

Perioperative Prognostic Value of Dipyridamole Echocardiography in Vascular Surgery A Large-Scale Multicenter Study in 509 Patients

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Background—Patients undergoing major vascular surgery are at a relatively high risk of cardiac events, and pharmacological stress echocardiography is increasingly used for perioperative risk stratification. The aim of the current study was to evaluate the value of dipyridamole echocardiography test (up to 0.84 mg/kg over 10 minutes) in predicting cardiac events in a large-scale, multicenter, prospective, observational study design.

Methods and Results—Five hundred nine patients (mean age 66 ± 10 years) were studied before vascular surgery by dipyridamole stress echocardiography in 11 different centers. All patients underwent preoperative clinical risk assessment according to the American Heart Association guidelines. No major complications occurred during dipyridamole stress echocardiography. Technically adequate images were obtained in all patients; however, in 4 patients only the low dipyridamole dose (0.56 mg/kg over 4 minutes) was given for limiting side effects. Eighty-eight (17.3%) had a positive test. Perioperative events occurred in 31 (6.1%) patients: 6 deaths, 11 myocardial infarctions, and 14 episodes of unstable angina. Sensitivity and specificity of dipyridamole stress echocardiography for predicting spontaneous cardiac events were 81% and 87%, respectively, with a positive predictive value of 28% and negative predictive value of 99%. By multivariate analysis, the difference between wall motion score index at rest and peak stress (Δ wall motion score index), test positivity, and ST-segment depression during dipyridamole infusion were independent predictors of any perioperative cardiac event.

Conclusions—Dipyridamole stress echocardiography is safe and well tolerated in patients undergoing major vascular surgery and provides an effective preoperative screening test for the risk stratification of these patients, mainly because of the extremely high negative predictive value, which is a potent predictor of complication-free procedure. (*Circulation*. 1999;100[suppl II]:II-269–II-274.)

Key Words: echocardiography ■ trials ■ stress ■ risk factors ■ surgery

Perioperative cardiovascular complications such as myocardial infarction, unstable angina, pulmonary edema, and serious ventricular arrhythmias are major causes of morbidity and death in surgical patients. This is particularly important in patients undergoing major vascular surgery, who have a relatively high rate of cardiovascular complications.¹ A variety of methods and noninvasive diagnostic procedures to predict perioperative risk have been evaluated over the last decade, including multifactorial clinical scoring systems,^{2–4} ambulatory ECG monitoring,⁵ radionuclide ventriculography,⁶ and pharmacological myocardial perfusion imaging.^{7–17} It has been suggested that the most accurate information can be derived by adding clinical data to those obtained by dipyridamole–thallium-201 myocardial perfusion imaging,⁹ which remains the most extensively studied noninvasive

approach to the risk stratification of patients undergoing noncardiac surgery. Recently, stress echocardiography with dobutamine^{18–22} or dipyridamole^{23–26} has been proposed for risk stratification in these patients. Pharmacological stress echocardiography proved to be a safe and sensitive technique for predicting perioperative cardiac events, with an excellent negative predictive power. The widespread availability and the relatively low cost of the technique make it a most appealing one for risk stratification. This study represents the extension of a previously reported multicenter prospective study with dipyridamole stress echocardiography in 136 patients undergoing major vascular surgery.²⁴ The aim of the study was to confirm the value of dipyridamole stress echocardiography as an effective preoperative screening test for risk stratification before noncardiac vascular surgery in a

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substantially larger patient population and to show the incremental value, if any, of the technique over conventional clinical variables.

Methods

Patient Population

Initially, 532 patients (mean age 66 ± 10 years) scheduled for elective noncardiac surgery, with a technically acceptable acoustic window, were prospectively enrolled in 11 different centers. Twenty-three patients were excluded from the study because of the presence of high-risk stress echocardiography response (dipyridamole time < 5 minutes and/or a peak wall motion score index > 2), which influenced the decision of the attending physician to either cancel or postpone the surgical intervention, so the final number of patients that were enrolled in this study was 509.

