METHODS

Dobutamine Stress Echocardiography: Correlation With Coronary Lesion Severity as Determined by Quantitative Angiography

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This study was performed 1) to determine the ability of dobutamine stress echocardiography to detect stenoses in individual coronary arteries by utilizing a new model of coronary artery distribution; 2) to evaluate its ability to detect coronary artery stenosis with a minimal lumen diameter <1 mm; and 3) to correlate the heart rate at which a positive test result occurs with the severity of coronary artery disease.

Eighty-five patients were identified who underwent both dobutamine stress echocardiography and quantitative coronary angiography. During incremental infusion of dobutamine, two-dimensional echocardiograms were obtained at rest, during low and peak stress and after stress. Echocardiograms were interpreted with use of a modified 16-segment model with an anterior-inferior overlap scheme. The overall sensitivity of the technique for the detection of significant coronary artery disease (diameter stenosis >50%) was 95%; specificity was 82% and accuracy 93%.

The sensitivity for detection of individual coronary artery lesions did not differ significantly (p > 0.05) in the three major coronary artery distributions (79% left anterior descending, 70% left circumflex, 77% right coronary artery). Among 35 stenoses with a minimal lumen diameter <1 mm, the test result was positive in 30 (86%). Test results were correctly positive for 88%, 82% and 86% of stenoses in the left anterior descending, left circumflex and right coronary artery distributions, respectively.

Multivessel disease was present in 11 of 16 patients with normal wall motion at rest who developed a wall motion abnormality at a heart rate <125 beats/min. The incidence of multivessel disease was statistically higher in patients with positive findings on a dobutamine stress echocardiogram at a heart rate <125/min.

In conclusion, dobutamine stress echocardiography has high sensitivity and specificity for the detection and localization of coronary artery disease. Detection of stenosis in individual coronary arteries is improved in those lesions with a minimal lumen diameter <1 mm. Patients with a positive test result at a heart rate <125 beats/min have a high likelihood of multivessel coronary artery disease.

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ography may provide a more accurate estimate of coronary artery narrowing (8-11). The percent diameter stenosis and the minimal lumen diameter of a specific lesion can be measured with quantitative angiographic techniques. Some studies (8,11) suggest that the minimal lumen diameter more closely correlates with coronary perfusion reserve than does a qualitative assessment of diameter stenosis. The accuracy of stress echocardiography for the detection of significant stenosis in the individual coronary arteries has varied widely (7,12-14).

Dobutamine stress echocardiography has potential advantages over more standard forms of exercise testing. Because the degree of cardiac stress can be controlled, the technique may provide a more accurate assessment of the physiologic significance of a coronary artery lesion. The ability to continuously acquire data not only contributes to the safety of the test but may allow for more physiologic assessment of the hemodynamic severity of a coronary artery lesion.

Therefore, the goals of the current study were threefold: 1) to determine the ability of dobutamine stress echocardiography to detect stenosis in the individual major coronary artery distributions by utilizing a new overlap model of segmental wall motion analysis; 2) to evaluate its ability to detect lesions with a minimal lumen diameter <1 mm; and 3) to correlate the heart rate at which a positive test result occurs with the severity of coronary artery disease.

Methods

Patient selection. Between June 1988 and August 1989, 97 nonconsecutive patients underwent both dobutamine stress echocardiography and cardiac catheterization. Patients were referred for dobutamine stress echocardiography because of prior stroke, claudication, severe arthritis or other conditions that prevented exercise stress testing. Twelve patients with prior coronary artery bypass grafting were excluded from this study. Results in the remaining 85 patients are reported. The mean age of the patients was 58.6 years (range 28 to 85); 52 were men. The protocols used in this study were approved by the Indiana University Institutional Review Board in May 1988. All patients gave informed, written consent for this study.

Dobutamine infusion protocol. Dobutamine was infused in increments beginning with a dose of 5 µg/kg per min and increasing by 5 µg/kg per min every 3 min. The electrocardiogram (ECG) and blood pressure were measured and recorded at the end of each stage. The dobutamine infusion was discontinued when any of the following end points were reached: 1) a new abnormality of regional wall motion or myocardial thickening in two or more contiguous segments; 2) ≥2-mm ST segment depression on the ECG; 3) >15-mm Hg decrease in systolic blood pressure from the baseline value; 4) significant side effects or arrhythmia; 5) maximal dose of 30 µg/kg per min; and 6) achievement of 85% of the age-predicted maximal heart rate.

