Latent Obstruction and Left Atrial Size Are Predictors of Clinical Deterioration Leading to Septal Reduction in Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Exercise echocardiography is a reliable tool to assess left ventricular (LV) dynamic obstruction in hypertrophic cardiomyopathy (HCM). The aim of this study was to determine the role of exercise echocardiography in the evaluation of latent obstruction and in predicting clinical deterioration in HCM patients.

Methods and Results: We considered 283 HCM patients studied with exercise echocardiography. The end point was clinical deterioration leading to septal reduction (myectomy or alcohol septal ablation). LV latent obstruction was present at enrollment in 67 patients (24%). During a mean follow-up of 42 ± 31 months, 42 patients had clinical deterioration leading to septal reduction therapy: in 12/67 (22%) patients with a latent obstruction at enrollment, in 28/84 (33%) patients with obstruction at rest, and in 2/132 (1.5%) with obstruction neither at rest or during stress. Multivariate analysis identified the following variables as independently associated with the end point: LV gradient >30 mm Hg at rest (hazard ratio [HR] 2.56, 95% CI 1.27−5.14; $P = .009$), LV gradient >30 mm Hg during stress (HR 4.96, 95% CI 1.81−13.61; $P = .002$), and indexed left atrial volume (LAVi) >40 mL/m^2 (HR 2.86, 95% CI 1.47−5.55; $P = .002$). In patients with a latent obstruction, the strongest independent predictor of outcome was LAVi >40 mL/m^2 (HR 3.75, 95% CI 1.12−12.51; $P = .032$).

Conclusions: Assessment of LV gradient during stress with exercise echocardiography is an important tool for the evaluation of latent obstruction in HCM and may have a role in risk stratification of these patients. (*J Cardiac Fail 2014;20:236−243*)

Key Words: Hypertrophic cardiomyopathy, exercise echocardiography, left ventricular obstruction.

Intracavitary left ventricular (LV) obstruction, typically across the left ventricular outflow tract (LVOT), is an important pathophysiologic feature of hypertrophic cardiomyopathy (HCM).[1] Twenty-five percent to 30% of patients with HCM have a significant LVOT gradient at rest.[2] In patients with HCM, LVOT obstruction at rest is considered to be a strong independent predictor of progression to severe symptoms of heart failure and death.[3]

The presence of a significant intraventricular gradient identifies a subgroup of patients in whom septal reduction interventions, such as surgical myectomy or alcohol septal ablation, are considered as therapeutic options.[4,5] It is now recognized that a sizable proportion of patients with minimal or absent LVOT gradients at rest develop significant gradients after exercise or provocative maneuvers. These patients may be minimally symptomatic or asymptomatic.[6] However, the burden of latent obstruction is variable in the different series analyzed, and its prognostic role is not clear.

The first aim of the present study was to describe the prevalence and features of patients with latent obstruction

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in a large population of patients with HCM studied with exercise echocardiography. The second aim was to assess whether latent obstruction is associated with a higher likelihood of worsening symptoms and exercise intolerance leading to septal reduction therapy.

Methods

Study Population

From the population of patients with HCM enrolled in the Stanford registry for inherited cardiovascular disease, 283 patients (mean age 50 ± 16 years, male sex 60%) referred for evaluation at Stanford University from January 2000 to January 2012 underwent exercise echocardiography at enrollment. For the present analysis we excluded 16 patients with ''pure'' apical HCM without significant intraventricular gradient at rest or stress.

The diagnosis of HCM was based on the presence of significant LV hypertrophy (end-diastolic wall thickness >15 mm with M-mode or 2-dimensional [2D] echocardiography) in the absence of other etiologies according to international criteria, or wall thickness of 13−15 mm in the presence of an abnormal electrocardiogram or familial history of inherited cardiomyopathies.[7] Patients with left ventricular (LV) systolic dysfunction at enrollment were included in the study if there was a clear documented history of HCM and preserved LV ejection fraction (LVEF) from earlier echocardiographic examinations performed at other institutions.

All subjects were stable and receiving optimal medical therapy at the time of testing. Written informed consents were obtained with the use of a protocol approved by the Stanford University Institutional Review Board. The investigation conformed with the principles outlined in the Declaration of Helsinki[8] and local legal requirements and was approved by the Institutional Review Board at Stanford University.

