Relationship between perioperative troponin elevation and other indicators of myocardial injury in vascular surgery patients

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Background. In 2000 the European Society of Cardiology and the American College of Cardiology published a consensus document revising the definition of myocardial infarction. The usefulness of this revised definition has been challenged. It has been suggested that, rather than any release of cardiac troponin being potentially diagnostic of myocardial infarction, a diagnostic threshold consistent with significant myocardial injury should be defined.

Methods. We studied 65 patients undergoing elective major vascular surgery to examine the relationship between the magnitude of cardiac troponin I (cTnI) and creatine kinase MB fraction (CK-MB) release and clinical signs or symptoms of myocardial injury. cTnI and CK-MB concentrations were measured preoperatively and on the first 4 postoperative days using the ACCESS® assay (Beckmann). Patients were considered to have suffered a perioperative myocardial infarction if they had either symptoms or ECG changes consistent with this diagnosis, together with cTnI release.

Results. Peak postoperative cTnI concentrations above the lower detection limit of the ACCESS® assay (0.06 μg litre⁻¹) occurred in 26 patients. Eight of these patients displayed symptoms or ECG changes consistent with myocardial injury. A cTnI level greater than 0.68 μg litre⁻¹ was found to be consistent with the clinical diagnosis of myocardial infarction. The optimal cut-off for the diagnosis of MI using CK-MB was 40.4 μg litre⁻¹.

Conclusions. These data suggest that further studies are required to define the optimal cardiac troponin diagnostic threshold for the diagnosis of myocardial infarction in the non-cardiac surgery population.

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Perioperative cardiac troponin release is common in patients undergoing major vascular surgery and has adverse prognostic implications.1 However, not all patients who demonstrate release of cardiac troponin in the perioperative period fulfil the clinical criteria for myocardial infarction (MI).2 Conversely, the symptoms and signs of myocardial ischaemia are common in these patients, but not all patients with these changes display cardiac biomarker release consistent with the diagnosis of MI. Deciding whether or not a patient is to be labelled as having suffered an MI can be difficult. In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) published a consensus document revising the definition of MI (Table 1).3 The authors of the ESC/ACC definition propose that it should be used in both the medical and the surgical setting.3 This redefinition is important from both an epidemiological and a clinical perspective. Devereaux and colleagues4 have suggested recently that the ESC/ACC

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definition should indeed form the basis of a definition of perioperative MI. For the epidemiologist and the clinical researcher, the use of a consistent definition of MI is essential, if studies are to be compared. From a clinical perspective, the management of patients who suffer either an ST-segment elevation (STEMI) or a non-ST-segment elevation (NSTEMI) MI is well described. The optimal postoperative management of patients who display cardiac troponin release in the perioperative period, but who do not display any symptoms or signs of myocardial ischaemia, is much less certain. The British Cardiac Society Working Group on the diagnosis of MI produced a report in 2004 which points out problems in the application of the ESC/ACC guidelines. In the ESC/ACC definition an elevated cardiac troponin is defined as a maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 h after the index clinical event. The British Cardiac Society document suggests that the diagnosis of MI should be made not on the basis of cardiac troponin being detectable in the blood, but should require troponin release above a diagnostic threshold. In this study, we sought to identify the level of troponin release consistent with a clinical diagnosis of MI in a population of patients undergoing major vascular surgery.

Methods
The study was approved by the South and West of England Multicentre Research Ethics Committee and subsequently approved by the Research Ethics Committees of the participating hospitals. Patients undergoing elective major vascular surgery in hospitals in Bristol, Leicester, Sheffield, Newcastle, Edinburgh and Plymouth were eligible for recruitment. Patients who had a documented history of cardiac disease or two or more risk factors for cardiac disease were approached for the study. After informed consent, data were collected on the patient’s age and sex and on the planned surgery. After surgery, patients were reviewed daily whilst in hospital. Symptoms and signs of cardiac complications were actively sought. These included ECG and clinical evidence of new MI, new or worsened angina, new or worsened heart failure, and cardiac rhythm changes. Other complications, including surgical complications, were also recorded. All in-hospital deaths were recorded. Deaths were classified as cardiac deaths when attributable to MI, arrhythmia or heart failure.

