CHAPTER 8

The performance of troponin I and troponin T in relation to conventional criteria for the detection of myocardial injury in patients undergoing major noncardiac surgery.

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Summary
Biochemical markers together with the ECG are commonly used parameters for the detection of peri-operative acute myocardial infarction (AMI) in patients undergoing major non-cardiac surgery. We investigated the performance of troponin I and troponin T in relation to the conventional criteria CKMB-activity, CKMB-mass and ECG changes for the detection of AMI in sixty patients undergoing major noncardiac surgery. AMI was diagnosed according to WHO-criteria. All biochemical parameters were analysed at the start and at the end of surgery, and six hours, one day and three days thereafter. Two patients experienced AMI, and both patients had elevated troponin I and troponin T concentrations, whereas one of these patients had elevated CKMB-act and both patients had elevated CKMB-mass concentrations. Another four patients had ischemia characterised by ECG changes, but no infarction, from who only one patient had slightly elevated troponin I concentrations. One patient had seriously elevated troponin I and troponin T concentrations without notification of ECG changes. Troponin I concentrations were elevated in five patients in at least one of the five timepoints, whereas this applies for troponin T concentrations in three patients. In contrast, twenty patients had elevated CKMB-act at at least one of the five timepoints and moreover, this was true for thirty-two patients concerning CKMB-mass concentrations. We conclude that troponin I and troponin T are more specific and reliable for the detection of myocardial injury after major noncardiac surgery than the conventional markers CKMB-act and CKMB-mass. Furthermore, the measurement of troponin I or troponin T looks like to be more accurate than (discontinuous) ECG monitoring for the detection of myocardial injury after major noncardiac surgery.

Introduction

Peri-operative myocardial infarction (AMI) has been known to be a serious complication in patients undergoing major noncardiac surgery (1). Chest pain complaints, ECG changes and elevation of biochemical markers in the blood are the three WHO-criteria to diagnose AMI in patients after ischemic episodes (2). For this reason, biochemical markers are, besides the ECG, of common use for the detection of AMI. Among the conventional biochemical markers, the creatine kinase (CK)MB isoenzyme has already for a long time been accepted as the gold standard for the detection of myocardial tissue injury (3). However, CKMB is not a specific parameter for myocardial tissue damage. In addition, the CKMB/CK total ratio is also used as a marker for myocardial tissue damage. But this ratio may be falsely negative, if myocardial tissue damage is accompanied by massive skeletal muscle damage (4). Therefore, this ratio is only reliable in patients with solitary ischemic myocardial damage. Thus, a correct interpretation of elevated CKMB-levels and CKMB/CK-total ratios in patients after (noncardiac) surgery may be a problem for reasons of the non-heart specificity of the CKMB isoenzym.
Recently, new biochemical parameters have been introduced for the detection of myocardial tissue damage. Troponin I (5) and troponin T (6) belong to this new category of biochemical parameters. Both troponins are related to the actin-myosin complexes of the thin filaments of striated muscle. Troponin I as well as troponin T are part of skeletal and myocardial muscle tissue and both have an unique protein structure (7,8). The sequence of amino acids of both troponin I and troponin T from skeletal muscle differs from those of myocardial muscle. For this reason, they can be separated immunochemically by the use of specific antibodies directed against these parts of the proteins for

which the sequences of the amino acids differ in skeletal from myocardial muscle tissue.
Several studies concerning myocardial damage in patients at the Intensive Care Unit (ICU) or after major non-cardiac surgery have been reported (9-13). Mostly, it concerns the investigation of only the troponin I or troponin T marker. Moreover, in most of these studies the first generation troponin T measurement has been used. This first generation troponin T reagent has been characterised by cross reactivity of the label-antibody with skeletal muscle troponin T (14).
The aim of this study is to investigate the performance of the new biochemical markers troponin I and the more heart specific second generation troponin T in relation to the conventional criteria CKMB-activity, CKMB-mass and ECG changes for the detection of myocardial injury in patients undergoing major noncardiac surgery. This study is part of a randomised and controlled trial studying the effects on clinical outcome of standard preoperative treatment at the ward compared to a preoperative haemodynamic optimisation at the ICU.

