Comparison of Valsalva Maneuver, Amyl Nitrite, and Exercise Echocardiography to Demonstrate Latent Left Ventricular Outflow Obstruction in Hypertrophic Cardiomyopathy

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Guidelines recommend exercise stress echocardiogram (ESE) for patients with hypertrophic cardiomyopathy (HC) if a 50 mm Hg gradient is not present at rest or provoked with Valsalva or amyl nitrite, to direct medical and surgical management. However, no study has directly compared all 3 methods. We sought to evaluate efficacy and degree of provocation of left ventricular outflow gradients by ESE, and compare with Valsalva and amyl nitrite. In patients with HC between 2002 and 2015, resting echocardiograms and ESEs within 1 year were retrospectively reviewed. Gradients elicited by each provocation method were compared. Rest and ESE were available in 97 patients (mean age 54 ± 18 years, 57% male); 78 underwent Valsalva maneuver and 41 amyl nitrite provocation. Median gradients (interquartile range) were 10 mm Hg (7,19) at rest, 16 mm Hg (9,34) with Valsalva, 23 mm Hg (13,49) with amyl nitrite, and 26 mm Hg (13,58) with ESE. ESE and amyl nitrite were able to provoke obstruction (≥30 mm Hg) and severe obstruction (≥50 mm Hg) more frequently than Valsalva. In patients with resting gradient <30 mm Hg (n = 83), provocation maneuvers demonstrated dynamic obstruction in 51%; in those with Valsalva gradient <30 mm Hg (n = 57), ESE or amyl nitrite provoked a gradient in 44%; and in those with amyl nitrite gradient <30 mm Hg (n = 20), ESE provoked a gradient in 29%. No demographic or baseline echocardiographic parameter predicted provocable obstruction. In conclusion, ESE is clinically useful; however, different provocation maneuvers may be effective in different patients with HC, and all maneuvers may be required to provoke dynamic obstruction in symptomatic patients. **(Am J Cardiol 2017;120:2265–2271)**

Left ventricular outflow tract obstruction (LVOTO) can cause symptoms and morbidity in patients with hypertrophic cardiomyopathy (HC).[1,2] The dynamic nature of the gradient can make obstruction challenging to identify. Valsalva maneuver and administration of amyl nitrite are techniques on resting echocardiography that can be used to elicit the highest possible gradient across the left ventricular outflow tract (LVOT). The 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines introduced a IIa indication for exercise stress echocardiogram (ESE) to help demonstrate latent obstruction in symptomatic patients with HC if LVOTO cannot be elicited by resting echocardiogram techniques.[1–5] Several studies have evaluated provocation of gradients in HC using Valsalva, amyl nitrite, and ESE.[3–16] Despite current recommendations, no study has compared all 3 techniques directly. Therefore, we sought to evaluate efficacy and degree of provocation of left ventricular outflow gradients on ESE, and to compare them with Valsalva maneuver and amyl nitrite.

Methods

The study was approved by the Mayo Clinic Institutional Review Board. All patients included had provided written informed consent. Consecutive patients with HC undergoing ESE at the Mayo Clinic echocardiography laboratory in Rochester, MN, between 2002 and 2015, were retrospectively reviewed. HC was defined using the standard definition as outlined in the current guidelines.[2] Patients who had dobutamine stress echocardiography were not included, as ESE is preferred for the evaluation of latent obstruction in HC, and dynamic intracavitary obstruction can be provoked with dobutamine in patients without HC.[17,18] Regularly administered medications were not held before ESE.

Inclusion criteria were clinically confirmed diagnosis of HC, and both resting and ESE performed within 1 year of each other. For patients with multiple resting or ESEs, only the first study was included. A total of 138 patients met these criteria. Excluded were patients who had ESE for regional wall motion abnormality without assessment of LVOT gradients (n = 20), those with previous myectomy or alcohol ablation procedure (n = 17), and those with poor or

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immeasurable Doppler tracings after peak exercise (n = 4). The remaining 97 patients were included for analysis.

Patient demographic data, symptoms, medical history, risk factors, physical data, medications, and indications for ESE were collected before each examination by a dedicated registered nurse, and recorded in a standardized electronic echocardiography database. Electronic medical records of all included patients were reviewed to confirm HC diagnosis, medications, medical history, and subsequent septal reduction therapy or death.

