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Dobutamine Stress Echocardiography in Women With Chest Pain

Pilot Phase Data from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE)

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OBJECTIVES The aim of this project was to assess the utility of dobutamine stress echocardiography (DSE) for evaluation of women with suspected ischemic heart disease.

BACKGROUND Most investigations addressing efficacy of diagnosis and treatment of coronary artery disease (CAD) have been performed in predominantly male populations. As part of the Women's Ischemia Syndrome Evaluation (WISE) study, DSE was assessed in women participating at the University of Florida clinical site.

METHODS Women with chest pain or other symptoms suggestive of myocardial ischemia and clinically indicated coronary angiography were eligible for the WISE study. Enrolled subjects underwent DSE using a modified protocol. Coronary stenosis was assessed by core laboratory quantitative coronary angiography (QCA).

RESULTS The 92 women studied ranged in age from 34 to 82 years (mean 57.5). All women had ≥1 major risk for CAD, and most (89, 97%) had ≥2 risk factors. In 78 women (85%), left ventricular wall motion was normal at baseline and during peak infusion. The remaining 14 women had wall motion abnormalities during DSE. By QCA, 25 women (27%) had ≥50% coronary stenosis, including 10 with single-vessel obstruction. Dobutamine stress echocardiography was abnormal in 10 of these 25 women, yielding overall sensitivity of 40%, and 60% for multivessel stenosis. Exclusion of women with inadequate heart rate response yielded overall sensitivity of 50%, and 81.8% for multivessel stenosis. Dobutamine stress echocardiography was normal in 54 of the 67 women with <50% coronary narrowing, specificity 80.6%.

CONCLUSIONS Dobutamine stress echocardiography reliably detects multivessel stenosis in women with suspected CAD. However, DSE is usually negative in women with single-vessel stenosis, and in the larger subset without coronary stenosis. Ongoing protocols of the WISE study are expected to improve diagnostic accuracy in women with single-vessel disease, as well as provide important data in the substantial number of women with chest pain but without epicardial coronary artery stenosis. (J Am Coll Cardiol 1999;33:1462–8) © 1999 by the American College of Cardiology

Most investigations addressing efficacy of diagnosis and treatment of coronary artery disease (CAD) have been performed in predominantly male populations. It is now recognized that the findings of these studies may not be strictly applicable to women. For example, noninvasive tests used for diagnosis of CAD in men have been reported to yield inferior results in women, largely due to poor specificity (1–5). There is concern that these limitations of testing and other ill-defined biases lead to delayed recognition of CAD in women, and hence may influence treatment and prognosis (5–9).

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Abbreviations and Acronyms

ANGIO = coronary angiography/angiographic
CAD = coronary artery disease
DSE = dobutamine stress echocardiography
ECG = electrocardiogram
ETT = exercise treadmill stress testing
WISE = Women's Ischemia Syndrome Evaluation

In response to these issues, the National Heart, Lung and Blood Institutes initiated a project to assess the utility of existing diagnostic tests as well as evaluate innovative methods for the diagnosis of ischemic heart disease in women. As part of this project, dobutamine stress echocardiography (DSE) was assessed in women participating in the study at the University of Florida clinical site. This article reports the findings of these studies during the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE).

METHODS

Women ≥18 years of age were enrolled in the WISE study if they met the following criteria: 1) chest pain or other symptoms suggestive of myocardial ischemia; 2) clinically indicated coronary angiography (ANGIO), and 3) ability to give informed, written consent. Criteria for exclusion included 1) acute myocardial infarction or unstable angina in the preceding 4 weeks; 2) uncontrolled systemic hypertension, defined as blood pressure >160/95 mm Hg on at least two occasions; 3) severe heart failure defined as New York Heart Association functional class IV; 4) coronary revascularization within the previous six months; 5) noncardiac conditions likely to influence outcome, and 6) factors related to ability to comply with study protocol. The protocol was approved by the University of Florida Institutional Review Board, and each patient gave informed consent. From November 1996 to May 1998, 944 patients were screened at the University of Florida clinical site; 801 were excluded for a variety of reasons. The most frequent reason for exclusion (in 72%) was lack of clinical indication for ANGIO (as determined by the referring physician) or refusal of ANGIO by the patient. The remaining excluded patients expressed disinterest in the study (23%), refused at the advice of their referring physician (4%) or had miscellaneous other reasons (1%).