Patients and methods

Sixty consecutive patients who underwent extensive non-cardiac surgery were included during a ten months period. The patients were characterised as high surgical risk according to criteria earlier described (15). These include: previous severe cardiorespiratory illness; extensive ablative surgery planned for carcinoma; age over 70 years and evidence of limited physiologic reserve of one or more vital organs; septicaemia, positive blood culture or septic focus, white blood cell count >13.000 /ml, spiking fever to 38.3 ^{o}C for 48 h; acute renal failure; and late stage vascular disease involving aortic abnormality. All patients were preoperatively screened by extensive interview, physical examination and resting ECG. When indicated, additionally non-invasive and invasive diagnostics were performed to evaluate the existence and severity of myocardial ischemia. The patients of the protocol group (n=31) were admitted to the ICU at the preoperative day for haemodynamic optimisation (15), whereas the control group patients (n=29) received standard treatment at the ward. Anaesthesia was standardised in both groups.
Peri-operative AMI was diagnosed according to WHO-criteria (2) on basis of 12-lead ECG's in combination with elevations of CK-total and CKMB-activity measurements at day 1 directly after surgery, at day 2, 3 and 4 and at the final day of the hospital stay before the patient was discharged from the hospital. New ST-T depression of more

Table 1. Patient and surgical characteristics.

Number of male (female) patients	37 (23)
Mean age in years (standard deviation, range)	65 (12, 32-81)
Type of surgery:	
Aorta surgery	14
Laparotomy for septic focus	2
Laparotomy for malignancy:	33
- upper digestive tract	6
- modified Whipple procedure	7
- liversurgery (hemihepatectomy / cryosurgery)	11

- cystectomy	3
- colonsurgery	2
- other	4
Restricted surgical procedure (inoperability):	11
- hepatico-jejunostomy / gastro-jejunostomy	5
- 'open-close'	4
- other	2
Per-operative period:	
- mean time of operation in minutes (standard deviation)	309 (164)
- mean peroperative bloodloss in ml (stand.dev., range)	1850 (2050, 0-10000)
epidural catheter	52

than 1 mm in 2 or more adjacent leads, in the absence of electrolyte disturbances and use of digoxin, was defined as ischemia. ST-T elevations of more than 1 mm in 2 or more adjacent leads together with T-top changes were defined as AMI. The ECG's made at the day of hospital discharge were screened for new Q's or T-top inversions;
AMI was defined as a Q wider than 1.5 mm and deeper than 3 mm.
Blood was collected at day 1 at the start (t_0) and at the end (t_1) of the surgical procedure; six hours after the end of the surgery (t_2); at day 2 (t_3) and at day 4 (t_4). The blood was centrifuged at 1000x g and at 20 ^{o}C. After this procedure the serum was separated from the cells. The CK-total and CKMB-activity measurements were performed immediately. Until analysis of CKMB-mass, troponin I and troponin T, the sera were stored at -20 ^{o}C.
The CK-total (upper reference limit (url) 70 U/l) and CKMB-activity (immune-inhibition, url 10 U/l) were measured on a Vitros 750C analyser (Ortho Clinical Diagnostics, Beerse, Belgium).
Troponin I (AMI cut off value 2.0 µg/l) measurements were performed on an AxSYM analyser (16) (Abbott Diagnostic Division, Hoofddorp, The Netherlands).
For troponin T (AMI cut off value 0.1 µg/l) and CKMB-mass (url 5.0 µg/l) measurements an Elecsys 2010 analyser was used (Roche-Boehringer Mannheim, Almere, The Netherlands). The more cardiac specific 'second generation' troponin T-antibodies were used for the troponin T measurements (14).
All test results were normalised by dividing the result of the assay by the corresponding url in order to be able to compare the various biochemical parameters. The parameters CKMB-mass, troponin I and troponin T were not of common use in our hospital. For these parameters the url's were used recommended by the particular manufacturers. The specificities and the positive predictive values (PPV's) with the corresponding exact 95% confidence intervals were calculated for the parameters CKMB-act, CKMB-mass, troponin I and troponin T by the use of StatXact-4 (Cytel Software Corporation, Cambridge, MA, USA).

Results

Patient and surgical characteristics are depicted in table 1. Eleven patients have undergone a less extensive surgical procedure than planned, because of (abdominal) metastasis (ten patients), and because of preoperative development of cardiac ischaemia during haemodynamic optimisation (one patient).

Two patients (patients A and B) have been classified as having experienced an AMI during hospital stay. Both patients have had elevated concentrations of CKMB-mass, troponin I and troponin T, whereas only patient B has had elevated CKMB-act. One patient (patient C) has initially been diagnosed at the ICU as experiencing a non Q-wave AMI because of ECG changes (ST-T depression), history of coronary artery disease and elevation of CK-total and CKMB-act (CK-total 176 U/L, CKMB-act 18 U/L). All troponin I and troponin T concentrations of this patient have been below the url's.

