



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

Perioperative myocardial infarction in non-cardiac surgery. Pathophysiology and clinical implications.

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

Perioperative myocardial infarction in non-cardiac surgery. Pathophysiology and clinical implications / Pietro Amedeo Modesti; Ignazio Simonetti; Giuseppe Olivo. - In: INTERNAL AND EMERGENCY MEDICINE. - ISSN 1828-0447. - STAMPA. - 1:(2006), pp. 177-186. [10.1007/BF02934735]

Availability:

The webpage <https://hdl.handle.net/2158/347466> of the repository was last updated on

Published version:

DOI: 10.1007/BF02934735

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

Perioperative myocardial infarction in non-cardiac surgery.

Pathophysiology and clinical implications

Pietro Amedeo Modesti, Ignazio Simonetti, Giuseppe Olivo

Clinical Medicine and Cardiology, Department of Critical Care Medicine and Surgery, University of Florence, Florence, Italy

Advances in surgical and anaesthetic techniques and an aging patient population have resulted in more complex procedures being performed in greater numbers of aged subjects and in patients with a high likelihood of significant cardiovascular disease. Nearly one fourth of non-cardiac surgical procedures (major intra-abdominal, thoracic, vascular, and orthopaedic procedures) performed in persons older than 65 years have been found to be associated with significant perioperative cardiovascular morbidity and mortality.

During previous years the main attempt was to define strategies

to accurately estimate perioperative cardiovascular risk based either on the characteristics of surgery and on patient characteristics. More recently preventive medical strategies have been proposed. Therefore, the physician has to be aware of the key elements useful to calculate the perioperative cardiovascular risk, and of the medical preventive treatment or further interventions to adopt in patients candidate to surgery.

(Intern Emerg Med 2006; 1 (3): 177-186)

Key words: cardiovascular risk, myocardial infarction, troponins

The dimension of the problem

Between April 1998 and March 1999 the National Confidential Enquiry into Patient Outcome and Death, collected a total of 32 956 in-hospital deaths within 30 days of an operative procedure (24 920 after emergency surgery and 8036 after non-emergency surgery¹). Total procedures were 2.3 million (644 463 emergency surgery and 1.7 million non-emergency surgery) resulting in an approximate mortality rate of 1.4% (3.9% after emergency surgery or 0.5% after non-emergency surgery)¹. Almost half of deaths occurred within the first 5 days with a distribution of the number of calendar days between operation (day 0) and death which has remained remarkably unchanged over the years² (Fig. 1). Patient disease is recognised as the most relevant of the three components of perioperative risk of death (anaesthesia, surgery and patient disease). More precisely, in a survey considering over 1 million cases of anaesthesia in a 1-year period (1987, about 485 850 operations), perioperative mortality was due to intercurrent disease in 44% of overall mortality, although the main cause was represented by the patient presenting disease (67% of overall mortality)³.

Cardiovascular diseases are now becoming the most common cause of perioperative death due to either cardiac-related death (heart failure, acute myocardial infarction [MI], left ventricular failure) or stroke-related death⁴, with pneumonia renal failure and sepsis being the next most common⁴ (Fig. 2).

When both mortality and morbidity data are considered, cardiac events occur in an estimated 1-5% of patients undergoing non-cardiac surgery, and the cardiovascular complication rate may reach 30% for patients undergoing vascular surgery^{5,6}. In recent years the introduction of troponin assay for the diagnosis of perioperative MI⁷⁻¹⁴ led to an apparent further increase in the frequency of perioperative MI from 1.4% with creatine kinase-MB assay to 6.6%¹¹. In a retrospective study¹⁵ performed on 869 patients who underwent major non-cardiac surgery, troponin I elevations ($> 0.4 \mu\text{g/l}$) were observed among 38% of patients with significant intraoperative events such as hypotension, hypertension or unexpected blood loss or readmitted to the intensive care unit for an acute event on the ward.

The overall frequency of MI in the whole surgical population may appear low ($< 1\%$), but the prevalence is particularly concentrated among patients who undergo major thoracic, abdominal or vascular surgery, especially when they are ≥ 70 years¹⁶⁻¹⁸, and among patients with underlying coronary artery disease (CAD). In particular, the risk of perioperative MI or cardiac death is $< 1\%$ for patients who do not have CAD¹⁹, but increases twice in the presence of known or suspected coronary or atherosclerotic vascular disease¹⁹⁻²⁵. A further 3 to 5-fold increase was reported in patients selected to undergo

Received 13 February 2006; revised 21 February 2006; accepted 22 February 2006.

Address for correspondence: Prof. Pietro Amedeo Modesti, Clinica Medica e Cardiologia, Dipartimento di Area Critica Medico Chirurgica, Università degli Studi, Firenze, Viale Morgagni 85, 50134 Firenze, Italy. E-mail: pa.modesti@unifi.it

© 2006 CEPI Srl

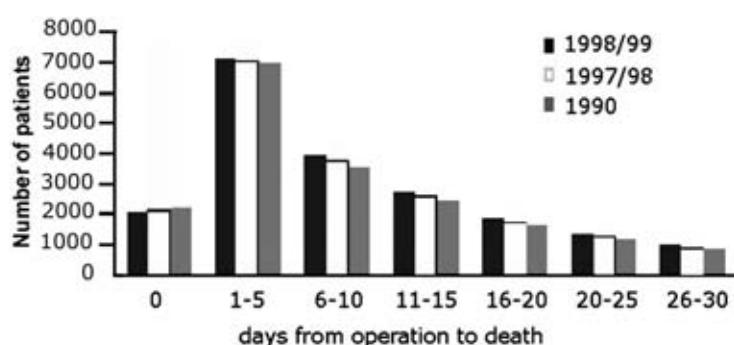


Figure 1. Distribution of the number of calendar days between operation (day 0) and death.

