Improved Cardiac Risk Stratification in Major Vascular Surgery With Dobutamine–Atropine Stress Echocardiography

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Objectives. This study sought to optimize preoperative cardiac risk stratification in a large group of consecutive candidates for vascular surgery by combining clinical risk assessment and semiquantitative dobutamine–atropine stress echocardiography.

Background. Dobutamine–atropine stress echocardiography has been used for the prediction of perioperative cardiac risk in a small group of patients scheduled for elective major vascular surgery on the basis of the presence or absence of stress-induced regional left ventricular wall motion abnormalities.

Methods. Clinical risk assessment and dobutamine–atropine stress echocardiography were performed in 302 consecutive patients presenting for major vascular surgery. The extent and severity of stress wall motion abnormalities and the heart rate at which they occurred, in addition to the presence of wall motion abnormalities at rest, were assessed.

Results. The absence of clinical risk factors (angina, diabetes, Q waves on the electrocardiogram, symptomatic ventricular tachyarrhythmias, age >70 years) identified a low risk group of 100 patients with a 1% cardiac event rate (unstable angina). Dobutamine–atropine stress echocardiographic findings were positive in 72 patients. Twenty-seven patients had a perioperative

cardiac event (cardiac death in 5, nonfatal infarction in 12, unstable angina pectoris in 10); all 27 patients had positive stress test results (positive predictive value 38%, negative predictive value 100%). The semiquantitative assessment of the extent and severity of ischemia did not provide additional prognostic information in patients with positive test results. In contrast, the heart rate at which ischemia occurred defined a high risk group with a low ischemic threshold (38 patients with 20 events [53%]) and an intermediate risk group with a high ischemic threshold (34 patients with 7 events [21%]). All 5 patients with a fatal outcome and 8 of 12 with a nonfatal myocardial infarction were in the high risk group with a low ischemic threshold.

Conclusions. Clinical variables identify 33% of patients at very low risk for perioperative complications of vascular surgery in whom further testing is redundant. In all other candidates, dobutamine–atropine stress echocardiography is a powerful tool that identifies those patients at intermediate risk and a small group at very high risk. Risk stratification with a combination of clinical assessment and pharmacologic stress echocardiography has the potential to facilitate clinical decision making and conserve resources.

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Perioperative cardiac complications are a leading cause of morbidity and mortality in patients undergoing major vascular surgery (1–4). For example, elective resection of an abdominal aortic aneurysm is associated with an operative mortality rate of 3% to 10% (2), with ~50% of deaths cardiac in origin. Effective preoperative risk stratification has the potential to facilitate decision making by enabling patients and physicians to better assess the risk/benefit ratio of proposed surgical procedures. Furthermore, unequivocal identification of a low risk group would permit their expeditious and cost-effective surgical management.

Several techniques for preoperative cardiac risk assessment

have been advocated. These include clinical evaluation (5–7), exercise electrocardiography (8), ambulatory electrocardiography (9,10), radionuclide ventriculography (11) and dipyridamole–thallium scintigraphy (12–14). Of these, dipyridamole–thallium myocardial perfusion scintigraphy has been most widely advocated. However, recent studies (15) have found dipyridamole–thallium scintigraphy to have poor predictive power and suggest that its routine use may not have been justified.

More recently, pharmacologic stress echocardiography with dobutamine or dipyridamole has been proposed as an alternative to dipyridamole–thallium scintigraphy for risk assessment in candidates for vascular surgery (16–21). This technique uses transthoracic echocardiography to detect ischemic left ventricular wall motion abnormalities induced by pharmacologic stress. Preliminary studies suggest that stress echocardiography is a safe (22) and sensitive technique for predicting perioperative cardiac events and has excellent negative predictive power (16–21). However, these previous studies had limitations: 1) Most did not enroll patients consecutively, so a referral bias