Dobutamine stress echocardiography protocol. Dobutamine stress echocardiography was performed using a protocol modified for the WISE study. Subjects were instructed to discontinue beta-adrenergic blocking agents, calcium channel blocking agents and long-acting nitrates on the evening before testing. Baseline images in standard views were obtained and recorded on 0.5-in. (1.27 cm) videotape. Dobutamine infusion was initiated at 5 μg/kg/min, and the dosage increased at 5-min increments to 10, 20, 30 and 40 μg/kg/min. Intravenous atropine (0.25 to 1.0 mg) was given after the 40-μg/kg/min dose if the target heart rate (i.e., 85% predicted maximum) was not achieved. Dobutamine infusion was terminated if any of the following occurred: 1) target heart rate; 2) new segmental wall motion abnormality or ≥2 mm ST segment depression; 3) complex ventricular ectopy or sustained supraventricular tachycardia; 4) hypotension defined as ≥20 mm Hg decrease from baseline systolic blood pressure and absolute pressure <90 mm Hg, or hypertension defined as systolic blood pressure ≥220 mm Hg; 5) severe chest pain, and 6) intolerable symptoms (e.g., dyspnea, nausea). Images at baseline, 5 μg/kg/min, peak and recovery were digitized in continuous loop and displayed in quad loop format using a commercially available on-line digitizing system (Hewlett-Packard Sonos 1000 model 77025A, Andover, Massachusetts, upgraded with Nova MicroSonics High Performance Acquisition Module, Mahwah, New Jersey), and were also recorded on videotape. A 12-lead electrocardiogram (ECG) was recorded at baseline, at the end of each 5-min stage and at recovery. The ECG, blood pressure (DynaMap, Tampa, Florida) and echocardiographic images were monitored throughout the procedure.

Wall motion analysis was performed by a single cardiologist experienced in interpretation of DSE studies and masked to clinical and ANGIO findings. Interpretation was performed from the digitized images, and videotaped images were reviewed only for clarification of questionable findings. For analysis, the left ventricle was divided into 16 segments as recommended by the American Society of Echocardiography (10). Segments were graded based on systolic thickening and excursion: 1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic. Wall motion score index was calculated as the total score (sum of grades of all segments) divided by the number of segments scored. An ischemic response to dobutamine infusion was considered present when the score in any segment increased with the exception of akinetic to dyskinetic. Abnormal segmental wall motion at baseline or peak infusion was considered indicative of CAD. Wall motion of basal left ventricular segments supplied by the posterior coronary circulation was interpreted as abnormal only when visualized in two echocardiographic views. Dobutamine stress echocardiography studies were further categorized as normal if no abnormality was observed at baseline or peak stress and target heart rate was achieved, abnormal if wall motion abnormality was present at baseline or developed at peak stress or indeterminate if no abnormality was observed at baseline or peak stress and target heart rate was not reached.

Observer variability of wall motion analysis at the University of Florida was established before initiation of the project by interpretation of 25 DSE studies by two experienced cardiologists. Intraobserver agreement for the WISE investigators was 90%, that is, exact grade for specific segments read on two separate occasions. Interobserver agreement on segment grades by the two cardiologists was

85%. Discrepancies in wall motion score >1 grade occurred in only 2% of segments.

