Prognostic value of dobutamine–atropine stress echocardiography for peri-operative and late cardiac events in patients scheduled for vascular surgery

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Cardiac events in the peri-operative phase and late after non-cardiac vascular surgery are a major cause of morbidity and mortality. Numerous tests and diagnostic strategies — usually consisting of a combination of analysis of clinical risk factors and additional non-exercise dependent stress testing, such as thallium scintigraphy, or stress echocardiography — have been developed to pre-operatively identify patients with increased risk. The tests ideally should identify three subpopulations in a group with a high prevalence of coronary artery disease; (1) low-risk patients who can be referred for surgery without extra cardiac intervention, (2) patients whose peri-operative cardiac risk outweighs the potential benefits of vascular surgery, (3) patients whose risk may be reduced by peri-operative therapeutic interventions.

This review will discuss the prognostic value of dobutamine stress echocardiography for risk stratification in patients scheduled for non-cardiac vascular surgery and discuss guidelines for future management.

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Key Words: Stress echocardiography, vascular surgery.

Introduction

Ideally, patients undergoing major surgery should emerge from the peri-operative period intact and survive long enough to enjoy the benefits of successful surgery. However, the occurrence of serious peri-operative and late cardiac complications frequently mars an otherwise excellent surgical result. Pre-operative cardiac risk stratification helps to identify which patients are likely to suffer a major cardiac event. By facilitating decision-making, precise risk assessment has the potential to improve clinical outcome at reduced costs.

Patients scheduled for elective major non-cardiac vascular surgery are an especially high-risk group, with respect to both peri-operative and late cardiac events [1–4]. Myocardial infarction is the major cause of peri-operative and late death in this population and although the operative mortality associated with elective major vascular surgery has declined from 13–6% in 1980 to 5–6% in 1990 [3], it remains relatively high, with late cardiac events occurring in 9–12% of survivors within 2 years of surgery [6–9]. Peri-operative mortality in vascular surgery has continued to decline despite increases in the number of elderly patients and in the frequency of extensive co-morbidity [10]. One reason for the improved peri-operative outcome in this group may be a greater recognition by attending physicians of the importance of underlying cardiac disease.

The ultimate goal of pre-operative risk stratification is to define three groups of patients: (1) low-risk patients who can be referred for surgery without cardiac screening with specialized tests or therapeutic interventions; (2) patients whose peri-operative cardiac risk outweighs the potential benefits of surgery; (3) patients whose increased risk may be reduced by peri-operative therapeutic intervention.

Patients presenting for major vascular surgery have a high incidence of underlying coronary artery disease. Hertz et al. [10] used routine coronary angiography in all vascular surgery candidates and found normal coronary arteries in only 8% of them. Even when clinical evidence of coronary artery disease was absent, there was still a 37% prevalence of significant coronary artery stenoses.
Historically, high-risk patients have been identified clinically. In the past high-risk patients were considered to be those with a history of a recent myocardial infarction. Later, a multifactorial approach to clinical risk stratification evolved, but despite a sophisticated statistical approach, these clinical risk indices lacked sensitivity. Although they are fairly good at identifying high-risk patients, approximately 40% of peri-operative cardiac events occur in patients predicted to be of low risk. The insensitivity of clinical risk indices may reflect their inability to detect significant, but silent, underlying coronary artery disease. This is especially important when exercise capacity is severely limited by non-cardiac systemic disease (e.g. chronic pulmonary disease or peripheral vascular disease with claudication). This explains the increasing reliance by clinicians on non-invasive tests which detect underlying coronary artery disease without requiring physical exercise. Dipyridamole-thallium scintigraphy, ventriculography, ambulant ST-segment monitoring, and pharmacological stress echocardiography have been increasingly employed in pre-operative cardiac risk assessment.