may have been present. 2) Clinicians caring for the patients usually had access to test results, and this may have altered management. In some studies, apparently high risk patients underwent coronary angiography or myocardial revascularization, or both, before vascular surgery. 3) A relatively small number of patients were studied. 4) Test results were classified simply as positive or negative, without including information about the extent and severity of inducible ischemia or the threshold heart rate at which ischemia developed. This latter defect might explain the relatively low positive predictive power of stress echocardiography in some studies (16,17). We attempted to overcome these limitations by evaluating the predictive power of dobutamine–atropine stress echocardiography in a large group of consecutive patients while blinding clinicians to test results. We also attempted to improve the predictive power of the test by using a quantitative approach that utilizes more of the information available from the test. This report represents an extension of our previous 136 consecutive patients (21).

Methods

Patient characteristics. Three-hundred two consecutive patients scheduled for elective major vascular surgery were studied during a 3-year period from 1991 to 1994. All patients were judged not suitable to be assessed by exercise testing. After a detailed history, physical examination and 12-lead electrocardiogram (ECG), Detsky's modification of Goldman cardiac risk index was calculated for each patient. By the method of Eagle et al. (13), the number of clinical risk factors (angina, diabetes requiring drug therapy, age >70 years, Q wave on the ECG and history of ventricular ectopic activity requiring treatment) present in each subject was counted. Minimal additional preoperative testing or therapy was undertaken. Three patients underwent dipyridamole–thallium myocardial scintigraphy, and none had coronary angiography or prophylactic myocardial revascularisation before operation.

Dobutamine–atropine stress test. The study protocol was approved by the hospital ethics committee, and all patients gave informed consent. No anti-ischemic medication was withdrawn before testing. A rest two-dimensional echocardiographic examination, including standard apical and parasternal views of the left ventricle, was performed for each patient and recorded on videotape. A rest 12-lead ECG was also recorded. Dobutamine was administered intravenously with an infusion pump, starting at 10 µg/kg body weight per min for 3 min (stage I). The infusion rate was increased by 10 µg/kg per min every 3 min to a maximum of 40 µg/kg per min (stage IV) and continued for 6 min. If signs and symptoms of ischemia were absent during stage IV, atropine was given to patients who did not reach their age-corrected target heart rate [(220 − Age) × 0.85 in men, and (200 − Age) × 0.85 in women]. Intravenous atropine was administered in 0.25-mg increments to a maximum of 1 mg while the dobutamine infusion was continued. During the test, the 12-lead ECG was monitored continuously and recorded each minute. Blood pressure was measured

noninvasively (Accutorr A1, Datascope Corp.) at rest and at each stage of the protocol. The two-dimensional echocardiogram was monitored continuously and recorded on videotape during the last minute of each stage. A quad-screen video display, for side-by-side comparison of rest and stress images, was used during the last 150 examinations (Vingmed CFM 800, Diasonics Sonatron). The criteria for stopping the test included a decline in systolic blood pressure >40 mm Hg from the rest value or a systolic blood pressure <100 mm Hg, significant cardiac arrhythmias, severe chest pain, horizontal or downsloping ECG ST depression ≥0.2 mV measured 80 ms after the J point, ST segment elevation ≥0.2 mV and severe or extensive new echocardiographic wall motion abnormalities.

Off-line assessment of echocardiographic images was performed by two investigators who knew the doses of dobutamine and atropine used but were unaware of clinical information. The left ventricular wall was divided into 16 segments (23), and wall motion in each was subjectively scored on a four-point scale: 1 = normal; 2 = hypokinetic; 3 = akinetic, and 4 = dyskinetic. The test results were considered positive when wall motion in any segment deteriorated one grade or more. Agreement between the two investigators was required for test results to be designated as positive. In the event of disagreement, a third investigator resolved the dispute.

For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress: *Severity of ischemia* was defined as the difference between these two values; *extent of ischemia* was defined as the number of segments exhibiting deteriorating wall motion during stress; and *ischemic threshold* was defined as the heart rate at which new echocardiographic wall motion abnormalities occurred, divided by the maximal age-related heart rate [(220 − Age) in men, and (200 − Age) in women].

