Dobutamine Stress Echocardiography for Noninvasive Assessment and Risk Stratification of Patients With Rheumatic Mitral Stenosis

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OBJECTIVES

We sought to evaluate the impact of dobutamine stress echocardiography (DSE) in patients with known rheumatic mitral stenosis (MS) in order to assess its safety, feasibility, and prognostic correlation to well-known clinical outcomes.

BACKGROUND

Noninvasive prognostic assessment of MS still represents an unresolved task in patients with clinically challenging disease.

METHODS

Dobutamine stress echocardiography was performed in 53 patients with MS (8 males; age 37.4 ± 11.3 years) with no major complications.

RESULTS

During follow-up (60.5 ± 11.0 months), 29 patients presented with clinical events: 16 hospitalizations, seven cases of acute pulmonary edema, and six symptomatic supraventricular arrhythmias. On multivariate analysis, the diastolic mitral valve mean gradient at peak DSE (DSE-MG) was the best predictor of clinical events (p = 0.008), especially in patients with moderate disease (p = 0.001). The best performance of DSE for the detection of clinical events was obtained at a cut-off value of 18 mm Hg DSE-MG (sensitivity 90%, specificity 87%, and accuracy 90%). The addition of DSE to the conventional cardiology work-up would allow a 17% increment for the detection of high-risk patients in the entire population and a 40% increment in patients with presumed moderate disease.

CONCLUSIONS

In patients with MS, DSE is a safe and highly feasible stress test. A DSE-MG ≥18 mm Hg identifies a subgroup of high-risk patients in whom a more aggressive approach may be warranted; on the other hand, patients with a DSE-MG <18 mm Hg predicts an uneventful clinical course and may justify a more conservative strategy. (J Am Coll Cardiol 2004;43:393–401) © 2004 by the American College of Cardiology Foundation

Management of patients with mitral stenosis (MS) is determined by the severity of the impending obstruction. In some patients, functional significance of a given obstruction may be difficult to establish. Management of patients with dyspnea and evidence of mild to moderate MS may present a major challenge, especially if other illness or complications are present (1–10). Despite recent advances in Doppler echocardiographic techniques and imaging quality, rest Doppler echocardiographic data may underestimate the real hemodynamic compromise of a given mitral inflow obstruction in some clinical scenarios (2,10–15). Thus, provocative tests to elicit the real hemodynamic burden and to establish a causal relationship with symptoms are attractive and may help manage clinically challenging patients (3,7–9).

Dobutamine stress echocardiography (DSE) is a well-known cardiovascular diagnostic technique commonly used to assess the extent, location, and severity of coronary artery disease (CAD) (16–18). Despite its versatility, only few studies have focused on the role of DSE in patients with MS (19,20), usually including patients with mild and/or moderate disease. Furthermore, no blinded follow-up data are available in patients with MS who had been submitted to DSE. Thus, the true prognostic information, feasibility, and safety of DSE for a given degree of mitral inflow obstruction remain to be established.

The purpose of the present study was to assess the usefulness of DSE in patients with MS and to determine its safety and feasibility, as well as to correlate DSE findings with clinical outcome, thus establishing its prognostic value.

METHODS

Patient selection. Between 1995 and 1998, 74 consecutive patients with known MS were prospectively evaluated. The protocol was approved by the Institutional Review Board Committee of Socor and Vera Cruz Hospitals, and all patients gave written, informed consent before stress testing. Mitral stenosis was defined by the presence of a reduced mitral valve orifice area (MVA), with characteristic echocardiographic features of rheumatic heart valve disease in the setting of a history of rheumatic fever. Patients were excluded if any other significant valvar involvement was...
identified by Doppler echocardiography with color flow mapping. Thus, patients with MS were not considered for the study if more than mild mitral regurgitation (MR) or tricuspid regurgitation (TR) were identified at baseline. Twenty-one potentially eligible patients were excluded because of the patient’s or physician’s refusal to participate (n = 6), New York Heart Association (NYHA) functional class IV (n = 5), pregnancy (n = 3), life-threatening medical conditions (n = 2), known episodes of tachyarrhythmias associated with hemodynamic instability precluding dobutamine infusion (n = 2), overt endocarditis (n = 2), and technical limitations on the measurement of MVA (n = 1).

