Clinical Relevance of Chest Pain during Dobutamine Stress Echocardiography in Women

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Summary

Background: Dobutamine stress echocardiography (DSE) is commonly used for diagnosis and management of patients with known or suspected coronary artery disease. Chest pain occurring during DSE potentially provides additional diagnostic accuracy. Our experience suggests that chest pain occurs frequently in women undergoing DSE.

Hypothesis: It was the purpose of this study to determine the frequency with which chest pain occurs in women undergoing DSE and the relation to inducible ischemia or coronary artery stenosis.

Methods: To determine the prevalence and clinical significance of chest pain during DSE, we reviewed the records of 154 consecutive women undergoing DSE in our laboratory. Of these, 59 patients (37.5%) also underwent coronary angiography. The presence or absence of chest pain was correlated with ECG changes, left ventricular wall motion abnormalities during DSE, and coronary stenosis by angiography.

Results: Forty-one women (26%) developed chest pain during DSE. Patients experiencing chest pain were older (58.5 ± 9.3 vs. 54.9 ± 12.6 ; $p = 0.05$), and had lower resting heart rates (71 ± 12.2 vs. 77.9 ± 14.9 ; $p = 0.008$), but received similar maximum doses of dobutamine and reached comparable peak heart rates (131.1 ± 17.4 vs. 133.5 ± 21.7 ; $p = \text{NS}$). Patients with chest pain more commonly exhibited ST-segment depression ≥ 1 mm during dobutamine infusion (13/41, 32%, vs. 17/113, 15%; $p = 0.02$), but chest pain showed no statistically significant correlation with abnormal DSE or with coronary stenosis.

Conclusions: In women undergoing DSE, chest pain occurs in 26% and does not appear to be related to inducible myocardial ischemia. Electrocardiographic changes occur more frequently in patients who experience chest pain, but are also often unrelated to inducible myocardial ischemia.

Key words: stress echocardiography, women, coronary artery disease

Introduction

Dobutamine stress echocardiography (DSE) has been employed in large numbers of patients with known or suspected coronary artery disease, with reported sensitivity ranging from 70 to 95% and specificity 85 to 100%.^{1–10} Most studies, however, have been applied to primarily male populations, and the observations may not be strictly applicable to women. In these investigations, chest pain occurring during DSE has been reported in 5 to 28% of subjects. The relation of chest pain to inducible myocardial ischemia, coronary artery disease, and gender are not entirely clear. It was the purpose of this study to determine the frequency with which chest pain occurs in women undergoing DSE and the relation to inducible ischemia or coronary artery stenosis.

Methods

Selection of Study Patients

The records of 154 consecutive women (aged 18–79 years, mean 54 years) undergoing DSE in our laboratory between May 1, 1996, and May 30, 1997, were reviewed. Patients were referred for evaluation of chest pain or other symptoms suspected to be due to coronary artery disease (86%), and as part of evaluation prior to renal (9%) or liver transplantation (5%). No patient had clinical evidence of active pericarditis or other readily identifiable explanation for chest pain.

Echocardiography Protocol

Patients were instructed to fast after midnight prior to testing. In addition, patients were instructed to take all medica-

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tions except beta-adrenergic blockers, but accurate listing of medications taken prior to DSE were not consistently available. Each patient underwent standard DSE with an infusion rate started at 5 mcg/kg/min and increased every 3 min (in 100 patients) or 5 min (in 54 patients who were part of a research project to evaluate ischemic heart disease in women) to a maximum of 40 mcg/kg/min. Atropine 0.25 mg–1.0 mg intravenously was given at the end of the 40 mcg/kg/min dose if target heart rate (i.e., 85% predicted maximum) was not achieved. Images were obtained at baseline, continuously monitored during dobutamine infusion and recovery, and taped on 0.5" videotape. Images at baseline, 5 mcg/kg/min, peak dose, and recovery were also digitized in continuous loop and placed in quad screen format for review and analysis. Analysis was done primarily from the digitized images, and videotape was reviewed only for clarification of findings on the digitized images. Blood pressure and electrocardiogram (ECG) were monitored throughout dobutamine infusion; 12-lead ECG was performed at baseline, at the end of each stage of stress, and at recovery. During DSE, patients were specifically questioned about the presence of precordial discomfort, including substernal heaviness and dull or aching pain. These anginal-type symptoms were systematically recorded.