Analysis of clinical outcomes. Patients were followed up throughout their stay in hospital. On the first, third and seventh postoperative days, serum levels of creatine kinase (CK) with MB fraction were measured, and a 12-lead ECG was recorded. These tests were repeated when necessary at the discretion of the treating physicians. Adverse clinical outcomes included 1) cardiac death (on the basis of clinical assessment, cardiac isoenzyme levels, the ECG and autopsy studies when available); 2) nonfatal myocardial infarction documented by cardiac isoenzyme levels (CK >110 U/liter with MB >10%) or ECG (new Q waves >0.03 s), or both; 3) unstable angina consisting of typical persisting chest pain at rest with transient ischemic ECG changes requiring prolonged stay or readmission to the intensive care unit and intravenous treatment with nitrates or percutaneous transluminal angioplasty, or both.

Statistical analysis. Univariable analysis was performed using the chi-square test with the Yates correction or Fisher exact test for categoric variables and the Student t test for continuous variables. Multivariable logistic regression models were fitted in stepwise manner to identify independent predictors of a cardiac event. Only the variables significantly associated with cardiac events by univariable statistics were entered into the multivariable analysis. The risk associated with a given

variable was expressed as an odds ratio with corresponding 95% confidence intervals. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. Receiver operating characteristic curves were used to determine the optimal ischemic threshold for the prediction of cardiac events.

Results

Patient characteristics. The study included 302 patients (257 men, 45 women; mean age 67 years, range 22 to 90) with a history of previous myocardial infarction in 93 (31%), angina pectoris in 60 (20%) and diabetes mellitus (with drug therapy) in 33 (11%). Two hundred seventy-five patients had a Detsky score of 0 to 15 points; 23 had 16 to 30 points; and 4 had >30 points. By the clinical risk factors of Eagle et al. (13), 100 patients had no clinical risk factors, 179 patients one or two risk markers, and 21 patients had three or more risk factors.

Dobutamine–atropine stress echocardiography. Two patients with severe pulmonary disease were excluded from the study because adequate echocardiographic images were not obtained. Atropine was administered in 101 of 300 patients. Patients taking beta-adrenergic blocking agents before the test required atropine more frequently (67 of 101) than those who were not (34 of 101) (p = 0.004). Test end points were target heart rate in 276 patients (92%), severe angina in 17 (5.6%) and side effects in 7 (2.3%). The side effects causing termination of the test were ventricular fibrillation in one patient, paroxysmal atrial fibrillation in two, hypotension in one, severe hypertension (240/130 mm Hg) in one and chills in two. Cardiac arrhythmias all occurred in the recovery phase of the test, and test results were available for these patients. In the four other patients the test was inconclusive; in the perioperative period no events occurred.

Cardiac arrhythmias developed in 15 patients (5%) (sustained ventricular tachycardia in 3, nonsustained ventricular tachycardia in 8, paroxysmal atrial fibrillation in 3). One patient developed ventricular fibrillation during stage IV. This arrhythmia was terminated with a single countershock, and the patient suffered no sequelae. Two patients with sustained ventricular tachycardia responded quickly to discontinuation of dobutamine, and another received intravenous metoprolol. Paroxysmal atrial fibrillation reverted to sinus rhythm after discontinuation of dobutamine plus administration of intravenous metoprolol in two patients and intravenous digoxin in one. Mild hypotension (decline in systolic blood pressure >20 mm Hg) occurred in 12 patients (4%), hypertension (systolic blood pressure >220 mm Hg) in 3 (1%) and chills in 7 (2%).

New wall motion abnormalities occurred in 72 of 300 patients, 12 of whom had normal wall motion at rest. Six patients had a left bundle branch block, making interpretation of ST segment changes impossible. New ST elevation or depression >1 mm during testing occurred in 68 patients and angina in 42. In all patients new wall motion abnormalities preceded the occurrence of stress-induced angina.

