Early Hemodynamic Changes Versus Peak Values: What Is More Useful to Predict Occurrence of Dyspnea During Stress Echocardiography in Patients with Asymptomatic Mitral Stenosis?

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Background: In asymptomatic mitral stenosis (MS), the usefulness of peak exercise Doppler echocardiography (DE) values is acknowledged, but the role of values recorded during the first stage of DE remains unclear.

Methods: DE was analyzed in 48 asymptomatic patients with significant MS and revealed dyspnea in 22 patients (46%).

Results: MS severity and rest and peak systolic pulmonary artery pressures (SPAPs) were not different between patients who did and did not develop dyspnea. Progressions of mean gradient and relative SPAP (ratio of SPAP/baseline SPAP) were significantly greater in patients who developed dyspnea compared with those who did not ($P < .01$), whereas no difference was observed for absolute SPAP progression ($P = .28$). Onset of dyspnea was associated with a high increase of relative SPAP (>90% at 60W, OR 2.31; CI, 1.2–4.8; $P = .02$) but not with the 60 mm Hg peak SPAP threshold (OR 1.3; CI, 0.7–43.1; $P = .40$).

Conclusion: DE reveals symptoms in 46% of patients who are considered asymptomatic. Despite similar peak values, these patients have different hemodynamic parameters during the first level of exercise compared with patients remaining asymptomatic. This may lead to the integration of early hemodynamic changes in the evaluation of exercise tolerance. (J Am Soc Echocardiogr 2011;24:392-8.)

Keywords: Asymptomatic, Exercise echocardiography, Mean transmitral gradient, Mitral stenosis, Systolic pulmonary pressure

In mitral stenosis (MS), indications for intervention, especially percutaneous mitral commissurotomy (PMC), are usually based on the degree of severity of MS and functional status.[1] Although intervention is clearly indicated in symptomatic patients with moderate to severe MS (valve area <1.5 cm^2), decision-making is more difficult in patients with no, or equivocal, symptoms.

According to the American College of Cardiology/American Heart Association guidelines, intervention is recommended in asymptomatic patients with a mean mitral gradient (MG) >15 mm Hg during exercise and systolic pulmonary artery pressure (SPAP) >60 mm Hg at peak exercise.[1,2] However, the additional value of peak hemodynamic parameters over exercise-induced symptoms for decision-making remains controversial.[3] Furthermore, no study has analyzed the pattern of progression of hemodynamic variables at each level of effort and its potential additional value in tolerance evaluation. These uncertainties led us to design the present study and to analyze the relationship between the pattern of progression of hemodynamic variables during exercise Doppler echocardiography (DE) and the onset of dyspnea in a group of asymptomatic patients with significant MS.

MATERIALS AND METHODS

Study Population

Patients were prospectively enrolled if they (1) claimed to be asymptomatic; (2) had moderate to severe predominant MS (defined as mitral valve area [MVA] ≤1.5 cm^2); and (3) were evaluated using semi-supine DE. Exclusion criteria were associated moderate to severe and severe mitral regurgitation (grade >2/4); concomitant significant aortic valve, congenital, or pericardial disease; previous valve repair or replacement; and inability to execute bicycle stress testing. All patients gave informed consent for the study.

Echocardiography

At baseline, all patients underwent a comprehensive Doppler echocardiographic study. Two-dimensional echocardiographic measurements included assessment of valve morphology, especially pliability of the anterior leaflet, presence of calcification, degree of commissural fusion, and subvalvular involvement. Mitral valve score was calculated according to the Wilkins score[4] and Cormier's score[5] (Table 1). MVA was

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Abbreviations

AV = Atrioventricular

DE = Doppler echocardiography

MG = Mitral gradient

MS = Mitral stenosis

MVA = Mitral valve area

PMC = Percutaneous mitral commissurotomy

SPAP = Systolic pulmonary artery pressure

assessed using two-dimensional planimetry method in the parasternal short-axis view, with the inclusion of the intercommissural space when a commissure was still open.[5] MVA was also assessed by Doppler using the pressure half-time method.[6] Doppler recordings of transmitral velocities allowed measurement of mean transmitral gradient (mean MG).

SPAP was calculated from the tricuspid regurgitant jet velocity by the modified Bernoulli equation, assuming a right atrial pressure of 10 mm Hg.[7]

To take into account the pattern of SPAP progression, we defined relative SPAP at each level of exercise expressed as a percentage of resting SPAP.