Cardiac Catheterization

In all, 59 patients underwent cardiac catheterization and coronary angiography at the discretion of their referring physician. Angiograms were interpreted by an experienced interventional cardiologist using visual estimation of luminal stenosis. Coronary disease was categorized as: <50%, ≥50%, and ≥70% luminal diameter stenosis.

Statistical Analysis

Continuous variables are expressed as a mean ± standard deviation (SD). Differences in continuous variables (e.g., age, blood pressures, heart rates) between patients with or without pain were tested using unpaired Student's *t*-test; $p \leq 0.05$ was considered significant. Chi-square analysis was used to test relation of noncontinuous variables between patients with or without chest pain (e.g., inducible myocardial ischemia, ST-segment depression, and coronary stenosis). Statistics were performed using SAS statistical software (SAS Institute, Inc., Cary, N.C., USA).

Results

Dobutamine stress echocardiography was terminated in most patients (74%) after achievement of target heart rate. In the remaining patients, the study was stopped after patients received maximum dose of dobutamine and atropine but did not achieve target heart rate (10%), developed intolerable symptoms (10%), developed obvious new segmental wall motion abnormality (2.5%), experienced a decrease in systolic blood pressure ≥ 20 mmHg from baseline and absolute pressure < 90

TABLE I Hemodynamic responses during dobutamine stress echocardiography among 154 women with or without chest pain

	Chest pain (n = 41)	No chest pain (n = 113)	p Value
Age (years)	58.5 ± 9.3	54.9 ± 2.6	0.05
Baseline HR (beats/min)	71.0 ± 12.2	77.9 ± 14.9	0.008
Baseline SBP (mmHg)	144.0 ± 27.4	145.3 ± 28.0	0.79
Baseline DBP (mmHg)	76.1 ± 14.2	81.7 ± 15.9	0.04
Max Dob Rate (mcg/kg/min)	38.8 ± 4.6	37.1 ± 6.5	0.06
Peak HR (beats/min)	131.1 ± 17.4	133.5 ± 21.7	0.5
Peak SBP (mmHg)	159.8 ± 35.3	156.0 ± 39.2	0.59
Peak DBP (mmHg)	72.5 ± 14.7	75.7 ± 20.2	0.28

Abbreviations: DBP = diastolic blood pressure, SBP = systolic blood pressure, HR = heart rate, Max Dob Rate = maximum rate of dobutamine infusion administered.

mmHg (2.5%), or experienced a sustained supraventricular arrhythmia (1%). Of the 154 women, 41 (26%) developed chest pain during DSE. Patients experiencing chest pain were older (58.5 ± 9.3 vs. 54.9 ± 12.6 ; $p = 0.05$) and had lower resting heart rates (71.0 ± 12.2 vs. 77.9 ± 14.9 ; $p < 0.008$). However, patients with and without chest pain received similar maximum doses of dobutamine and reached comparable levels of peak heart rate (Table I). Peak heart rate did not differ among patients receiving dobutamine at 3- or 5-min increments (133.9 ± 20.6 vs. 130.9 ± 20.8 , respectively; $p = 0.39$), and mean wall motion score index at peak stress was identical (1.05 ± 0.02) in the two infusion protocols.

Relation of Chest Pain to Dobutamine Stress Echocardiography

Abnormal DSE studies occurred in 14 of the 154 patients (9%) (Fig. 1). Eleven women had evidence of inducible myocardial ischemia, and 3 others had abnormal baseline wall motion that remained unchanged at peak stress (Table II). The occurrence of chest pain during DSE was similar between women with normal or abnormal DSE studies (Table III).