Cardiac events. Twenty-seven patients experienced cardiac events between days 1 and 7 (fatal myocardial infarction in 5, nonfatal myocardial infarction in 12, unstable angina in 10).

Predictive value of clinical variables and stress test. The Detsky score was significantly higher in patients with than without a cardiac event (12.0 ± 8.1 vs. 6.5 ± 5.4, respectively, p < 0.01). Cardiac events occurred in 22 of 275 low risk patients (0 to 15 points), 4 of 23 intermediate risk patients (16 to 30 points) and 1 of 4 high risk patients (>30 points).

One cardiac event occurred among 100 patients (1%) with no clinical risk factors (i.e., low risk) according to the criteria of Eagle et al. (13). The event rate was 11% (20 of 181) in intermediate risk patients with one or two risk factors and increased to 29% (6 of 21) in high risk patients with more than two risk factors (p < 0.001).

Univariable analysis. *Clinical variables.* Significant univariable clinical predictors of perioperative events were a history of angina (odds ratio [OR] 4.6, 95% confidence interval [CI] 2.0 to 10), previous myocardial infarction (OR 4.1, 95% CI 1.8 to 9.2) and diabetes mellitus (OR 3.2, 95% CI 1.3 to 8.4). Other clinical variables, including age, gender, history of hypertension, smoking, heart failure, use of antianginal medication and type of operation (abdominal vs. infrainguinal), were not predictive of perioperative events.

Echocardiographic variables. Perioperative cardiac events were more frequent in patients with echocardiographic wall motion abnormalities at rest (OR 3.7, 95% CI 1.6 to 8.3). All 27 patients with a cardiac-related event had new wall motion abnormalities during stress. Consequently, patients with positive test results were more likely to have a cardiac event (OR 124, 95% CI 17 to 934). The positive predictive value of new wall motion abnormalities in the present study was 38% (95% CI 26 to 50). Ischemic ST segment changes were less strongly correlated with perioperative events (OR 4.9, 95% CI 2.2 to 11), and the occurrence of angina during stress was unrelated to outcome (OR 1.8, 95% CI 0.6 to 4.6).

Multivariable analysis of clinical data and stress test results revealed only one independent predictor of cardiac events—new wall motion abnormalities (OR 124, 95% CI 17 to 934).

Among patients with new wall motion abnormalities, quantification of the extent and severity of stress-induced wall motion abnormalities was not correlated with perioperative cardiac events (Table 1). However, the heart rate threshold at which ischemia occurred provided additional prognostic information. Among patients with a cardiac event, the ischemic threshold was 67% (95% CI 63% to 71%) of the age-corrected maximal heart rate compared with 80% (95% CI 77 to 83) in patients without an event (p < 0.01). On the basis of receiver operating characteristic curve analysis, the best "cutoff" point for the heart rate ischemic threshold was estimated to be 70%. There were 20 postoperative cardiac-related events among 38 patients in whom ischemic wall motion abnormalities developed at a heart rate ≤70% of the age-corrected maximal heart rate (positive predictive power 53%). In contrast, there were seven cardiac-related events among 34 patients with a heart rate threshold >70% (positive predictive power 21%). All

Table 1. Semiquantitative Analysis of Dobutamine–Atropine Stress Test in Patients With Positive Test Results: New Wall Motion Abnormalities During Stress (n = 72)

Ischemia	All Cardiac Events (n = 27)	CD/MI (n = 17)	No Cardiac Events (n = 45)	p Value
Threshold	67 (63–71)	62 (57–67)	80 (77–83)	< 0.01
Extent	3.3 (2.3–4.3)	3.4 (2.2–4.6)	3.6 (2.5–4.7)	NS
Severity	1.5 (1.4–1.7)	1.5 (1.3–1.7)	1.6 (1.4–1.8)	NS

Data presented are mean value (95% confidence interval). Extent = number of ischemic segments during stress; Severity = difference between wall motion score at peak stress and rest; Threshold = heart rate increment at which echocardiographic myocardial ischemia occurs [(Heart rate at ischemia − Heart rate at rest/Age-predicted maximal heart rate − Heart rate at rest) %].

patients with cardiac death had a low ischemic threshold of 65% (95% CI 58% to 71%).

