Long-term prognostic value of dipyridamole echocardiography in vascular surgery: a large-scale multicenter study

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**Background** Late cardiac events after non-cardiac major vascular surgery are an important cause of morbidity and mortality. The aim of the present study was to assess the value of a preoperative dipyridamole echocardiography test (up to 0.84 mg/kg over 10 min) in predicting late cardiac events in survivors of major non-cardiac vascular surgery.

**Design** Large-scale, multicenter, prospective, observational study design.

**Methods** Two hundred and seventy-six patients (mean age 66 ± 9 years) were studied prior to vascular surgery by dipyridamole stress echocardiography in four different centres. All patients underwent preoperative clinical risk assessment according to the American Heart Association guidelines. All underwent dipyridamole stress echocardiography according to standard high-dose protocol.

**Results** No major complications occurred during dipyridamole stress echocardiography. Sixty-three patients (23%) had a positive test. Patients were followed up for a median of 20 months. Cardiac events occurred in 43 patients (16%): five deaths, 18 myocardial infarctions and 20 cases of unstable angina. The difference between wall-motion score index (WMSI) at rest and peak stress (delta WMSI), using multivariate analysis, was an independent predictor of late cardiac death.

**Conclusion** Dipyridamole stress echocardiography performed before major vascular surgery identifies patients at high risk for late cardiac events. Stress echocardiographic parameters outperformed clinical variables in the long-term risk stratification in this set of patients. *Coron Artery Dis* 13:49–55 © 2002 Lippincott Williams & Wilkins

**Keywords:** dipyridamole, stress echocardiography, prognosis, non-cardiac surgery

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patients. Two hundred and seventy-six patients recruited in four different centres were followed up for a median of 20 months after major vascular surgery.

Materials and methods

Patient population

The patient population was selected from a population of 509 consecutive patients enrolled in a multicentre prospective study aimed at assessing the value of dipyridamole stress echocardiography for the prediction of perioperative events after major vascular non-cardiac surgery [16]; from the previous population we excluded seven centres that did not perform long-term monitoring; for the other four centres long-term follow-up was obtained for all patients. Two hundred and seventy-six patients (mean age 66 ± 9 years) recruited in four different centres were followed up for a median of 20 months after major vascular surgery from January 1994 until December 1999. Demographic characteristics of the study patients are presented in Table 1. Stress test results were available to the referral physician.

Dipyridamole stress echocardiography

The standard protocol for dipyridamole stress echocardiography (cumulative dose 0.84 mg/kg, over 10 min) was used [17]. During the procedure, two-dimensional echocardiographic, 12-lead electrocardiographic 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 [18]. 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) or dyskinetic—paradoxical wall motion away from the left ventricular centre in systole (score 4). Test positivity was defined as the occurrence of at least one of the following conditions [19]: (1) new dyssynergy in a region with normal rest function (that is, normokinesia becoming hypokinesia, akinnesia or dyskinesia) in at least two adjacent segments; (2) worsening of rest dyssynergy (that is, hypokinesia becoming akinnesia or dyskinesia; rest akinnesia becoming dyskinesia was not considered a positivity criterion) [19]. 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 min) was given at the end of the test. Echocardiographic monitoring was performed throughout dipyridamole infusion and up to at least 5 min 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 (the time between start of infusion and the onset of a regional dyssynergy) was arbitrarily assumed to be 17 min (when aminophylline was given).

Quality control of stress echo performance and reading in enrolled centres has been previously described in depth [20]. Briefly, the reader from each recruiting centre met the predefined criteria for stress echo reading. At that point, the centre could start recruiting patients and the readings of stress echo from the recruiting centre were directly entered into the data bank.

Follow-up data

Follow-up data were obtained from at least one of four sources: a review of the patient’s hospital record, personal communication with the patient’s physician and review of the patient’s chart, a telephone interview with the patient conducted by trained personnel and a staff physician visiting the patient at regular intervals in the out-patient clinic [20]. Events were defined as cardiac death, non-fatal myocardial infarction and unstable angina. In patients who died in hospital or at home, the cause of death was elucidated from the medical record, the family and the local physician who signed the death certificate. The definition of cardiac death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In the case of deaths out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. Myocardial infarction was defined as a cardiac event requiring admission to hospital with development of new electrocardiogram (ECG) changes and an increase in cardiac enzyme level. Unstable angina was defined by accelerating anginal symptoms requiring hospital readmission (no enzyme elevation, or new wall-motion dyssynergy at resting echocardiogram or new Q waves on resting ECG) or progression of symptoms requiring