Coronary angiography protocol. Cardiac catheterization was performed using standard clinical techniques. Coronary angiography was performed using the WISE study protocol. Multiple projections of the left and right coronary arteries were recorded with particular care taken to achieve adequate opacification and visualization of proximal and middle portions of each coronary artery without overlapping or distortion. Images were recorded on 35-mm film at ≥30 frames per second. All films were interpreted by the WISE Angiography Core Laboratory without knowledge of clinical or DSE findings using previously published methods (11). Briefly, all angiograms were first reviewed for quality, and only those graded satisfactory or superior were further analyzed. These angiograms were then analyzed qualitatively for the presence or absence of lumen outline irregularities. Arteries with irregularities that reduce the lumen diameter (measured by electronic calipers) ≥20% were considered to have coronary artery stenosis. Stenoses were further classified as minimal (20% to 49% narrowing), moderate (50% to 69%) or severe (≥70%). An angiography severity score which incorporates percent luminal, extent and location of stenosis as well as the presence of collaterals was also calculated (11). A severity score of 5.0 was assigned to angiograms with only minor irregularities reducing the lumen diameter ≤20%; larger scores indicate increasing severity of angiographic disease.

Statistical methods. Continuous variables were summarized as mean ± SD. Sensitivity of DSE was calculated as the number of abnormal tests divided by the number of subjects with significant (≥50%) coronary stenosis; specificity was calculated as the number of normal tests divided by the number of subjects without significant coronary stenosis. Comparisons among patient groups (i.e., those with normal, abnormal and indeterminate DSE) were made using chi-square or Fisher exact tests for categorical variables, and Kruskal-Wallis rank-sum tests for ordinal and continuous variables such as number of CAD risk factors and age. McNemar test was used to compare the accuracy of wall motion score, chest pain and ST segment changes, alone and in combination, during DSE. Statistical significance was considered present at $p < 0.05$.

RESULTS

Patient population. A total of 143 women met all criteria for inclusion. Of these, 51 women were excluded for a variety of reasons: inadequate acoustic window (15 subjects), test cancellation by referring physician because of perceived contraindication (4 subjects), tenderness at mastectomy site (1 subject), refusal or withdrawal of consent (22 subjects), failure to complete testing (4 subjects) and coronary angioplasty performed shortly after qualifying ANGIO (5 subjects). The remaining 92 women completed DSE and constituted the study population.

Table 1. Characterization of Women Undergoing Dobutamine Stress Echocardiography (n = 92)

	Value	(n)*
Age (yr)	57.5 ± 10.1	(92)
Systolic BP (mm Hg)	136.8 ± 22.2	(91)
Diastolic BP (mm Hg)	76.0 ± 10.9	(91)
Current tobacco use	17 (18.7%)	(91)
Hypertension	51 (56.0%)	(91)
Dyslipidemia	52 (65.0%)	(80)
Family history of CAD	55 (61.1%)	(90)
Postmenopausal status	83 (90.2%)	(92)
Diabetes mellitus	21 (23.1%)	(91)
Prior revascularization (No., %)	6 (6.5%)	(92)
Total cholesterol (mg/dl)	209.4 ± 44.2	(52)
HDL (mg/dl)	48.0 ± 14.8	(50)
LDL (mg/dl)	127.5 ± 40.5	(44)
Triglycerides (mg/dl)	178.0 ± 123.9	(52)
Hormone replacement therapy (No., %)	33 (36.7%)	(90)
Beta-blockers (No., %)	27 (30.3%)	(89)
Calcium channel blockers (No., %)	34 (38.2%)	(89)
ACE inhibitors (No., %)	20 (22.5%)	(89)

*Number of women with listed baseline data.
ACE = angiotensin-converting enzyme; BP = blood pressure; CAD = coronary artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein.

These 92 subjects were recruited from the cardiovascular clinic (56%) or inpatient cardiology service (41%), or referred by the cardiology consultation service and emergency department (3%). Chest pain was the most frequent indication for evaluation and was present in 83 women (90%). The remaining nine women were referred for evaluation of dyspnea or because of an abnormal exercise stress test. The ages of the 92 women ranged from 34 to 82 years (mean 57.5). The majority (71, 77%) were white, 18 (20%) were African-American and the remaining 3 (3%) were Hispanic or Asian. All women had at least one risk factor for CAD including age ≥65 years, tobacco use, hypertension, dyslipidemia, family history of CAD, postmenopausal status or diabetes mellitus, and most (89, 97%) had two or more risk factors (Table 1). Pretest probability of CAD in 77 women (excluding 15 with history of myocardial infarction or revascularization) was assessed based on age, gender and symptoms (12). Probability was determined to be low (<10%) in 5 (6.5%), moderate (10% to 80%) in 60 (77.9%) and high (>80%) in 12 (15.6%). Subjects had taken a variety of medications, including beta-blockers, calcium channel blockers and angiotensin-converting enzymes inhibitors, before testing (Table 1). Although all subjects complied with instructions to discontinue medications on the evening before testing, 20 (24%) women had taken beta-blockers within 24 h of DSE.