Discussion

The present study demonstrates the utility of dobutamine–atropine stress echocardiography for preoperative cardiac risk stratification in candidates for major vascular surgery. The test was especially effective for identifying a low risk group with a very low incidence of perioperative cardiac complications. There were no cardiac events among 228 patients with negative test results (negative predictive power 100%, 95% CI 98% to 100%). Positive test results greatly increased the likelihood of a perioperative cardiac event (OR 124, 95% CI 17 to 934) and was the sole independent predictor of cardiac events. Seventy-two patients with positive stress test results had 27 perioperative cardiac complications (positive predictive power 38%, 95% CI 26% to 50%).

Quantifying the extent and severity of stress-induced wall motion abnormalities did not provide additional risk stratifi-

cation among patients with positive test results. However, consideration of the heart rate threshold at which ischemia occurred significantly enhanced risk stratification. Ischemia occurred at significantly lower heart rates in patients with than without a cardiac event (67%, 95% CI 63% to 71% vs. 80%, 95% CI 77% to 83%) of the age-corrected maximal heart rate). An ischemic threshold of 70% of the age-corrected maximal heart rate provided optimal risk stratification. This threshold defined a high risk group of 38 patients with an ischemic threshold (<70%) in which 20 cardiac events occurred (positive predictive value 53%). This high risk group included all 5 patients with cardiac-death and 8 of 12 with a nonfatal infarction (76% of "hard" cardiac events). There were only seven events in an intermediate risk group of 34 patients with new wall motion abnormalities at a high ischemic threshold (positive predictive value 21%) (Fig. 1).

Heart rate threshold was not influenced by the concomitant use of beta-blockers. When the same patients were studied with and without beta-blockers, the heart rate at which ECG-detected ischemia occurred was unchanged. The dobutamine

Figure 1. Breakdown of clinical variables and dobutamine stress test results for perioperative outcomes as applied to the present group of 300 patients. Clinical variables are age >70 years, angina, diabetes requiring treatment, Q wave on the electrocardiogram and history of ventricular ectopic activity. DSE = dobutamine–atropine stress test; events = cardiac death, nonfatal myocardial infarction (MI) and unstable angina pectoris; high (low) threshold = new echocardiographic wall motion abnormalities occurred at >70% (≤70%) of maximal age-corrected heart rate; ischemic threshold = heart rate at which new echocardiographic wall motion abnormalities occurred, divided by the maximal age-corrected heart rate (220 − Age in men, 200 − Age in women); neg (pos) = negative (positive) test results.
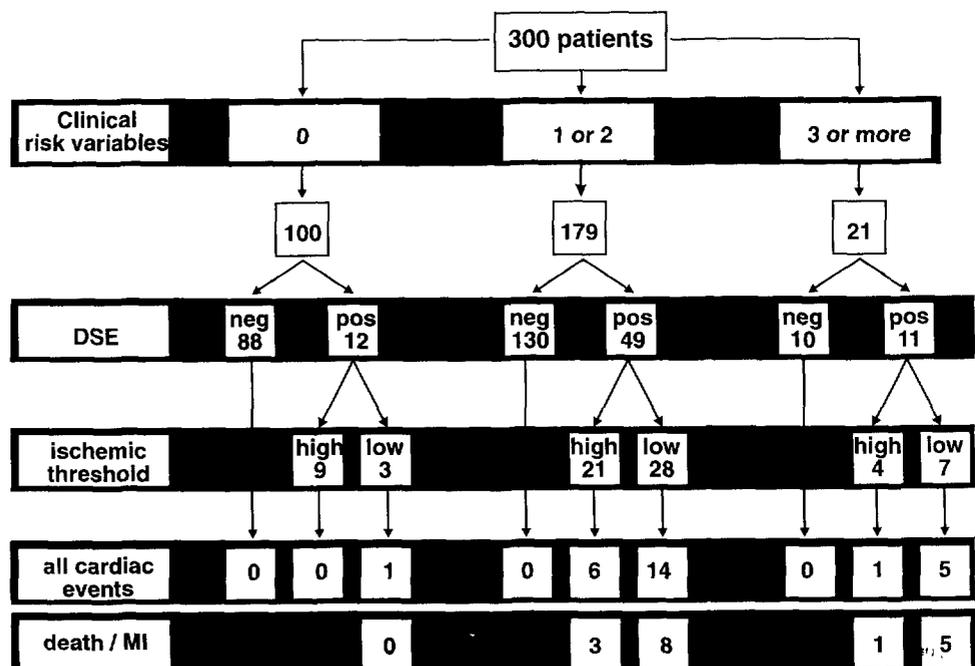
Table 2. Review of Value of New Wall Motion Abnormalities Detected by Stress Echocardiography for Preoperative Risk Stratification of Perioperative Cardiac Events in Patients Scheduled for Major Vascular Surgery