Two-dimensional echocardiography. An ultrasound imaging system (Sonos 2000, Hewlett-Packard, Andover, Massachusetts) was used for imaging and Doppler studies, using 2.5- to 3.5-MHz transducers. Chamber dimensions and MVA by planimetry were measured according to standard techniques (21). Left ventricular (LV) ejection fraction was calculated by the area-length method, using combined orthogonal apical four- and two-chamber views (22,23). Flow velocity across the mitral valve, aortic, and tricuspid valve was obtained by continuous-wave Doppler echocardiography in the four-chamber view and Doppler-derived peak and mean diastolic mitral gradients and diastolic mitral flow (ml/s of diastole), and TR velocity was calculated using a computerized off-line system.

Protocol for DSE. The DSE protocol was developed from previously published studies (16,18,24). Patients were advised to not stop any medications before the test, including beta-adrenergic antagonists. After obtaining a 12-lead electrocardiogram (ECG) at rest, dobutamine was administered intravenously by a continuous infusion pump, starting at 10 µg/kg/min for 5 min. The infusion rate was then increased by 10 µg/kg/min every 3 min to a maximum of 40 µg/kg/min. Throughout the test, the 12-lead ECG, transcutaneous oximetry, and vital signs were monitored continuously and recorded at the end of each dose. The two-dimensional echocardiogram and Doppler images (color flow mapping, pulsed and continuous wave) of mitral and tricuspid inflow were continuously monitored and recorded on videotape during the last 20 s of each dose for an off-line analysis. End points were predefined as a maximum protocol dose, heart rate >75% of the age-adjusted maximum heart rate, dyspnea, or a mean diastolic mitral valve gradient at peak DSE (DSE-MG) ≥25 mm Hg obtained at any dose. If major collateral effects and/or symptoms, such as severe hypertension, hypotension, symptomatic arrhythmias, severe nausea, or vomiting developed, the examination would be interrupted, even if the end points had not been reached. A 5-min post-infusion time was allowed for recovery to the basal hemodynamic condition. Off-line assessment of two-dimensional and Doppler images was performed by two investigators who were aware of the dose of dobutamine that had been used, but who were blinded to clinical data.

To assess intra- and inter-observer variability for interpretation of Doppler echocardiographic data obtained at rest and during DSE, a random sample of 20 patients was selected according to a systematic sample framework to represent a broad range of mitral valve orifice reduction. Two independent observers measured all echocardiographic M-mode and Doppler recordings at rest and during each dose of dobutamine infusion.

Follow-up. Follow-up data were obtained by an independent observer and updated at three-month intervals by review of medical records, clinical appointments, or telephone interviews. The physician who obtained the follow-up data and the attending cardiologist were both blinded to the results of DSE, because, at that time, the test was still considered investigational for patients with MS. Therefore, any clinical decision during the follow-up period was made without knowledge of the results obtained by DSE. Patients were carefully monitored for evidence of development of clinical end points, defined as: 1) hospitalization for progressive dyspnea, overt pulmonary edema, or complications associated with mitral valve disease; 2) mitral valve interventions (surgical or percutaneous balloon mitral commissurotomy, mitral valve replacement), as indicated by the attending cardiologist using conventional work-up; 3) atrial and/or ventricular arrhythmias associated with hemodynamic instability requiring hospitalization and/or urgent cardioversion; and 4) death.

Statistical analysis. Data are expressed as the mean value ± SD for continuous variables and as the frequency (%) for categorical variables. Differences between groups were analyzed using the unpaired Student t test or Mann-Whitney U test, and categorical data were evaluated by the Fisher exact test. Kaplan-Meier life-table estimates of spontaneously occurring event-free outcomes were used to summarize the follow-up experience of these patients. The capability of certain variables to predict subsequent outcome was assessed by the Cox proportional hazard model (SPSS for Windows 95). To determine the incremental value of DSE, the best model including clinical and rest two-dimensional echocardiography variables was compared with the best model including DSE variables. Receiver-operating
characteristics (ROC) analysis was adopted to determine the optimal positivity criterion for prediction of clinical events with respect to Doppler echocardiographic variables obtained at peak dobutamine infusion. The best cut-off point was identified as the point with the highest sum of sensitivity and specificity.

