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Dobutamine stress echocardiography: Prevalence of a nonischemic response in a low-risk population

The problems of population referral bias in the calculation of specificity in diagnostic testing for coronary artery disease have been previously described. Previous studies investigating the sensitivity and specificity of dobutamine stress echocardiography (DSE) have been subject to pretest and posttest referral biases, largely as a result of the requirement for coronary arteriography. This study determines the normalcy rate for DSE by examining a population at statistically low risk for coronary artery disease. The probability of significant coronary artery disease was determined for 828 consecutive patients referred for DSE at the University of Michigan, and groups were identified with <10% and <5% probability of disease. Four of 72 patients (5.6%) with a normal baseline echocardiogram and a probability of coronary artery disease of <10%, and three of 38 (7.9%) with a probability of <5% were found to have an abnormal DSE, yielding normalcy rates of 94.4% and 92.1%, respectively. The area of abnormality involved the posterior circulation in three of four patients (75%). This study demonstrates that DSE has a normalcy rate of 92% to 94% and is an accurate test for excluding the presence of significant coronary artery disease. (*AM HEART J* 1993;125:1257.)

David S. Bach, MD, Anne Hepner, MD, Pamela A. Marcovitz, MD, and
William F. Armstrong, MD *Ann Arbor, Mich.*

Dobutamine stress echocardiography (DSE) is an accurate and feasible method for the noninvasive de-

tection of coronary artery disease.¹⁻¹⁰ Using selective coronary angiography as a measure of accuracy, the sensitivity of DSE for the detection of coronary artery disease has been high, ranging from 68% to 97%.³⁻¹⁰ The specificity of DSE, however, has been more variable, ranging from as high as 100%⁴ to as low as 45%.³ Several factors may be responsible for the low test specificity in these studies. In addition to the possibility of error in test interpretation, pretest

From the Division of Cardiology, Department of Internal Medicine, University of Michigan Medical Center.

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Reprint requests: David S. Bach, MD, University of Michigan Hospital, UH B1F245-Box 0022, 1500 E. Medical Center Dr., Ann Arbor, MI 48109.

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and posttest selection biases may have been introduced in the selection of study populations. These biases exist to a large extent because of the requirement of invasive coronary arteriography for the documentation of coronary artery disease, and have been noted previously to influence the specificity of examinations in "unselected" patient populations.¹¹

Several studies have addressed the problems of specificity calculation for diagnostic testing in the exclusion of coronary artery disease.¹²⁻¹⁵ Pretest selection bias occurs^{16,17} when the study population is made up of patients with a high pretest probability of disease. In the case of DSE, factors contributing to this include the conduction of studies in the setting of university-based tertiary referral hospitals where the incidence and severity of coronary artery disease is greater than in the general population, and the inclusion of patients in the study population who already have the established diagnosis of coronary artery disease. This includes patients undergoing testing following myocardial infarction, and patients referred for DSE following cardiac catheterization for the assessment of the significance of already detected coronary artery disease.

Inclusion of patients with nonischemic cardiac disease may also contribute to pretest referral bias. These patients often have wall motion abnormalities at rest and thus are more likely to have false positive DSEs than are patients without underlying cardiac diseases.³ Additionally, they are more likely to undergo diagnostic cardiac catheterization. As such, the pool of patients undergoing cardiac catheterization includes a disproportionate number of patients preselected to have a false positive test.

Posttest referral bias may also contribute to a poor specificity for DSE. As the test has gained clinical use since its introduction, patients are more likely to undergo subsequent diagnostic cardiac catheterization following a positive DSE than following a negative test. As such, most patients with a false positive test will undergo coronary arteriography, while the majority of patients with negative results will not. As has been previously described,¹⁶ this will result in a decline in the measured test specificity.

These referral biases may be responsible for the relatively poor test specificity of DSE in previous studies. Given these constraints on population selection, alternative means must be used for determining the ability of the test to accurately predict the absence of disease. Precedent exists in clinical studies for the use of normalcy, the occurrence of a negative test in a population at statistically low risk for disease,^{18,19} to decrease the selection bias accompanying the requirement for invasive coronary angiog-

raphy. This study was designed to assess the normalcy rate of DSE by reviewing tests performed in patients who are at statistically low risk of having significant coronary artery disease.