Serial 12-lead ECGs were performed on the evening before surgery and 24, 48, 72 and 96 h after surgery. These were examined by a consultant cardiologist (A.B.) who was blinded to the clinical outcome of the patients and the cTnI (cardiac troponin I) and CK-MB (MB isoform of creatine kinase) assay results. New ECG changes were noted. Significant changes were considered to be new ST-segment elevation in two or more contiguous leads as described in Table 1, new ST-segment depression of greater than 1 mm in leads I, II, aVL, aVF, or V1–4 (Minnesota code IV1), new T-wave flattening or inversion in leads I, II or V2–6 (Minnesota code V), and the development of new pathological Q-waves in leads I, II or V2–6 (Minnesota codes II or 2).

Blood was obtained for assays of cTnI and CK-MB on the evening before surgery and 24, 48, 72 and 96 h after surgery. Samples were cold centrifuged and frozen locally and were transported to the Department of Cardiac, Anaesthetic and Radiological Sciences at the University of Bristol for analysis. Analyses for cTnI and CK-MK were performed using the ACCESS® immunoassay system (Beckman Instruments, UK). The lower detection limit of this cTnI assay is between 0.0055 and 0.0092 μg litre⁻¹, with a mean of 0.007 μg litre⁻¹. The lowest value with a coefficient of variation of 10% is 0.06 μg litre⁻¹ and this was therefore considered as the lower limit of reliable detection. The ACCESS® assay for CK-MB has a range derived in a healthy population of 0.3–4.0 μg litre⁻¹ (i.e. the range between the lower limit of detection and the 95th percentile). The assay has acceptable precision at the upper limit of the normal range, with a coefficient of variation of 8.2% at a CK-MB concentration of 3.2 μg litre⁻¹.

Data were analysed using Intercooled Stata version 7 for Windows (Stata Corporation, TX). Data for both cTnI and CK-MB had markedly skewed distributions, with a small number of high values and are reported as median values with interquartile ranges and maximum and minimum values. cTnI concentrations in patients with and without clinical symptoms of MI were compared using the Mann–Whitney U-test. The effect of type of anaesthesia on cardiac troponin release was examined using one-way ANOVA. The diagnosis of MI required the occurrence of either symptoms or ECG changes consistent with myocardial ischaemia together with the presence of cTnI above the lower detection limit of our chosen assay (0.06 μg litre⁻¹). New ECG changes consistent with myocardial ischaemia were changes that fulfilled the criteria given above.
Results

Sixty-five patients from six centres were studied. The mean age of the patients was 70.3 (45–86) yr. Fifty-seven (88%) of the patients were male. Thirty-one patients (48%) underwent surgery for abdominal aortic aneurysm (including one thoraco-abdominal aneurysm), 8 (12%) patients abdominal aortic surgery for aorto-iliac occlusive disease, 10 (15%) patients carotid endarterectomy, 15 (23%) patients lower limb revascularization and 1 (2%) patient repair of a subclavian artery aneurysm.

In 16 patients (25%) surgery was carried out under general anaesthesia alone, in 8 patients (12%) a local or regional technique was used and in 41 patients (63%) combined general and regional anaesthesia was used. There was no difference in peak postoperative cTnI concentrations between patients who had received different types of anaesthesia (one-way ANOVA, F=0.14, P=0.87).

cTnI elevation and MI

No patient had a cTnI concentration above 0.06 µg litre\(^{-1}\) before surgery (Table 2). Twenty-six patients had a cTnI concentration above 0.06 µg litre\(^{-1}\) on at least 1 postoperative day (POD). A cTnI concentration above 0.06 µg litre\(^{-1}\) was first recorded on the first POD in 11 patients, the second POD in 10 patients and the third POD in 5 patients. No patient had a cTnI elevation above 0.06 µg litre\(^{-1}\) first recorded on the fourth POD.