RESULTS

Study group. The study group consisted of 53 patients (45 females and 8 males; mean age 37.4 ± 11.3 years [range 18 to 60]) whose characteristics are listed in Table 1. Nine patients (17%) were in NYHA class III, 23 (43%) in class II, and 21 patients (40%) in class I. Thirty-one patients (58%) had a previous mitral valve commissurotomy. Sixteen patients were on beta-blockers at the time of DSE. In 13 patients (10 females), MVA was <1.0 cm²; in 22 patients (19 females), MVA was between 1.0 and 1.5 cm²; and in 18 patients (16 females), MVA was >1.5 cm². Five patients with inclusion criteria had chronic stable atrial fibrillation (AF) and were included in the study group.

Dobutamine stress echocardiography. Dobutamine was infused to a mean peak dose of 29 ± 8 μg/kg/min. The heart rate increased from a mean of 73 ± 12 beats/min at rest to 118 ± 22 beats/min at peak dose (p < 0.0001), and systolic blood pressure increased from 135 ± 19 to 167 ± 22 mm Hg (p < 0.0005). In all patients, at least a minimum dobutamine dose of 10 μg/kg/min was used; in 50 patients, a dose of 20 μg/kg/min was reached; and 37 patients completed the dose of 30 μg/kg/min and 11 completed the full proposed protocol (40 μg/kg/min infusion dobutamine dose). Predefined end points were achieved in 43 patients, including the five patients with chronic AF. Eight of the 10 patients in whom predefined end points were not achieved had the test interrupted at the completion of 30 μg/kg/min dobutamine infusion. Side effects precluding continuity of DSE infusion included arrhythmias (n = 2), hypotension (n = 2), anxiety (n = 1), and light-headedness and/or dizziness (n = 2). Chronotropic incompetence was observed in five patients, all on beta-adrenergic antagonist therapy. Among these two patients, two achieved predefined end points during DSE. Patients on beta-adrenergic antagonist therapy elicited a blunted heart rate response to dobutamine infusion (100 ± 27 vs. 125 ± 14 beats/min, p < 0.0001). No myocardial segments were found to have an abnormal wall motion response to dobutamine infusion.

Because of exclusion criteria, TR was observed in only 17 patients (32%), being mild in all. For the same reason, mild MR occurred in 22 patients (41%). All but three had a significant decrease of the Doppler signal of TR and MR during DSE.

Inter-observer variability. In 20 randomly selected tests, rest two-dimensional Doppler echocardiography and DSE were reviewed for assessment of inter-observer variability. There was an excellent agreement between the two independent observers in the assessment of MVA (kappa = 0.91, 95% confidence interval [CI] 0.86 to 0.95) and the mean diastolic mitral gradient at rest (kappa = 0.90, 95% CI 0.87 to 0.94) and at peak dobutamine infusion (kappa = 0.87, 95% CI 0.81 to 0.92). Over 90% agreement between the two observers (kappa >0.83) was also obtained for all measurements and Doppler calculations. Both observers had 100% agreement on wall motion interpretation both at rest and during DSE.

Clinical-morphologic dissociation. Overall, we identified 21 patients in NYHA class I (17 of them had a previous mitral commissurotomy). The clinical examination indicated mild disease in 17. After adding rest Doppler echocardiographic data, attending cardiologists changed their minds about five patients who were in NYHA class I: four patients had moderate disease with a mean diastolic mitral gradient of >10 mm Hg and one had MVA <1.0 cm² and a mean diastolic mitral gradient of 8 mm Hg. As for the 23

Table 1. Clinical and Rest Echocardiographic Characteristics Among 53 Patients Submitted to Dobutamine Stress Echocardiography According to the Mitral Valve Orifice Area Measured at Rest