Dobutamine stress echocardiography. Reasons for termination of DSE included attainment of target heart rate (62 subjects, 67%), maximum infusion dose and administration

Table 2. Wall Motion Score and Coronary Anatomy in Women With Abnormal Dobutamine Stress Echocardiography

ID No.	Baseline WMSI	Low dose WMSI	Peak WMSI	Angiography Findings, No. (Vessels) ≥50% stenosis	Angiography Severity Score*
30002	1.0	1.0	1.25	3 (lad, lcx, rca)	41.75
30006	1.5	1.37	1.50	2 (lad, lcx)	51.00
30008	1.0	1.0	1.25	2 (lad, rca)	23.75
30010	1.5	1.31	1.50	3 (lad, lcx, rca)	56.50
30011	1.0	1.0	1.25	1 (lad)	41.00
30031	1.0	1.0	1.19	0	5.00
30043	1.87	1.6	2.06	3 (lm, lad, rca)	78.50
30077	1.0	1.0	1.25	0	5.00
30114	1.19	1.19	1.44	2 (rca, lad)	27.75
30117	1.00	1.0	1.25	2 (lad, lcx)	27.75
30120	1.62	1.5	1.87	2 (lad, rca)	39.0
30122	1.50	1.37	1.62	3 (lad, rca, lcx)	56.0
30123	1.00	1.0	1.38	0†	24.0
30131	1.19	1.06	1.12	0	5.0

*Larger score is indicative of more extensive disease; see text for details. †Subject with 49% stenosis in right coronary artery.
lad = left anterior descending; lcx = left circumflex; lm = left main; rca = right coronary artery; WMSI = wall motion score index (see text for details).

of atropine without reaching target heart rate (8 subjects, 9%), anginal chest pain (15 subjects, 16%), new wall motion abnormality (3 subjects, 3%), hypotension (3 subjects, 3%), hypertension (4 subjects, 4%) and other intolerable symptoms such as dyspnea or extreme anxiety (8 subjects, 9%); 13 subjects (14%) had more than one reason for termination. Two tests were terminated due to ventricular tachycardia or sustained supraventricular tachycardia. Most women (70, 76%) received a maximum infusion rate 30 to 40 μg/kg/min (mean dose 32.2 ± 9.3); 22 (24%) also received atropine. A variety of other symptoms were reported at peak stress, but did not result in premature termination of DSE. These symptoms included atypical chest pain 43 (47%), nausea 18 (20%) and lightheadedness 8 (9%). No symptoms were reported in 31 (34%) subjects.

Wall motion analysis. The majority of women (78, 85%) had normal left ventricular wall motion at baseline and during peak dobutamine infusion. This included 64 women who reached target heart rates, and 14 with studies considered "indeterminate" because of inadequate chronotropic response; that is, target heart rates were not achieved. The remaining 14 women had segmental wall motion abnormalities during dobutamine infusion, seven of these with baseline abnormalities. Data from these 14 women are summarized in Table 2.