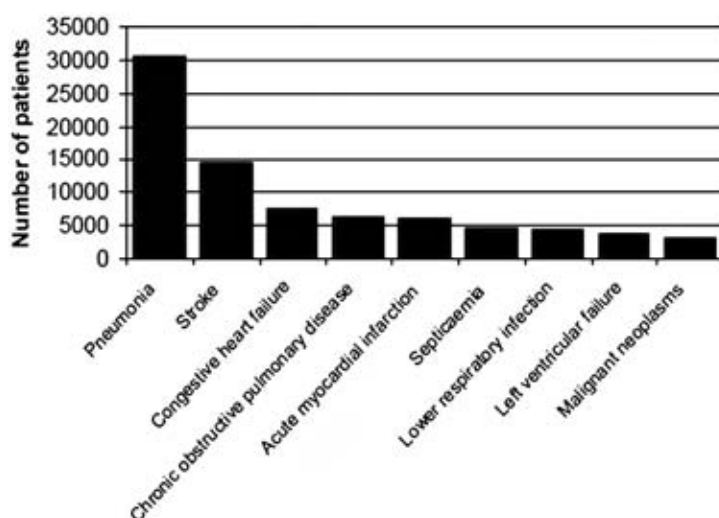


Figure 2. Final primary diagnosis of perioperative death (n = 310 274) collected by the National Confidential Enquiry into Patient Outcome and Death between 1 April 2003 and 31 March 2004.

preoperative thallium scintigraphy²⁶⁻³¹. In addition, the prevalence of cardiovascular disease increases with age and nearly one fourth of non-cardiac surgical procedures (major intra-abdominal, thoracic, vascular, and orthopaedic procedures) performed in subjects > 65 years have been associated with significant perioperative cardiovascular morbidity and mortality³². Therefore, in the preoperative evaluation, special attention should be placed to identify patients at risk of myocardial ischaemia³².

Almost half of the patients who experience cardiac morbidity develop other types of non-cardiac complications and mortality³³. To control healthcare costs, hospital stays have been shortening in western countries to bring hospital expenditure in line with diagnosis-related group reimbursement. Likewise, ambulatory surgery or same day admission for major surgery are now widely used with the introduction of critical pathways and the development of protocols reducing the use of routine laboratory diagnostic tests for

preoperative evaluation³⁴. This aspect is critical because failure in preoperative evaluation or immediately perioperative care may result in increased costs. One million people having perioperative cardiac complications over the 27 million men and women having surgery each year in the United States, require approximately 20 billion in costs of in-hospital and long-term care³⁵.

To better understand the key elements useful to calculate the perioperative cardiovascular risk in patients referred to the surgeon it is important to know the pathophysiological mechanisms responsible for perioperative MI.

Pathophysiology of perioperative myocardial infarction

Perioperative MI mainly occurs either at the end of the surgical procedure or 24-96 h after non-cardiac surgery³⁶⁻³⁸.

Although the mechanism underlying perioperative MI is unknown, it was assumed to resemble that of non-surgical MI³⁹, that is, acute plaque rupture and coronary thrombosis^{40,41}. This hypothesis mainly stems from the large prevalence of ulcerated plaques and coronary thrombosis (> 45%) found in retrospective studies performed on autopsy records of patients who underwent elective or emergency non-cardiac surgery and fatal perioperative MI between 1980 and 1990^{39,42}. However, in high-risk patients undergoing vascular surgery under electrocardiographic monitoring⁷, the majority of ischaemic events (67%) including those culminating in MI, were reported to start between 50 min before and 60 min after the end of surgery and during the emergence from anaesthesia, a time characterised by an increase in heart rate, blood pressure, and sympathetic discharge⁴³. In 67% patients with perioperative MI, the troponin levels reached values above the 99th percentile of the reference population (diagnosis of MI) within < 18 h after the end of surgery with no ST-segment elevation or Q-wave MI⁷. In addition, coronary angiography performed in a small subgroup of patients with perioperative MI within 7 days of MI revealed the presence of chronic severe CAD without thrombus or ulcerated plaques⁷. These findings support the hypothesis that haemodynamic changes may play a prevalent role at the end of surgery and in the early postoperative hours. A significant decrease in coronary and myocardial blood flow may indeed occur as a consequence of tachycardia in the presence of fixed, but severe, coronary artery stenosis, due to shortening of the diastolic time period^{44,45}. Vasoconstriction secondary to ischaemia may further decrease coronary blood flow^{46,47}. The hypothesis that prolonged tachycardia and stress-induced ischaemia underlie the evolution of perioperative MI is further supported by the reduction in cardiac death rates from 34 to 3.4% by prophylactic preoperative bisoprolol treatment in high-risk patients undergoing major vascular surgery⁴⁸. Therefore, the pathophysiology of early perioperative MI seems to be related to a prolonged imbalance between myocardial oxygen supply and demand in the setting of CAD.