<table>
<thead>
<tr>
<th>Mitral Valve Orifice Area</th>
<th>&lt;1.0 cm² (n = 13)</th>
<th>1.0–1.5 cm² (n = 22)</th>
<th>&gt;1.5 cm² (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>35.2 ± 12.6</td>
<td>39.0 ± 11.1</td>
<td>36.0 ± 10.5</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>71</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>NYHA class I/II/III (%)</td>
<td>1/6/6</td>
<td>6/13/3</td>
<td>14/4/0</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3 (23%)</td>
<td>1 (5%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Mitral commissurotomy (%)</td>
<td>36</td>
<td>44</td>
<td>85</td>
</tr>
<tr>
<td>Beta-blocker therapy (%)</td>
<td>36</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>MVA (cm²)</td>
<td>0.8 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>48.0 ± 7.9</td>
<td>45.7 ± 5.6</td>
<td>43.4 ± 5.9</td>
</tr>
<tr>
<td>Peak gradient* (mm Hg)</td>
<td>23.5 ± 9.1</td>
<td>17.2 ± 4.2</td>
<td>11.1 ± 4.7</td>
</tr>
<tr>
<td>Mean gradient* (mm Hg)</td>
<td>13.5 ± 4.5</td>
<td>9.1 ± 0.2</td>
<td>5.5 ± 2.6</td>
</tr>
<tr>
<td>Mitral flow* (ml/s)</td>
<td>146.7 ± 38.4</td>
<td>178.1 ± 27.8</td>
<td>231.0 ± 58.1</td>
</tr>
</tbody>
</table>

*Of the diastolic mitral valve. Data are presented as the mean value ± SD, number (%) of patients, or frequency.

MVA = mitral valve orifice area; NYHA = New York Heart Association.
patients in NYHA class II, 10 were considered to have mild disease by clinical examination. The subgroup with moderate MS by Doppler echocardiographic criteria (n = 22) is the most heterogeneous in terms of NYHA class (8 patients in NYHA class I, 10 in class II, and 4 in class III).

Follow-up data. Patients were followed up to 73 months (mean 61 ± 11), and no death was observed during the follow-up period. Twenty-nine patients (55%) presented clinical events at follow-up. Sixteen patients were hospitalized due to progressive dyspnea, seven developed acute pulmonary edema, and the remaining six were admitted to the emergency care unit with supraventricular arrhythmias and hemodynamic instability. In this subgroup, 21 patients (72%) were submitted to mitral valve intervention at their clinician’s discretion. The remaining eight patients who did not undergo mitral valve intervention had significant clinical deterioration, despite intensive medical treatment. Four of these patients refused mitral valve intervention. The other four patients (acute pulmonary edema [n =1], progressive pulmonary hypertension by serial Doppler echocardiography [n = 3]) were still being followed by their attending cardiologist at last follow-up. Mitral valve intervention had been indicated for all patients in NYHA class III and in all but three patients with MVA <1.0 cm² after initial evaluation by their attending cardiologist.

No difference was found in peak dobutamine dose and heart rate response during dobutamine infusion between patients with and without clinical events during the follow-up period (27.1 ± 8.1 vs. 30.8 ± 7.2 μg/kg/min, p = 0.09 and 115.5 ± 24.6 vs. 121.3 ± 18.2 beats/min, p = 0.35, respectively), nor for patients with stable chronic AF versus sinus rhythm (127.7 vs. 117.2 beats/min, p = NS). Performance of DSE was also similar for both groups, with an average peak dobutamine dose of 24.0 μg/kg/min for patients with AF and 29.3 μg/kg/min for patients in sinus rhythm (p = NS).

Follow-up of the NYHA class I subgroup demonstrated clinical events in six patients thought to have moderate disease on the conventional cardiology work-up. All of them had been considered to have hemodynamically severe MS by DSE. Among 21 patients in NYHA class II, clinically important events were found in 15 (7 thought to have moderate MS by clinical findings and severe MS by DSE). In the subgroup of patients considered to have moderate MS (n = 22), all patients who presented with clinical events had a DSE profile compatible with severe MS.

Predictors of clinical events. Univariate predictors of clinical events at follow-up are shown in Table 2. Multivariate analysis identified the MVA and DSE-MG as independent predictors of clinical events (Table 3). Because patients with MVA <1.0 cm² are already known to have a poor prognosis if left untreated, we performed a multivariate analysis excluding this subgroup. For patients with an MVA >1.0 cm², the DSE-MG and diastolic mitral valve flow obtained at rest Doppler echocardiography (ml/s) were independent predictors of clinical events (Table 4). The correlation between the DSE-MG and clinical events at follow-up is shown in Figure 1. A marked increment in the mean diastolic mitral gradient, associated with a mild increase in diastolic mitral flow, was observed in patients presenting with clinical events at follow-up.