Table 1 Patient and stress echocardiographic characteristics

<table>
<thead>
<tr>
<th>Cardiac events</th>
<th>No cardiac events</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (mean ± SD)(years)</td>
<td>64 ± 9</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Women (%)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Current or past cigarette use (%)</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59</td>
<td>51</td>
</tr>
<tr>
<td>History of angina (%)</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Previous CABG or PTCA (%)</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>Rest WMSI</td>
<td>1.16 ± 0.25</td>
<td>1.13 ± 0.28</td>
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<tr>
<td>Peak WMSI</td>
<td>1.4 ± 0.34</td>
<td>1.17 ± 0.32</td>
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<tr>
<td>Test positivity (%)</td>
<td>60</td>
<td>16</td>
</tr>
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MI, myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; WMSI, wall motion score index; NS, not significant.
revascularization. Therefore the outcome events were hard cardiac events (defined as cardiac death or non-fatal myocardial infarction) for infarction-free survival or spontaneously occurring events (death, non-fatal myocardial infarction, unstable angina) for spontaneous event-free survival. Only the most severe outcome was considered an endpoint when follow-up was censored during revascularization procedures.

**Statistical analysis**
The statistical analyses included descriptive statistics (frequency and percentage of categorical variables and mean and standard deviation of continuous variables), Kaplan–Meier survival curves and Cox proportional hazard models. Differences between survival curves were compared with the log-rank test. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, USA), and *P* values <0.05 were considered to be statistically significant.

**Results**

**Patient characteristics**
The study included 276 patients (233 men, 43 women, mean age 66) with a history of previous myocardial infarction in 83 (30%), angina pectoris in 51 (18%), diabetes mellitus in 73 (26%), hypertension in 160 (58%) and a history of previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty in 56 (20%). Ninety-three (34%) reported either a past or current smoking habit. One hundred and twenty-nine (47%) patients underwent abdominal aortic aneurysm repair, 69 (25%) aortoiliac and aortofemoral reconstruction and 78 (28%) carotid artery thromboendarterectomy. Twenty-one (7%) experienced a non-fatal perioperative cardiac event.

**Resting echocardiographic findings**
Resting WMSI was 1.14 ± 0.27. Regional wall-motion abnormalities were present in the baseline examination of 91 patients (33%).

**Stress echocardiographic findings**
Using inclusion criteria, technically adequate images were obtained in all patients. No major complications occurred during the test. The dipyridamole echocardiography test was positive in 63 patients (23%) and negative in 213 (77%). WMSI at peak dipyridamole was 1.6 ± 0.3 in positive compared with 1.1 ± 0.24 in negative tests (*P* < 0.0001).

**Follow-up data**
Cardiac events occurred during follow-up in 43 patients (16%): five cardiac deaths, 18 non-fatal myocardial infarctions and 20 episodes of unstable angina. One patient experienced a fatal stroke. Among 21 patients who experienced a non-fatal perioperative cardiac event, seven late spontaneous cardiac events occurred during follow-up and four patients underwent coronary revascularization. Twenty-seven (62%) of the 43 who had cardiac events had a positive dipyridamole stress echocardiography test. Of the 63 patients with a positive test, 13 (20.6%) had a multivessel distribution of myocardial ischemia and four (31%) of them experienced a long-term cardiac event (one cardiac death, two non-fatal myocardial infarctions and one unstable angina). Sensitivity and specificity of the test for predicting spontaneous cardiac events were 60.4 and 84%, respectively. The overall accuracy of the test was 80%. The positive predictive value of the test was 41% and the negative predictive value 92%.

**Cardiac-related death**
When cardiac-related death was considered, three deaths occurred in patients with a positive test and two in those with a negative test (5% compared with 0.9%, *P* < 0.001) (Table 2). Using univariate analysis, dipyridamole test positivity (χ² = 5.2, *P* < 0.0217), angina during dipyridamole stress echocardiography (χ² = 9.2, *P* < 0.0024), a WMSI-at-peak-dipyridamole stress test (χ² = 9.8, *P* < 0.0017), dipyridamole-time (χ² = 13.6, *P* < 0.0008) and delta WMSI (χ² = 17.1, *P* = 0.0000) were the best predictors of late cardiac death. Using stepwise analysis only delta WMSI (HR = 406.2, 95% confidence intervals (CI) = 26.5–6.209, *P* < 0.0001) was an independent predictor of cardiac death. In Figure 1, the cumulative survival rates in patients with a positive compared to those with a negative dipyridamole stress test are shown.

