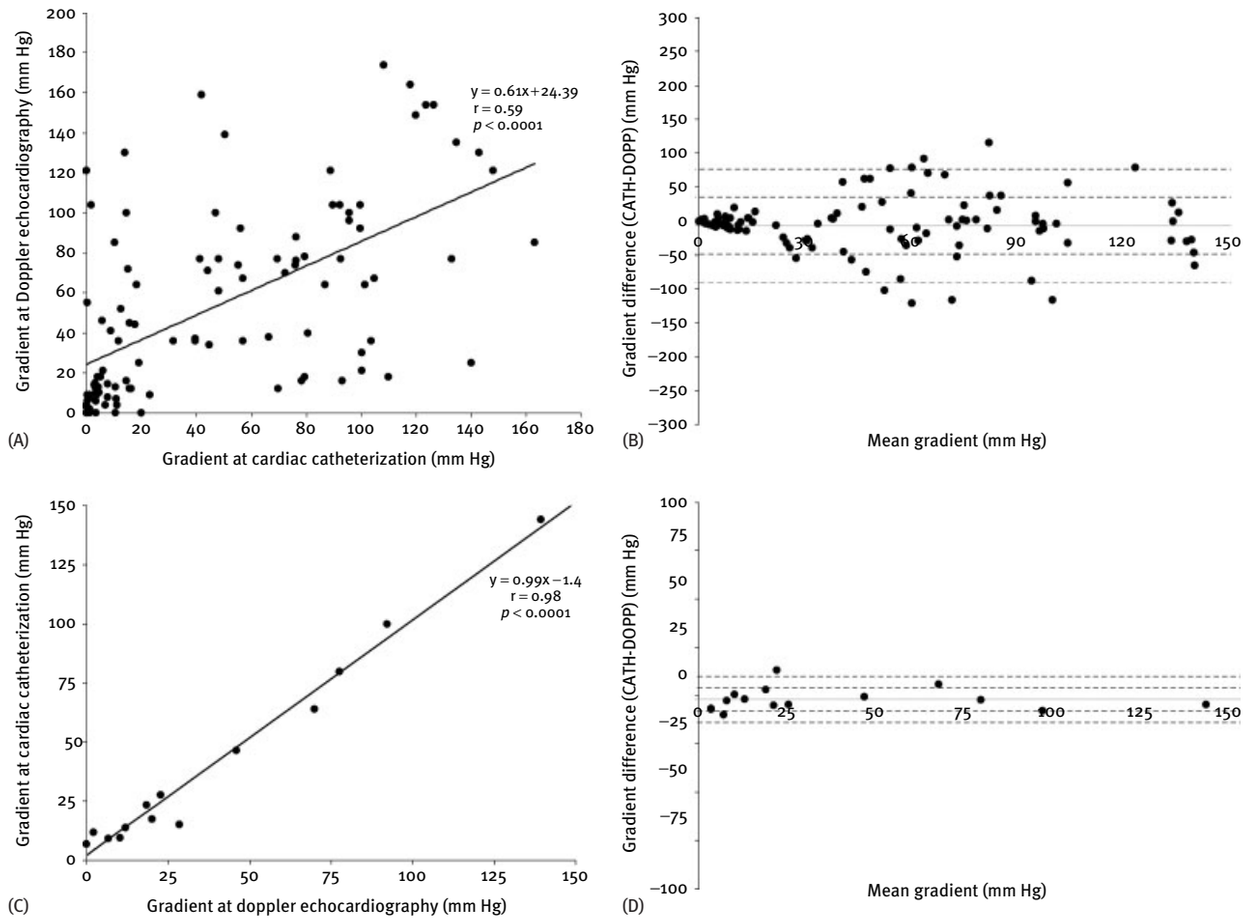

Figure 3. Correlation of outflow tract gradient. (A) Linear regression of LVOT gradient measured by DOPP and CATH in all patients. (B) Bland-Altman correlation of LVOT gradient in all patients. (C) Linear regression of simultaneous, same-beat LVOT gradient DOPP and CATH. (D) Bland-Altman correlation of LVOT gradient for simultaneous, same-beat analysis. Abbreviations: CATH, cardiac catheterization; DOPP, doppler transthoracic echocardiography; LVOT, left ventricular outflow tract.

alleviation of LVOT obstruction. Prior studies have reported residual gradients evaluated by different methodology and under varying hemodynamic states (eg, general anesthesia, conscious sedation, recent cardioplegia). A single measurement of LVOT gradient may not be sufficient to determine an appropriate management approach or determine the results of therapy.

Conclusions

It is important to recognize the daily variability of LVOT obstruction in patients with HCM. Over 20% of patients may be misclassified as to the presence or absence of severe outflow obstruction, which has important implications for determining optimal therapy in these patients.