Echocardiographic and Doppler Study

Echocardiographic images were acquired with the use of Philips IE 33 or HP 5500 systems depending on the period of enrollment (Andover, Massachusetts). We considered only the examination performed at enrollment. HCM was classified according to ventricular morphology as: 1) hypertrophy with reverse septal curvature; 2) hypertrophy with proximal septal bulge; 3) concentric hypertrophy with normal shape (symmetric); or 4) indefinite if the morphology did not fit any of the other subgroups.[9] Using M-mode and 2D, we measured LV diameters and shortening fraction, thickness of the interventricular septum (IVS) and LV posterior wall (PW), and left atrial end-systolic diameter; all measurements were performed according to recommendations of the American Society of Echocardiography (ASE).[10,11] With the use of 2D, the sites and maximal extent of ventricular hypertrophy were assessed and measured in end-diastole. LV volumes and EF were assessed from the apical 4-chamber view, with the use of the biplane method of discs. LVEF was considered to be depressed when it was <50%.

At Doppler examination, the systolic intraventricular gradient was quantified with the use of the continuous-Doppler technique. A peak gradient of >30 mm Hg at rest was considered to be significant. LV filling was assessed by pulsed Doppler interrogation at the level of mitral opening tips. In accordance with earlier studies and with ASE guidelines,[12,13] the pattern of LV filling was classified as: 1) restrictive filling pattern: E-deceleration time <120 ms or an E/A ≥2 associated with E-deceleration time <160 ms; 2) abnormal relaxation: E/A <1 associated with E-deceleration time >220 ms; or 3) normal (or ''pseudonormal''): intermediate filling pattern. Mitral and tricuspid valve regurgitation were assessed according to the ASE guidelines.[14]

Left ventricular myocardial performance index (MPI) was measured from mitral inflow and LV outflow Doppler tracings, as previously described by Tei et al.[15] From tissue Doppler imaging we considered peak myocardial early diastolic velocity measured at the lateral mitral annulus and the assessment of transmitral to TDI early-diastolic velocity ratio (E/e′).[16] Tricuspid annular plane systolic excursion (TAPSE) was measured from the systolic excursion of the tricuspid lateral annulus. In accordance with ASE guidelines, right ventricular systolic dysfunction was considered to be present when fractional area contraction (apical 4-chamber view) was <35% and/or TAPSE was <16 mm.[17] We defined the development of new wall motion abnormalities as the presence of alterations in segmental kinesis not observed during resting echocardiography and worsening of mitral regurgitation (MR) from mild to moderate/severe or from moderate to severe MR, according to ASE guidelines.[18]

Patients were stressed with the use of the ramp Bruce protocol. The Borg scale[19] and the peak respiratory exchange ratio (RER) were used as measures of adequate stress. After the treadmill exercise test, patients were immediately placed in the left lateral decubitus position. Imaging was performed by an experienced technician. The peak gradient was measured first, and degrees of MR were then assessed.

Patients were classified according to the presence of a significant gradient at rest and/or during stress in the following 3 groups: group 1: patients nonobstructive either at rest or stress; group 2: patients obstructive only at stress (latent obstruction); and group 3: patients obstructive at rest.

Follow-Up Assessment

Patients were periodically followed with clinical/laboratory assessment. The frequency of evaluations was established according to the clinical needs of a given patient. The end point of the study was clinical deterioration leading to septal reduction therapy (surgical myectomy or alcohol septal ablation). Clinical deterioration was defined as an evolution from a condition considered to be manageable with medications to severe symptoms (New York Heart Association [NYHA] functional class III−IV) despite optimal medical therapy (OMT). Septal reduction therapy during follow-up was considered only when significant symptoms (NYHA functional class III−IV) despite OMT, associated with a significant resting LVOT gradient, occurred. The patients that at enrollment were symptomatic (NYHA functional class III) showing a significant obstruction at rest and/or at stress were initially medically treated with closer follow-up. Information regarding study end points was obtained directly from the clinical follow-up evaluations or by telephone interview with the patient, their relatives, or general practitioner or obtained by the residence birth/death registries. For patients without events, the end of follow-up was considered to be June 1, 2012. During follow-up, 3/67 (4%) in group 2, 5/84 (6%) in group 3 and 7/132 (5%) in group 1 died or underwent heart transplantation (P = NS). We did not consider this end point for the present study, focusing our attention on clinical deterioration leading to septal reduction.