Study (ref no.)	Stress	No. of Pts	Se	Sp	+PV	−PV	No. of Events	Event
Tischler et al. (20)	Dipy	109	88	98	78	99	8	CD, MI, UAP, CHF
Lane et al. (17)	Dobu	38	100	56	21	100	4	CD, MI, UAP
Poldermans et al. (21)	Dobu	131	100	83	42	100	15	CD, MI, UAP, CHF
Lalka et al. (18)	Dobu	60	85	44	29	95	13	CD, MI, UAP
Eichelberger et al. (16)	Dobu	70	100	66	19	100	5	MI, UAP

CD = cardiac death; CHF = congestive heart failure; Dipy = dipyridamole; Dobu = dobutamine; MI = myocardial infarction; pts = patients; ref = reference; Se = sensitivity (%); Sp = specificity (%); +PV = positive predictive value (%); −PV = negative predictive value (%); UAP = unstable angina pectoris.

dose used to achieve this heart rate increased with beta-blocker medication.

Our results regarding the prognostic value of the ischemic "threshold" during dobutamine stress testing are in agreement with those reported by Cutler et al. (8) using exercise electrocardiography. They found that cardiac complications occurred most frequently in patients who developed ischemic ST segment depression at <75% of the predicted maximal age-related heart rate.

Semiquantitative analysis. Quantifying the extent and severity of stress-induced ischemia did not enhance the predictive power of dobutamine–atropine stress echocardiography. Other investigators (24), using quantitative dipyridamole–thallium myocardial scintigraphy, have demonstrated that the extent and severity of redistribution defects enhanced the predictive value of this test. This discrepancy is difficult to explain. A tentative explanation for these different findings is that dipyridamole–thallium scintigraphy detects not only myocardial ischemia, but malperfusion that may be associated with mild coronary artery stenoses (25). It is conceivable that such mild stenoses become clinically relevant if they subtend a large myocardial territory.

Side effects. The dobutamine–atropine stress test caused serious complications in three patients in the present study (ventricular fibrillation in one, paroxysmal atrial fibrillation in two). There were no fatal complications, which confirms previous findings (22) about the safety of the stress test.

The present study has several unique features compared with previous echocardiographic studies: 1) We studied a large group of consecutive patients; 2) test results were not used for clinical decision making; 3) a comprehensive analysis of stress test results, including severity, extent and heart rate threshold of ischemia, was applied. These features increase our confidence in the reliability of our results. The findings are consistent with previous work, including our own. All earlier studies found that preoperative pharmacologic stress echocardiography has excellent negative predictive power for perioperative cardiac events (95% to 100%) (Table 2). Moreover, most early studies found the positive predictive power to be relatively low (21% to 42%). The exception is the work of Tischler et al. (20). In the only study using dipyridamole stress echocardiography,