**Hard cardiac events**
When only hard cardiac events (cardiac death and non-fatal myocardial infarction) were considered, there were three cardiac-related deaths and 13 non-fatal myocardial infarctions in patients with a positive test result compared with two cardiac deaths and five non-fatal myocardial infarctions in those with a negative test result (25% compared with 3%, *P* = 0.0000). Using univariate analysis, electrocardiographic changes during a dipyridamole stress test (χ² = 7.4,

<table>
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<td>Positive findings</td>
<td>Negative Findings</td>
</tr>
<tr>
<td>(n = 63)</td>
<td>(n = 213)</td>
</tr>
<tr>
<td>Cardiac-related death</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>11 (43%)</td>
</tr>
</tbody>
</table>

DET, Dipyridamole echocardiography test.
history of a previous coronary revascularization ($\chi^2 = 9.3$, $P < 0.0022$), a WMSI at peak dipyridamole stress test ($\chi^2 = 18.3$, $P = 0.0000$), dipyridamole test positivity ($\chi^2 = 23.7$, $P = 0.0000$), angina during dipyridamole test echocardiography ($\chi^2 = 33.1$, $P = 0.0000$), delta WMSI ($\chi^2 = 32.6$, $P = 0.0000$) and dipyridamole–time ($\chi^2 = 47.3$, $P = 0.0000$) were the best predictors of late hard cardiac events. Using stepwise analysis, dipyridamole test positivity (HR = 2.69, 95% CI = 1.09–6.61, $P = 0.0305$) and dipyridamole–time (HR = 1.5, 95% CI = 1.36–1.87, $P = 0.0000$) were independent predictors of late hard cardiac events. In Figure 2 cumulative survival rates free of hard cardiac events in patients with a positive compared to those with a negative dipyridamole stress test are shown.

**Spontaneous events**

Patients with positive test results had a higher incidence of spontaneous events than those with negative results (43% compared with 7.5%, $P = 0.0000$): three cardiac-related deaths, 13 non-fatal myocardial infarctions, 11 episodes of unstable angina in patients with positive results compared with two cardiac-related deaths, five non-fatal myocardial infarctions and nine episodes of unstable angina). Using univariate analysis, history of a previous coronary revascularization ($\chi^2 = 11.1$, $P < 0.0008$), history of angina ($\chi^2 = 13.7$, $P < 0.0002$), electrocardiographic changes during a dipyridamole stress test ($\chi^2 = 44.4$, $P = 0.0000$), angina during dipyridamole test echocardiography ($\chi^2 = 45.5$, $P = 0.0000$), delta WMSI ($\chi^2 = 53.2$, $P < 0.0000$) and dipyridamole–time ($\chi^2 = 70.7$, $P = 0.0000$) were the best predictors of late cardiac death. Using stepwise analysis dipyridamole–time (HR = 1.33, 95% CI = 1.24–1.43, $P = 0.000$) and history of angina (HR = 2.2, 95% CI = 1.16–4.3, $P < 0.0154$) were independent predictors of late spontaneous events. In Figure 3 cumulative survival rates free of spontaneously occurring cardiac events in patients with a positive compared to those with a negative dipyridamole stress test are shown.

**Discussion**

In patients undergoing major vascular surgery, long-term survival is related to the presence and extent of inducible ischemia.
ischemia as expressed by the variation of WMSI between rest and stress after dipyridamole infusion. Extent, severity and timing of inducible regional myocardial dysfunction at pharmacological stress echocardiography with dipyridamole predict an ominous long-term outcome with a high incidence of hard and spontaneous cardiac events. Stress echocardiography parameters outperform clinical variables in this set of patients. The history of typical angina as a clinical correlate of the presence of coronary artery disease is an independent predictor of all late spontaneous cardiac events. Test negativity is related to a good long-term prognosis in survivors of non-cardiac vascular surgery.

Comparison with previous studies

These results are consistent with previous studies in non-surgical patients demonstrating a relation between stress-induced wall-motion abnormalities and the risk of subsequent cardiac events in patients with known or suspected coronary artery disease [20–23]. The prognostic power of stress echocardiography for long-term risk stratification in patients with known or suspected coronary artery disease or in survivors of an uncomplicated myocardial infarction is well established [20–23]. Although patients undergoing major vascular surgery represent a particularly high-risk population for future cardiac events, because of the high prevalence of coronary artery disease associated with peripheral vascular disease few prospective studies have evaluated the long-term prognosis in this set of patients [1,2,4,5,12,24–26]. Magano et al. [2], analysing a high-risk population on clinical grounds undergoing non-cardiac surgery, found a 14-fold increase in the rate of subsequent cardiac complications within 2 years following surgery in those who experienced a perioperative myocardial infarction. Holter monitoring has been used for the long-term follow-up of patients undergoing major vascular surgery; in the Cox model the presence of myocardial ischemia was the only independent predictor of late outcome, with a relative risk of 5.4 [24]. With scintigraphic techniques the presence of a reversible or a fixed thallium defect was associated with a significant risk of cardiac death and non-fatal myocardial infarction during late follow-up, with a relative risk ranging between 5 and 6 [4,5,25,26]. Poldermans et al. [27] showed 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 hard cardiac events with a relative risk of 8.8.