Quantitative coronary angiography. Single-plane coronary angiograms were obtained by the Judkins technique with a standard cineangiographic system interfaced to a digital radiographic computer system (ADAC DPS 400C). Cinefilm images were projected on a cine viewer optically coupled to a video camera. Quantitative angiographic measurements of percent diameter stenosis and minimal lumen diameter were performed by an investigator who had no knowledge of the clinical history or results of stress echocardiography and echocardiography. Single-frame cinefilm images best demonstrating a stenosis were digitized into a 512 × 512 × 8-bit pixel matrix for quantitative angiography. To minimize any possible effects of pincushion distortion, attempts were made to image the stenotic area and catheter in the central portion of the radiographic field.

All images were analyzed without mask subtraction by using an automated quantitation program described in detail elsewhere (15). Briefly, single cine images best demonstrating a stenosis in its most severe narrowing were chosen for quantitation. An automatic edge detection method was used in the following manner. A calibration factor was obtained by using the catheter shaft of known diameter as a reference. A circular region of interest was positioned over the catheter shaft and a centerline was automatically derived. After linear density profiles perpendicular to the centerline were calculated along the chosen catheter segment, a weighted average of the first and second derivatives of the density profiles was used to determine edge points. The initial gradient-determined edge points were examined for spatial continuity; outliers were discarded and replaced in a smoothing process by linear interpolation between adjacent valid edge points. Calibration was achieved by entering the known catheter diameter resulting in a calibration factor (mm/pixel) for quantitative analysis.

In a similar fashion, a circular region of interest was positioned over each stenotic segment. A centerline and edge points were derived automatically for each stenosis in the manner just described. Stenosis severity was quantified in the following manner. First, multiple lumen diameters in an operator-designated "normal" segment proximal to the stenotic lesion were averaged by the computer program to provide a baseline normal lumen diameter. The operator then designated the most stenotic segment to obtain the geometric diameter percent stenosis and minimal lumen diameter. For the purposes of this study, the location of stenoses in the individual coronary arteries as determined by geometric diameter percent stenosis and minimal lumen diameter were correlated with the area of dobutamine-induced wall motion abnormalities. Stenoses in branch vessels were assigned to the contributing major vessel. Multivessel disease was defined as the presence of ≥50% diameter stenosis in more than one epicardial coronary artery. Single-vessel disease was defined as the presence of ≥50% diameter
stenosis in only one vessel. Patients were not separated on the basis of left or right dominant circulation.

**Echocardiography.** After the patient was placed in the left lateral decubitus position, two-dimensional echocardiograms were obtained with commercially available equipment using a 3 MHz transducer. All studies were monitored by an investigator. Studies were recorded on 0.5-in. (1.27-cm) VHS videotape and digitally acquired on-line and stored on a 5.25-in. (13.44-cm) floppy disk. Four views (parasternal long-axis, parasternal short-axis at the papillary muscle level, apical four-chamber and two-chamber) were obtained at rest, at low (5 µg/kg per min) dose and peak dose and at 5 min after termination of infusion. The echocardiograms were arranged in a quad screen display so that images obtained at rest and at low and peak dose and after infusion could be directly compared during playback in a continuous loop format.

**Echocardiographic analysis.** The digitized studies were independently interpreted by two investigators who had no knowledge of the patient's history or results of the stress ECG or coronary angiograms. Videotape recordings were available on request but were not routinely reviewed. A third investigator reviewed the echocardiograms in blinded manner if the first two investigators were not in agreement. A normal response was defined as a progressive increase in systolic myocardial thickening or wall motion, or both, during the sequential stages of dobutamine infusion. An abnormal response was defined as a reduction of systolic thickening or wall motion at any stage in the protocol compared with the previous stage. A lack of increase in wall motion or systolic thickening, or both, with incremental infusion of dobutamine was considered abnormal.