Defining normality of DSE. The diagnostic performance of DSE in this population was evaluated according to the presence or absence of predefined clinical end points during follow-up. The DSE-MG was tested according to its ability

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Events</th>
<th>Events</th>
<th>Student t Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>38.0 ± 11.2</td>
<td>36.9 ± 11.7</td>
<td>0.421</td>
<td>0.676</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.4 ± 0.6</td>
<td>2.0 ± 0.7</td>
<td>†</td>
<td>0.005</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>43.4 ± 5.9</td>
<td>47.4 ± 6.3</td>
<td>‑2.359</td>
<td>0.024</td>
</tr>
<tr>
<td>Mitral valve orifice area (cm²)</td>
<td>2.1 ± 0.5</td>
<td>1.0 ± 0.2</td>
<td>9.476</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak diastolic mitral gradient at rest (mm Hg)</td>
<td>12.0 ± 5.0</td>
<td>20.5 ± 7.7</td>
<td>‑4.595</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean diastolic mitral gradient at rest (mm Hg)</td>
<td>5.9 ± 2.7</td>
<td>11.6 ± 4.0</td>
<td>‑5.732</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic mitral valve flow at rest (ml/s)</td>
<td>225.4 ± 54.6</td>
<td>161.2 ± 37.0</td>
<td>4.789</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak dobutamine infusion (μg/kg per min)</td>
<td>30.8 ± 7.2</td>
<td>27.1 ± 8.1</td>
<td>‡</td>
<td>0.066</td>
</tr>
<tr>
<td>DSE peak diastolic mitral valve gradient (mm Hg)</td>
<td>20.2 ± 8.6</td>
<td>39.9 ± 9.9</td>
<td>‑7.649</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DSE mean diastolic mitral valve gradient (mm Hg)</td>
<td>10.8 ± 5.0</td>
<td>24.4 ± 6.8</td>
<td>‑8.358</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DSE diastolic mitral valve flow (ml/s)</td>
<td>304.2 ± 67.4</td>
<td>228.5 ± 53.6</td>
<td>4.511</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Dependent variable: clinical events at follow-up. †Fisher exact test. ‡z = 0.066 (Mann-Whitney U test). Data presented as the mean value ± SD.

DSE = dobutamine stress echocardiography; NYHA = New York Heart Association.

Table 3. Multivariate Analysis of Clinical and Doppler Echocardiographic Variables* Obtained at Rest and During Maximal Dobutamine Infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>ET</th>
<th>Wald</th>
<th>Slg. p Value</th>
<th>Exp (beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve area (cm²)</td>
<td>−4.29</td>
<td>0.81</td>
<td>27.76</td>
<td>&gt;0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td>DSE-MG (mm Hg)</td>
<td>0.05</td>
<td>0.03</td>
<td>6.10</td>
<td>0.014</td>
<td>1.05</td>
</tr>
</tbody>
</table>

*Dependent variable: clinical events at follow-up. Multivariate analysis was performed using the Cox model including all patients (n = 53). Variables included in this model: at rest—NYHA class, left atrium, peak and mean diastolic mitral valve gradients, and diastolic mitral valve flow (ml/segment); at peak DSE—mean and mean diastolic mitral valve, and diastolic mitral valve flow (ml/s).

DSE-MG = mean diastolic mitral valve gradient at peak dobutamine stress echocardiography.
to identify clinical events, as demonstrated by multivariate analysis. Sensitivity and specificity of DSE were determined considering hypothetical cut-off values for positivity, ranging from 10 to 22 mm Hg. A mean diastolic mitral gradient of 18 mm Hg was identified as the best cut-off point (Fig. 2). All but two patients who presented with clinical endpoints at follow-up had been correctly classified by DSE as high-risk patients. Conversely, two patients classified as high risk by DSE did not show any of the predefined clinical events. The definition of normality of DSE in this population was also tested using ROC curve analysis. A DSE-MG cut-off of 18 mm Hg was identified as having the best accuracy for prediction of clinical events in this series.