The onset of postoperative inflammatory reaction seems to play a role in the occurrence of MI in the following postoperative days. In particular, the inflammatory activation may be responsible for fluid shifts^{16,23,49}, for the creation of a hypercoagulable environment, and for functional alterations in distant organs. Major surgery and, in particular, abdominal aortic surgery are followed by extensive changes in the plasma levels of coagulation factors and in thromboelastographic parameters leading to a hypercoagulable state. An early impairment of fibrinolysis with higher amounts of plasminogen activator inhibitor-1 was observed in the early postoperative period (24 h) after infra-inguinal

reconstruction⁵⁰ and in patients undergoing lower-extremity vascular reconstruction⁵¹ and remained elevated through the second day. A return to baseline values of plasminogen activator inhibitor-1 and fibrinolysis was observed at day 3. Marked decreases in the naturally occurring anticoagulants, protein C and antithrombin III, and in alpha₂-macroglobulin were also reported in the following days (days 2-4)⁵². When patients undergoing abdominal aortic surgery, carotid endarterectomy and femoro-popliteal bypass were compared, an increase in plasma fibrinogen and factor VIII coagulant activity was observed in all the three procedures. Conversely, there was a decrease in antithrombin and protein C, and an increase in thrombin-antithrombin complex levels in the abdominal aortic group only⁵³. This temporary increase of the tissue plasminogen activator inhibitor may be responsible for an impairment of fibrinolysis and an increase in the risk of myocardial ischaemia⁵⁴.

After major non-cardiac surgery, in particular major abdominal surgery⁵⁵, cancer surgery⁵⁶, and vascular surgery⁵⁷, an early increase in plasma concentrations of both pro- and anti-inflammatory cytokines was also reported. A close relationship between cytokine release and the extension of surgical trauma⁵⁸⁻⁶⁰, and in particular with the extension of ischaemia and reperfusion⁶¹, was observed in aortic aneurysm surgery. Recent findings indicate that proinflammatory cytokines affect vascular function and endothelium-derived factors involved in blood pressure regulation. Tumour necrosis factor-alpha and interleukin-6 were both shown to induce structural as well as functional alterations in endothelial cells⁶². These cytokines enhance the formation of a number of endothelial cell substances, such as endothelin; reduce acetylcholine-induced vasodilatation; and destabilise the mRNA of endothelial nitric oxide synthase^{62,63}. Thus, proinflammatory cytokines may contribute to cause endothelial dysfunction in postoperative days.

Attempts have been made to define the systemic inflammatory reaction on the basis of simple clinical criteria, but their clinical meaning in the postoperative period remains to be established. During the early days in intensive care unit after surgery, the percentage of patients with positive criteria for a systemic inflammatory response (temperature > 38°C, leucocytosis, tachypnoea, and tachycardia) is much higher (93%) than mortality (8.2%) of the same group⁶⁴, so that the prognostic value of systemic inflammatory response syndrome (SIRS) was questioned. Indeed, part of these criteria may be related to sympathetic activation (postoperative pain) rather than to inflammation. However, when SIRS criteria persists for 2 consecutive days after postoperative day 3, the negative prognostic value is high^{61,66}.

Preoperative evaluation and clinical prediction

To reduce the incidence of perioperative cardiovascular complications and to minimise the costs of redundant perioperative tests, the American College of Cardiology (ACC), the American Heart Association (AHA) and the American College of Physicians produced practice guidelines for perioperative evaluation in non-cardiac procedures³². Two main factors contribute to perioperative risk, the first related to the type of surgery and degree of haemodynamic cardiac stress associated with surgery-specific techniques, the second related to patient characteristics³². In some cases, such as in vascular surgery for peripheral vascular disease, the two conditions coexists due to frequent co-morbidities (CAD, congestive heart failure, cerebrovascular disease, and renal and pulmonary disease)⁶⁷⁻⁷⁶.

Considerable risk is also present when surgery is performed as an emergency procedure especially in the elderly. However, a first relevant consideration is that preoperative cardiac evaluation has to be adapted to the circumstances that have required consultation and the nature of the illness. Therefore, at variance with elective surgical procedures, both in acute emergency and when good care requires prompt surgery (bleeding cancer), only limited essential critical tests (vital signs, volume status, renal function) are required and it is often not necessary to perform additional tests, especially when coronary revascularisation is not an option.

Perioperative evaluation for elective surgery often represents the first careful cardiovascular evaluation for the patients over the years. The visit should therefore be considered as an ideal opportunity to affect long-term treatment of a patient with cardiac disease or at risk of such disease and the referring physician should be informed of the results of the evaluation. History should be especially addressed to investigate serious cardiac conditions (prior angina, recent or past MI, heart failure, symptomatic arrhythmias, pacemaker, implantable cardioverter-defibrillator), co-morbid diseases (peripheral vascular disease, cerebrovascular disease, diabetes mellitus, renal impairment, peripheral vascular disease, cerebrovascular disease, renal failure) and risk factors. Diabetes, hypertension, angina or heart failure may often be diagnosed for the first time at preoperative consultation. It is well recognised that undiagnosed diabetes in the US population aged 20-74 years was 2.0 and 2.4% in the years 1976-1980 and 1999-2000, respectively, with a prevalence of 3.3 and 5.8% of diagnosed diabetes⁷⁷. Risk factors, such as hypertension and chronic pulmonary disease, seem to play a role as predictors of outcome⁷¹⁻⁷⁵. Patients with poorly controlled hypertension or labile preoperative hypertension have an increased risk for perioperative dysrhythmias and myocardial ischaemia³². Poor

pulmonary function is also often described as a significant predictor of perioperative mortality⁷¹⁻⁷⁵. Combination of different perioperative strategies designed to emphasise respiratory therapy in high-risk patients may reduce the risk of pulmonary⁷⁸ and subsequent cardiac³³ complications.