The left ventricle was divided into 16 segments with use of a standard model. The location of segmental wall motion abnormalities was correlated with coronary artery distribution by using a scheme modified from that proposed by Bourdillon et al. (8) (Fig. 1). The apical lateral and apical inferior segments were considered overlap areas. The apical lateral segment was considered to be a part of the left anterior descending coronary artery distribution in association with additional septal or anterior wall motion abnormalities. The same segment was considered to be a part of the left circumflex coronary artery distribution in association with posterior or posterolateral wall motion abnormalities.
The apical inferior segment was grouped with the right coronary artery distribution if there were additional inferior wall motion abnormalities. It was grouped in the left anterior descending region in the presence of anterior or anteroseptal wall motion abnormalities. Data were analyzed separately for patients with normal and abnormal wall motion at rest. Segmental wall motion was graded as previously reported for patients with normal and abnormal wall motion at rest.

Statistics. For statistical comparison between two groups of unequal size the Fisher exact test was utilized. For comparisons among more than two groups, chi-square analysis was performed. For the purposes of this study, a p value <0.05 was considered significant.

Results

Overall findings. Of the 85 patients (3 patients underwent two dobutamine stress echocardiograms and cardiac catheterizations for a total of 88 studies), 66 had abnormal findings as defined by the presence of >50% narrowing in a coronary artery. Results of the dobutamine stress echocardiogram were abnormal in 63 of the 66, yielding an overall sensitivity of 95%. The test correctly identified normal status (stenosis <50%) in 18 patients, yielding a specificity of 82% (18 of 22). The accuracy of the test in this group was 92%. For the subgroup with normal wall motion at rest, the sensitivity was 90% (27 of 30) and the specificity was 86% (18 of 21).

Individual coronary artery stenoses (Table 1). A total of 114 coronary artery lesions were identified with a stenosis ≥50% in diameter. Of 39 stenoses in the left anterior descending coronary artery, 31 (79%) were identified on the basis of a wall motion abnormality in a region supplied by that vessel. Of the eight stenoses that were not detected, five had <70% lumen narrowing and a minimal lumen diameter >1 mm and one lesion was in a diagonal vessel.

Of 27 lesions identified in the left circumflex coronary artery distribution, 19 (70%) were detected by dobutamine stress testing. Of the eight lesions that were not attributed to the circumflex distribution, the dobutamine test identified five in the right coronary artery distribution (four of five were associated with significant right coronary artery disease).

Of the 48 right coronary artery lesions, 37 (77%) were detected by dobutamine stress echocardiography. Of the 11 lesions that were not detected, 8 were interpreted as a left circumflex coronary artery lesion or were supplied by collateral flow. There was no significant difference in the percent of positive studies detected among the three coronary artery distributions.

Patients with minimal lumen diameter <1 mm (Table 2). Thirty-five patients had a stenosis with a minimal lumen diameter <1 mm. Results of the dobutamine stress echocardiogram were abnormal in 31 (86%) of these 35 patients. Of the five stenoses missed, one was in a diagonal branch of the left anterior descending coronary artery, two were in patients with multivessel disease whose study was stopped before the target heart rate was reached, one lesion was in a left circumflex coronary artery and one was in a heavily collateralized left anterior descending coronary artery. The test result was positive for 15 (88%) of 17 lesions in the left anterior descending coronary artery, 9 (82%) of 11 lesions in the left circumflex coronary artery and 6 (86%) of 7 lesions in the right coronary artery. There was no significant difference in the percent of positive study results among the three coronary artery distributions.

Effect of Heart Rate on Accuracy

Normal wall motion at rest. Results of the dobutamine stress echocardiogram were positive in 31 patients with normal wall motion at rest. The results became positive in 16 of these 31 patients at a heart rate ≤125 beats/min. Multivessel coronary artery disease was present in 11.

In 15 patients the test results became positive at a heart rate >125 beats/min. Four of these 15 patients had multivessel disease. Of the 11 remaining patients, 2 had a false positive test result and 9 had single-vessel disease.

The likelihood of multivessel disease was significantly higher in patients whose test result became positive at a heart rate ≤125 beats/min (p < 0.05). There was no statistically significant difference (p > 0.6) in the rate-pressure product between patients with or without multivessel disease.

Abnormal wall motion at rest. Wall motion was abnormal at rest in 37 patients. In 29 of these, the test result became positive at a heart rate ≤125/min. Multivessel disease was detected in 17 patients and 7 patients had single-vessel disease with a >75% diameter stenosis.