Outcome. The actual event rates observed in this study group were stratified by DSE, considering the cut-off point of 18 mm Hg. Patients with a DSE-MG value ≥18 mm Hg showed a higher incidence of clinical events than did those with a mean gradient <18 mm Hg (Fig. 3).

Incremental value of DSE. Considering the results of DSE in this population and the incidence of clinical events at follow-up, the incremental prognostic value of this technique over conventional clinical evaluation and rest Doppler echocardiographic data could be derived. Clinical and rest Doppler echocardiographic data, particularly MVA obtained by planimetry, showed good prognostic information. However, the addition of the DSE-MG provided significant incremental power over clinical and rest Doppler echocardiographic data, allowing for the detection of 17% additional cases, considering all patients submitted to DSE (n = 53; p < 0.008).

Overall data show variable performance of DSE in the detection of patients at a high risk for clinical events during follow-up, when considering subgroups based on the standard clinical work-up (clinical and baseline Doppler echocardiographic data). Dobutamine stress echocardiography adds no incremental prognostic information over a standard clinical work-up for patients with MVA <1.0 cm², as both methods correctly identify patients in whom more aggressive management is warranted. However, in patients with MVA >1.0 cm², DSE has consistently demonstrated incremental prognostic power, compared with classic cardiac evaluation, correctly classifying an additional 22% of patients in this subgroup (n = 40) as high-risk (p = 0.003). Indeed, the best performance of DSE for the identification of high-risk patients was observed in the subgroup with MVA between 1.0 and 1.5 cm², detecting, in this series of selected patients, an overall diagnostic increment of 40% (conventional evaluation [n = 5] and DSE [n = 13]), indicating that eight new cases were correctly classified as hemodynamically severe disease by DSE [n = 22]; p < 0.001). For patients with MVA >1.5 cm², the test has shown only a small increment in prognostic power (5% additional cases detected; p = NS).

**DISCUSSION**

To the best of our knowledge, this study was the first to compare data obtained during DSE in patients with rheumatic MS and try to associate these variables with the clinical outcome obtained by strict observation of clinical events during long-term follow-up. Because DSE was an investigational tool at the time of this study, the results were not available to the attending cardiologist and thus did not interfere with patient management. Clinical decisions in this group were made by the attending physicians, based solely on well-established strategies, ranging from clinical examination to invasive hemodynamic assessment of mitral valve obstruction.

The present study demonstrated that DSE is a safe and

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**Table 4. Multivariate Analysis of Clinical and Doppler Echocardiographic Variables* Obtained at Rest and During Maximal Dobutamine Infusion in Patients With a Mitral Valve Area >1.0 cm²**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>ET</th>
<th>Wald</th>
<th>p Value</th>
<th>Exp (beta) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSE-MG</td>
<td>-0.037</td>
<td>0.071</td>
<td>13.43</td>
<td>&gt;0.0001</td>
<td>1.29 (1.12–1.49)</td>
</tr>
<tr>
<td>Rest diastolic mitral valve flow (ml/s)</td>
<td>0.261</td>
<td>0.013</td>
<td>8.63</td>
<td>0.003</td>
<td>0.96 (0.94–0.98)</td>
</tr>
</tbody>
</table>

*Dependent variable: clinical events at follow-up. Multivariate analysis was performed using the Cox model for patients with mitral valve area >1.0 cm² (n = 40). Same variables presented in Table 3 were included in this model.

CI = confidence interval; DSE-MG = mean diastolic mitral gradient at peak dobutamine stress echocardiography.

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**Figure 1.** Correlation between mean diastolic mitral valve (MV) gradient (mm Hg) and MV flow (ml/s) in 53 patients with rheumatic mitral stenosis and clinical events (dashed lines) and in patients without clinical events (solid lines). Data were obtained at rest and during peak dobutamine stress echocardiography.
feasible stress technique in patients with rheumatic MS in NYHA classes I, II, and III, regardless of the MVA obtained at rest Doppler echocardiography. Patients had a low incidence of side effects, and no major complications were observed, even in patients with a small MVA. Moreover, the results of the present study also support the concept that DSE is useful for risk stratification of patients with rheumatic MS. The absolute increase in the DSE-MG allowed identification of subgroups with a high or low incidence of significant clinical events at follow-up. In particular, a DSE-MG ≥18 mm Hg was found to have a sensitivity of 90%, specificity of 87%, and overall accuracy of 90% for detection of clinical events at follow-up.