Dipyridamole stress echocardiography through the variation between stress and rest WMSI (delta WMSI) seems to better predict late cardiac death compared with the other techniques used with this aim. Moreover, in our study revascularization procedures were not included in the analysis in order to avoid the inflation of cardiac events to improve the performance of testing. In agreement with previous studies [2,12,28], we also found that patients who experienced a perioperative cardiac event (namely a myocardial infarction or an episode of unstable angina) had a significantly increased risk of late cardiac events. Rest WMSI was not a predictor of outcome in this patient population; this is probably due to the fact that the average value of rest WMSI was 1.14, identifying patients with a preserved left ventricular function.

The present study is the first report with dipyridamole stress echocardiography addressing the issue of long-term prognosis in patients undergoing non-cardiac surgery collected on a large-scale multicenter basis and demonstrating its safety, tolerability and power of prognostication.

Clinical implications

Risk stratification for survivors after major vascular surgery remains a major issue in clinical practice due to the large volume of vascular surgery undertaken and the high mortality rate in this set of patients. This has important clinical and practical implications: (1) to ensure the safe performance of surgery and a perioperative period free of adverse cardiac events; (2) to identify patients with a poor long-term prognosis. If stress echocardiography is able to identify those patients who will face a major surgical intervention with little or no risk, the question of the future outcome of those survivors with significant coronary artery disease identified by the presence of stress echocardiographic inducible ischemia remains to be established. Therefore the assessment of long-term prognosis is critical for the future management of these patients by affecting the overall risk/benefit ratio of the surgical procedure. In fact, perioperative stratification is important but the long-term implications of severe left main or triple-vessel disease are no less ominous following any type of surgery than they are in any other patient. On the other hand, the presence of peripheral vascular disease appears to be per se a strong independent predictor of long-term mortality in patients with known coronary artery disease or undergoing coronary artery bypass surgery [29,30]. The watchful surveillance advised in this set of patients in the perioperative period apparently fades progressively over the months so that the incidence of events increases at a constant rate. Therefore, the management of these patients, in the presence of a positive test, involves the need for intensive follow-up with aggressive medical therapy and coronary catheterization and revascularization when suitable. Stress echo test results were not blinded to referral physicians that used this information according to their clinical judgement (3.2% of the patient population underwent a coronary revascularization). It has been recently demonstrated that the use of \( \beta \)-blocking agents can significantly reduce perioperative cardiac death in
patients with a positive stress echocardiography test [31], and that the long-term use of these agents reduces mortality from major vascular surgery at 2 years [32]. Despite the absence of prospective randomized trials, practical conclusions might be drawn: (1) selection of a patient population in order to identify high-risk patients on clinical grounds and on surgery-specific risks; (2) the use of stress echocardiography should be reserved for only high-risk patients; (3) aggressive medical treatment with β-blocking agents should be used in the case of test positivity; (4) coronary revascularization should be reserved for only those patients with an extensive inducible ischemia in order to influence their long-term care [33].

Study limitations

The present population was selected from a previous study [16] on the basis of the availability of a long-term follow-up. This is, however, unlikely to have introduced a selection bias because all patients recruited by the four centres who had a long-term follow-up program entered the study. Stress test results were not blinded to the referring physician because this is an observational study. This influenced the selection of the initial series of patients that underwent coronary revascularization before peripheral surgery or had the intervention cancelled [16]. This setting might have lowered the predictive power of testing excluding those at higher risk of future cardiac events.

Conclusions

Pharmacological stress echocardiography with dipyridamole is feasible and safe in a set of patients with a high prevalence of coronary artery disease such as those with peripheral vascular disease [1,16]. The prognostic gradient offered by stress echocardiography through its main parameters (variation of WMSI between rest and stress echocardiography (extent and severity of ischemia) and time of dyssynergy appearance) has to be taken into consideration in clinical decision making avoiding the exclusion of patients with less extensive inducible ischemia from the surgical list and treating in a more aggressive way those with low-dose, short-time and extensive response to stress echocardiography, because this may change their future outcome.

Reference