Dipyridamole-thallium myocardial perfusion scintigraphy, often combined with clinical risk assessment, has been used extensively for risk stratification, and although initial reports indicated that patients who exhibited scintigraphic myocardial perfusion defects during dipyridamole infusion that normalized within 3-4 h or upon reinjection of thallium were at increased risk, later studies questioned these promising initial results. Mangano et al. found a sensitivity of 46% and a negative predictive value of only 82% in a study of vascular surgery patients, and although this study has been criticized for its small number of patients and few cardiac events, the results have been confirmed by Baron et al. and Marwick et al. Possible explanations for these disappointing and disparate results with dipyridamole-thallium scintigraphy include the following: (1) the test is now being used widely in a the general population instead of in selected patients with clinical risk factors; (2) clinicians responsible for peri-operative care were blinded to the results of dipyridamole-thallium scintigraphy; (3) repeat imaging 3-4 h after thallium infusion may not allow sufficient time for thallium redistribution to regions perfused by severely stenotic coronary arteries. These regions may thus be falsely classified as ‘fixed defects’ when, in fact, they contain viable myocardium; and (4) in patients with severe and diffuse coronary artery disease, thallium uptake may be uniformly reduced, so that discrete perfusion defects are not detectable.

Pharmacological stress echocardiography is a promising tool in vascular surgery for pre-operative and late cardiac risk stratification. It provides information about resting left ventricular function and inducible myocardial ischaemia, the respective hallmarks of peri-operative ischaemic complications and long-term survival. We will discuss the different stressors currently used and compare their prognostic value for peri-operative and late cardiac events.

**Pathophysiology of peri-operative cardiac morbidity**

Peri-operative cardiac events are principally caused by myocardial ischaemia due to coronary artery disease. The impact of a stenotic lesion can be magnified by factors which increase oxygen demand and reduce supply. Studies using Holter tape monitoring emphasize the role of sinus tachycardia in the induction of myocardial ischaemia, preceding the cardiac event, suggesting that an excess of myocardial oxygen demand is the key factor for ischaemic events. These results are confirmed by Raby et al. who showed that patients with cardiac events have higher peak heart rates (106 beats.min⁻¹ vs 99 beats.min⁻¹), and more prolonged ischaemic episodes (six ischaemic episodes vs three ischaemic episodes) than patients without cardiac events. Oxygen demand can also be increased by hypertension, sympathomimetic drugs, interruption of beta blocker medication, and stress. Acute coronary artery occlusion due to plaque rupture may occur as a result of increased stress and elevated catecholamine levels. Supply can be further decreased by hypotension, vasospasm, plaque rupture, anaemia, and hypoxaemia.

The awareness of peri-operative ischaemic risk has, somewhat paradoxically, made the intra-operative period one of relatively low-risk compared to the early postoperative period: as the patient returns to the ward after a period in intensive care, the chance of a cardiac event increases. Extravascular fluid is mobilized, pain increases adrenergic activity and a hypercoagulable state develops. All this occurs in a setting of decreased monitoring capacity. This explains why peak morbidity and mortality occurs between 1 and 7 days after surgery.

**Selection of stressor**

Stress echocardiography relies on exercise or drugs to increase myocardial oxygen demand and/or reduce oxygen supply. In patients with haemodynamically significant coronary artery disease this stress induces transient myocardial ischaemia. The onset of ischaemia is associated with transient segmental myocardial wall motion abnormalities which are detectable with standard two-dimensional echocardiographic techniques. Thus, stress echocardiography detects the functional consequences of physiologically important coronary artery disease. This should be compared to the static anatomical evaluation made with coronary angiography.

Physical exercise was the first stressor to be combined with echocardiography. Exercise stress has several disadvantages. It is difficult to perform continuous, high-quality echocardiographic monitoring during exercise because of posture, movement and hyperventilation. Transfer from the upright position, in which bicycle or treadmill exercise is usually performed, to the supine has to be swift, otherwise ischaemic segmental wall motion abnormalities might resolve before imaging.
The echocardiographic hallmark of myocardial ischaemia is the appearance of stress-induced ventricular wall motion abnormalities. Dobutamine is an ‘exercise simulator’ and is more effective at inducing new wall motion abnormalities in coronary artery disease than dipyridamole[33,34]. This can be explained by the different mechanisms by which dobutamine and dipyridamole influence myocardial oxygen demand and supply. Dobutamine increases myocardial oxygen demand by augmentation of heart rate and contractility. In patients with significant coronary artery disease, oxygen demand may exceed oxygen supply, leading to ischaemia which results in new wall motion abnormalities. Dipyridamole infusion results in a flow heterogeneity with reduction in flow in regions supplied by a stenotic coronary artery. In patients with moderate coronary artery disease no significant ischaemia will occur, which explains the reduced sensitivity of dipyridamole stress echocardiography in detecting moderate coronary artery disease.