Although symptoms of dyspnea, fatigue, and elevated rest pulmonary artery pressures in the setting of severe valvular obstruction are generally accepted as indications for surgical intervention, similar symptoms in patients with only mild or moderate obstruction represent a more challenging situation. Severe valvular obstruction without symptoms represents a somewhat unexpected finding. Symptoms may develop insidiously, allowing patients to adapt to their limitations by self-restricting physical activities and making it difficult for the patient to have a clear perception of developing symptoms (25). On the other hand, the converse might be observed for patients with mild MS in whom symptoms may not have a direct association with documented obstruction.

Clinical-morphologic dissociation. Discrepancies between presumed NYHA functional class and planimetered MVA (clinical-morphologic dissociation) account for up to 30% of patients with MS. These discrepancies, also demonstrated in this series, are responsible for the broad interfaces among the various phases of the natural history of MS (2,10,26). Establishing a causal relationship between impending obstruction and symptoms may be necessary in such cases in order to provide adequate data to support

Figure 2. Sensitivity, specificity, and accuracy of dobutamine stress echocardiography (DSE) for prediction of clinical events during follow-up of patients with rheumatic mitral stenosis (variable adopted: DSE-mean diastolic mitral valve gradient).

Figure 3. Kaplan-Meier product-moment event rates in patients with mitral stenosis. The cut-off point (18 mm Hg) was derived from the obtained performance of the test according to the presence or absence of clinical events during follow-up.
mitral valve interventions. Because of its proven ability to elicit significant stress to the cardiovascular system, DSE appears to be a particularly useful stress technique, which may be comparable to exercise, and allows for the detection of important changes in the adaptative rest hemodynamics in these patients. It also discloses severe hemodynamic obstruction in a patient classified, by the use of more conventional clinical and noninvasive strategies, as having moderate or even mild MS.

**Prognostic impact of DSE in patients with rheumatic MS.** Natural history studies have pointed out the high rate of significant clinical events in patients with MS (11,27). Thus, correct estimation of the hemodynamic burden of a given MS might optimize clinical management and provide an indication for mitral valve intervention at a more appropriate time, before clinical complications ensue. Furthermore, DSE may help estimate this time window owing to its ability to correctly identify a subgroup of patients with hemodynamic severe mitral valve inflow compromise, independent of MVA, who may present with significant clinical complications at follow-up.

Patients with presumed moderate disease were found to have the strongest prognostic benefit from DSE, as the test allowed the detection of 40% more patients in this particular subgroup, increasing the performance of detecting potentially high-risk patients in whom a more aggressive approach is recommended. Thus, in this series, DSE would have had a direct influence on patient management, including the decision to proceed with or delay mitral valve intervention, if the results had been available to the attending cardiologist. Also, patients with clinical-morphologic dissociation may particularly benefit from DSE, as it may help clarify whether symptoms are related to significant augmentation of gradients across the stenotic mitral valve. As expected, patients with either presumed mild or severe disease may not have a significant benefit from DSE, because, in this series, conventional strategy correctly identified the prognosis in both extremes of hemodynamic burden. Despite the observed safety of the test for these subgroups, the decision to perform DSE in such cases must be carefully evaluated on a risk-benefit basis. The DSE test is especially useful in situations of clinical-morphologic dissociation, if this remains an unresolved question after standard evaluation.

Although only five patients with AF were included in this analysis, the test proved to be useful in this setting. The low percentage of patients with AF in this series can be explained by the fact that patients were relatively younger (most series are composed of older patients with degenerative MS, in whom a higher incidence of AF is expected) and had isolated MS, so massive enlargement of the left atrium (more commonly seen if associated significant MR is present) was not observed.

No segmental wall motion abnormalities were found during DSE infusion in this series. Despite the fact that DSE has established diagnostic prognostic accuracy for the detection of CAD, this is a relatively young group of patients in whom CAD is not expected. Thus, whether DSE has diagnostic utility for the detection of CAD in patients with MS remains to be established.