Among the 26 patients with an increase in cTnI, 8 displayed either, or both of, ischaemic symptoms or ECG changes consistent with myocardial ischaemia or infarction. Of these patients, one developed a classic MI with new Q-waves, ST-segment elevation and T-wave inversion on the ECG and symptoms of chest pain and heart failure. This patient died from heart failure on the fifth POD. Six patients developed ST-segment depression or T-wave inversion on one or more postoperative ECG recordings. In two cases, this was accompanied by chest pain. One patient displayed a marked troponin increase to a peak concentration of 7.7 µg litre\(^{-1}\) and suffered chest pain, but did not develop new ECG changes. The range of peak cTnI concentrations among these eight patients was 0.16–14.42 µg litre\(^{-1}\).

Eighteen patients had a cTnI concentration above 0.06 µg litre\(^{-1}\) on at least one POD, but did not display symptoms or ECG changes consistent with MI. These patients had peak cTnI concentrations ranging from 0.07 to 0.56 µg litre\(^{-1}\). One of the 18 patients had an episode of heart failure. He had a peak cTnI value of 0.3 µg litre\(^{-1}\) on the third POD. The remaining 17 patients had no signs or symptoms of cardiac complications.

Amongst the patients with a cTnI elevation, there was very limited overlap in peak cTnI values between the patients who were considered to have had a MI and those who were not (Fig. 1). Peak cTnI concentrations were significantly higher amongst patients with clinical evidence of myocardial ischaemia or infarction (P=0.0004). Among the eight patients who were considered to have had a MI...
had an MI, only one had a peak cTnI that fell within the range for those who did not have clinical evidence of MI. The peak value in this patient was 0.16 \( \mu \text{g litre}^{-1} \). In the remaining seven patients the range of peak cTnI concentrations was 0.68–14.42 \( \mu \text{g litre}^{-1} \).

A receiver operator characteristic (ROC) curve was plotted to determine the cut-off for cTnI that resulted in the maximum number of patients who had suffered an MI being correctly classified (Fig. 2). This value was 0.68 \( \mu \text{g litre}^{-1} \). This threshold gave positive predictive value of 100% and a negative predictive value of 98.3% for the diagnosis of MI by clinical criteria.

The number of patients for whom the data are available decline over the four PODs of the study. There are two reasons for this. First, patients undergoing carotid endarterectomy were generally discharged after 2–3 days. Some data were lost because of early discharge in nine carotid endarterectomy patients, four after the first POD, three after the second and two after the third. Second, a number of patients withdrew consent for blood sampling when no routine postoperative blood sample was required and an extra venepuncture was required for the study, particularly on the fourth POD. One patient withdrew from the study on the first POD, seven patients withdrew on the third and thirteen on the fourth. Of the patients who withdrew, one had undergone a carotid endarterectomy, one repair of a subclavian artery aneurysm, twelve lower limb surgery and the remainder had aortic surgery.

Other cardiac events

Seven other patients suffered clinically evident cardiac events in the study period. Five patients developed heart failure in the postoperative period. In two cases this was associated with the development of new atrial fibrillation. Two patients had episodes of chest pain accompanied by ST-segment depression on the ECG. In all seven patients cTnI concentrations were below 0.06 \( \mu \text{g litre}^{-1} \) on all four PODs.

**CK-MB**

Data are incomplete because 27 samples were lost because of technical problems in the assay process (Table 2). Six patients in whom at least two consecutive postoperative CK-MB samples were not available were excluded from this analysis. Complete CK-MB data were available on all but one of the patients considered to have suffered an MI by the ESC criteria. Thirty-three patients (56%) had a peak CK-MB value above this concentration.

A ROC curve was plotted to determine the optimal CK-MB threshold for the diagnosis of MI as defined by a cTnI increase together with clinical or ECG evidence of MI (Fig. 3). The peak value of CK-MB was examined for each subject. The optimal threshold was found to be 40.4 \( \mu \text{g litre}^{-1} \). This threshold gave a positive predictive value of 66.7% and a negative predictive value of 98.2%.