Net atrioventricular (AV) compliance[8] was calculated from the deceleration rate of the mitral velocity profile (E-wave downslope) and effective MVA, determined by quantitative Doppler based on the continuity equation with measurement of transmitral velocity-time integral and aortic stroke volume. As demonstrated in earlier studies, AV compliance = 1270 (MVA/E-wave downslope) where AV compliance is expressed in cm^3/mm Hg if MVA is expressed in cm^2 and the E-wave downslope in cm/s^2.[7]

Of note for each measurement, three cardiac cycles were averaged in sinus rhythm and in patients with atrial fibrillation at least five consecutive cardiac cycles, representing the mean heart rate, were averaged and used for further calculations.

Exercise Protocol

All patients underwent symptom-limited bicycle exercise Doppler study in a semi-supine left lateral position on a tilting exercise table, with the table tilted up 45 degrees in the left lateral decubitus position, which allows the recording of Doppler measurement during the test.[9,10] The initial workload was set at 20W, and exercise intensity was increased by 20W every 3 minutes. In each case, patients were encouraged to perform maximal exercise. Exercise was continued until patients developed symptoms (significant dyspnea, leg fatigue, or exhaustion). According to the type of symptoms, patients were categorized as symptomatic for dyspnea or asymptomatic (without dyspnea during the test). Patients were considered as developing significant dyspnea if breathlessness occurred at low-level exercise, increased during the test, and led us to stop exercise. Conversely, we did not consider patients with only mild dyspnea at peak exercise as symptomatic, which resolved rapidly during the recovery phase. Peak exercise was defined as maximum work load achieved.

Doppler parameters (mean MG, SPAP, and relative SPAP) were recorded during the last 30 seconds of each level of exercise and at peak exercise. Heart rate, blood pressure, and electrocardiogram were monitored continuously during exercise. Of note, beta-blockers were interrupted a few hours before the test except for patients in atrial fibrillation.

Therapeutic Decisions

The therapeutic decisions included medical follow-up, PMC, or referral to surgery. They were mainly based on the onset of dyspnea during exercise[3] and collected prospectively.

Table 1 Assessment of mitral valve anatomy according to the cormier score[5]

Three echocardiographic groups are defined:
- Group 1 Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e., thin chordae ≥10 mm long)
- Group 2 Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e., thickened chordae <10 mm long)
- Group 3 Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

Statistical Analysis

Quantitative variables were expressed as mean ± SD, or percentage. Comparisons of clinical and echocardiographic characteristics at baseline and at peak exercise between patients who developed dyspnea or remained asymptomatic during exercise used Student *t* test or chi-square as appropriate. Univariate associations of baseline characteristics with occurrence of dyspnea during exercise were tested with logistic regression.

Multivariate logistic regressions were performed to define baseline independent determinant of dyspnea during exercise.

Comparisons of progression of mean gradient, absolute SPAP, and relative SPAP values between groups used analysis of variance for repeated measures at each level of exercise. To ensure the maximum number of patients in the models, we chose to analyze the progression of hemodynamic parameters at low level, until 60W, which was reached in 84% of cases. To analyze the impact of heart rate increase on MG and SPAP progression, we compared the progression of MG and SPAP in patients with a high increase in heart rate as defined by peak heart rate − rest heart rate above the median value of 60 beats/min, and those with a low increase in heart rate defined by peak heart rate − rest heart rate below the median value of 60 beats/min.

To account for the pattern of SPAP progression, we looked at the relative increase in SPAP at 60W (mean relative increase 87% ± 40%). Two categories were defined: high increase (≥90%) for values above the mean and low increase (<90%) for values below the mean. The odds of the occurrence of dyspnea or referral to intervention were calculated using logistic regression for the high increase group. With logistic regression, we also calculated the odds of occurrence of dyspnea and referral to intervention associated with SPAP ≥60 mm Hg at peak exercise. In addition, the association between rest SPAP and relative SPAP was tested using linear regression analysis. To take into account the potential difficulties of obtaining reproducible measurements in case of atrial fibrillation, we defined a subgroup of patients in sinus rhythm only and re-performed the analyses in this subgroup. A P value $< .05$ was considered significant.

RESULTS

Patient Characteristics

A total of 48 patients (mean age 51 ± 14 years, 33% were male) were enrolled in the study. Atrial fibrillation was recorded in only eight patients (17%). Patient characteristics are listed in Table 2. Overall MVA was 1.22 ± 0.16 cm^2, and mean MG was 7 ± 2 mm Hg. Resting SPAP ranged from 23 to 45 mm Hg. Thirty-two patients (67%) had undergone previous PMC. Cormier's score was 2 in 20 patients (42%) and 3 in 28 patients (58%), and Wilkins score was 8.7 ± 2.3 overall. Twenty-seven patients (56%) were taking beta-blocking agents.

For stress data, mean exercise time was 10 ± 4 minutes. Maximum work load was 40W in 6 patients (12%), 60W in 19 patients (40%),