A simple esteem of the functional capacity of the patient can be obtained during the history³² (Table 1). Poor functional capacity in patients with CAD is associated with increased incidence of subsequent cardiac events and exercise test was one of the first non-invasive technologies used in preoperative cardiac risk stratification. In most ambulatory patients the test of choice is exercise electrocardiographic testing. The positive predictive value of postoperative death or MI of abnormal results of an exercise test ranges from 5 to 25% with a negative predictive value of normal results of a maximal test exceeding 90%³². In patients unable to perform adequate exercise (30-50% of cases)⁷⁹, a non-exercise stress (dipyridamole myocardial perfusion imaging testing and dobutamine echocardiography test) has to be considered. The expertise of the local laboratories is often more important than the particular type of test³² (Table 2).

Table 1. Estimated energy requirements for various activities.

1-4 METS	
Can you take care of yourself?	
Eat, dress, or use the toilet?	
Walk indoors around the house?	
Walk a block or two on level ground at 2-3 mph or 3.2-4.8 km/h?	
Do light work around the house like dusting or washing dishes?	
4-10 METS	
Climb a flight of stairs or walk up a hill?	
Walk on level ground at 4 mph or 6.4 km/h?	
Run a short distance?	
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	
> 10 METS	
Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	

Table 2. Predictive value of three preoperative stress tests.

	Predictive value (%)		No. studies
	Positive	Negative	
Exercise			
ECG stress test	5-25	90-100	10
Non-exercise*			
Myocardial perfusion imaging	4-27	95-100	27
Dobutamine stress echo	7-33	93-100	11

* patients who cannot exercise, left bundle branch block, preexcitation (Wolff-Parkinson-White), pacemaker, ST-segment depression at rest > 1 mm.

In patients with CAD three aspects should be clarified: 1) the amount of damaged myocardium, 2) the ischaemic threshold, and 3) the ventricular function. Clarification of these three questions represents an important goal of preoperative evaluation and supplemental testing may sometimes be required. The decision to require a test represents a balance between the possibility of identifying advanced or non-suspected CAD, which might result in significant cardiac morbidity or mortality either perioperatively or in the long term, and the risks from the test and treatment in itself which may offset and even exceed the potential benefit of evaluation. Perioperative therapy, and in particular beta-blockade, represents an excellent strategy in patients at increased risk for perioperative mortality, especially when coronary revascularisation for long-term benefits is not a serious consideration.

Perioperative interventions

On the basis of two studies^{5,80}, the ACC/AHA task force on guidelines for non-cardiac surgery recommended perioperative beta-blockers for patients with preoperative stress test ischaemia having vascular surgery (class I recommendation) and for patients with established CAD, risk factors for CAD, or untreated hypertension having non-cardiac surgery (class IIa recommendation)³². In these two major studies, preoperative administration of beta-blockers titrated to a dose to achieve a resting heart rate of 50-60 bpm showed favourable effects on perioperative MI in high-risk patients undergoing major vascular surgery^{5,80}.

In the first study the administration of atenolol (5-10 mg i.v. 30 min before and after surgery followed by 50-100 mg/day up to 7 days) to patients at risk of CAD (previous MI, typical angina, positive stress test, age > 65 years, hypertension, current smoking, plasma cholesterol > 240 mg/dl, diabetes mellitus) significantly reduced both the primary endpoint (death in patients who survived to hospital discharge) and the combined endpoint (MI, unstable angina, need for coronary artery bypass grafting, congestive heart failure) at 6 months, 1 and 2 years after operation⁸⁰. The study by Mangano et al.⁸⁰ was criticised because in-hospital deaths and adverse events were ignored in the analysis, patients who were already on beta-blockers had them discontinued on entry and results of "intention-to-treat" analysis were not given⁸¹. When the six deaths that occurred during the period when patients received the study drug are appropriately included in the intention-to-treat analysis, the reduction in the risk of death with atenolol is no longer significant.

The second study evaluated the effect on 1-month mortality in patients with positive dobutamine stress echo

who were not already on beta-blockers⁵. In particular, any patient with a risk factor (age > 70 years; angina; prior MI on the basis of history or a finding of pathologic Q waves on electrocardiography; compensated congestive heart failure or a history of congestive heart failure; current treatment for ventricular arrhythmias; current treatment for diabetes mellitus; or limited exercise capacity, defined as the inability to perform most normal daily activities) underwent dobutamine echocardiography. Patients with a positive result at dobutamine test were considered at high risk. Patients were excluded if they had extensive wall motion abnormalities (wall motion index > 1.70 at rest), asthma, or strong evidence during stress testing of left main or three-vessel CAD. Bisoprolol, a selective beta₁-adrenergic receptor antagonist, was started (5 mg/day orally) at least 1 week before surgery and the dose was increased after 1 week (10 mg/day) if heart rate remained > 60 bpm. The same dose of bisoprolol was then continued postoperatively (30 days) except in patients who were unable to take medication orally or by nasogastric tube postoperatively. These patients received intravenous metoprolol to keep the heart rate < 80 bpm. Bisoprolol was withheld if the heart rate was < 50 bpm or the systolic blood pressure was < 100 mmHg immediately before each scheduled dose. The *interim* analysis of the Poldermans study demonstrated a 100% risk reduction in non-fatal MI (diagnosed at electrocardiography and by assay of serum creatine kinase level with the MB fraction) and a 80% risk reduction in cardiovascular death during the perioperative period (30 days); therefore the trial was stopped early.