Peri-operative cardiac complications tend to occur more often in patients with extensive coronary artery disease. The evidence for this is (1) during exercise electrocardiography patients who develop ischaemia at ‘low’ heart rates have a relatively high peri-operative risk[35]; (2) during dipyridamole-thallium scintigraphy, extensive and severe redistribution defects are associated with more peri-operative complications[36]; and (3) patients with three or more of Eagle’s criteria for cardiac disease have an increased peri-operative risk compared to patients with fewer factors[17]. If patients undergoing vascular surgery are stratified by an overly sensitive test which detects relatively mild coronary artery disease, inappropriate interventions may result. For example, patients may be subjected to unnecessary invasive testing or have needed surgery delayed.

The lower sensitivity for moderate coronary artery disease of dipyridamole stress echocardiography might explain the favourable results of Tischler et al.[33] in pre-operative cardiac risk stratification. They found a positive predictive value of 78%, and a negative predictive value of 99%. Unfortunately, these results have not been confirmed by other studies. At the moment we do not have enough data to conclude which ‘stressor’ is best.

When the two agents were compared with respect to side effects, feasibility and accuracy in a group of 360 patients who underwent both tests[36] no major complications occurred during either test. During the dobutamine-atropine infusion 37/360 tests had to be interrupted due to side effects; however, during dipyridamole-atropine infusion only 7/360 (P<0.01) were interrupted. Both tests had comparable accuracy.

**Predictive value of different stressors for peri-operative events**

Peri-operative cardiovascular complications such as cardiac death, myocardial infarction, unstable angina, and pulmonary oedema, are potentially avoidable causes of mortality and morbidity in surgical patients.
Pre-operative cardiac evaluation has the potential to reduce costs and improve outcome by tailoring peri-operative and long-term to accord with quantified risk. Cardiac risk stratification in this setting is one of the most promising clinical applications of pharmacological stress echocardiography.

The various studies employing dobutamine stress echocardiography for pre-operative risk stratification are heterogeneous and difficult to compare (Table 1). Patients were often not studied consecutively, a referral bias was often introduced, and test results were used for pre-operative management, particularly the decision to introduce coronary angiography and subsequent coronary revascularization before vascular surgery. Some studies included patients scheduled for either vascular surgery or general surgical procedures. The inclusion of less stressful surgical procedures may have reduced the pre-test probability of a peri-operative cardiac event. In most studies, the attending physicians were aware of the dobutamine stress echocardiography results, and this knowledge may have altered pre-operative patient management. It is significant that, in some studies patients underwent pre-operative coronary angiography with or without subsequent myocardial revascularization procedures or were denied surgery. The study of Poldermans et al. in 1995 overcame these major shortcomings. All patients referred for vascular surgery were studied consecutively. The attending physicians were blinded to the results of dobutamine stress echocardiography, so patient management was not altered. In particular, pre-operative coronary angiography and myocardial revascularization were not performed.

The initial study by Poldermans et al. in 1993 performed in 136 vascular surgery patients, demonstrated that new regional wall motion abnormalities induced by dobutamine stress echocardiography were associated with a greatly increased risk of peri-operative cardiac events, such as cardiac death, non-fatal myocardial infarction, and unstable angina (odds ratio 95, 95% confidence interval 11–822). Wall motion abnormalities at rest and clinical and electrocardiographic indicators of ischaemia during stress were not independently predictive. Clinical data, even combined in a risk index such as the Detsky score, provided little useful information about risk. In order to confirm these preliminary results the study was extended, using the same protocol, to 300 patients. The findings were essentially unchanged (Fig. 1). The absence of diabetes mellitus, as a pre-operative cardiac risk marker in the Detsky score decreased the predictive value compared to Eagle’s clinical risk factors. Dobutamine stress echocardiography was superior to clinical data for the prediction of peri-operative cardiac events (Table 2). However, as a screening test, dobutamine stress echocardiography had some limitations. These include the cost of routinely screening all vascular surgery patients, and secondly the relatively low positive predictive value (38%) of a positive test.