**Discussion**

In this study, cTnI concentrations above the detection limit of the assay were observed on at least one occasion in 26 out of 65 (40%) high-risk patients undergoing major vascular surgery. Eighteen patients had an increase in cTnI (range 0.07–0.56 \( \mu \text{g litre}^{-1} \)) but did not display the symptoms and signs of MI. Eight patients (12%) had clinical evidence of MI. Seven of them had peak cTnI concentrations in the range 0.68–14.4 \( \mu \text{g litre}^{-1} \). The remaining patients considered to have suffered an MI had a peak cTnI of 0.16 \( \mu \text{g litre}^{-1} \). Most papers examining the incidence of perioperative cardiac complications base their definition of MI on the WHO criteria (i.e. at least two of typical chest pain, a cardiac enzyme increase and ECG changes). The ESC/ACC definition of MI mirrors this definition, except it explicitly requires ‘a typical increase and gradual decrease (troponin) or more rapid increase and decrease (CK-MB) of biochemical markers of myocardial necrosis’ and the detection of any cardiac troponin in the blood is considered to...
be abnormal. In our study, the patients who had both a troponin increase and symptoms or ECG changes consistent with MI displayed a pattern of cTnI increase and decrease and had relatively large troponin elevations. In contrast, several patients without symptoms of ischaemia or ECG changes had isolated and relatively small cTnI elevations on 1 day only.

This is the first study to explicitly examine the impact of applying the ESC/ACC definition of MI to the diagnosis of perioperative MI in patients undergoing vascular surgery. Our findings suggest that the previously highlighted problems with the ESC/ACC definition apply to patients undergoing major vascular surgery. Patients in whom cardiac troponin was released were divided into two groups: those with low troponin concentrations and no other evidence of myocardial injury, who did not fulfil the criteria for MI; and those with higher troponin concentrations and clinical evidence of myocardial injury, who did fulfil the ACC/ESC definition of an MI. A cut-off of 0.68 \( \mu g \) litre\(^{-1}\) almost dichotomized patients between these two groups, with only one patient who suffered an MI having a peak cTnI value of less than this.

The ESC Task Force on the management of acute coronary syndromes without persistent ST-segment elevation proposes that the ESC/ACC definition of MI should apply in all clinical settings including following percutaneous coronary intervention or coronary artery bypass grafting. By inference, this should apply equally to patients undergoing major vascular surgery. Our data suggest that vascular surgery patients with low concentrations of troponin release are unlikely to fulfill the definition of an MI.

Published studies of surgical patients have used a range of different cut-off values to identify perioperative MI. Some studies, adhere to the convention of using the lower detection limit of the relevant troponin assay. \(^{13,14}\) Others have defined the threshold for cardiac troponin elevation in a number of different ways. In setting a threshold for the diagnosis of perioperative MI it is important to choose an appropriate control group for the definition of the ‘normal’ range. For the diagnosis of MI in medical patients presenting with chest pain it is appropriate to define the normal troponin level in terms of a healthy population as healthy individuals would not be expected to have detectable concentrations of cardiac troponin in their plasma. In contrast, there are a number of reasons apart from MI for the appearance of cardiac troponin in the plasma of patients in hospital. \(^{15}\) Some of these (heart failure and pulmonary embolism) are frequent in high-risk surgical patients. This is illustrated by the two studies of patients undergoing vascular or spinal surgery, where the cut-off for an elevated cTnI was considered as 3.1 \( \mu g \) litre\(^{-1}\), based on the upper limit of normal in a population of hospital patients without cardiac disease. The threshold was revised to 0.6 \( \mu g \) litre\(^{-1}\) when the assay was commercialized, recognizing that a variety of conditions apart from MI may produce a cardiac troponin elevation.

How should the diagnostic threshold for cardiac troponin elevation be decided for surgical patients? Metzler and colleagues\(^{16}\) studied 67 patients undergoing non-cardiac surgery. They made a distinction between those patients who had a relatively modest increase in troponin T of 0.32–0.99 \( \mu g \) litre\(^{-1}\) and who did not suffer obvious cardiac complications and eight patients with higher values in the range 0.47–9.8 \( \mu g \) litre\(^{-1}\) in whom there were clinically evident cardiac complications. Landesberg and colleagues\(^{2}\) studied 447 consecutive patients undergoing 501 major vascular operations. An MI was defined on the basis of cardiac troponin release. Two different troponin assays were used at different stages in the study and three different cut-offs were examined for each of the two assays. When the lowest threshold was used 107 patients (25%) would have been diagnosed as having an MI because they had a cardiac troponin level above this threshold. However, only 20% of these patients had other criteria for diagnosis of MI. Even using a higher troponin threshold concentration, many patients did not fulfill the criteria for MI.

