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

Rosa Sicari, MD, PhD; Andrea Ripoli, PhD; Eugenio Picano, MD, PhD; Ana Djordjevic-Dikic, MD; Raniero Di Giovanbattista, MD; Giovanni Minardi, MD; Simon Matskeplishvili, MD; Sergei Ambatiello, MD; Giovanni Pulignano, MD; Mario Accarino, MD; Anna Maria Lusa, MD; Gian Franco Del Rosso, MD; Roberto Pedrinelli, MD; Yuri Buziasvili, MD; on behalf of the EPIC (Echo Persantine International Cooperative) Study Group

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 (Δwall 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.

Key Words: echocardiography ■ trials ■ stress ■ risk factors ■ surgery
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. 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. 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). 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 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 χ² 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

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

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 (χ² 11.1, P < 0.0008), resting WMSI (1.11 ± 0.25, P < 0.0001), and stress WMSI (variation between rest and stress WMSI) (1.11 ± 0.25, P < 0.0001) were the best predictors of adverse outcome. By stepwise analysis, only test positivity (HR 5.46, 95% CI 1.25 to 23.8, P < 0.00001), and peak ΔWMSI (ΔWMSI (global χ² 33.504, df 4, P < 0.00001).

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

<table>
<thead>
<tr>
<th></th>
<th>Positive Findings (n=88)</th>
<th>Negative Findings (n=421)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Cardiac-related death</td>
<td>6 (6.8%)</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9 (10.2%)</td>
<td>2 (0.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>10 (11.4%)</td>
<td>4 (1%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

DET indicates dipyridamole echocardiography test.

TABLE 3. Stepwise Predictors of Cardiac Death

<table>
<thead>
<tr>
<th>Predictor</th>
<th>χ²</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔWMSI</td>
<td></td>
<td></td>
<td>973.5 (43.3 to 21.874)</td>
</tr>
</tbody>
</table>

WMSI at peak stress (χ² 12.7, P < 0.0003), and peak ΔWMSI (χ² 18.8, P < 0.0000) reached the highest value. By stepwise analysis, only ΔWMSI (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 ΔWMSI (global χ² 33.504, df 4, P < 0.00001).

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 < 0.0000). By univariate analysis, angina during dipyridamole test (χ² 11.0, P < 0.0009), ST-segment depression during dipyridamole test (χ² 16.0, P < 0.0001), WMSI at peak stress (χ² 12.9, P < 0.0003), dipyridamole time (χ² 22.3, P < 0.0000), test positivity (χ² 24.3, P < 0.0001), and ΔWMSI (variation between rest and stress WMSI) (χ² 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 (χ² 17.4, P < 0.0000), ST-segment deviation during dipyridamole test (χ² 30.2, P < 0.0000), WMSI at peak stress (χ² 30.3, P < 0.0000), dipyridamole time (χ² 37.8, P < 0.0000), test positivity (χ² 48.7, P < 0.0000), and peak ΔWMSI (χ² 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 ΔWMSI (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.
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%. 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. 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-
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 through pharmacological protection—in patients with less severe ischemic responses during stress.14

References

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Circulation. 1999;100:II-269-II-274
doi: 10.1161/01.CIR.100.suppl_2.II-269

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