Dipyridamole Stress Echocardiography

The standard protocol for dipyridamole stress echocardiography (cumulative dose 0.84 mg/kg over 10 minutes) was used.²⁴ During the procedure, 2-dimensional echocardiographic, 12-lead ECG, and blood pressure monitoring were continuously performed. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model.²⁷ In all studies, segmental wall motion was semiquantitatively graded as follows: normal, normal wall motion at rest, with normal/increased wall motion after dipyridamole (score 1); hypokinetic, marked reduction in endocardial motion (score 2); akinetic, virtual absence of inward motion (score 3); and dyskinetic, paradoxical wall motion away from the left ventricular center in systole (score 4). Test positivity was defined as the occurrence of ≥ 1 of the following conditions: (1) new dyssynergy in a region with normal rest function (ie, normokinesia becoming hypokinesia, akinesia, or dyskinesia); and (2) worsening of rest dyssynergy (ie, hypokinesia becoming akinesia or dyskinesia; rest akinesia becoming dyskinesia was not considered a positivity criterion).²⁸ The wall motion score index (WMSI) was derived by dividing the sum of individual segments by the number of interpretable segments. Aminophylline (up to 240 mg over 3 minutes) was given at the end of the test. Echocardiographic monitoring was performed throughout dipyridamole infusion and up to at least 5 minutes after the end of the infusion. Two-dimensional echocardiographic images were recorded at baseline and at the end of each dipyridamole dose. In negative tests, the dipyridamole time (ie, the time between start of infusion and the onset of a regional dyssynergy) was arbitrarily assumed to be 17 minutes (when aminophylline was given).

Quality control of stress echocardiography performance and reading in enrolled centers was previously described in depth.²⁹ Briefly, the reader from each recruiting center met the predefined criteria for stress echocardiography reading. At that point, the center could start recruiting patients and reading of stress echocardiography from recruiting center was directly entered in the data bank.

Preoperative Risk Assessment

Preoperative risk assessment was evaluated according to the American College of Cardiology/American Heart Association Task Force guidelines.³⁰ Patients were evaluated according to the presence of clinical predictors of increased perioperative cardiovascular risk and to the risk inherent to the type of noncardiac surgical procedure.

Postoperative Follow-Up

Patients were followed up throughout their hospital stay. During the first 3 days after surgery and when clinically indicated, serum levels of creatine kinase with isoenzymes were measured and a 12-lead ECG recorded.

Events were defined as cardiac-related death, nonfatal myocardial infarction, and unstable angina. The definition of in-hospital cardiac-related death required documentation of significant arrhythmias, cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precip-

itating factor. Myocardial infarction was diagnosed in the presence of the development of new ECG changes and cardiac enzyme level increases (MB fraction $> 5\%$). Unstable angina was defined by accelerating anginal symptoms with no enzyme level elevation or new wall motion dyssynergy on the resting echocardiogram or new Q waves on the resting ECG.

Statistical Analysis

Values are expressed as mean \pm SD.

The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (SPSS software package for Windows, 1995). The analysis was performed according to the unmodified forward selection stepwise procedure. In this case, the variables were entered into the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relation to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable), but in this case this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model. We also analyzed the data according to a modified stepwise procedure, in which the significant individual variables were included in the model in the same order in which they are actually considered by the cardiologist (historic and clinical data first, preoperative risk variables second, and the dipyridamole stress echocardiography variables third).

Variables selected for examination were age, sex, previous myocardial infarction, history of angina, history of coronary revascularization, hypertension, smoking, diabetes, WMSI at baseline, WMSI at peak stress, the variation between rest and stress WMSI (Δ WMSI), test positivity, dipyridamole time (ie, the time from the beginning of infusion to the development of regional dyssynergy at echocardiography), ECG modification during dipyridamole infusion, and angina during dipyridamole infusion.