Relation of DSE to ANGIO findings. By quantitative coronary angiography, 67 women (73%) had minimal or no disease (<50% narrowing). The other 25 women (27%) had moderate or severe narrowing (≥50%) in one or more coronary arteries. This included 10 women with single-vessel, 10 with two-vessel and 5 with three-vessel obstruction. Of the 25 women with ≥50% coronary stenosis, 10 had abnormal DSE studies at peak infusion (Table 2). The remaining 15 women had no wall motion abnormality at baseline or peak stress; 10 of these reached target heart rate, and five were considered indeterminate studies due to inadequate chronotropic response (two of these five had taken beta-blockers within 24 h of DSE). Thus, overall sensitivity of DSE for detection of ≥50% coronary narrowing was 40%, but was 60% in patients with two- or three-vessel stenosis. Sensitivity of DSE in women without baseline wall motion abnormality was 21% overall, and 33.3% in patients with two- or three-vessel disease. Analysis of data with exclusion of women with indeterminate DSE yielded overall sensitivity of 50%, and 81.8% for two- or three-vessel stenosis; in women without baseline wall motion abnormalities, sensitivities were 28.6% overall and 60% for multivessel disease. All cases of ANGIO stenosis in the absence of segmental wall motion abnormality during DSE occurred in the presence of single-vessel coronary narrowing, <70% stenosis or indeterminate studies due to inadequate chronotropic response (Table 3). Among the 14 women with indeterminate DSE studies, five (35.7%) had significant coronary stenosis. In the 92 study subjects, accuracy of DSE was 69.6%, with positive predictive value of 71.4% and negative predictive value of 84.4%. Accuracy of DSE was also assessed using a combination of other potential markers of CAD including ischemic ST segment changes and chest pain during dobutamine stress. No significant improvement in accuracy was observed by combination of these markers ($p = 0.48$).

Coronary angiography severity score in the 67 patients with no or minimal disease (coronary stenosis <50%) ranged from 5.0 to 24.0 (mean 6.7). Mean severity score in the 25 patients with ≥50% coronary narrowing ranged from 8.8 to 78.5 (mean 28.7). Angiography severity score was highest in women with abnormal DSE, lowest in women

Table 3. Findings in Women With Significant Angiographic Coronary Disease and Normal or Indeterminate Dobutamine Stress Echocardiography

ID No.	Results of DSE	Angiography Findings, No. (Vessels) ≥50% stenosis	Angiography Severity Score*
30007	Normal	1 (rca)	16.25
30015	Normal	1 (lad)	19.50
30018	Normal	1 (lcx)	11.25
30020	Normal	2 (lad, lcx)†	14.75
30021	Normal	1 (lad)†	9.00
30059	Normal	1 (lad)	16.00
30068	Normal	1 (lad)†	24.25
30074	Normal	1 (rca)†	14.50
30094	Normal	1 (rca)†	8.75
30125	Normal	(3 lad, lcx, rca)†	20.50
30003	Indeterminate	2 (lad, rca)	25.50
30047	Indeterminate	2 (lad, rca)†	26.00
30055	Indeterminate	2 (lad, rca)	34.50
30082	Indeterminate	2 (lm)†	21.00
30130	Indeterminate	1 (lad)†	12.25

*Larger score is indicative of more extensive disease; see text for details. †Coronary stenosis <70%.
Abbreviations as in Table 2.

with normal DSE and intermediate in those with indeterminate studies (Table 4). An angiography severity score of ≥35.0 was always associated with abnormal DSE; a score ≥25 was consistently associated with abnormal DSE, except in individuals with indeterminate tests (Tables 3 and 4). Alternately, a score of <25 was associated with abnormal DSE in only 5 women.

Dobutamine stress echocardiography was interpreted as normal in 54 of the 67 women with <50% coronary narrowing, yielding a specificity of 80.6%. Nine of these 54 women had indeterminate studies. Wall motion abnormalities in four occurred at peak stress and were confined to basal inferior and basal inferior septal segments (2 subjects), apical inferior and apical septal segments (1 subject) and midanterior segment (1 subject).

Electrocardiographic analysis. At peak dobutamine infusion rate, ECGs demonstrated ischemic type ≥1-mm ST depression in 10/92 (13%) women. Of the 25 women with ≥50% coronary narrowing, six developed ≥1-mm ST segment depression during stress (sensitivity 24%); 2/9 with ≥70% narrowing showed ST segment depression (22.2%). In the 67 women with <50% narrowing by ANGIO, six showed ischemic ST segment changes, yielding a specificity of 91%.

Comparisons among women with normal, abnormal or indeterminate DSE. Analysis of findings among subjects with normal, abnormal or indeterminate DSE revealed lower peak heart rate in women with abnormal DSE and more frequent use of beta-blockers among those with abnormal or indeterminate studies (Table 4). The most frequent reasons for termination of DSE in the 14 patients with indeterminate studies were chest pain (in five patients, 35.7%) and hypertension (in four patients, 28.6%). Studies were terminated in the other five patients because of hypotension, severe dyspnea or ventricular tachycardia during maximum infusion rate.