The inclusion of these two studies in a recent meta-analysis considering randomised controlled trials published from 1996-2004 evaluating perioperative beta-blockers in non-cardiac surgery (6 studies for a total of 632 patients)⁸² led to favourable conclusions showing a decrease in long-term cardiac mortality from 12 to 2% and a decrease in myocardial ischaemia from 33 to 15%. All outcomes except perioperative overall mortality had improvements ($p < 0.02$), with a number needed to treat of 20, 11, 10, 14 and 9 for perioperative cardiac mortality, long-term overall mortality, long-term cardiac mortality, MI and myocardial ischaemia, respectively⁸². Those conclusions were challenged by a contemporary meta-analysis⁸¹ which questioned the robustness of the evidence included by McGory et al.⁸². The study considered 22 randomised controlled trials with a total of 2437 patients, but for predefined quality reasons excluded from calculations both the two studies considered by the ACC/AHA task force guidelines^{5,80}. On the basis of included studies, perioperative beta-blockers showed only a statistically significant beneficial relative risk reduction (0.44; 95% confidence interval [CI] 0.20-0.97, 99% CI 0.16-1.24, $p < 0.04$) for the composite outcome of cardiovascular mortality, non-fatal MI, and

non-fatal cardiac arrest with no statistically significant beneficial effects on any of the individual outcomes⁸¹. The individual safety outcomes in patients treated with perioperative beta-blockers showed a relative risk for bradycardia needing treatment of 2.27 (95% CI 1.53-3.36, 99% CI 1.36-3.80) and a nominally statistically significant relative risk for hypotension needing treatment of 1.27 (95% CI 1.04-1.56, 99% CI 0.97-1.66). However, the meta-analysis by Devereux et al.⁸¹ included also studies performed either on low-risk patients, or on low-risk surgery, two conditions not strictly considered in the ACC/AHA recommendations for the perioperative use of beta-blockers.

A new large trial is now ongoing, the Perioperative Ischaemic Evaluation (POISE) trial, which plans to recruit 10 000 patients, and has already recruited more than 4000 patients in 18 countries. While awaiting clear evidence from the results of the POISE study, the use of beta-blockers can be considered for patients with positive preoperative stress test ischaemia having vascular surgery (class I recommendation) and for high-risk patients having non-cardiac surgery³².

The group of patients at high risk for clinical risk factors and non-invasive testing often has considerable perioperative mortality despite beta-blocker use⁷². For these patients undergoing non-cardiac procedures including major vascular surgery, a combination of beta-blockers with statins may offer additional prevention⁸³⁻⁸⁵. In patients in whom, despite the combination of beta-blockers and statins, the estimated probability remains high and there is clear indication for coronary revascularisation independent of the need for vascular surgery, a coronary intervention should be considered³². After surgery, cardiovascular secondary prevention has to be especially considered when postoperative troponin elevation is detected.

Which prognostic role for perioperative troponin rise?

In the vast majority of postoperative patients the elevations of cardiac-specific markers is caused by thrombotic obstruction and/or impaired myocardial perfusion in the context of an acute coronary syndrome⁸⁶. However, several studies have also raised the question of the unexpectedly high percentage of elevated troponin levels in surgical intensive care unit patients without underlying coronary syndromes^{87,88}.

The release of cardiac troponin can be due to irreversible or reversible cell damage⁸⁹. In prolonged ischaemia, the increase in troponin I is related with irreversible damage of cardiomyocytes⁹⁰ but patients with unstable angina have only transient troponin elevations, with values returning to baseline within a few hours⁹¹. In a study by

Suleiman et al.⁹², short periods (3 min) of regional ischaemia and reperfusion resulted in the release of significant amounts of troponin. Moreover, animal studies and other indirect clinical evidence have also suggested that troponin can be released in reversible ischaemia⁹³. Therefore the ACC/AHA guidelines do indicate that MI should be diagnosed in conjunction with other supportive evidence¹⁴.

In the setting of postoperative inflammatory states (SIRS/sepsis), the release of myocardial depressant substances, such as tumour necrosis factor, might cause degradation of free troponin *in situ* to lower-molecular-weight fragments⁹⁴. With increased membrane permeability, those smaller troponin fragments could be released into the systemic circulation. In this setting, myocyte damage may not be permanent, and thus cell necrosis does not occur⁹⁵. A high incidence of abnormal troponin I was found in septic patients (17/20, 85%) independently of CAD as demonstrated by coronary angiography, stress echocardiography or histologic findings on the available autopsies⁹⁵. Likewise, ver Elst et al.⁹⁶, in half of the autopsy cases with a positive *pre-mortem* troponin I, did not demonstrate irreversible myocyte necrosis (e.g. contraction band necrosis)⁹⁶. The assessment of whether troponin elevation is expression of myocardial ischaemia or is caused by reversible non-ischaemic myocardial injury can be, therefore, challenging. Ischaemic electrocardiographic changes, chest pain, wall motion abnormalities on echocardiography, irreversible deficit on radionuclide imaging (thallium) and the presence of atherosclerotic risk factors may be associated with a thrombotic origin of troponin elevation⁹⁷. On the other hand, in patients with a low pre-test probability of CAD the main goal is to identify the underlying cause of troponin elevation, which frequently becomes evident during a perioperative period (such as myocarditis, pericarditis, sepsis, pulmonary embolism)⁸⁹. Troponins maintain their diagnostic and prognostic value also in patients with chronic renal failure, being predictive not only of cardiovascular mortality but also of general mortality in this patient group^{98,99}.