FIG. 1 Pie diagrams illustrating findings in 154 consecutive women during dobutamine stress echocardiography. Left pie summarizes the results of wall motion analysis. □ = Normal, ■ = ischemia, ■ = baseline abnormal. Right pie demonstrates large percentage of women with chest pain during dobutamine stress echocardiography. ■ = Chest pain, □ = no chest pain. See text for details.

TABLE II Occurrence of chest pain in patients with abnormal wall motion during dobutamine stress echocardiography (DSE)

Case No.	Chest pain during DSE	Baseline WMSI	Peak WMSI
1	Yes	1.0	1.25
5	No	1.125	1.50
7	Yes	1.0	1.25
9	Yes	1.5	1.5
10	Yes	1.0	1.25
40	Yes	1.875	2.062
56	No	1.0	1.375
62	No	1.0	1.1875
71	No	2.0	2.0
82	No	1.2	1.2
129	No	2.0	2.4
136	No	1.5	1.75
144	Yes	1.25	1.375
146	No	1.5	1.625

Abbreviations: WMSI= wall motion score index (see text for description).

Relation of Chest Pain to Electrocardiographic Changes

ST-segment depression during DSE was observed in 31 (20%) of the 154 women (Table III). Patients with chest pain more commonly demonstrated ischemic ECG, that is, ≥ 1 mm ST-segment depression in at least one lead [13 of 41 (32%) vs. 18 of 113 (16%); $p = 0.02$]. However, ischemic ECG changes were present in only 6 women (54%) with inducible myocardial ischemia by echocardiography, but were absent in 120/145 women (83%) without echocardiographic evidence of inducible myocardial ischemia.

Relation of Chest Pain to Coronary Angiography

In the subset of 59 patients who underwent coronary angiography, severe stenosis ($\geq 70\%$ luminal diameter stenosis) was found in 18, including 11 with single-vessel disease, 4 with double-vessel disease, and 3 with triple-vessel disease. Chest pain occurred during DSE in 32 of these 59 patients. The presence of severe coronary artery stenosis did not differ significantly between women with or without chest pain (Table III). Coronary artery stenosis $\geq 50\%$ was also similar between women with and without chest pain. In this subset of 59 women undergoing coronary angiography, DSE was abnormal in 6 of the 18 women with significant coronary stenosis, yielding a sensitivity of 30%; DSE was normal in 40 of 41 women without significant coronary stenosis, yielding a specificity of 97%.

Discussion

Chest pain during noninvasive testing for coronary artery disease potentially adds supportive diagnostic information. This study in women demonstrates that while chest pain occurs commonly during DSE (in about one-fourth), demonstra-

TABLE III Chi-square analysis of relation of chest pain to dobutamine stress echocardiography, dobutamine ECG, and coronary angiography

No. of patients (%)	Chest pain (n = 41)	No chest pain (n = 116)	p Value
ECG changes	13 (31.7)	18 (15.5)	0.02
Abnormal DSE	5 (12)	6 (5)	0.13
Abnormal echo	6 (15)	8 (7)	0.13
$\geq 70\%$ stenosis	12 (37) ^a	6 (28) ^a	0.2
$\geq 50\%$ stenosis	16 (50) ^a	10 (37) ^a	0.3

^a Numbers and percentages of patients with coronary stenosis among the 59 patients undergoing coronary angiography.

