**PAPER**

Dobutamine stress echocardiography in women with systemic lupus erythematosus: increased occurrence of left ventricular outflow gradient

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Dobutamine stress echocardiography (DSE) is an accurate noninvasive test used for the diagnosis and evaluation of patients with known or suspected coronary artery disease (CAD). The aim of this study was to determine the rate of positive findings in DSE, to define the echocardiographic and clinical characteristics of women with systemic lupus erythematosus (SLE) and to evaluate the safety of DSE in SLE patients. Thirty consecutive SLE patients were enrolled in the study and underwent DSE study. The mean age of patients was 44 years (range 20–76). Mean duration of SLE was 8.1 years and mean SLEDAI was 5.5. None of the DSE tests performed were positive for myocardial ischaemia. A left ventricular outflow gradient (LVOG) was found in 15/28 (54%) patients who completed the test, a result higher than the reported 20% prevalence of this finding in the literature. There were no significant differences in baseline characteristics between patients who developed a gradient and patients in whom a gradient was not found. There were no significant adverse effects during the study. In the general population, LVOG has been reported to be associated with an increased rate of chest discomfort and with a significantly lower prevalence of CAD. Whether this is true for SLE patients requires further study. *Lupus* (2004) 13, 101–104.

**Key words:** dobutamine stress echocardiography; ischaemic heart disease; systemic lupus erythematosus

**Introduction**

Cardiac involvement is common among patients with systemic lupus erythematosus (SLE). All anatomic parts of the heart have been reported to be involved in SLE patients.¹ Valvular abnormalities have been reported in more than 50% of SLE patients.² Coronary artery disease (CAD) contributes significantly to the morbidity and mortality of SLE patients and is related to atherosclerosis, arteritis, antiphospholipid antibodies related thrombosis, embolism, and coronary artery spasm. It develops in SLE patients who are younger and have less traditional risk factors for CAD, than CAD patients without SLE.³ Systemic lupus erythematosus patients are 9–50 times more likely to develop CAD than the general population.⁴

The diagnosis of CAD in women differs from the diagnosis of CAD in men. Chest pain or discomfort characteristic for angina is a less specific marker for ischaemic heart disease in women compared with men.⁵ Electrocardiographic changes, induced by stress testing and indicative of CAD, are believed to be more commonly false-positive in women than in men.⁶ Finally, diagnostic testing for CAD in women demonstrates higher levels of test variability compared with men, possibly due to cycling reproductive hormone levels.⁷

The high prevalence of asymptomatic CAD in SLE patients has led to attempts to find a diagnostic paradigm that will enable early detection of CAD in SLE patients. In one such study, myocardial perfusion imaging was performed in SLE patients; perfusion abnormalities were found in 40% of the patients, the majority of whom had no previous diagnosis of CAD.⁸

Dobutamine stress echocardiogram (DSE) is a relatively novel test in which two-dimensional echocardiographic imaging is performed during the infusion of increasing doses of dobutamine to induce
myocardial stress. This test has been validated in many studies, particularly in the setting of intermediate pre-test probability for CAD. Advantages of stress echocardiography as compared with other stress modalities are the avoidance of ionizing radiation, the increased ability to image cardiac structures and function, and the relatively accurate diagnosis of ischaemia without dependence on ECG changes. Imaging of the heart valves is particularly advantageous in SLE patients who have an increased occurrence of valvular disorders. Limitations of DSE include reduced accuracy for single vessel coronary disease and 50–70% stenotic lesions.

A meta-analysis of exercise testing in women analysed 19 studies on exercise ECG testing, exercise echocardiography, and exercise thallium scans. Stress echocardiography was found to have the highest sensitivity (weighted mean sensitivity 0.86) and specificity (weighted mean specificity 0.79) for women as compared to all other exercise testing modalities. The accuracy of exercise echo is similar for men and women. The prognostic value of DSE in women was demonstrated in a study of 2476 women undergoing DSE; in women with no inducible wall motion abnormalities, cardiovascular event-free survival was 97%.

In the present study we performed an evaluation of the characteristics of female SLE patients undergoing elective DSE studies. A search of the English language literature found no previously published studies of DSE in SLE patients.

Patients and methods

Patients

Thirty consecutive female SLE patients, with no known CAD, attending the lupus clinic were enrolled in the study. All patients fulfilled the American College of Rheumatology (ACR) classification criteria for SLE. Patients with known severe valvular abnormalities or CAD were excluded. Disease activity was evaluated by using the SLE Disease Activity Index (SLEDAI).

Our institute’s ethics committee approved the study and all patients gave their informed consent before participation in the study. Patients treated with beta-adrenergic blockers were required to stop these medications one day prior to the study.