Continuous variables were compared by the unpaired 2-sample *t* test. Proportions were compared by the χ^2 statistic; a Fisher's exact test was used when appropriate. A value of $P < 0.05$ was considered statistically significant

Results

Type of Surgery

Two hundred seventy (53%) patients underwent abdominal aortic aneurysm repair, 125 (24%) aortoiliac and aortofemoral reconstruction, and 114 (22%) carotid artery thromboendarterectomy.

Patient Characteristics

The study included 509 patients (450 men, 59 women, mean age 66 ± 10 years), with a history of previous myocardial infarction in 103 (20%), angina pectoris in 63 (12.3%), diabetes mellitus in 54 (11%), hypertension in 249 (52%), and 51 (10%) with a history of previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Two hundred four (40%) patients reported either past or current smoking habit. According to the guidelines for preoperative risk assessment, the patient population comprised 394 (77.4%) with a high risk and 115 (22.6%) with an intermediate risk of developing perioperative cardiac events (Table 1). Nineteen percent of the patients were receiving antianginal therapy during the test (nitrates and/or calcium-channel blockers and/or β -blockers).

TABLE 1. Patient Characteristics

Age, y	66±10
Sex, male/female	450/59
Patients with previous myocardial infarction	103 (20%)
History of angina	63 (12.3%)
Diabetes mellitus	54 (11%)
Hypertension	249 (52%)
Previous coronary artery bypass grafting or coronary angioplasty	51 (10%)
Current or past cigarette use	204 (40%)
Preoperative risk	
High	394
Intermediate	115
Resting WMSI	1.11±0.25

Resting Echocardiographic Findings

Resting WMSI was 1.11±0.25. Regional wall motion abnormalities were present in the baseline examination in 131 (26%) patients. Mean ejection fraction was 56±10%.

Stress Echocardiographic Findings

By inclusion criterion, technically adequate images were obtained in all patients. No major complications occurred during the test. In 4 patients, only the low dipyridamole dose (0.56 mg/kg over 4 minutes) was given for limiting side effects. The feasibility of the test was 99%. The dipyridamole echocardiography test was positive in 88 (17.3%), and negative in 421 (82.7%). WMSI at peak dipyridamole was 1.5±0.37 in positive versus 1.10±0.26 in negative tests, ($P<0.0001$).

Follow-Up Data

Perioperative cardiac events occurred in 31 (5%) patients: 6 deaths, 11 myocardial infarctions, and 14 episodes of unstable angina.

Twenty-five (81%) of the 31 who had cardiac events had a positive dipyridamole stress echocardiography test. Sensitivity and specificity of the test for predicting spontaneous cardiac events were 81% and 87%, respectively. The positive predictive value of the test was 28%, with a negative predictive value of 99%.

Cardiac-Related Death

When cardiac-related death was considered, all the 6 deaths occurred in patients with a positive test (Table 2). By univariate analysis, dipyridamole time (χ^2 11.1, $P<0.0008$),

TABLE 2. Event Rate Occurrence in Relation to Dipyridamole Stress Echocardiographic Results

	DET		P
	Positive Findings (n=88)	Negative Findings (n=421)	
Cardiac-related death	6 (6.8%)	0	0.0001
Nonfatal myocardial infarction	9 (10.2%)	2 (0.5%)	0.0001
Unstable angina	10 (11.4%)	4 (1%)	0.0001

DET indicates dipyridamole echocardiography test.

TABLE 3. Stepwise Predictors of Cardiac Death

	χ^2	P	HR (95% CI)
Δ WMSI	18.07	0.0000	973.5 (43.3 to 21.874)

WMSI at peak stress (χ^2 12.7, $P<0.0003$), and peak Δ WMSI (χ^2 18.8, $P<0.0000$) reached the highest value. By stepwise analysis, only Δ WMSI (hazard ratio [HR] 973.5, 95% CI 43.3 to 21.874, $P<0.0000$) was an independent predictor of cardiac death (Table 3). When variables were entered into the model according to an interactive clinically realistic approach, clinical variables and perioperative risk were not able to predict the adverse outcome; when considering stress echocardiography parameters, the model was able to predict cardiac death through the Δ WMSI (global χ^2 33.504, df 4, $P<0.0001$).