METHODS

Study population. Clinical characteristics and DSE results were retrospectively reviewed for all patients referred for DSE at the University of Michigan Medical Center between January 1990 and September 1991. The probability of significant coronary artery disease was established using a previously described nomogram.²⁰ Probability was based on the age and sex of the patient, a history of diabetes, hyperlipidemia or tobacco use, previous history of myocardial infarction or abnormalities on electrocardiography, and a history of typical or atypical chest pain. Based on these criteria, patients were identified with a probability of significant coronary artery disease of less than 10%. Additionally, subsets of patients with a probability of coronary artery disease of less than 5% and those with a probability of disease between 5% and 10% were identified.

Dobutamine echocardiography. Dobutamine stress echocardiograms were performed using a previously reported protocol.¹⁰ The protocol was undertaken after approval of the University of Michigan Human Subjects Committee, and informed consent was obtained from each patient. Dobutamine was administered as a continuous intravenous infusion in 3-minute stages at doses of 5, 10, 20, and 30 $\mu\text{g}/\text{kg}/\text{min}$. Heart rate was continuously monitored. Images were obtained in standard parasternal long- and short-axis views, and in apical four-chamber and two-chamber views. Two-dimensional echocardiograms were recorded at baseline and at each stage of dobutamine infusion. Blood pressure and 12-lead electrocardiography were obtained at baseline, at the completion of each stage, and at 5 minutes following infusion termination. Indications for discontinuation of the protocol included the development of significant chest pain or a new wall motion abnormality on echocardiography. Echocardiographic images were digitized at baseline, during 5 $\mu\text{g}/\text{kg}/\text{min}$ infusion, at peak dobutamine infusion, and at 5-minutes of recovery.

All analyses were completed by a highly experienced observer (WFA). Echocardiograms were interpreted prospectively, intermixed with other daily stress and dobutamine stress studies, and nomogram-derived probabilities of coronary artery disease were subsequently calculated. As such, the interpreter was blinded to the nomogram-derived probability of coronary artery disease at the time of interpretation of the echocardiogram.

A normal response to dobutamine infusion is hyperdynamic motion in all visualized areas of the left ventricle. An abnormal test for the detection of coronary artery disease was defined as the presence of a resting wall motion abnormality, or the induction of a new or worsened wall motion abnormality during dobutamine infusion. The latter was considered as evidence of inducible ischemia.

Catheterization. Cardiac catheterization was performed between 0 and 149 (mean 47.5 ± 61.3 , median 8) days of the DSE in nine patients in whom there was a clinical indica-

Table I. Patient demographics

CAD probability	Population size (n)	Age range (yr)	Age mean (yr)	Age median (yr)	No. male	No. female	Atypical chest pain	Diabetes mellitus	Hypercholesterolemia	Tobacco use	ST segment/T wave abnormalities
<10%	75	19-65	41.8	41	20	55	37	4	1	4	3
<5%	39	19-52	37.5	37	9	30	13	1	1	1	1

CAD, Coronary artery disease.

Table II. Normalcy rate of dobutamine stress echocardiography (DSE)

CAD probability	All subjects		Normal baseline echocardiogram		%	Normalcy
	Population size (n)	Abnormal DSE	Population size (n)	Abnormal DSE		
<10%	75	5	72	4	5.6	94%
<5%	39	4*	38	3†	7.9	92%
5%-10%	36	1*	34	1†	2.9	97%

Abbreviations as in Table I.

* $p = 0.36$.

† $p = 0.62$.

tion for the procedure. The angiograms were reviewed and interpreted by an experienced observer. Significant obstructive coronary artery disease was felt to be present if there was a 50% or greater stenosis in any of the major epicardial coronary arteries.