Dobutamine stress echocardiography

Prior to DSE, a regular transthoracic echo was performed according to the American Society of Echocardiography guidelines. Dobutamine stress echocardiography was performed according to a previously described protocol. Blood pressure and a 12-lead ECG were recorded at baseline, at the end of each stage of dobutamine infusion and during recovery. A two-dimensional echo-Doppler was performed in parasternal and apical views at each stage of the protocol. The DSE was to be terminated when 85% of the predicted maximal pulse (calculated as 220 – patient age in years) was reached, if new regional wall motion abnormalities developed accompanied by severe anginal pain, if significant haemodynamic changes, significant arrhythmia, or if significant side effects occurred.

Statistical analysis

All data were analysed with the SPSS statistical package. Continuous variables were compared with the unpaired two-tailed Student \( t \)-test. Categorical variables were compared using the chi-square test. Results were considered significant at \( P < 0.05 \).

Results

Thirty women were enrolled in the study. The mean age of the patients was 44 years (range 20–76), mean duration of SLE was 8.1 ± 6 years and the mean SLEDAI was 5.5 ± 4.4 (range 0–20). Table 1 shows the baseline characteristics of the patients. The main clinical features of the SLE patients, occurring at any time during the SLE disease duration, included: skin rash (73%), butterfly rash (50%), photosensitivity (60%), arthritis (63%), vein thrombosis (6.7%), livedo reticularis (16.6%), lupus nephritis (36.6%), nephrotic syndrome (23.3%), renal failure (20%), and neuro-psychiatric symptoms (10%). Two patients had a history of stroke and one patient had a history of mesenteric vasculitis. The cardiovascular and pulmonary features are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients (n = 30)</th>
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</thead>
<tbody>
<tr>
<td>Age (years) [range]</td>
<td>44 [20–76]</td>
</tr>
<tr>
<td>Duration of SLE (years) [range]</td>
<td>9.4 [1–22]</td>
</tr>
<tr>
<td>SLE disease activity index (score) [range]</td>
<td>5.2 [0–20]</td>
</tr>
<tr>
<td>Cardiovascular risk factors (number) [%]</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 [10%]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 [33%]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8 [26.7%]</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>4 [13.3%]</td>
</tr>
<tr>
<td>Average number of risk factors per patient</td>
<td>0.83</td>
</tr>
<tr>
<td>Antiphospholipid antibodies (number) [%]</td>
<td>15 [50%]</td>
</tr>
<tr>
<td>Cardiovascular and respiratory manifestations of SLE</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>5 [16.7%]</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>6 [20%]</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>2 [6.7%]</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>2 [6.7%]</td>
</tr>
<tr>
<td>Shrinking lung</td>
<td>1 [3.3%]</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1 [3.3%]</td>
</tr>
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</table>
The majority of patients (20/30) had previous complaints of chest pain or effort dyspnea. The average number of conventional risk factors for CAD was 0.83 (range 0–3), the most common of which was hypertension in one-third of the patients. Anti-cardiolipin (IgG or IgM) antibodies were found in 50% of the patients.

Medical treatment included corticosteroids in 75% of the patients; the average dose of prednisone was 12.5mg/day. Additional medications given during the diseases course included chloroquine in 21 of the patients (70%), methotrexate in five patients (16.6%), azathioprine in nine patients (30%), and cyclophosphamide in seven patients (23%). Three patients were treated with warfarin and five patients with aspirin for antiphospholipid syndrome. Pre-existing treatment with beta-adrenergic blocking drugs was stopped prior to performance of DSE in five patients.

Laboratory manifestations included antinuclear antibodies (96.6%), anti-DNA antibodies (76.6%), IgG anti-cardiolipin antibodies (ACL) (50%), and IgM ACL (50%).

Transthoracic echocardiography revealed valvular disorders in 33% of the patients. The majority of these were mitral valve insufficiency. None of the patients in this study were found to have a pericardial effusion.

All the DSE studies were negative for myocardial ischaemia. Left ventricular function was normal in all patients. None of the patients had ventricular hypertrophy or obstructive cardiomyopathy.

A left ventricular outflow gradient (LVOG) developed in 15/28 patients during the infusion of dobutamine. The mean gradient was 46.3mmHg (range 16–109). This gradient resolved in all the patients during the recovery period following the study. The development of LVOG was not associated with symptoms or with a decrease in arterial blood pressure. We found no difference between patients who developed a gradient and patients who did not (Table 2). Since there were no positive DSE, we could not assess whether LVOG was an indication of a lesser likelihood for CAD.

Dobutamine stress echocardiography was not performed in one patient who was found during the initial transthoracic echocardiogram to have previously undiagnosed severe aortic stenosis. An additional patient’s test had to be stopped because she developed significant hypertension. Minor side effects were headache and tremor, which each developed in three patients. Two patients complained of nausea and two of chest discomfort. One patient had mild hypotension at the end of the study.