Tischler et al. found a positive predictive power of 78%. There are several possible explanations for this different result: 1) Dipyridamole-induced ischemia might be a less sensitive but more specific indicator of severe coronary artery disease than that caused by dobutamine/atropine. Consistent with this hypothesis, the sensitivity of dipyridamole stress echocardiography was 88% in the study of Tischler et al. versus 100% in our study and two other reports (16,17,21). 2) Methodologic differences might explain the results. The study by Tischler et al. was relatively small (n = 109), and there were few cardiac events (n = 8). In addition, differences in study patients and selection criteria may have been operative. These differences in study design make it impossible to draw definite conclusions about the relative efficacy of dipyridamole or dobutamine as pharmacologic stressors.

Clinical risk assessment. Our experience shows that clinical risk assessment using the Detsky scoring system is too insensitive for use as a screening tool in candidates for vascular surgery. In our study, 22 of 27 cardiac events occurred in patients with a relatively low Detsky score of 0 to 15 points. The Detsky system is a modification of the cardiac risk index of Goldman et al. (26), which is itself a specific but relatively insensitive indicator of risk. Furthermore, the cardiac risk index was derived from a general surgical population undergoing a variety of surgical procedures rather than the relatively unique vascular surgery cohort of the present study.

In contrast, the clinical risk factors defined by Eagle et al. (13) in a study of candidates for vascular surgery were useful in our study group. There was only one cardiac event (unstable angina pectoris) among 100 patients with none of the five clinical factors of Eagle et al. (angina, diabetes requiring drug therapy, age >70 years, Q wave on ECG and history of ventricular ectopic activity requiring treatment). The negative predictive power of none of the criteria of Eagle et al. was 99% (95% CI 98% to 100%). This finding is consistent with the negative predictive power of 96.9% in the study by Eagle et al. (13) and 96.8% noted by Lette et al. (6). This result is not surprising, considering that the three univariable clinical predictors of perioperative cardiac risk that we observed (angina, diabetes and previous myocardial infarction) are similar to those seen by Eagle et al. In contrast to the study by Eagle et

al. (13), the positive predictive value remained present, even in patients with three or more cardiac risk factors. This result may be explained by the superior positive predictive value of dobutamine–atropine stress echocardiography compared with that for dipyridamole–thallium scintigraphy for perioperative cardiac events.

On the basis of our results, we do not recommend routine preoperative pharmacologic stress echocardiography for all candidates for vascular surgery. Patients with none of the clinical risk factors of Eagle et al. appear to represent a low risk group (33% of our patients) for whom further cardiac evaluation may be unnecessary. We recommend that the remaining patients (with one or more clinical risk factors) undergo stress echocardiography preoperatively. This test identifies another large low risk group (70% of our remaining patients) with negative test results. Avoiding additional testing or expensive risk-reduction strategies (e.g., coronary angiography and myocardial revascularization), or both, in these patients has the potential to conserve health care resources. The test also defines an intermediate risk group with positive stress test results but a high ischemic threshold. The optimal management of these patients is unclear.

Patients with positive pharmacologic stress test results and a low ischemic threshold (heart rate <70% of the age-corrected maximal heart rate) are at extremely high risk, and the advisability of operation should be carefully reconsidered.

The optimal management of the very high risk patient who must undergo major vascular surgery because of life- or limb-threatening disease is unknown. Various risk-reduction strategies, including intensive perioperative monitoring and intervention (2,6,27), perioperative beta-adrenergic blockade with ultrashort-acting beta-blockers like esmolol (2), prophylactic myocardial revascularisation (3,28) and stress suppression with regional anesthesia and analgesia (29), have been proposed. However, the efficacy of these techniques has not been adequately investigated, and their benefits are unproved.

Dobutamine–atropine stress echocardiography clearly identifies a high risk group of patients in whom the utility of previously untested risk-reduction strategies can be prospectively assessed and may represent the most immediate application of the test.

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