The issue of cost was dealt with by defining a low-risk patient group which did not require dobutamine stress echocardiography pre-operatively. We

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**Table 1 Results of pre-operative dobutamine-atropine stress echocardiography for peri-operative cardiac risk stratification in patients scheduled for non-cardiac vascular surgery**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Cardiac events</th>
<th>Sens</th>
<th>Spec</th>
<th>pos PV</th>
<th>neg PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davila-Roman et al.</td>
<td>91</td>
<td>4</td>
<td>100</td>
<td>78</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Eichelberger et al.</td>
<td>75</td>
<td>5</td>
<td>100</td>
<td>69</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Lalka et al.</td>
<td>60</td>
<td>13</td>
<td>85</td>
<td>44</td>
<td>29</td>
<td>95</td>
</tr>
<tr>
<td>Lane et al.</td>
<td>57</td>
<td>4</td>
<td>100</td>
<td>56</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>Poldermans et al.</td>
<td>300</td>
<td>27</td>
<td>100</td>
<td>84</td>
<td>38</td>
<td>100</td>
</tr>
<tr>
<td>Pellikka et al.</td>
<td>80</td>
<td>8</td>
<td>86</td>
<td>76</td>
<td>29</td>
<td>98</td>
</tr>
<tr>
<td>Langan et al.</td>
<td>74</td>
<td>3</td>
<td>100</td>
<td>79</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>737</td>
<td>64</td>
<td>95</td>
<td>76</td>
<td>28</td>
<td>99</td>
</tr>
</tbody>
</table>

No. of patients = number of patients who underwent dobutamine stress echocardiography and vascular surgery, without additional coronary artery interventions (CABG or PTCA); Cardiac events = cardiac death, non-fatal myocardial infarction, congestive heart failure or unstable angina pectoris; Sens = sensitivity (%); Spec = specificity (%); pos PV = positive predictive value (%); neg PV = negative predictive value (%).

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Figure 1 Dobutamine stress test results and peri-operative cardiac complications in patients undergoing non-cardiac vascular surgery (n=300). Death = cardiac death; myocardial infarction = nonfatal myocardial infarction; UAP = unstable angina pectoris.
Table 2  Multivariate predictors of peri-perative cardiac events in patients undergoing major non-cardiac vascular surgery (n=300)

<table>
<thead>
<tr>
<th>Clinical risk variables</th>
<th>Odds ratios (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New wall motion abnormalities</td>
<td>124 (17-934)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.8 (1.2-12)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>3.5 (1.4-8.9)</td>
</tr>
</tbody>
</table>

determined that patients with none of the clinical risk factors defined by Eagle et al. (age >70 years, angina, diabetes mellitus, Q wave on ECG, and symptomatic ventricular tachyarrhythmias) have a low peri-operative cardiac risk (1%). In this large group (100/300 patients) additional stress testing was unnecessary. We also found that patients with three or more clinical risk factors comprised a high-risk group, with a 29% rate of peri-operative complications (Figs 2 and 3). However, in contrast to Eagle et al. [17], we found that dobutamine stress echocardiography provided further useful risk stratification in this high risk group. Patients with three or more risk factors, and a positive dobutamine stress echocardiography had a peri-operative event rate of 55% compared to 0% in patients with a negative test.

The positive predictive value of dobutamine stress echocardiography was improved by adopting a semi-quantitative analysis of the stress test results. By considering the heart rate threshold at which ischaemia occurred, patients with a positive test were divided into two groups; (1) ischaemia at a low heart rate (≤70% of the age related maximal heart rate) (38/72 patients), and (2) ischaemia at high heart rate (>70% of the age related maximal heart rate) (34/72 patients). Patients who developed ischaemia at a low heart rate were at highest risk for peri-operative cardiac events (positive predictive value of 66%). All five fatal complications occurred in this group (n = 38). When ischaemia occurred at a high heart rate, patients had an intermediate risk of peri-operative cardiac events (16%).