Hard Cardiac Events

When only hard cardiac events (cardiac death and nonfatal myocardial infarction), were considered, there were 6 cardiac-related deaths and 9 nonfatal myocardial infarctions in patients with positive test results versus no cardiac death and 2 nonfatal myocardial infarctions in those with negative test results (17% vs 0.5%, $P<0.000$). By univariate analysis, angina during dipyridamole test (χ^2 11.0, $P<0.0009$), ST-segment depression during dipyridamole test (χ^2 16.0, $P<0.0001$), WMSI at peak stress (χ^2 12.9, $P<0.0003$), dipyridamole time (χ^2 22.3, $P<0.0000$), test positivity (χ^2 24.3, $P<0.0001$), and Δ WMSI (variation between rest and stress WMSI) (χ^2 33.3, $P<0.0000$) were the best predictors of adverse outcome. By stepwise analysis, only test positivity (HR 38.8, 95% CI 8.56 to 175.8, $P<0.001$) was an independent predictor of hard cardiac events.

Spontaneous Events

Patients with positive test results had a higher incidence of spontaneous events than those with negative results (28% vs 1.4, $P<0.05$; 6 cardiac-related deaths, 9 nonfatal myocardial infarctions, 10 episodes of unstable angina in patients with positive results vs no cardiac-related death, 2 myocardial infarctions, 4 episodes of unstable angina). By univariate analysis, angina during dipyridamole test (χ^2 17.4, $P<0.0000$), ST-segment deviation during dipyridamole test (χ^2 30.2, $P<0.0000$), WMSI at peak stress (χ^2 30.3, $P<0.0000$), dipyridamole time (χ^2 37.8, $P<0.0000$), test positivity (χ^2 48.7, $P<0.0000$), and peak Δ WMSI (χ^2 53.3, $P<0.0000$) were the best predictors of spontaneous events. By stepwise analysis, ST-segment deviation during dipyridamole test (HR 2.64, 95% CI 1.0 to 6.9, $P<0.0479$), test positivity (HR 5.46, 95% CI 1.25 to 23.8, $P<0.0237$), and peak Δ WMSI (HR 38.1, 95% CI 2.0 to 726.9, $P<0.0154$) were independent predictors of adverse outcome. With an interactive procedure, we analyzed the predictivity of the model considering the variables in clinical order: historic parameters first, preoperative risk assessed on clinical grounds, and stress echocardiographic parameters (Figure 1); still stress echocardiographic parameters added significant prediction to the model compared with historic and clinical variables.

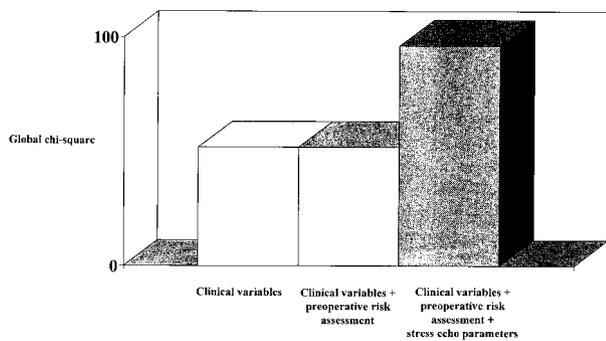


Figure 1. Global χ^2 value of significant predictor modeling of spontaneous events (cardiac death, nonfatal myocardial infarction, unstable angina) according to an interactive procedure. In the model, stress echocardiographic parameters still added significant information to historic clinical variables and preoperative risk parameters.