Statistical analysis. The incidence of positive DSE for the groups with probability of coronary artery disease of less than 5% and for those with probability of disease of 5% to 10% were compared using a Fisher exact test (two-tail). The Fisher exact test was also used for comparison of the incidence of a positive DSE among male and female patients. A significant difference was defined as $p < 0.05$.

RESULTS

Patient demographics. Clinical characteristics of 828 patients referred for DSE were reviewed. Of these, 75 patients were identified with a probability of significant coronary artery disease of less than 10%. This group included 20 (27%) men and 55 (73%) women. The age range was 19 to 65 years, with a mean of 41.8 years. The age range of the male patients was 19 to 45 (mean 33.1 ± 5.1) years, and that of the female patients was 26 to 65 (mean 44.8 ± 9.6) years. Clinical characteristics are summarized in Table I.

Indications for referral for DSE included evaluation of chest pain in 30 patients, preoperative cardiac risk assessment in 23 (including eight patients undergoing evaluation for lung transplantation), evaluation of palpitations or arrhythmia in seven, evaluation of dyspnea or conduction abnormality in two each, evaluation of syncope or dilated cardiomyopathy in one patient each, and completion of other

protocols in six patients. No indication was available in three patients.

Thirty-seven patients (49%) had a history of atypical chest pain. Only 11 patients (15%) had one or more risk factors that increased the probability of coronary artery disease, using the nomogram of Pryor et al.²⁰ These risk factors included diabetes in four patients, hyperlipidemia in one patient, a history of tobacco use in four patients, and baseline ST segment or T wave abnormalities on resting electrocardiography in three patients. A single patient had two risk factors; a 30-year-old man with diabetes and resting ST segment abnormalities on electrocardiography, who was referred for DSE as part of a preoperative cardiac evaluation. No patients had a history of previous myocardial infarction or electrocardiographic evidence of a previous myocardial infarction. Thirty-nine patients had a probability of coronary artery disease of less than 5%.

Dobutamine stress echocardiography. The DSE protocol was completed in all 75 patients. No patients developed chest pain during the infusion. Among all patients with a probability of coronary artery disease of less than 10%, DSE was positive for ischemia in five patients (6.7%), including four (80%) women. These data are summarized in Table II. The incidence was 7.2% (4 of 55) in women and 5.0% (1 of 20) in men ($p = 1.0$). The age range for these patients was 31 to 52 (mean 41.4 ± 8.8) years. One patient, whose status was evaluated 4 days after pericardiocentesis, had a resting inferior wall motion abnormality and a small residual pericardial effusion. None of the other

Table III. Abnormal dobutamine stress echocardiograms (DSEs)

Age (yr)	Sex	Probability of CAD	DSE indication	CAD risk factors	Baseline echocardiogram	Induced wall motion abnormality	Abnormal circulation	Coronary angiogram	Other
31	M	<5%	Atyp CP	None	Normal	Inferior	Posterior	N/A	
34	F	<5%	Preop	Tobacco	Normal	Inferior	Posterior	Normal	
43	F	<5%	Atyp CP	None	Normal	Inferior	Posterior	Normal	
47	F	<5%	Preop	ST abn	Inferior WMA	Septal	Anterior	N/A	PEF*
52	F	<10%	Atyp CP	None	Normal	Infero-posterior	Posterior	Normal	

Atyp CP, Atypical chest pain; Preop, preoperative assessment; ST abn, ST segment abnormalities; WMA, wall motion abnormality; N/A, not available; other abbreviations as in Table I.

*Residual pericardial effusion 4 days following pericardiocentesis.

four patients had a resting wall motion abnormality. The area of induced wall motion abnormality was anterior in one patient, inferior in three, and infero-posterior in one. Three of these five patients underwent coronary arteriography. None of these three patients, nor any of the other six patients with negative DSEs undergoing coronary arteriography had evidence of significant coronary artery disease. Four of 39 patients (10.2%) with a less than 5% probability of coronary artery disease, and one of 36 patients (2.8%) with a probability of coronary artery disease between 5% and 10% had an abnormal DSE (Table II). Induced wall motion abnormalities involved the inferior wall in three and the anterior wall in one patient. The clinical and echocardiographic characteristics of these patients are summarized in Table III.