Resting and ESE images of all included patients were reviewed for LV and hemodynamic parameters. HC morphology was evaluated on apical long-axis images, and classified as according to septal contour of sigmoid, neutral, reverse curve, or apical. Presence of systolic anterior motion of the mitral valve was evaluated on two-dimensional images, and color Doppler imaging was reviewed to confirm level of obstruction and degree of mitral regurgitation. LVOTO was defined as a maximal instantaneous gradient (MIG) on continuous-wave (CW) Doppler ≥30 mm Hg and severe obstruction as MIG ≥50 mm Hg.[2]

ESE peak gradients were obtained by experienced sonographers immediately after cessation of exercise on treadmill and the patient assuming the supine position, and during peak exercise for supine bike ESE. Care was taken to avoid mitral regurgitation flow on CW Doppler. Resting gradients were obtained before provocation maneuvers. CW Doppler-derived gradients were reviewed on all resting and ESE examinations, and were available, after Valsalva maneuver or administration of amyl nitrite. A small proportion of patients had intracavitary obstruction, and these were combined in the analysis with patients with LVOT obstruction, as the study question was to investigate how obstruction can be provoked.

Rest and ESE examinations were reviewed for regional wall motion abnormalities, stress-induced leaflet systolic anterior motion and change in degree of mitral regurgitation, peak ejection fraction, right ventricular systolic pressure using CW Doppler, and medial E/e′ using tissue Doppler.[19,20] However, jet eccentricity (a hallmark of systolic anterior motion mediated mitral regurgitation) precluded quantitation of mitral regurgitation beyond visual assessment. Clinical parameters from ESE were also collected, including exercise capacity, heart rate and blood pressure (BP) response, and symptoms induced by exercise. Drop in BP was defined as a reduction of systolic BP at peak stress by >10 mm Hg compared with baseline measurement, and blunted BP response was defined as failure of BP to rise >20 mm Hg with peak exercise.[21,22]

Statistical analyses were performed using SAS (version 9.3, SAS Institute Inc., Cary, NC). Continuous variables are presented as means ± standard deviation for normally distributed data or median (interquartile range) for skewed data. Categorical variables are presented as frequencies with percentages. Comparison of patient variables across groups was performed using analysis of variance methods on raw data or ranks for continuous variables and chi-square test for categorical variables. LVOT gradients were compared between methods using paired *t* tests. Kaplan-Meier methods were used to look at events (subsequent myectomy, alcohol septal ablation, or death) during follow-up, and subjects were censored at last known follow-up and compared between groups using the log-rank test. Two-sided tests were used, and statistical significance was defined as $p < 0.05$.

Results

Included were 97 patients with HC, age 54 ± 18 years, 55 (57%) male. The time interval between resting and ESE was 2 (1,18) days. Valsalva maneuver was performed in 78 (79%) and amyl nitrite in 41 (41%). Thirty-six (36%) patients had all 3 provocation maneuvers performed. Forty-one (41%) patients had no significant obstruction (MIG <30 mm Hg), 14 (14%) had resting obstruction (MIG ≥30 mm Hg), and 42 (42%) had latent or provocable obstruction (rest MIG <30 mm Hg and Valsalva, amyl nitrite, or ESE gradient ≥30 mm Hg), which was severe (MIG ≥50 mm Hg) in 28 (28%) (Figure 1).

There was no difference in patient characteristics between patients who had no significant obstruction, latent obstruction, or resting obstruction, aside from family history of HC, which was more frequent in the no obstruction group (Table 1). No resting or stress echocardiographic characteristics or exercise parameters were associated with the presence of provocable obstruction (Tables 2 and 3).

Obstruction and severe obstruction were elicited more frequently by ESE and amyl nitrite administration, than by

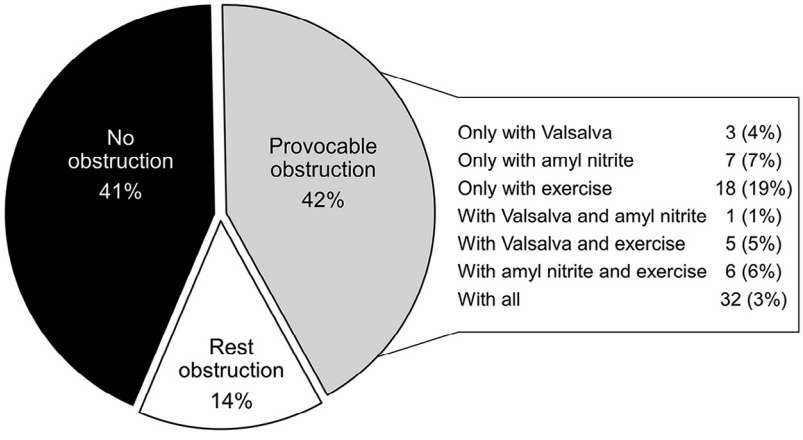

Figure 1. Proportion of patients with HC with no obstruction, resting obstruction, and provocable obstruction by each technique.