Results of eight studies were positive at a heart rate
>125/min. Five of the eight studies were in patients with multivessel disease, and four of the five were in patients with either collateral flow or no lesion with >75% diameter stenosis. Heart rate was not a statistically significant discriminator for the presence of multivessel disease in patients with wall motion abnormalities at rest.

**Discussion**

Dobutamine stress echocardiography has been proposed (2-6) as a clinically useful noninvasive, nonexercise test for the evaluation of patients with coronary artery disease. We recently reported (6,16) our initial clinical experience with dobutamine stress echocardiography for the detection of coronary artery disease and preoperative risk assessment.

In the current study, the overall sensitivity of the test was 95%, specificity 82% and accuracy 92%. In the group with normal wall motion at rest the sensitivity was 90% and specificity 86%, findings very similar to those previously reported (6).

Detection of individual coronary artery stenoses. This study demonstrated no statistically significant difference in the test's ability to detect coronary artery lesions in the three vascular territories. Prior studies (7,12-14,17) have found that lesions in the left circumflex coronary artery territory are detected less accurately than those in the left anterior descending or right coronary artery. This difficulty has been attributed to the overlap in perfusion areas between the right and left circumflex coronary arteries. The improved accuracy for the detection of left circumflex coronary artery lesions in the current study is most likely attributable to the use of an overlap method for determining the proper coronary distribution of wall motion abnormalities. This method takes into account the overlap in perfusion that is possible between the left circumflex and right coronary arteries as well as the overlap between the left anterior descending and right coronary arteries.

Several studies (9-11) have demonstrated that visual estimation of coronary artery lesions is less accurate than results obtained with quantitative angiography. In addition, a body of published data (18-22) suggests that the minimal lumen area or diameter may be a more physiologic marker for the severity of coronary artery lesions than is percent diameter stenosis. In this study the correct assignment of wall motion abnormalities to coronary lesions was enhanced when evaluation was confined to lesions with a minimal lumen diameter <1 mm. This finding supports the view that the latter lesions with quite variable percent diameter stenoses were hemodynamically significant.

A well established tenet in stress testing is that an “early positive” test result identifies a patient with more severe coronary artery disease. Our observations support this concept. In patients with normal wall motion at rest, a positive result on a dobutamine stress echocardiogram at a heart rate ≤125 beats/min was more frequently associated with multivessel disease, whereas patients whose test result became positive at a higher rate had a greater prevalence of single-vessel disease. Heart rate did not discriminate among patients with wall motion abnormalities at rest. A previous study (23) demonstrated that in patients with wall motion abnormalities at rest, there is an increased prevalence of multivessel coronary artery disease. Thus, in this subgroup multivessel coronary artery disease is already suggested at rest. It is currently unknown whether an early (heart rate ≤125/min) positive result on a dobutamine stress echocardiogram provides significant prognostic information.

**Study limitations.** Our study has several limitations. It was retrospective and some bias may have been introduced. Attempts were made to limit any potential sources of bias by analyzing and interpreting all data in blinded fashion.

Although no echocardiograms were believed to be uninterpretable, some were of marginal quality (“technically difficult”). No patient with adequate rest images had technically unacceptable stress images. In patients with a poor transthoracic window, transesophageal imaging during dobutamine infusion may provide an acceptable alternative test (24).

Finally, the heart rate at which the test result became positive was determined from retrospective analysis of the data. It is possible that more studies were positive at a heart rate ≤125 beats/min than were documented. In addition, using a heart rate of 125 beats/min as an independent discriminator will require prospective validation. Although the development of a new wall motion abnormality during the test is an end point, subtle wall motion abnormalities may not be appreciated during the study. Medications that block beta-adrenergic receptors may influence the peak heart rate response to dobutamine.

**Conclusions.** Dobutamine stress echocardiography is equally sensitive for the detection of coronary artery disease in all three major coronary artery distributions. Lesions with a minimal lumen diameter <1 mm are more likely to be correctly identified. A dobutamine stress echocardiogram that becomes positive at a heart rate ≤125 beats/min is suggestive of multivessel coronary artery disease.

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**References**