Discussion

The current study confirms in a larger patient population the results of a previous report²⁴ on the risk stratification power of dipyridamole stress echocardiography in patients undergoing noncardiac vascular surgery. In this analysis, test positivity identified as the variation between rest and stress WMSI (peak Δ WMSI) was the best predictor of perioperative in-hospital cardiac death. Stress echocardiographic results outperform the clinical variables routinely used to estimate the risk in this set of patients. Moreover, the current study demonstrates that the dipyridamole echocardiography test is safe and well tolerated in a population of consecutive patients enrolled on a multicenter basis who are undergoing major vascular surgery, providing an effective preoperative screening for the risk stratification mainly as a result of the extremely high negative predictive value.

Comparison With Previous Studies

These results are consistent with previous reports that used pharmacological stress echocardiographic imaging techniques to predict perioperative ischemic events in patients undergoing noncardiac vascular surgery. The experience of several groups with either dobutamine^{18–22} or dipyridamole indicates,^{23–26} in univocal terms, that these tests have a very high negative predictive value (between 90% and 100%): A negative test is associated with a very low incidence of cardiac events and allows a safe surgical procedure. Much lower is the positive predictive value (between 25% and 45%). In the series by Poldermans et al,²¹ the presence of a new wall motion abnormality was a powerful determinant of an increased risk for perioperative events after multivariate adjustment for different clinical and echocardiographic variables. The same group³¹ reported that dobutamine stress echocardiography is the most powerful predictor of late cardiac events after major vascular surgery and is superior to simple clinical risk assessment. In fact, multivariate analysis indicated that the extent of ischemia was an independent predictor of late cardiac events.³¹ The lower positive predictive value of the test in the current study compared with the study by Poldermans et al is probably caused by the fact that referring physicians were not blinded to stress echocardiographic results in our study. This situation was the only

feasible one in our setting because of ethical and practical reasons. In this way, patients with “high-risk” dipyridamole stress echocardiography response are excluded because they are either referred to revascularization or vascular surgery is postponed. This ultimately deflates the predictive value of a positive test. Myocardial perfusion imaging with dipyridamole has been used widely for the preoperative evaluation of patients before vascular surgery. The positive predictive value of thallium redistribution ranged from 4% to 20% in reports that included >100 patients.^{9,10,12–17} The negative predictive value of a normal scan remains high, at 99% for myocardial infarction and/or cardiac death. Recently Baron et al¹⁶ raised the need for caution in routine screening with dipyridamole thallium stress testing of all patients before vascular surgery. In this review of 457 patients undergoing elective abdominal aortic surgery, the presence of definite coronary artery disease and age >65 years were better predictors of cardiac complications than perfusion imaging. In a recent meta-analysis of 15 studies³² comparing intravenous dipyridamole–thallium-201 imaging and dobutamine echocardiography for risk stratification before vascular surgery, it has been demonstrated that the prognostic value of noninvasive stress imaging abnormalities for perioperative ischemic events is comparable between available techniques but that the accuracy varies with coronary artery disease (CAD) prevalence. The results obtained with dipyridamole stress echocardiography were added to the previous meta-analysis: The current study shows comparable results but a narrower confidence interval because of the large patient population analyzed (Figure 2).

Clinical Implications

Risk stratification in noncardiac vascular surgery recently has become a major clinical issue in clinical practice. Several large studies have demonstrated that perioperative cardiac morbidity is particularly high in patients who undergo vascular surgery, especially when they are ≥ 70 years old, with an incidence of angiographically significant CAD as high as 75%.³³ Patients who require vascular surgery appear to have an increased risk for cardiac complications as the result of different factors: First, many of the risk factors contributing to peripheral vascular disease are also risk factors for coronary artery disease; second, the usual presentation for CAD may be obscured by exercise limitations imposed by advanced age, intermittent claudication, or both; third, major arterial operations may be associated with substantial fluctuations in intravascular fluid volumes, cardiac filling pressures, systemic blood pressure, or heart rate. The need of risk stratification for the preoperative assessment of CAD in peripheral vascular patients is well established, and guidelines from the AHA/ACC Committee have been drawn to focus this clinical problem.³⁰ The diagnostic-prognostic algorithm takes into consideration patients at high, intermediate, and minor cardiovascular risk who should undergo any type of vascular surgery considered as a high-risk procedure. In the current conceptual and practical framework, the evidence of inducible ischemia during noninvasive stress imaging is a crucial determinant of future risk, whereas clinical variables do not provide an adequate power of stratification. Pharma-