Findings of exercise treadmill stress testing (ETT). Exercise treadmill stress testing was performed in 57 of the 92 women with DSE. Of these, 12 had ST segment changes considered positive for ischemia; two of these 12 women also had wall motion abnormalities during DSE, but 10 were normal. Exercise treadmill stress testing in the remaining 45 women was normal; 39 of these 45 also had normal DSE, and 6 showed wall motion abnormalities. No significant correlation was found between ETT and DSE findings ($p = 0.5$). Compared to quantitative coronary angiography, sensitivity of ETT (using ST segment criteria) for detection of coronary stenosis ≥50% was 25%; specificity was 80%.

Table 4. Comparisons Among Women With Normal, Abnormal and Indeterminate Dobutamine Stress Echocardioraphy

	Normal (n = 64)	Abnormal (n = 14)	Indeterminate (n = 14)	p Value
Age (yr)	57.1 ± 10.5	59.4 ± 9.1	57.3 ± 9.5	0.68
Baseline HR (bpm)	72.4 ± 12.1	74.5 ± 15.2	66.3 ± 15.0	0.41
Baseline SBP (mm Hg)	145.4 ± 24.8	138.1 ± 30.1	161.1 ± 28.8	0.08
Peak HR (mm Hg)	141.0 ± 11.3	127.8 ± 18.6	98.4 ± 21.3	—
Peak SBP (mm Hg)	164.8 ± 30.1	162.7 ± 40.2	186.7 ± 43.9	0.15
Max dose (μg/kg/min)	33.3 ± 7.8	30.0 ± 9.6	29.1 ± 14.0	0.46
Atropine (number, %)	19 (29.7%)	2 (14.3%)	1 (7.0%)	0.14
Beta-blocker (number, %)	10 (15.6%)	5/12 (41.7%)	5 (35.7%)	0.05
Number CAD risk factors	3.8 ± 1.4	4.5 ± 1.7	5.1 ± 1.1	0.0084
Angiography severity score	7.8 ± 4.3	34.4 ± 21.8	12.9 ± 9.7	0.0001

CAD = coronary artery disease; HR = heart rate; Max dose = maximum rate of dobutamine infusion; SBP = systolic blood pressure.

DISCUSSION

Dobutamine stress echocardiography has been applied to large numbers of subjects with known or suspected CAD with reported sensitivities ranging from 72% to 95%, and specificities from 77% to 97% (13–23). Discrepancies among these studies have generally been attributed to differences in patient populations with regard to prevalence of CAD and inclusion of patients with previous myocardial infarction. However, nearly every study comprises predominantly male subjects, and little is known about the effect of gender on these findings.

Major findings of the present study. The present investigation reveals several important observations. First, in a cohort of women evaluated for chest pain and multiple risk factors for CAD, angiographic evidence of significant CAD was present in only 27%. Moreover, 40% of these women had important stenosis in only one vessel. Dobutamine stress echocardiography applied to this population showed an overall sensitivity of 40%. However, in women with multivessel stenosis, and excluding those with indeterminate studies, sensitivity of DSE was 81.8%, similar to findings in predominantly male cohorts (13–15,17,22).

Comparison with previous studies. Noninvasive testing for CAD in women has generally been hampered by poor specificity (2,5,24). Previous observations, although limited, suggest that DSE shares this limitation (25,26). In a study by Bach et al. of patients with false positive DSE, women were more likely to have false positive studies, accounting for 72% of the group (25). Women had a fourfold incidence of false positive studies, nearly 20% compared with only 5% in men. This differs substantially from the findings of our study which demonstrate a very low false positive rate and specificity of approximately 81% in patients without angiographic evidence of significant disease. This discrepancy likely relates to methodologic differences. In particular, postcatheterization referral biases observed in prior studies in which only abnormal DSE responses are referred for ANGIO artificially deflate test specificity. The WISE study design, conversely, in which all subjects underwent DSE and ANGIO, eliminates this bias. In addition, the low overall prevalence of abnormal DSE and significant coronary artery narrowing likely contributed to the high specificity observed in this study.