The possibility of performing strategies of myocardial reperfusion in perioperative MI is limited because of the high risk of bleeding. Therefore, the issue of cardiovascular risk in these patients with isolated (without other clinical signs of myocardial ischaemia) troponin increase at medium and long-term follow-up becomes relevant. In a prospective study performed in 229 patients undergoing aortic or infrainguinal vascular surgery¹⁰⁰, at 6-month follow-up an abnormal troponin serum level (> 1.5 ng/ml) in the perioperative period was associated with a 6-fold increased risk of mortality (adjusted odds ratio [OR] 5.9; 95% CI 1.6-22.4) and a 27-fold increased risk of MI (OR 27.1; 95% CI 5.2-142.7). At

1-year follow-up, about 16% of patients with CAD or at high risk of CAD undergoing major non-cardiac surgery ($n = 173$) died¹⁰¹. Elevation of troponin I ($> 2 \text{ g/l}$ on the first and/or second postoperative mornings) was strongly associated with the 12-month all-cause mortality (OR 6.5, 95% CI 2.6-16). During a 1 to 5-year follow-up period (mean 32.3 ± 13.8 months), 82 out of 447 consecutive patients who underwent major vascular surgery patients died (18.3%)¹⁰². Increased troponin measured immediately after surgery and every morning in the first 3 postoperative days, was found an independent predictor of long-term mortality at both low (troponin I $> 0.6 \text{ ng/ml}$ and/or troponin T $> 0.03 \text{ ng/ml}$) and high cut-off levels (troponin I $> 3.1 \text{ ng/ml}$ and/or troponin T $> 0.2 \text{ ng/ml}$) (OR 2.30, 95% CI 1.49-3.55, and 3.41, 95% CI 1.81-6.43, respectively)¹⁰².

These data indicate that an isolated troponin increase in patients without clinical evidence for ischaemia should not be dismissed as false positive results and that these patients may warrant further cardiac evaluation.

Conclusions

The identification of patients at the highest risk of perioperative MI is one of the main goals of preoperative evaluation. In the clinical course of the surgical patient, a first phase characterised by an increased sympathetic discharge, corresponding to the end of surgery and emergence from anaesthesia, is followed by a second phase in which different factors contribute to create a hypercoagulable and proinflammatory environment (SIRS). Perioperative myocardial ischaemia may occur in both phases with different mechanisms requiring different prevention strategies. The early identification and management of subclinical myocardial injury is particularly relevant to start secondary prevention early in order to avoid the progression to myocardial failure.

References

1. National Confidential Enquiry into Patient Outcome and Death. 2003/04 Death data. Available at <http://www.ncepod.org.uk/pdf/200304DeathData.pdf>; accessed 10 February 2006.
2. National Confidential Enquiry into Patient Outcome and Death. General data. Available at <http://www.ncepod.org.uk/pdf/2000/tan/TaNGen.pdf>; accessed 10 February 2006.
3. Lunn JN, Devlin HB. Lessons from the confidential enquiry into perioperative deaths in three NHS regions. *Lancet* 1987; 2: 1384-6.
4. National Confidential Enquiry into Patient Outcome and Death. Surgery. Available at <http://www.ncepod.org.uk/pdf/2000/tan/TaNSurg.pdf>; accessed 10 February 2006.
5. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; 341: 1789-94.
6. Auerbach AD. Chapter 25: Beta-blockers and reduction of perioperative cardiac events. Available at <http://www.ahcpr.gov/CLINIC/PTSAFETY/chap25.htm>; accessed 10 February 2006.
7. Landesberg G, Mosseri M, Zahger D, et al. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. *J Am Coll Cardiol* 2001; 37: 1839-45.
8. Adams JE 3rd, Sicard GA, Allen BT, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med* 1994; 330: 670-4.
9. Katus HA, Looser S, Hallermayer K, et al. Development and in vitro characterization of a new immunoassay of cardiac troponin T. *Clin Chem* 1992; 38: 386-93.
10. Adams JE 3rd, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993; 88: 101-6.
11. Lee TH, Thomas EJ, Ludwig LE, et al. Troponin T as a marker for myocardial ischemia in patients undergoing major noncardiac surgery. *Am J Cardiol* 1996; 77: 1031-6.
12. Metzler H, Gries M, Rehak P, Lang T, Fruhwald S, Toller W. Perioperative myocardial cell injury: the role of troponins. *Br J Anaesth* 1997; 78: 386-90.
13. Sarko J, Pollack CV Jr. Cardiac troponins. *J Emerg Med* 2002; 23: 57-65.
14. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined - a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36: 959-69.
15. Relos RP, Hasinoff IK, Beilman GJ. Moderately elevated serum troponin concentrations are associated with increased morbidity and mortality rates in surgical intensive care unit patients. *Crit Care Med* 2003; 31: 2598-603.
16. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med* 1990; 323: 1781-8.
17. Backer CL, Tinker JH, Robertson DM, Vlietstra RE. Myocardial reinfarction following local anesthesia for ophthalmic surgery. *Anesth Analg* 1980; 59: 257-62.
18. Greenburg AG, Saik RP, Pridham D. Influence of age on mortality of colon surgery. *Am J Surg* 1985; 150: 65-70.
19. Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med* 1993; 118: 504-10.
20. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med* 1986; 1: 211-9.
21. Foster ED, David KB, Carpenter JA, et al. Risk of noncardiac operation in patients with defined coronary disease: the Coronary Artery Surgery Study (CASS) registry experience. *Ann Thorac Surg* 1986; 41: 42-50.

22. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; 72: 153-84.
23. Raby KE, Goldman L, Creager MA, et al. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989; 321: 1296-300.
24. Shah KB, Kleinman BS, Rao TLK, Jacobs HK, Mestan K, Schaafsma M. Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. *Anesth Analg* 1990; 70: 240-7.
25. Baron JF, Mundler O, Bertrand M, et al. Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. *N Engl J Med* 1994; 330: 663-9.
26. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989; 110: 859-66.
27. Hendel RC, Whitfield SS, Villegas BJ, Cutler BS, Leppo JA. Prediction of late cardiac events by dipyridamole thallium imaging in patients undergoing elective vascular surgery. *Am J Cardiol* 1992; 70: 1243-9.
28. Lette J, Waters D, Cerino M, Picard M, Champagne P, Lapoint J. Preoperative coronary artery disease risk stratification based on dipyridamole imaging and a simple three-step, three-segment model for patients undergoing noncardiac vascular surgery or major general surgery. *Am J Cardiol* 1992; 69: 1553-8.
29. Brown KA, Rowen M. Extent of jeopardized viable myocardium determined by myocardial perfusion imaging best predicts perioperative cardiac events in patients undergoing noncardiac surgery. *J Am Coll Cardiol* 1993; 21: 325-30.
30. McFalls EO, Doliszny KM, Grund F, Chute E, Chesler E. Angina and persistent exercise thallium defects: independent risk factors in elective vascular surgery. *J Am Coll Cardiol* 1993; 21: 1347-52.
31. Bry JD, Belkin M, O'Donnell TF Jr, et al. An assessment of the positive predictive value and cost-effectiveness of dipyridamole myocardial scintigraphy in patients undergoing vascular surgery. *J Vasc Surg* 1994; 19: 112-24.
32. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery – executive summary. A report of American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002; 105: 1257-67.
33. Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. *Am J Med* 2003; 115: 515-20.
34. Fischer SP. Development and effectiveness of an anesthesia preoperative evaluation clinic in a teaching hospital. *Anesthesiology* 1996; 85: 196-206.
35. Liu LL, Wiener-Kronish JP. Preoperative cardiac evaluation of women for noncardiac surgery. *Cardiol Clin* 1998; 16: 59-66.
36. Tarhan S, Moffitt EA, Taylor WF, Giuliani ER. Myocardial infarction after general anesthesia. *JAMA* 1972; 220: 1451-4.
37. Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; 59: 499-505.
38. Becker RC, Underwood DA. Myocardial infarction in patients undergoing noncardiac surgery. *Cleve Clin J Med* 1987; 54: 25-8.
39. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996; 57: 37-44.
40. Rosing DR, Brakman P, Redwood DR, et al. Blood fibrinolytic activity in man. Diurnal variation and the response to varying intensities of exercise. *Circ Res* 1970; 27: 171-84.
41. Green LH, Seropian E, Handin RI. Platelet activation during exercise-induced myocardial ischemia. *N Engl J Med* 1980; 302: 193-7.
42. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999; 8: 133-9.
43. Breslow MJ, Parker SD, Frank SM, et al. Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. *Anesthesiology* 1993; 79: 1202-9.
44. Indolfi C, Ross J Jr. The role of heart rate in myocardial ischemia and infarction: implications of myocardial perfusion-contraction matching. *Prog Cardiovasc Dis* 1993; 36: 61-74.
45. Landesburg G, Zhou W, Aversano T. Tachycardia-induced subendocardial necrosis in acutely instrumented dogs with fixed coronary stenosis. *Anesth Analg* 1999; 88: 973-9.
46. Nabel EG, Selwyn AP, Ganz P. Large coronary arteries in humans are responsive to changing blood flow: an endothelium-dependent mechanism that fails in patients with atherosclerosis. *J Am Coll Cardiol* 1990; 16: 349-56.
47. Sambucetti G, Marzilli A, Maraccini P, et al. Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease. *Circulation* 1997; 95: 2652-9.
48. Morrow DA, Cannon CP, Rifai N, et al, for the TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA* 2001; 286: 2405-12.
49. Raby KE, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L. Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. *JAMA* 1992; 268: 222-7.
50. Killewich LA, Macko RF, Gardner AW, Cox K, Lilly MP, Flinn WR. Defective fibrinolysis occurs after infrainguinal reconstruction. *J Vasc Surg* 1997; 25: 858-64.
51. Rosenfeld BA, Beattie C, Christopherson R, et al, for the Perioperative Ischemia Randomized Anesthesia Trial Study Group. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. *Anesthesiology* 1993; 79: 435-43.
52. Gibbs NM, Crawford GP, Michalopoulos N. Postoperative changes in coagulant and anticoagulant factors following abdominal aortic surgery. *J Cardiothorac Vasc Anesth* 1992; 6: 680-5.