Safety of dobutamine-atropine stress test in patients with non-cardiac vascular disease

Published experience with dobutamine stress echocardiography includes 737 patients who underwent dobutamine stress echocardiography for pre-operative cardiac risk assessment [37-44]. Only one major adverse event was recorded. This patient, a 55-year-old male with a history of symptomatic ventricular tachyarrhythmias, developed ventricular fibrillation during the peak dose of dobutamine. He was successfully resuscitated with a single countershock and experienced no sequelae. Specific information about safety and the presence of aortic aneurysm is provided in the study of Pellikka et al. [42], who studied 80 patients with symptomatic and asymptomatic aortic aneurysms of more than 4 cm in diameter. In this group no serious side effects occurred. This could be expected, as the most threatening complication in these patients, hypertension, rarely occurs during the dobutamine stress test [32,43].

Minor side effects consisting primarily of minor cardiac arrhythmias and hypotension occur more frequently [32,43]. In a group of 451 patients [32] significant cardiac arrhythmias occurred in about 4% of patients. These consisted of sustained and non-sustained ventricular tachycardia, paroxysmal atrial fibrillation, and supraventricular tachycardia. There was a strong association between a history of previous ventricular arrhythmias and the risk of dobutamine induced arrhythmias (odds ratio 9-9, 95% confidence index
2–45). Hypotension, defined as a decrease in systolic blood pressure of >20 mmHg occurred in about 3% of patients. This mild degree of hypotension was well tolerated, and most patients successfully completed the test. Hypotension occurred significantly less frequently in patients receiving concomitant beta-adrenergic blocking agents (odds ratio 4:1, 95% confidence index 2:1–8:7). Hypertension, defined as a systolic blood pressure >220 mmHg, a potentially serious complication in patients with abdominal aortic aneurysm, occurred only in ±1% of the patients. These side effects were not caused by the induction of myocardial ischaemia and are similar to those reported by Picano et al.(94).

In a study of 2799 patients, cardiac arrhythmias and hypotension were the most frequent side effects. Serious cardiac side effects (myocardial infarction, symptomatic ventricular arrhythmias, severe hypotension, and prolonged ischaemia) occurred in 9/2799 patients (0:3%). Compared to the side effects of dobutamine stress echocardiography, dipyridamole–thallium scintigraphy(95), and exercise electrocardiography(96) we think dobutamine stress echocardiography is safe and highly feasible and we would advise an alternative stress test, for instance dipyridamole–thallium scintigraphy, only in patients with a history of paroxysmal cardiac arrhythmias or severe hypertension.

**Predictive value of different stressors for late events**

Coronary artery disease is a major cause of late morbidity and mortality in survivors of major vascular surgery. For example, Krupski et al.(97) found that late cardiac events occurred in 19% of 129 patients followed-up for 2 years after vascular surgery. This high incidence reflects the severity of underlying coronary artery disease. Hertz et al.(98) obtained coronary angiograms in 1000 vascular surgery candidates and found severe correctable coronary artery disease in 36% of patients with aortic aneurysms and in 28% of those with lower extremity ischaemia. Therefore, the pre-operative evaluation of vascular surgery candidates should assess the risk of late postoperative cardiac events, since these will determine the likelihood that individual patients will survive to enjoy the benefits of successful surgery.

Several clinical and laboratory variables have been associated with an increased risk of late cardiac events after major surgery. Clinical predictors include a history of coronary artery disease or congestive heart failure. Of particular interest is the finding by Mangano et al.(99) that patients who survived a peri-operative myocardial infarction or episode of unstable angina had a 20-fold increase in the odds of a late cardiac event. Non-invasive laboratory indicators of late cardiac risk include left ventricular dilatation and thallium redistribution on dipyridamole–thallium scintigraphy, fixed defects on dipyridamole–thallium scintigraphy(100), impaired left ventricular function on radionuclide ventriculography(101) and ischaemic ST-segment changes during peri-operative ambulatory electrocardiographic monitoring(102). Recently, we showed that inducible ischaemia during dobutamine stress echocardiography was an independent predictor of the risk of late cardiac events in patients with suspected or proven coronary artery disease(103).

We recently studied 318 survivors of major vascular surgery(104) who had undergone pre-operative dobutamine stress echocardiography and clinical evaluation for the presence of cardiac risk factors (smoking, hypertension, angina, diabetes, previous infarction and age >70 years). Patients were followed for 19±11 months (range 6–36) postoperatively and the occurrence of cardiac events was noted. One patient was lost to follow-up. Thirty-two cardiac events occurred (11 cardiac deaths, 11 nonfatal myocardial infarctions and 10 patients with unstable angina). Univariable and multivariable regression analysis of clinical history and stress test results were performed for the prediction of late cardiac events.

The univariable predictors of late cardiac events are presented in Table 3, as are the sensitivity, specificity and likelihood ratios for each variable. A history of angina, myocardial infarction, or diabetes mellitus, and the occurrence of a non-fatal peri-operative cardiac event were significant predictors of late cardiac events. Stress test results were also predictive. Left ventricular dysfunction at rest (>3 segments), extensive new wall motion abnormalities during stress (≥3 segments), and stress-induced angina or ST-segment changes also predicted late cardiac events. The severity of ischaemia during stress and the heart rate threshold for ischaemia were not predictive.

Multivariable regression analysis was performed on all clinical risk factors and stress test results (Table 4). Like Mangano et al.(98), we found that the occurrence of a non-fatal peri-operative cardiac event at the time of major vascular surgery was the most powerful predictor of late cardiac events. New wall motion abnormalities during stress, especially extensive new wall motion abnormalities and a history of myocardial infarction was also an independent predictor of late cardiac events. Event-free survival curves for patients with a normal stress test, and those with stress-induced new wall motion abnormalities are presented in Fig. 4. There is a significant decrease in event-free survival in patients with extensive new wall motion abnormalities.

This study demonstrates the incremental prognostic value that dobutamine–atropine stress echocardiography adds to the presence of a previous myocardial infarction for predicting late cardiac events after major vascular surgery. The additional prognostic value of dobutamine stress echocardiography and especially the extent of ischaemia during stress is presented in Table 5.

We noted with interest a relationship between the extent of ischaemia observed during dobutamine
Table 3  Univariate predictors of all cardiac events (cardiac death, myocardial infarction or coronary revascularization) and 'hard cardiac events' (cardiac death or myocardial infarction), after major vascular surgery (n=316, follow-up period 19 ± 11 months)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All cardiac events, hazard ratios (95% CI)</th>
<th>Hard cardiac events, hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative cardiac events</td>
<td>4.7 (2.5-9.6)</td>
<td>3.4 (1.6-7.4)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4.5 (2.2-9.0)</td>
<td>3.4 (1.5-7.4)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>3.1 (1.2-9.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>3.1 (1.5-6.0)</td>
<td>2.9 (1.2-7.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.6 (1.2-5.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Ischaemia ≥ 3 segments</td>
<td>9.0 (4.5-18.2)</td>
<td>8.8 (3.7-20)</td>
</tr>
<tr>
<td>NWMA</td>
<td>7.9 (3.7-17)</td>
<td>5.6 (2.5-12)</td>
</tr>
<tr>
<td>Low ischaemic heart rate threshold</td>
<td>5.6 (2.5-12)</td>
<td>4.5 (1.6-12)</td>
</tr>
<tr>
<td>Severity of ischaemia</td>
<td>3.1 (1.4-6.8)</td>
<td>ns</td>
</tr>
<tr>
<td>ST changes during stress</td>
<td>3.1 (1.5-6.0)</td>
<td>3.9 (1.8-9.0)</td>
</tr>
<tr>
<td>Angina during stress</td>
<td>2.9 (1.2-7.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Resting wall motion abnormalities ≥ 2</td>
<td>2.7 (1.3-5.5)</td>
<td>2.4 (1.1-5.5)</td>
</tr>
</tbody>
</table>

NWMA = any new wall motion abnormalities, Low ischaemic threshold: echocardiographic-detected ischaemia at a heart rate of <70% of the maximal age- and sex-related heart rate; Severity of ischaemia: difference between wall motion score at peak stress – wall motion score at rest >0.14; CI = confidence interval; ns = not significant.

Table 4  Multivariate predictors of all cardiac events (cardiac death, myocardial infarction or coronary revascularization) and 'hard cardiac events' (cardiac death or myocardial infarction) after major vascular surgery (n=316, follow-up period 19 ± 11 months)

<table>
<thead>
<tr>
<th></th>
<th>All cardiac events, hazard ratios (95% CI)</th>
<th>Hard cardiac events, hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia during stress  ≥ 3 segments</td>
<td>6.5 (3.0-15)</td>
<td>5.8 (2.5-15)</td>
</tr>
<tr>
<td>Ischaemia during stress 1–2 segments</td>
<td>2.9 (1.1-7.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>3.8 (1.6-8.2)</td>
<td>2.8 (1.1-6.7)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ns = not significant.

Guidelines for the pre-operative assessment of vascular surgery patients

We suggest the following approach, based on a combination of clinical risk factors, exercise capacity, and additional dobutamine stress echocardiography in patients with risk factors and/or limited physical activity, for pre-operative cardiac risk stratification in patients scheduled for major vascular surgery.

1) Clinical assessment

Patients with unstable cardiac disease, such as unstable angina pectoris, congestive heart failure, and symptomatic arrhythmias should be excluded from elective non-cardiac vascular surgery until the problem has been
identified and treated. Patients without any risk factor (age >70 years, diabetes requiring treatment, angina, Q waves on ECG, and history of symptomatic ventricular arrhythmias or congestive heart failure) can undergo surgery expeditiously and without additional pre-operative cardiac investigations or extensive post-operative monitoring.

(2) Dobutamine stress echocardiography

This test should be performed in all patients with one or more risk factors or limited physical ability which may conceal angina pectoris. Patients with a negative test have an event rate of 1% (unstable angina pectoris) and can be sent for surgery without extra investigations.

(3) Positive dobutamine stress echocardiography

Patients who develop ischaemia at a high heart rate (≥70% of the maximum age-related heart rate) are at intermediate risk, with a peri-operative event rate of 16%. With this in mind, we recommend that medical treatment for ischaemia, including beta-adrenergic blocking agents, be initiated pre-operatively and maintained throughout the peri-operative period. Intra-operative and postoperative electrocardiographic ischaemia monitoring is also indicated. Patients who develop ischaemia during or after surgery should remain in the Intensive Care and receive additional treatment.

Patients who develop ischaemia at a low heart rate represent an extremely high-risk group with a predicted peri-operative event rate of 66%, and a mortality rate of 16-7%. The optimal approach in this group has not yet been established. Available options include cancellation of surgery or substitution of a less invasive procedure, such as percutaneous transluminal angioplasty or stent implantation. A second possibility is evaluation of coronary artery disease by angiography and performance of a myocardial revascularization procedure with a view to reducing peri-operative and late cardiac event rates. The final treatment alternative would be to proceed with essential surgery while utilizing some combination of anti-ischaemic and/or antithrombotic therapy, invasive haemodynamic monitoring, peri-operative monitoring for ischaemia and a prolonged postoperative Intensive Care Unit admission.

The value of 'prophylactic' coronary revascularization, just because these patients undergo non-cardiac surgery is questionable. This aggressive approach requires careful prospective evaluation before it can be recommended[53]. The cumulative mortality rate associated with angiography, myocardial revascularization and subsequent vascular surgery might prove to be substantial in this elderly, high-risk population. In view of the current data concerning the pathophysiology of peri-operative myocardial ischaemia[54], we would also advise a more prudent approach in this group starting with 'optimal' anti-ischaemic medical treatment, including beta-blockers. We would recommend coronary angiography and myocardial revascularization only in patients with disabling angina despite maximal medical therapy and/or if dobutamine stress echocardiography results show diffuse myocardial ischaemia.