Sensitivity of DSE in women. The explanation for the poor overall sensitivity of DSE in this group of women also relates in part to the relatively low overall prevalence of severe coronary artery narrowing. Previous reports have included cohorts with from 42% to 87% prevalence of angiographic disease (13,16,17,22,27,28). For example, Elhendy et al. evaluated the accuracy of DSE in women (28) and found overall sensitivity of 76%. Prevalence of CAD in the cohort of women studied was 65%, substantially higher than the present investigation, and over one half of women studied had prior myocardial infarction. The lower prevalence of coronary stenosis in WISE patients may be a consequence of several factors. Most patients had no previously documented myocardial infarction, and individuals with unstable symptoms were excluded from study. Also, the intent of our study was to evaluate a broadly representative cohort of women undergoing evaluation for suspected myocardial ischemia, as well as to include other possible causes for ischemia such as microvascular dysfunction. As a consequence, the cohort of women in this study may indeed reflect a more accurate representation of women being evaluated for chest pain. Nonetheless, our cohort of women had clinical indication for coronary angiography based on the presenting symptoms and prevalence of risk factors. Findings in these patients may not be applicable to other groups of women with chest pain syndromes without clinical indication for coronary angiography, and lower sensitivity of DSE might be expected in such individuals.

Another contributing factor to the low overall sensitivity of DSE in the WISE study relates to 40% prevalence of single-vessel involvement in women with epicardial coronary artery stenosis. The lower sensitivity of DSE for detection of single-vessel stenosis has been reported by most previous investigations and has ranged from 50% to 80% (16,21–23,29). Moreover, myocardial ischemia is influenced by factors other than luminal narrowing, such as lesion morphology and collateral circulation. The relation of DSE findings to angiography severity score used in the present study underscores this more complex relationship between inducible myocardial ischemia and lesion description. In the present study, sensitivity was lower in women with single-vessel stenosis and low angiographic severity score, potentially representing individuals with low risk for inducible myocardial ischemia of sufficient severity to result in wall motion abnormalities. For example, an angiography severity score less than 25 was rarely associated with inducible myocardial ischemia, whereas a score $\geq$35 was invariably associated with abnormal wall motion.

Adverse effects and indeterminate DSE. Few patients (15%) did not achieve target heart rates during DSE. These "indeterminate" tests were due largely to premature termination of DSE because of intolerable symptoms of chest pain or dyspnea, or important cardiovascular side effects including hypertension and hypotension. Of note, a hypertensive response to dobutamine infusion in one third of the prematurely terminated studies was consistently observed only in women with history of hypertension, and was likely exacerbated by the routine cessation of medication before testing. These findings are comparable to those of previous investigations (22,30–32). In a study of over 3,000 patients (32), Secknus and Marwick reported premature termination of DSE in 15% of patients, most of these for cardiovascular side effects. In the present study, the presence of severe coronary artery stenosis in one third of women with inde-

terminate DSE underscores the need for further evaluation and testing in these patients with inconclusive findings.

Conclusions. In summary, DSE reliably detects multivessel stenosis in women with suspected CAD. However, DSE is usually negative in women with single-vessel disease, and in the larger subset of women with chest pain and without angiographic coronary stenosis. The findings of the present study constitute pilot phase data from the WISE study and require confirmation in the larger group of women subsequently enrolled. Protocols performed during the ensuing years of the WISE study are expected to improve diagnostic accuracy in women with single-vessel disease. In particular, because the low overall sensitivity in single-vessel stenosis results in part from smaller stress-induced wall motion abnormalities, the efficacy of contrast echocardiography for improved endocardial visualization of wall motion will be assessed in this cohort. With regard to the substantial number of women with chest pain but without epicardial coronary artery stenosis, a protocol testing the relation between abnormal coronary flow reserve and myocardial ischemia using phosphorus-31 nuclear magnetic resonance spectroscopy is in progress (33).

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