References

1. Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. i. a description of the disease based upon an analysis of 64 patients. *Circulation*. 1964; 30(suppl 4):3–119.
2. Maron BJ, Gottdiener JS, Arce J, Rosing DR, Wesley YE, Epstein SE. Dynamic subaortic obstruction in hypertrophic cardiomyopathy: analysis by pulsed Doppler echocardiography. *J Am Coll Cardiol*. 1985;6:1–18.
3. Klues HG, Leuner C, Kuhn H. Left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy: increase in gradient after exercise. *J Am Coll Cardiol*. 1992;19:527–533.
4. Kizilbash AM, Heinle SK, Grayburn PA. Spontaneous variability of left ventricular outflow tract gradient in hypertrophic obstructive cardiomyopathy. *Circulation*. 1998;97:461–466.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594 © 2009 Wiley Periodicals, Inc.

5. Schoendube FA, Klues HG, Reith S, Flachskampf FA, Hanrath P, Messmer BJ. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. *Circulation.* 1995;92:II122–127.
6. McCully RB, Nishimura RA, Tajik AJ, Schaff HV, Danielson GK. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. *Circulation*. 1996;94: 467–471.
7. Franke A, Schondube FA, Kuhl HP, et al. Quantitative assessment of the operative results after extended myectomy and surgical reconstruction of the subvalvular mitral apparatus in hypertrophic obstructive cardiomyopathy using dynamic three-dimensional transesophageal echocardiography. *J Am Coll Cardiol*. 1998;31:1641–1649.
8. Nagueh SF, Ommen SR, Lakkis NM, et al. Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol*. 2001;38:1701–1706.
9. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol*. 2003;41: 987–993.
10. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;348:295–303.
11. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol*. 2005;45:1076–1080.
12. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:470–476.
13. Elliott PM, Gimeno JR, Tome MT, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2006;27:1933–1941.
14. Wigle ED, Henderson M, Rakowski H, Wilansky S. Muscular (hypertrophic) subaortic stenosis (hypertrophic obstructive cardiomyopathy): the evidence for true obstruction to left ventricular outflow. *Postgrad Med J*. 1986;62:531–536.
15. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. *Am J Cardiol*. 1979;43:1242–1244.
16. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation*. 1996;93:841–842.
17. Wigle ED, Marquis Y, Aucer P. Muscular subaortic stenosis. Initial left ventricular inflow tract pressure in the assessment of intraventricular pressure differences in man. *Circulation*. 1967;35: 1100–1117.
18. Nishimura RA, Schwartz RS, Tajik AJ, Holmes DR Jr. Noninvasive measurement of rate of left ventricular relaxation by Doppler echocardiography. Validation with simultaneous cardiac catheterization. *Circulation*. 1993;88:146–155.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
20. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Prog Cardiovasc Dis*. 1985;28:1–83.
21. Jiang L, Levine RA, King ME, Weyman AE. An integrated mechanism for systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy based on echocardiographic observations. *Am Heart J*. 1987;113:633–644.
22. Sherrid MV, Gunsburg DZ, Moldenhauer S, Pearle G. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2000;36:1344–1354.
23. Braunwald E, Brockenbrough EC, Morrow AG. Hypertrophic subaortic stenosis—a broadened concept. *Circulation*. 1962;26: 161–165.
24. Wilson WS, Criley JM, Ross RS. Dynamics of left ventricular emptying in hypertrophic subaortic stenosis. A cineangiographic and hemodynamic study. *Am Heart J*. 1967;73:4–16.
25. Glancy DL, Shepherd RL, Beiser D, Epstein SE. The dynamic nature of left ventricular outflow obstruction in idiopathic hypertrophic subaortic stenosis. *Ann Intern Med*. 1971;75:589–593.
26. Shah JS, Esteban MT, Thaman R, et al. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart*. 2008;94:1288–1294.
27. Nishimura RA, Trusty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol*. 1997;29:435–441.
28. Ryan TJ. Doppler echocardiographic measurement of outflow tract gradient in hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 1988;1:471–472.
29. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*. 2006;114:2232–2239.
30. Sorajja P, Nishimura RA, Ommen SR, Ackerman MJ, Tajik AJ, Gersh BJ. Use of echocardiography in patients with hypertrophic cardiomyopathy: clinical implications of massive hypertrophy. *J Am Soc Echocardiogr*. 2006;19:788–795.
31. Yock PG, Hatle L, Popp RL. Patterns and timing of Doppler-detected intracavitary and aortic flow in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1986;8:1047–1058.
32. Sasson Z, Yock PG, Hatle LK, Alderman EL, Popp RL. Doppler echocardiographic determination of the pressure gradient in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1988;11: 752–756.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20594