Dobutamine infusion seems to have advantages over exercise in the setting of mitral valve inflow obstruction. Through its beta1-agonist action, dobutamine increases the heart rate and contractility, with a resultant increase in cardiac output, whereas pulmonary and peripheral vascular resistance may fall due to its beta2-agonist effects (28). The net hemodynamic effect of DSE in patients with MS is similar to that of exercise, but it is associated with lower LV end-diastolic, systolic pulmonary artery, and pulmonary wedge pressures than exercise at similar degrees of hemodynamic stress, as shown by Hwang et al. (20). Perhaps these findings may explain the lower incidence of dyspnea observed during DSE, even in the setting of severe MS.

**Study limitations.** We focused on stable ambulatory patients with MS, without any significant associated valvular disease or myocardial dysfunction. Therefore, the effects of associated valvular disease, especially significant MR, TR, or LV dysfunction, on gradients could not be established. This highly selected population was necessary as a first step to identify the feasibility and effectiveness of DSE without confounding variables, such as associated valvular diseases. Moreover, a somewhat homogeneous group would help make correct assumptions about Doppler echocardiographic data during DSE.

Another potential bias was the use of planimetry as a standard measurement of MVA by echocardiography in this study. Although the mitral valve reaches its maximal excursion in early diastole and can be easily quantified by two-dimensional echocardiography, this might not be the case during stress testing, considering the technical difficulties that may arise (e.g., increasing rotation and translation of the heart during dobutamine infusion, tachycardia, tachypnea), leading to significant variations of measured MVA (29). Calculation of MVA by the continuity equation may represent an average of the instantaneous values throughout diastole and thus a better measurement at rest, but it was not used in the present study because of its limitations during tachycardia. In vitro models have suggested that peak MVA cannot be further increased, but the mean valve area can be enhanced simply by acceleration of the opening and closing phases (30). This may result in an increase of the calculated MVA due to an increase in the contraction coefficient, which is the ratio of effective to anatomic valve areas (31).

Because the test was considered investigational in the early stage of the study, DSE was terminated in some patients who had minor side effects. As the investigators became more comfortable with the protocol, a more aggressive approach was employed throughout the study, without observation of significant side effects. In this series, when early termination of DSE was decided upon, the test still elicited significant changes in the rest hemodynamic profile. However, to increase the diagnostic accuracy of DSE, if no major side effects are observed during dobutamine infusion,
we strongly recommend continuing the test until established end points are reached.

Because, according to established inclusion criteria, patients with more than mild MR or TR were not included, these findings only apply for patients with isolated MS. Furthermore, Doppler detection of mild regurgitation at peak dobutamine was technically demanding in this series, even when using continuous wave, pulsed wave, and color flow mapping. Further studies are needed to address the effect of MR and TR on DSE gradients in patients with predominant MS.

**Clinical implications.** This is the first prospective, long-term, longitudinal study of patients with MS submitted to DSE. Doppler echocardiography data derived from the test were analyzed in agreement with true predefined end points of well-established adverse events identified during prospective long-term follow-up of the entire population. As such, the obtained cut-off point of 18 mm Hg for the DSE-MG does not represent a hypothetical assumption, but a true cut-off point derived from observation of clinical events. It reflects the real hemodynamic burden of a given mitral valve inflow obstruction, with an expected low probability of bias, as attending cardiologists were blinded to the results of DSE for their clinical decisions during follow-up. A representative sample of all degrees of MS was observed, considering the broad range of mitral inflow obstruction present in this population.

Multi-stage DSE was safe and effective, allowing for the detection of different hemodynamic subsets of patients with MS in all values of MVA, ranging from mild to critical stenosis. The protocol used is reproducible, noninvasive, and not time-consuming and can be performed at a low cost. The technique is widely available, and interpretation of the results does not depend on extensive expertise on interpreting the images and Doppler data.

**Conclusions.** Doppler stress echocardiography is a feasible stress-testing technique with a low rate of complications in patients with MS. It seems to offer important information, not only by helping to classify the underlying hemodynamic burden of the impending obstruction, but also by providing data that adequately allow for correct identification of a subgroup of high-risk patients during follow-up, in whom a more aggressive approach should be attempted.

**REFERENCES**


24. Pellikka PA, Roger VL, Oh JK, et al. Stress echocardiography. II: