Low negative predictive value of dobutamine stress echocardiography before abdominal aortic surgery

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Background. According to previous studies, a negative dobutamine stress echocardiography (DSE) test before major vascular surgery indicates that postoperative myocardial necrosis is very unlikely. We believe that the use of new cardiac troponin assays which can detect small amounts of myocardial necrosis results in a lower DSE negative predictive value for myocardial necrosis.

Methods. A total of 418 consecutive patients were screened using the ACC/AHA Guideline for Perioperative Cardiovascular Evaluation for Noncardiac Surgery before scheduled abdominal aortic surgery. Of these 143 met ACC/AHA criteria for non-invasive testing and underwent DSE. Patients with a negative DSE were deemed to be fit for surgery. A positive DSE led to a coronary angiogram. DSE was negative in 110 (77%) and positive in 33 (23%) patients. Myocardial necrosis was monitored up to the third postoperative day by daily cardiac troponin I (cTnI) measurement and a daily 12-lead ECG.

Results. Coronary angiography showed artery stenosis in 27 (84%) of 32 patients with a positive DSE. The negative predictive value of DSE for cTnI elevation was 92.7% (95% CI 86.2–96.8%). This was significantly lower than the lowest value of negative predictive value for myocardial necrosis assessed in previous studies.

Conclusion. A negative DSE prescribed before scheduled aortic surgery according to ACC/AHA guidelines does not rule out postoperative myocardial necrosis.

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Introduction

Postoperative myocardial damage revealed by cardiac troponin I (cTnI) release is associated with an increase in short- and long-term mortality in vascular surgery patients.¹–⁸ Non-invasive preoperative coronary testing, such as dobutamine stress echocardiography (DSE), had been proposed to identify patients who are at high risk for postoperative cardiac complications.³ The negative predictive value of DSE for myocardial necrosis has been widely assessed in vascular surgery patients⁹–¹⁵ and ranges from 97.6 to 100%. These assessments used old biomarkers of myocardial infarction such as creatinine kinase (CK-MB) or a high cut-off value of the more recent cardiac troponin biomarkers. The negative predictive value of DSE for any postoperative cTnI elevation above the threshold of detection has never been assessed. Furthermore, the negative predictive value of DSE applied according to the AHA/ACC Guideline for Perioperative Cardiovascular Evaluation for Noncardiac Surgery has never been assessed.

The main purpose of our study was to evaluate the negative predictive value of DSE for myocardial necrosis detected by cTnI release in a population of consecutive patients scheduled for abdominal aortic surgery screened according to the ACC/AHA guidelines and to compare this with published negative predictive values. Myocardial necrosis was defined as a cTnI level above the 99th percentile. Patients with postoperative
cTnl elevation above 0.2 ng ml\(^{-1}\) measured using the Stratus autoanalyzer Dade-Behring (Dade-Behring, Paris La Défense, France) were considered to have developed myocardial necrosis. The second aim of the study was to evaluate the ability of DSE to predict the finding of abnormal coronary arteries on coronary angiography.

**Material and methods**

We performed a prospective observational study in a single centre. The study was approved by our institutional ethical committee (Comité de Protection des Personnes, Pitié-Salpêtrière, Paris, France). Under French legislation, no informed consent was needed to collect, analyse and publish these data.

**Population**

At a pre-anaesthetic consultation all patients scheduled for an abdominal aortic surgery from January 1, 2002 to January 31, 2004 were screened for myocardial risk, according to the ACC/AHA criteria.\(^3\) They could either be cleared for surgery without further cardiac investigations or DSE or specific cardiologic management (such as a coronary angiography) could be requested.

All patients eligible for preoperative DSE according to the ACC/AHA guidelines were included in the study. Patients were excluded if they underwent emergency surgery, if they had had recent coronary revascularization, a recent coronary angiogram or stress test, if they underwent stress echocardiography not indicated under the ACC/AHA guidelines or in cases with very poor echocardiographic imaging. We performed a retrospective medical records review to ensure that all patients who merited a DSE underwent this test.

**Dobutamine stress echocardiography**

Beta-blockers were discontinued 24 h before testing, and restarted immediately after the procedure. The 12-lead ECG was monitored continuously and recorded at each stage of the protocol. Arterial blood pressure was measured non-invasively at rest and at each stage of the protocol. DSE consisted of four echocardiographic views recorded at baseline and at the end of each 3 min stage. Data were digitally stored for off-line analysis. I.V. incremental doses of dobutamine were infused, starting at 10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\), and increasing by 10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) every 3–5 min until 40 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) in order to reach the target heart rate (maximal heart rate predicted for age). Supplemental atropine (0.25–1 mg) could be administered i.v. in order to facilitate the increase of heart rate. DSE was considered positive if myocardial ischemia was identified as new extensive wall motion abnormalities or worsening wall motion abnormalities in at least two segments, greater than 2 mV downsloping ST-segment depression measured 80 ms after the J point as compared with baseline, or both. DSE was also considered positive if it demonstrated myocardial viability (regional function improvement with low dose dobutamine).\(^{16}\)

Criteria for termination of the dobutamine infusion were achieving the target heart rate or the occurrence of either myocardial ischemia as previously defined, severe angina or other intolerable symptoms, severe hypertension (systolic arterial blood pressure >230 mm Hg), symptomatic hypotension or decrease in systolic arterial blood pressure of >40 mm Hg or severe arrhythmias.

**Coronary angiography**

Preoperative coronary angiography was performed in patients with positive DSE tests as recommended in the ACC/AHA guidelines. Postoperative coronary angiography could be performed in patients with postoperative myocardial necrosis who had not had preoperative coronary angiography. Significant coronary artery disease was defined as a 50% or more decrease in lumen diameter in at least one coronary artery. If one artery had more than one significant stenosis, we recorded the value of the most important one. Coronary angiography could lead to coronary revascularization,\(^{17}\) medical treatment, or both.

**Preoperative and intraoperative management**

Antiplatelet agents (clopidogrel and aspirin) were withdrawn 7 days before surgery. Angiotensin converting enzyme inhibitors and angiotensin receptor blocking drugs were withdrawn 24 h before surgery. Beta-blockers, statins and calcium channel inhibitors were given on the day of surgery. Beta-blocker therapy was initiated in patients with cardiac risk factors, as recommended by ACC/AHA guidelines.\(^3\) In patients with a contraindication to beta-blockers diltiazem therapy was substituted. All patients were premedicated with oral midazolam (5 mg). A standard anaesthetic technique was followed in all patients. A radial artery catheter was inserted under local anaesthesia, and all patients received 10 ml kg\(^{-1}\) of Ringer’s solution before induction of general anaesthesia. Anaesthesia was slowly induced with sufentanil (0.5 \(\mu\)g kg\(^{-1}\)) and target-controlled propofol infusion (effect site concentration of 1.5 ng ml\(^{-1}\)). Three minutes after atracurium administration (0.6 mg kg\(^{-1}\)), orotracheal intubation was performed. Patients were ventilated using a mixture of 50% oxygen and 50% nitrous oxide. Sufentanil, propofol and atracurium infusions were maintained throughout the operative period. Heparin (50 iu kg\(^{-1}\)) was administered before aortic cross clamping. Intraoperative monitoring included invasive arterial blood pressure monitoring, pulse pressure variation analysis, heart rate, haemoglobin levels (Hemocue\(^8\), Hemocue AB, Angelholm, Sweden), transoesophageal echocardiography (when available) and fluid replacement and transfusion was guided by blood loss.

All patients spent the first 24 h after surgery in an intensive care unit. Particular attention was paid to volaemic status, haemoglobin concentration and central core temperature before and after emergence from anaesthesia. Postoperative analgesia was provided using propacetamol (1 g i.v. every 6 h) and morphine chlorhydrate. Morphine titration
started at the time of tracheal extubation based on the Visual Analogue Pain Score and a Patient-Controlled Analgesia device was connected.

Postoperative follow-up
As is our usual practice, all patients were monitored for cardiac ischemia on the day of surgery with computerized ST-segment analysis. A plasma cTnI measurement (Stratus autoanalyzer, Dade-Behring, Paris La Défense, France) was performed 6 h after the end of the surgery. The coefficient of variation of this assay at the 99th percentile of normal (0.07 ng ml$^{-1}$) is 8.2%. A plasma concentration above 0.2 ng ml$^{-1}$ is considered abnormal in our institution. This assay shows no cross-reactivity with skeletal muscle troponin I or other cardiac proteins. Cardiospecificity of cTnI is related to the absence of expression in the skeletal muscle, even in patients with end-stage renal disease or with dialysis. In myocardial infarction, in patients with renal disease the peak value of cTnI is not overestimated, the only effect because of renal disease being an increased delay in the decline of cTnI to normal.

Cardiac ischemia was monitored up to the third day with a daily 12-lead ECG and daily plasma cTnI measurements were performed. If a troponin concentration $>0.2$ ng ml$^{-1}$ was found additional measurements were performed every 6 h until levels returned to normal.

Statistical analysis
The lowest reported value negative predictive value for DSE for the detection of myocardial necrosis is 97.6%. In a preliminary study, we observed that the negative predictive value of DSE for myocardial necrosis was only 92.7%. We performed a power calculation based on a 5% one-sided $\chi^2$-test which indicated that a sample of 93 patients with a negative DSE test would be needed to provide the study with 80% power to detect a difference between the value reported in the literature and the negative predictive value from our pilot study.

Continuous variables are expressed as mean (SD). Categorical variables are presented as percentage, and differences were compared using the $\chi^2$-test or Fisher’s exact test as appropriate. All statistical comparisons were two-tailed and a $P$-value of less than 0.05 was considered significant. 95% CIs were calculated using the binomial exact test. Statistical analyses were performed using Stata 8 software (StataCorp Lt, College Station, TX).

Results
Patients’ characteristics
The flow chart of the study is presented in Figure 1. A total of 418 patients were screened, and 143 patients (34%) met...
the criteria for DSE testing. Their characteristics are reported in Table 1.

### DSE results

Thirty-three patients had a positive DSE. Fourteen subjects (42%) had a positive test on echocardiographic criteria alone and a further 15 subjects (45%) had other criteria for a positive test in association with changes on echocardiography (5 ECG, 1 clinical and 9 both clinical and ECG). In four patients, both new wall motion abnormalities (NWMA) and worsening resting wall motion abnormalities (WRWMA) were seen. Dobutamine stress echocardiography was considered positive on isolated ECG criteria in four subjects. No DSE test was positive on clinical criteria alone. Six of seven patients (5%) did not reach their target heart rate because of induced ischemia.

Post-DSE complications occurred in two subjects (1% of the group tested): 2 days of sustained atrial fibrillation occurred in one patient and a transient isolated ST-segment down-sloping without cTnI release in another.

### Negative DSE and postoperative follow-up

cTnI rose above 0.2 ng ml\(^{-1}\) (defining myocardial necrosis) in 8 of 110 patients (7%) who had a negative DSE. The negative predictive value of DSE for myocardial necrosis was 92.7% (95% CI 86.2–96.8%), which is significantly less than the lowest value reported previously (P<0.001).†

Subjects 1, 2 and 4 in Table 2 displayed ST-segment elevation whereas Subjects 6 and 8 displayed down-sloping ST-segment depression. One patient required re-operation. None of the negative DSE test patients experienced congestive heart failure or died during their hospital stay.

### Positive DSE and preoperative follow-up

Of the 33 patients who had a positive DSE test, 32 underwent coronary angiography. One did not because of severe renal failure (creatinine clearance 29 ml min\(^{-1}\)). Angiography demonstrated a coronary artery stenosis in 27 (84%) of the 32 patients. The stenosis was less than 50% of vessel lumen in 8 (25%) patients. The positive predictive value of DSE for a >50% stenosis on coronary angiography was 59.4% (95% CI 40.6–76.3%). There was stenosis of one vessel in nine patients, two vessels in six patients and three vessels in four patients. Two of the four patients whose positive DSE result was based solely upon ECG criteria had a coronary artery stenosis of over 50%. Coronary angiographic findings led to percutaneous transluminal angioplasty in 12 (37%) patients, coronary artery bypass grafting in 1 patient (3%) and medical treatment alone in 12 (37%) patients. The positive predictive value of DSE for stenosis accessible to revascularization was 40.6% (95% CI 23.7–59.4%) and does not differ from incidence of correctable coronary artery disease assessed in previous studies. Positive findings on coronary angiography were not associated with particular DSE positivity criteria (Table 3, P=0.553). One patient with positive DSE test developed a high level of postoperative cTnI release (peak 12 ng ml\(^{-1}\)) and 3 days of ST-segment elevation.

### Overall follow-up

Among the 275 patients without criteria for DSE testing, 33 experienced myocardial necrosis. Patients who underwent DSE experienced less postoperative myocardial necrosis than non-tested patients, whatever the result of DSE (6% vs 12%, P=0.037). Patients with positive DSE did not experience more myocardial necrosis than those with negative DSE (3% vs 7%, P=0.379).

### Discussion

We assessed the prognostic value of preoperative DSE used as recommended by ACC/AHA guidelines, in patients scheduled for infra-renal aortic surgery and observed that its negative predictive value for postoperative myocardial necrosis was 92.7%. The positive predictive value of DSE for revascularizable coronary stenosis was 40.6%. Three out of four DSE tests were negative. Patients who underwent DSE experienced fewer cardiac events than non-tested patients, irrespective of DSE results.

In the first study defining postoperative myocardial infarction by a cTnI increase, the 1.5 ng ml\(^{-1}\) cTnI threshold...
corresponded to the detection threshold at that time. In subsequent studies, authors did not take account of improvements in cTnI measurement methods that reduced 99th percentile threshold from 1.5 to 0.2 ng ml\(^{-1}\) and used the higher threshold to define postoperative myocardial infarction. Recently, Le Manach and colleagues reported that low levels of postoperative cTnI release indicating myocardial damage (cTnI above the threshold detection of 0.2 ng ml\(^{-1}\) but below 1.5 ng ml\(^{-1}\)) were associated with increased mortality and predicted delayed postoperative myocardial infarction. Because of the continuous association between postoperative cTnI release and mortality, and the lack of consensus for a clear cTnI cut-off we classified all the patients with abnormal postoperative cTnI as having suffered myocardial necrosis. We did not distinguish between postoperative myocardial damage and postoperative myocardial infarction.

Our criteria for coronary followed the ACC/AHA guidelines. Recently, several studies have reported the lack of benefit of coronary revascularization in patients with stable coronary disease presenting for non-cardiac surgery. Our strategy could be responsible for the lack of significant difference observed between the positive and negative DSE groups of patients. However, our study was not powered to test this and this hypothesis requires further evaluation.

The negative predictive value of preoperative DSE for postoperative myocardial necrosis was lower than the lowest value reported in previous studies, that used CK-MB for the diagnosis of myocardial injury and whose enrolment criteria were close to ACC/AHA recommendations except with regard to functional capacity. Our study is original because it relies upon cTnI instead of CK-MB for the diagnosis of myocardial necrosis. This is justified by a clear relationship between troponin release and postoperative mortality. The shift from CK-MB to cTnI has improved test precision and both sensitivity and specificity in the diagnosis of myocardial necrosis. Small amounts of myocardial necrosis that were not diagnosed in previous studies can now be detected, thereby reducing false negative rates for the detection of myocardial necrosis. Thus, cTnI has been shown to increase the rates of diagnosis of myocardial infarction by between 12 and 227% so reducing methodological bias.

To our knowledge, elevation of cTnI above the detection threshold had never been used to evaluate the negative predictive value of DSE. More than 7% (1 in 14) of the patients with preoperative negative DSE will experience postoperative myocardial necrosis. According to Le Manach and colleagues 24% of the patients with postoperative myocardial damage (cTnI between 0.2 and 1.5 ng ml\(^{-1}\)) will develop subsequent myocardial infarction. All these patients have an increase in postoperative predicted mortality dependant on cTnI concentration. The prognostic value of preoperative DSE for mortality remains to be assessed.

Table 2: Coronary events in negative dobutamine stress echocardiography patients (n=8). MN, myocardial necrosis; PTCA, percutaneous transluminal coronary angioplasty; AIV, anterior interventricular coronary artery; RCA, right coronary artery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Postoperative cTnI peak (ng ml(^{-1}))</th>
<th>Postoperative ECG abnormalities</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>22.70</td>
<td>ST-segment elevation</td>
<td>Immediate redo surgery for aortic graft thrombosis. Myocardial necrosis on day 2. PTCA of occluded AIV coronary artery</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>2.62</td>
<td>ST-segment elevation</td>
<td>Typical chest pain on day 7. PTCA on RCA stenosis coronary rupture. 48 h intra-stent thrombosis</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>2.32</td>
<td>None</td>
<td>Previous coronary angiogram showed lesions beyond revascularization</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>1.50</td>
<td>ST-segment elevation</td>
<td>No coronary angiogram was performed because of severe chronic renal failure</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>1.40</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>0.47</td>
<td>Down-sloping ST-segment depression</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>0.36</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>0.35</td>
<td>Down-sloping ST-segment depression</td>
<td>Postoperative anemia</td>
</tr>
</tbody>
</table>

Table 3: Coronary angiography findings in patients with positive DSE tests according to criteria for a positive DSE. Angina, chest pain on stress testing; Echo positive, echocardiographic changes on stress testing; ECG positive, ECG changes on stress testing

<table>
<thead>
<tr>
<th>DSE results</th>
<th>Coronary angiogram findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Angina Echo positive ECG negative</td>
<td>1</td>
</tr>
<tr>
<td>Angina Echo positive ECG positive</td>
<td>9</td>
</tr>
<tr>
<td>No angina Echo negative ECG positive</td>
<td>4</td>
</tr>
<tr>
<td>No angina Echo positive ECG positive</td>
<td>5</td>
</tr>
<tr>
<td>No angina Echo positive ECG negative</td>
<td>14</td>
</tr>
</tbody>
</table>
Low NPV for preoperative DSE

DSE for cardiological assessment. This may be because of a higher false negative rate as the result of the inability of DSE to reproduce all components of surgical stress, whereas cardiological patients are exposed during their daily life to lower stress levels than during DSE. DSE cannot simulate systemic factors such as hypovolemia, anaemia, vasoconstriction, inflammation, hypercoagulability because of high fibrinogen concentration, easily activated platelets and reduced fibrinolysis.

The incidence of positive DSE tests in our study does not differ from the one reported by Boersma and colleagues, using similar criteria to select patients for testing. After two levels of selection (clinical evaluation then DSE) no more than 40% of DSE positive patients had coronary stenosis eligible for revascularization according to ACC/AHA guidelines. Whatever the benefits of coronary revascularization, this result suggests that DSE does not perform better than simple clinical screening to identify patients whose coronary angiogram reveals high cardiac risk. However, our study was not powered to test this and this finding requires further study.

High-risk patients who underwent DSE developed less postoperative myocardial necrosis than low-risk patients not eligible for non-invasive testing, irrespective of the DSE result. This is consistent with previous results. Such paradox may rely upon more aggressive perioperative care, such as the use of beta-blockers and statins in high-risk patients. Thus the criteria for DSE testing alone identify patients that benefit from therapeutic modifications. Again, our study is not powered to test this and such a conclusion requires further evaluation.

Conclusion

This study points out that a negative DSE performed before aortic surgery according to ACC/AHA guidelines does not exclude perioperative myocardial necrosis as previously reported. This result suggests that a negative DSE does not support withdrawal of any perioperative diagnostic or therapeutic strategies recommended in high-risk patients.

Acknowledgements

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References

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