In addition to the patient with residual pericardial effusion and a baseline inferior wall motion abnormality 4 days following pericardiocentesis, two patients in the group had a severe dilated cardiomyopathy. Excluding patients with underlying cardiomyopathy, pericardial or valvular disease, 3 of 38 patients (7.9%) with a probability of coronary artery disease of less than 5%, and 1 of 34 patients (2.9%) with a probability of disease between 5% and 10% had a DSE positive for ischemia. There was no statistically significant difference between these groups with respect to the incidence of an abnormal DSE ($p = 0.62$). In the group of 72 patients with a probability of coronary artery disease of less than 10% and a normal baseline echocardiogram, four patients (5.6%) had an abnormal DSE.

DISCUSSION

Previous studies assessing the accuracy of DSE for the detection of coronary artery disease have been performed using patient populations subject to pretest and posttest referral bias. Study populations

have been drawn from university-based settings and have included patients following acute myocardial infarction, patients referred from the cardiac catheterization laboratory, and patients referred for cardiac catheterization based on the results of the DSE. In each case, either pretest selection bias existed such that the population under study had a greater prevalence of coronary artery disease than would be expected in a general population referred to the echocardiography laboratory, or posttest referral bias existed as a result of referral for subsequent cardiac catheterization based on the results of the echocardiogram. Because of these selection biases, the study populations may have contained fewer than expected numbers of patients without coronary artery disease, and determination of the test specificity may have been subsequently impaired. To circumvent these selection biases, this study was designed to assess the ability of DSE to exclude the presence of significant coronary artery disease in a population at very low risk for disease. As risk for coronary artery disease was used for selection criteria, none of the biases in patient selection that accompany studies requiring cardiac catheterization as a comparative standard were operative. Clinical characteristics were reviewed for patients referred for DSE, and patients with a less than 10% or a less than 5% probability of having significant coronary artery disease were identified using a previously described nomogram for the prediction of coronary artery disease probability in an individual. Particularly in the lowest probability group, the patient population was skewed to contain a predominance of women and patients under 40 to 50 years of age, as well as patients without significant independent risk factors for coronary artery disease. The patients were otherwise representative of patients referred for DSE.

The incidence of an abnormal and presumed false

positive DSE was 6.7% (5 of 75 patients). Excluding patients who had baseline cardiomyopathy, pericardial or valvular disease, the incidence was 5.6%. The incidence was 7.9% among those with a probability of coronary artery disease of less than 5%, and 5.6% in the group of patients with a probability of less than 10%, yielding normalcy rates for DSE of 92% and 94%, respectively. A higher incidence of an abnormal DSE was noted in the group with a lower predicted coronary disease probability, but the difference is not statistically significant and is most likely a function of the relatively small size of the two groups. The normalcy rate of 92% to 94% is in close agreement with the specificity of 91% for DSE in patients with normal baseline echocardiograms previously reported from our laboratory.¹⁰ This population of patients with normal resting function excludes many patients with nonischemic cardiac diseases, and results in fewer false positive tests.

The majority of false positive DSEs in this study were in the posterior circulation, with only one patient developing an inducible abnormality in the anterior circulation. This is consistent with findings in previous studies that inducible abnormalities in the posterior circulation are more likely to represent false positive DSEs than do anterior circulation abnormalities.¹⁰ The mechanism underlying this observation is uncertain, but many represent either observer error because of suboptimal visualization in this area, or wall motion abnormalities related to nonischemic but as yet unidentified mechanisms.

Conclusions. DSE has been previously demonstrated to be highly sensitive for the detection and localization of coronary artery disease. Test specificities ranging from 100% to 45% in previous studies may have been compromised by potential pretest and posttest referral biases in the populations studied. This study demonstrates that DSE has a normalcy rate of 92% to 94% in patients at low likelihood of having disease, with false positive tests predominantly involving the posterior circulation. DSE is a reasonable test for excluding the presence of significant coronary artery disease in nonselected patient populations.

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