53. Gibbs NM, Crawford GP, Michalopoulos N. A comparison of postoperative thrombotic potential following abdominal aortic surgery, carotid endarterectomy, and femoropopliteal bypass. *Anaesth Intensive Care* 1996; 24: 11-4.
54. Wiman B. Plasminogen activator inhibitor 1 in thrombotic disease. *Curr Opin Hematol* 1996; 3: 372-8.
55. Sarbinowski R, Arvidsson S, Tylman M, Oresland T, Bengtsson A. Plasma concentration of procalcitonin and systemic inflammatory response syndrome after colorectal surgery. *Acta Anaesthesiol Scand* 2005; 49: 191-6.
56. Mokart D, Merlin M, Sannini A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. *Br J Anaesth* 2005; 94: 767-73.
57. Swartbol P, Truedsson L, Norgren L. The inflammatory response and its consequence for the clinical outcome following aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2001; 21: 393-400.
58. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; 79: 757-60.
59. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Ann Surg* 1993; 218: 769-76.
60. Swartbol P, Parsson H, Truedsson L, Sjöholm A, Norgren L. Aortobifemoral surgery induces complement activation and release of interleukin-6 but not tumour necrosis factor- α . *Cardiovasc Surg* 1996; 4: 483-91.
61. Groeneveld AB, Raijmakers PG, Rauwerda JA, Hack CE. The inflammatory response to vascular surgery-associated ischaemia and reperfusion in man: effect on postoperative pulmonary function. *Eur J Vasc Endovasc Surg* 1997; 14: 351-9.
62. Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes. Part I: Introduction and cytokines. *Circulation* 2006; 113: e72-75.
63. Giardina JB, Green GM, Cockrell KL, Granger JP, Khalil RA. TNF- α enhances contraction and inhibits endothelial NO-cGMP relaxation in systemic vessels of pregnant rats. *Am J Physiol Regul Integr Comp Physiol* 2002; 283: R130-R143.
64. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med* 1995; 21: 302-9.
65. Haga Y, Beppu T, Doi K, et al. Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. *Crit Care Med* 1997; 25: 1994-2000.
66. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: effect of intensive care unit resuscitation. *Arch Surg* 1999; 134: 81-7.
67. Kertai MD, Boersma E, Klein J, et al. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med* 2005; 165: 898-904.
68. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982; 247: 2543-6.
69. Hertzner NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; 199: 223-33.
70. Meldrum DR. Tumor necrosis factor in the heart. *Am J Physiol* 1998; 274 (Pt 2): R577-R595.
71. L'Italien GJ, Cambria RP, Cutler BS, et al. Comparative early and late cardiac morbidity among patients requiring different vascular surgery procedures. *J Vasc Surg* 1995; 21: 935-44.
72. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001; 285: 1865-73.
73. Lederle FA, Wilson SE, Johnson GR, et al, for the Aneurysm Detection and Management Veterans Affairs Cooperative Group. Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002; 346: 1437-44.
74. Schinkel AF, Elhendy A, van Domburg RT, Bax JJ, Roelandt JR, Poldermans D. Prognostic value of dobutamine-atropine stress (99m Tc-tetrofosmin myocardial perfusion SPECT in patients with known or suspected coronary artery disease. *J Nucl Med* 2002; 43: 767-72.
75. Bond R, Rerkasem K, Shearman CP, Rothwell PM. Time trends in the published risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Cerebrovasc Dis* 2004; 18: 37-46.
76. Eagle KA, Lim MJ, Dabbous OH, et al, for the GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; 291: 2727-33.
77. Gregg EW, Cadwell BL, Cheng YJ, et al. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the US. *Diabetes Care* 2004; 27: 2806-12.
78. Smetana GW. Medical evaluation of the surgical patient. In: Kasper DL, Braunwald E, Fauci AS, et al, eds. *Harrison's principles of internal medicine*. 16th ed. New York, NY: McGraw-Hill, 2005: 60-71.
79. Chaitman BR, Miller DD. Perioperative cardiac evaluation for noncardiac surgery noninvasive cardiac testing. *Prog Cardiovasc Dis* 1998; 40: 405-18.
80. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; 335: 1713-20.
81. Devereux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in noncardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; 331: 313-21.
82. McGory ML, Maggard ML, Ko CY. A meta-analysis of perioperative beta blockade: what is the actual risk reduction? *Surgery* 2005; 138: 171-9.
83. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003; 107: 1848-51.
84. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004; 291: 2092-9.

85. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004; 39: 967-75.
86. Landesberg G, Mosseri M, Shatz V, et al. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. *J Am Coll Cardiol* 2004; 44: 569-75.
87. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA* 1995; 273: 1945-9.
88. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. *Crit Care Med* 1999; 27: 1775-80.
89. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med* 2005; 142: 786-91.
90. Higgins JP, Higgins JA. Elevation of cardiac troponin I indicates more than myocardial ischemia. *Clin Invest Med* 2003; 26: 133-47.
91. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992; 327: 146-50.
92. Suleiman MS, Lucchetti V, Caputo M, Angelini GD. Short periods of regional ischaemia and reperfusion provoke release of troponin I from the human hearts. *Clin Chim Acta* 1999; 284: 25-30.
93. Wu AH, Ford L. Release of cardiac troponin in acute coronary syndromes: ischemia or necrosis? *Clin Chim Acta* 1999; 284: 161-74.
94. Wu AH. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? *Intensive Care Med* 2001; 27: 959-61.
95. Ammann P, Fehr T, Minder EI, Gunter C, Bertel O. Elevation of troponin I in sepsis and septic shock. *Intensive Care Med* 2001; 27: 965-9.
96. ver Elst KM, Spapen HD, Nguyen DN, Garbar C, Huyghens LP, Gorus KK. Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. *Clin Chem* 2000; 46: 650-7.
97. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: summary article. A report of American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation* 2002; 106: 1893-900.
98. Buhaescu I, Izzedine H, Covic A. Cardiac troponins in renal failure - time for an optimistic consensus? *Int J Clin Pract* 2005; 59: 1317-25.
99. Kontos MC, Garg R, Anderson FP, Tatum JL, Ornato JP, Jesse RL. Outcomes in patients admitted for chest pain with renal failure and troponin I elevations. *Am Heart J* 2005; 150: 674-80.
100. Kim LJ, Tinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation* 2002; 106: 2366-71.
101. Filipovic M, Jeger R, Probst C, et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol* 2003; 42: 1767-76.
102. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003; 42: 1547-54.