These recommendations are in accordance with the guidelines recently provided by the report of the

### Table 5 Hazard ratios for all late cardiac events as a function of the presence of a previous myocardial infarction and the extent of stress-induced ischaemia

<table>
<thead>
<tr>
<th>Ischaemic segments during dobutamine stress echocardiography</th>
<th>Previous myocardial infarction</th>
<th>No. patients</th>
<th>Event rate</th>
<th>Hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no</td>
<td>183</td>
<td>7/183 (4%)</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>0</td>
<td>yes</td>
<td>49</td>
<td>4/49 (8%)</td>
<td>3.1 (1.4–6.6)</td>
</tr>
<tr>
<td>1–2</td>
<td>no</td>
<td>13</td>
<td>1/15 (7%)</td>
<td>2.9 (1.1–7.8)</td>
</tr>
<tr>
<td>1–2</td>
<td>yes</td>
<td>22</td>
<td>6/22 (27%)</td>
<td>8.8 (3.1–25.2)</td>
</tr>
<tr>
<td>≥3</td>
<td>no</td>
<td>26</td>
<td>3/26 (12%)</td>
<td>10.3 (4.5–23.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>yes</td>
<td>21</td>
<td>11/21 (52%)</td>
<td>31.5 (11.4–87.3)</td>
</tr>
</tbody>
</table>

DSE = dobutamine stress test; CI = confidence interval.

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American College of Cardiology and American Heart Association Task Force\textsuperscript{55,56}. First patients are stratified by the presence of unstable cardiac disease, followed by: (1) clinical cardiac risk factors; (2) exercise capacity; and (3) type of surgery. The clinical risk factors are stable angina pectoris, previous myocardial infarction, history of congestive heart failure and diabetes mellitus. Age \textgreater 70 years was not included as a clinical risk factor, although in previous studies this was considered as an independent risk factor\textsuperscript{17,26}. With a well defined evaluation of functional capacity as described in the report by Eagle \textit{et al.}\textsuperscript{56}, the risk factor age \textgreater 70 may become redundant. If the patient has undergone coronary revascularization during the past 5 years or coronary angioplasty from 6 months to 5 years and the clinical status has remained stable without recurrent signs or symptoms of ischaemia no further stress testing is warranted, since these patients have a very low risk of peri-operative and late cardiac events. Also the report stresses the importance of different types of surgery. Since our recommendations are related to 'major' vascular surgery only, this was omitted in the guidelines. Carotid endarterectomy is not considered as high risk surgery and in this patient group the presence of only one risk factor may not warrant additional stress testing. The use of coronary revascularization, just to get the patient through surgery, is also not recommended\textsuperscript{54,56}.

\textbf{Future directions for stress testing and peri-operative management}

The risk assessment algorithm developed in conjunction with our dobutamine stress echocardiography programme is of more than academic interest. First, we have demonstrated that clinical assessment alone followed by dobutamine stress echocardiography in patients with risk factors can define a very large population of patients who can proceed to surgery without extensive investigation or intensive peri-operative management. This information has the potential to substantially reduce costs by avoiding potentially hazardous and unnecessary tests and interventions. Further, our ability to quantify cardiac risk in vascular surgery sets the stage for future risk-reduction trials designed to define the efficacy of various interventions to reduce risk in high-risk patients.

Future risk-reduction studies will face several problems and must be carefully designed. Potential problems include the following: (1) the number of peri-operative cardiac events in non-cardiac surgery is decreasing over the time due to improved surgical and anaesthesiological care; (2) surgeons are likely to refer high-risk candidates to less invasive procedures such as percutaneous transluminal coronary angioplasty or stents, without extensive cardiac screening; (3) peri-operative cardiac events are heterogeneous and need to be classified uniformly. For example a 'chemical myocardial infarction', diagnosed solely on a finding of elevated cardiac enzymes must be clearly differentiated from transmural Q-wave infarction. Ideally one would study only 'hard' cardiac events such as cardiac death and definite myocardial infarction. This would necessitate studying larger numbers of patients, as the number of 'end-points' will decrease.

Some risk-reduction strategies that deserve prospective investigation include: (1) peri-operative beta-adrenergic blockade; (2) continuous electrocardiographic ischaemia monitoring with aggressive anti-ischaemic management; (3) coronary angiography with prophylactic myocardial revascularization with PTCA; (4) antithrombotic therapy. In all these potential trials stress echocardiography can play a crucial role for the inclusion of the patients at increased risk.

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\textbf{References}

Prognostic value of dobutamine stress echocardiography