In the medical setting, Fox and colleagues\(^{7}\) propose that the troponin diagnostic threshold for the diagnosis of MI should be 1.0 \( \mu g \) litre\(^{-1}\) for troponin T or 0.5 \( \mu g \) litre\(^{-1}\) for the AccuTnI assay. This is based on the fact that patients with cardiac troponin concentrations above these thresholds have outcomes similar to those seen in patients diagnosed using the 1979 WHO definition of MI. It is recommended that laboratories using other assays should estimate equivalent troponin concentrations. For the ACCESS troponin assay that we used a cut-off of 0.15 \( \mu g \) litre\(^{-1}\) is suggested as consistent with the diagnosis of MI.\(^{5}\) However, our finding of a cut-off of 0.68 \( \mu g \) litre\(^{-1}\) suggests that this threshold may not be appropriate in the setting of vascular surgery. Large cohort studies are required to establish diagnostic thresholds for the diagnosis of MI in the setting of non-cardiac surgery.

We recognize that this study has some limitations. We report a high cardiac event rate (25%). However, we studied a high-risk population with either documented cardiac disease or two or more risk factors for such disease, and is comparable to other studies.\(^{17}\) As patients were monitored with a daily 12-lead ECG, rather than with Holter monitoring, some episodes of myocardial ischaemia may have been missed. However, a recent study in vascular surgery patients showed a 72% concordance between continuous monitoring and the 12-lead ECG for the detection of myocardial ischaemia.\(^{18}\) Thus, while not as sensitive as Holter monitoring, the daily 12-lead ECG is a reasonably reliable method for the detection of postoperative myocardial ischaemia. A number of patients were lost to the study upon early discharge from hospital, or patient withdrawal. Many of those who withdrew had undergone lower limb surgery. It can be argued that the majority of the patients who were lost to the study had lower risk procedures and that we observed a disproportionately high incidence of cardiac troponin release. However, some data suggest
that the incidence of perioperative cardiac complications is comparable in patients undergoing aortic and carotid surgery, and that patients undergoing infrainguinal vascular surgery are at increased risk.19 Thus, if the drop-out rate from our study does confer a bias, it is not clear in what direction it will act. Our primary aim was to report not the incidence of troponin release, but the proportion of cases in which this was associated with a formal diagnosis of MI. No patient was discharged home having suffered a large troponin increase the previous day and no patient was readmitted with a cardiac complication. Thus, we feel that our data give an accurate picture of the difference between patients with small, transient troponin increases, and those with larger elevations consistent with MI. It is notable that a number of patients suffered adverse cardiac events in the absence of increases in cTnI or CK-MB. Our data confirm the lack of sensitivity and specificity of CK-MB for the diagnosis of MI using conventional cut-off values, but suggest that a markedly increased threshold may improve the specificity of the assay. This may be of clinical relevance in the early diagnosis of perioperative MI in the first 12–24 h after surgery when cardiac troponin concentrations may not yet have increased.

In summary, these data confirm that patients should not be diagnosed as suffering a perioperative MI on the basis of minor elevations in cTnI. We suggest that if cTnI is elevated after surgery in asymptomatic patients a further assay should be performed the following day. Only relatively large cardiac troponin elevations should be considered as consistent with the diagnosis of MI. Lesser elevations of cardiac troponin do have prognostic significance and we did not examine long-term outcome in this study.1 However, from an epidemiological perspective or in clinical trials, not every patient who displays some perioperative cardiac troponin release should be considered to have suffered an MI. Our data suggest a threshold for cTnI of 0.68 μg ml⁻¹ but further studies are required. We disagree with Devereaux and colleagues5 that the current ESC/ACC definition of MI is applicable in the perioperative setting. Further studies are needed to clarify the definition of perioperative MI and to determine the optimal threshold for the diagnosis of perioperative MI for the other commonly used troponin assays. If CK-MB is being used for the early diagnosis of postoperative MI only marked elevations of this enzyme should be considered significant.

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