**Discussion**

Later mortality and morbidity in SLE is largely caused by atherosclerosis. The atherosclerotic process is usually widespread and may affect the aorta, coronary arteries, carotid arteries, cerebral arteries, and femoral arteries. Early detection of CAD allows early intervention and possibly retarding the development of symptomatic cardiovascular disease. Studies using technetium 99m sestamibi single photon emission tomography, have found an increased rate (40%) of positive nuclear scans. However, the findings of coronary angiography may be normal in some of these patients, suggesting a microvascular disease or a high rate of false-positive nuclear scan in women without CAD.

In the present study, there were no positive DSE tests among consecutive SLE patients with no known CAD, despite the large percentage (70%) of patients who complained of chest discomfort or dyspnea prior to testing. Since the sensitivity of DSE in detecting ischaemic lesions is related to the severity of atherosclerosis, radius of the coronary arteries, and number of vessels involved, the data indicate that DSE is not a sensitive tool for detecting early CAD before the development of critical stenosis.

Although signs of ischaemia were not observed in our SLE patient, 54% of the patients developed LVOG during the DSE. The range of the gradient was between 16 and 109mmHg. This rate of LVOG is much higher than the rate of LVOG seen in non-SLE patients at our center and is more than double the reported rate in the general population.

In a large prospective study of non-SLE patients, LVOG developed in 17.5% of 394 consecutive patients undergoing DSE. Among women, LVOG developed in 47/222 women (21.2%). The characteristics associated with the development of LVOG were female gender, history of chest pain, no known history of CAD, and asymmetric septal hypertrophy. Only 2/69 (2.9%) of the patients who developed LVOG had positive DSE for ischaemia as opposed to 100/325 (30.8%) in patients who did not develop LVOG.

Another study, designed to assess the clinical significance of LVOG, assessed 73 patients who underwent DSE, nuclear cardiac scanning, and coronary

**Table 2** Characteristics of patients according to the presence or absence of left ventricle outflow gradient (LVOG)

<table>
<thead>
<tr>
<th></th>
<th>Patients with LVOG (n = 15)</th>
<th>Patients without LVOG (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.7 ± 15.1</td>
<td>39.5 ± 13.3</td>
<td>0.33</td>
</tr>
<tr>
<td>SLE duration</td>
<td>9 ± 6.8</td>
<td>7.4 ± 5.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Presence of chest pain</td>
<td>53%</td>
<td>47%</td>
<td>1</td>
</tr>
<tr>
<td>SLE disease activity index</td>
<td>5.1 ± 2.8</td>
<td>5.6 ± 5.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Antiphospholipid Abs (%)</td>
<td>64.3</td>
<td>40</td>
<td>0.17</td>
</tr>
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</table>

Dobutamine dose reached (mcg/kg/min)

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angiography. The percentage of patients developing LVOG was 21%. These patients had symptoms of chest discomfort induced during the DSE. The coronary angiography of only one of the 16 patients developing LVOG demonstrated coronary artery disease. This patient underwent coronary artery bypass grafting and, following surgery had a DSE that performed again demonstrated LVOG of the same degree. Patients who developed LVOG were treated with beta-adrenergic blocking agents and remained symptom free during a one year follow-up. The authors of the study concluded that development of LVOG during DSE is associated with a significantly decreased prevalence of CAD. They also concluded that the LVOG might be responsible in an unclear mechanism for the symptoms of chest pain and that treatment of this group of patients with beta-adrenergic blocking drugs completely alleviates these symptoms.20

These studies indicate that the development of LVOG during DSE in the general population is associated with a decreased prevalence of CAD. Chest pain in these patients is probably not caused by CAD, and might subside following treatment with beta-adrenergic blocking drugs.

The significance of the high rate of LVOG among SLE patients is not clear. Further research is warranted to assess the possibility that the development of LVOG during DSE is a marker of low risk for CAD in female SLE patients as it has been suggested in the general population. However, the development of LVOG may be the result of other causes. Possible mechanisms include autonomic dysfunction, endothelial dysfunction, impaired heart rate variability, and impaired T2-weighted relaxation time by cardiac magnetic resonance imaging. The role of all these possibilities in the development of LVOG needs to be determined.

The rate of valvular disorders in our study is similar to that found in previous studies, after adjusting for our exclusion of patients with known severe valvular disease.

Conclusions

Female SLE patients are significantly more likely than the general population to develop LVOG during DSE. This increased occurrence of LVOG was found in a population with an increased prevalence of chest pain, and no positive DSE for cardiac ischaemia. The finding of LVOG might be an indicator of a lower prevalence of CAD in this population or it may be associated with other pathological processes seen in SLE. Dobutamine stress echocardiography is safe in female SLE patients.

Further research with a larger group of patients and a longer follow-up period is required to further elucidate the significance of LVOG development in SLE patients.

Acknowledgement

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References