Abbreviations: Abnormal echo = wall motion abnormality at baseline or at peak dobutamine infusion, abnormal DSE = new wall motion abnormality during peak dobutamine infusion, ECG = electrocardiogram, ECG changes = ST-segment depression ≥ 1 mm in one or more leads.

tion of concomitant inducible myocardial ischemia is uncommon. These findings differ substantially from previous studies performed primarily in male patients, which suggests that chest pain either occurs uncommonly,^{1, 8, 11, 12} or is usually associated with coronary artery disease and inducible myocardial ischemia.^{4, 13, 14} Indeed, chest pain in male cohorts in the absence of inducible myocardial ischemia or angiographic coronary disease appears to be unusual.^{1, 15, 16}

The etiology of chest pain during DSE in the absence of inducible myocardial ischemia demonstrable by echocardiography is unclear. Since one-third of patients with chest pain had ECG abnormalities with stress, it might be hypothesized that the pain occurred as a consequence of ischemia, not detected by echocardiography. In this regard, dobutamine ECG has previously been shown to have poor sensitivity and specificity for diagnosis of coronary artery disease.^{8, 16, 17} Using criteria similar to those in the present study, Mairesse *et al.* demonstrated sensitivity of 18% and specificity of 93%.⁸ Other investigators evaluating the use of dobutamine ECG have reported sensitivity $< 30\%$.^{8, 16, 17} Also, the temporal relationship between ECG changes and development of wall motion abnormalities occurring during the "ischemic cascade" has been well documented, and it is unlikely that chest pain due to myocardial ischemia would be marked by ECG changes prior to development of wall motion abnormalities.¹⁸

The apparent relation between chest pain and ECG changes during dobutamine stress echocardiography has also been observed by Panza *et al.* in a group of 70 patients with angiographically normal coronary arteries and angina-like chest pain.¹⁹ These investigators found an 84% incidence of chest pain during DSE. ST-segment depression during dobutamine infusion was common among these patients, but wall motion abnormalities were not observed in any patient. The authors suggested that chest pain in their patients (63% of whom were women) was not a consequence of myocardial ischemia, but rather due to abnormal cardiac nociception. The inotropic and chronotropic effects of dobutamine may, in some patients, re-

sult in significant chest discomfort in the absence of angiographic coronary disease or inducible myocardial ischemia. Finally, chest pain may occur as a consequence of microvascular disease²⁰ coupled with a dobutamine-induced increase in myocardial oxygen demand. This also seems unlikely, and indeed the issue of chest pain believed to be due to endothelial dysfunction or microvascular disease, without other demonstrable evidence of ischemia, has received recent scrutiny,²¹ and merits further investigation.

Limitations of the Study

A significant limitation of the study is the lack of angiographic data in all patients. The decision to perform coronary angiography is often contingent on abnormal DSE findings or symptoms, and the greater prevalence of chest pain among patients undergoing angiography compared with the overall cohort underscores this bias. In this regard, the apparently low sensitivity of DSE for detection of coronary stenosis should be interpreted with caution. The prevalence of single-vessel stenosis (61%) in this cohort of women undoubtedly also contributed to the low sensitivity observed.

The small percentage of patients with abnormal DSE findings (i.e., 9%) also presents a limitation for assessment of chest pain. Our findings, however, are similar to those of a study of 3,011 patients (56% men) undergoing DSE in which evidence of ischemia was present in only 15 to 20%.²² These low percentages of positive studies undoubtedly reflect pretest referral bias; that is, patients believed to have moderate to high likelihood of disease may be preferentially referred directly for coronary angiography, while those with low to moderate likelihood are referred for noninvasive testing. The present study likely contains similar biases.

Conclusions

This study of women undergoing dobutamine stress echocardiography for evaluation of ischemic heart disease suggests that chest pain is a frequent occurrence which is usually not attributable to demonstrable myocardial ischemia or angiographic coronary artery disease.