Univariate odds ratio for intravenous dipyridamole-thallium-201 (TI-201) myocardial perfusion, dobutamine and dipyridamole stress echocardiographic imaging

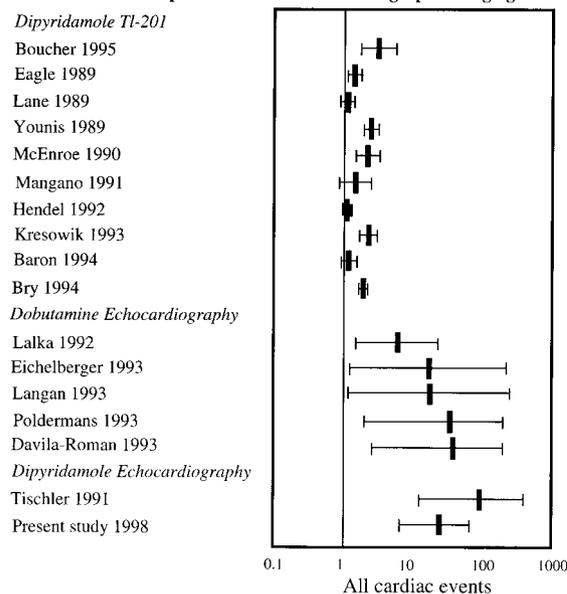


Figure 2. Univariate hazard ratio for intravenous dipyridamole-thallium-201 myocardial perfusion, dobutamine stress echocardiography, and dipyridamole stress echocardiography for each of the 17 published reports (redrawn and updated from Reference 32).

cardiological stress echocardiography might play a central role in the workup of the vascular patient, mainly through the information on the extent and severity of inducible ischemia. Moreover, pharmacological stress echocardiography is a low-cost, widely available technique, highly suited for routine clinical risk stratification. On the basis of the current data, a negative stress echocardiography test is associated with a very low incidence of cardiac events and allows a safe surgical procedure. In the presence of a positive stress echocardiography test, the approach should be weighed from case to case and on the basis of the stress echocardiography response, which should not be read as a “yes or no” gate-keeper to vascular surgery. In fact, a stress echocardiography response has different shades of severity, taking into consideration the time of appearance of the wall motion abnormalities (the shorter the time the higher the probability of an extensive CAD), the extent of wall motion abnormalities (a high number of the segments is related to an extensive disease), and the severity of the inducible dyssynergy. Therefore, on the basis of these parameters, it is possible to grade the response and consequently the therapeutic approach to the patient, which is different from case to case because patients with a high-risk stress echocardiography result should (and this was our approach for ethical reasons) undergo coronary angiography and postpone cardiac surgery; on the other end, a low-risk stress echocardiography positivity (small extent of the inducible ischemia and/or high dose threshold) is not sufficient to cancel the surgical procedure but should indicate a more aggressive medical approach. Nonetheless, not all patients should undergo risk stratification. The decision to recommend further testing for the individual patient must take into consideration the estimated probabilities of effectiveness versus risk. It is possible that in the stratification process, the risks from the tests and treatments may offset the potential benefit of evaluation. To date, in the absence of prospective randomized trials, it appears reasonable to perform coronary revascularization before peripheral vascular

surgery in the presence of a markedly positive result of stress echocardiography and to adopt a more conservative approach—with a watchful cardiological surveillance coupled with through pharmacological protection—in patients with less severe ischemic responses during stress.³⁴

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