References

1. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, Fineberg NS, Armstrong WF, Feigenbaum H: Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991;83:1605-1614
2. Marcovitz PA, Armstrong WF: Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. *Am J Cardiol* 1992;69:1269-1273
3. Martin TW, Seaworth, Johns JP, Pupa LE, Condos WR: Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. *Ann Intern Med* 1992;116:190-196
4. Mazeika PK, Nadazdin A, Oakley CM: Dobutamine stress echocardiography for detection and assessment of coronary artery disease. *J Am Coll Cardiol* 1992;19:1203-1211
5. Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H: Dobutamine stress echocardiography correlation with coronary lesion of severity as determined by quantitative angiography. *J Am Coll Cardiol* 1992;19:1197-1202
6. Forster T, McNeil AJ, Salustri A, Reijts AEM, El-Said E-SM, Roelandt JRTC, Fioretti PM: Simultaneous dobutamine stress echocardiography and technetium-99m isonitrite single-photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1993;21:1591-1596
7. Marwick T, D'Hondt A-M, Baudhuin T, Willemart B, Wijns W, Detry J-M, Melin J: Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: Combination with echocardiography or scintigraphy, or both? *J Am Coll Cardiol* 1993;22:159-167
8. Mairesse GH, Marwick TH, Vanoverschelde J-L J, Baudhuin T, Wijns W, Melin JA, Detry J-MR: How accurate is dobutamine stress electrocardiography for detection of coronary artery disease? Comparison with two-dimensional echocardiography and technetium-99m methoxyl isobutyl isonitrite (Mibi) perfusion scintigraphy. *J Am Coll Cardiol* 1994;24:920-927
9. Dagianti A, Penco M, Agati L, Sciomer S, Dagianti A, Rosanio S, Fedele F: Stress echocardiography: Comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. *J Am Coll Cardiol* 1995;26:18-25
10. Geleijnse ML, Fioretti PM, Roelandt JRT: Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;30:595-606
11. Davila-Roman VG, Waggoner AD, Sicard GA, Geltman EM, Schechtman KB, Perez JE: Dobutamine stress echocardiography predicts surgical outcome in patients with an aortic aneurysm and peripheral vascular disease. *J Am Coll Cardiol* 1993;21:957-963
12. Poldermans D, Arnesen M, Fioretti PM, Salustri A, Boersma E, Thomson IR, Roelandt JRTC, Van Urk H: Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995;26:648-653
13. Previtali M, Lanzarini L, Farrario M, Tortorici M, Mussini A, Montemartini C: Dobutamine versus dipyridamole echocardiography in coronary artery disease. *Circulation* 1991;83(suppl III):III-27-III-31
14. Cohen JL, Ottenweller JE, George AK, Duvvuri S: Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. *Am J Cardiol* 1993;72:1226-1231
15. Bach DS, Heper A, Marcovitz PA, Armstrong WF: Dobutamine stress echocardiography: Prevalence of a nonischemic response in a low-risk population. *Am Heart J* 1993;125:1257-1261
16. Beleslin BD, Ostojic M, Stepanovic J, Djordjevic-Dikic A, Stojkovic S, Nedeljkovic M, Stankovic G, Petrasinovic Z, Gojkovic L, Vasiljevic-Pokrajacic Z, Nedeljkovic S: Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. *Circulation* 1994;90:1168-1176
17. Marwick T, Willemart B, D'Hondt A-M, Baudhuin T, Wijns W, Detry J-M, Melin J: Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99mTc-MIBI single photon emission computed tomography. *Circulation* 1993;87:345-354
18. Nesto RW, Kowalchuk GJ: The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol* 1987;57:23-27
19. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilsizian D, Cannon RO: Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;29:293-301
20. Quyyumi AA, Cannon RO III, Panza JA, Diodati JG, Epstein SE: Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation* 1992;86:1864-1871
21. Cannon RO: Does coronary endothelial dysfunction cause myocardial ischemia in the absence of obstructive coronary artery disease? *Circulation* 1997;96:3251-3254
22. Secknus M-A, Marwick TH: Evolution of dobutamine echocardiography protocols and indications: Safety and side effects in 3,011 studies over 5 years. *J Am Coll Cardiol* 1997;29:1234-1240