Another three patients (patients D, E and F) have had a period of ischemia without AMI. All troponin I and troponin T concentrations from the patients D and E have not been elevated at any of the five time points. From patient F the maximum troponin I concentration (2.4 µg/l) has been slightly elevated, whereas the maximum troponin T concentration (0.08 µg/l) has remained below the url.

Another patient (patient G) has had elevated maximum troponin I (30.4 µg/l) and maximum troponin T (0.78 µg/l) concentrations without notification of ECG changes.

In figure 1 the normalised results are shown of the biochemical parameters CKMB-act, CKMB-mass, troponin I and troponin T at the five different time points. CKMB-act has been elevated in twenty patients at at least one of the five time points. Moreover, this is true for thirty-two patients concerning the CKMB-mass concentration. In contrast, the troponin I concentration has been elevated in five patients at any of the five time points, whereas this applies for the troponin T concentration in three patients.

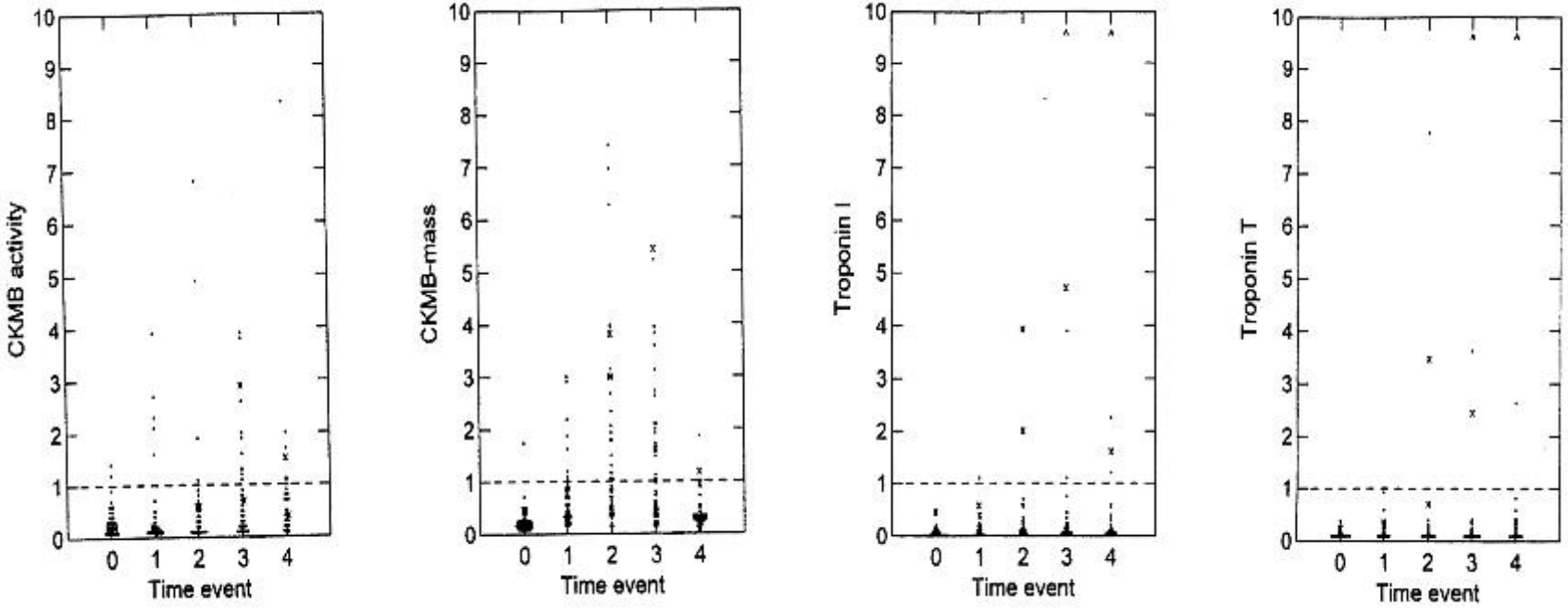

Figure 1.The normalised values between 0 and 10 at five timepoints for CKMB-activity, CKMB-mass, troponin I and troponin T from sixty patients undergoing major noncardiac surgery. Two patients experienced an acute myocardial infarction. The values of these 2 patients are indicated with (x). ^ indicates a value beyond 10.

Table 2. The specificities and positive predictive values (PPV's) with their corresponding 95% confidence intervals of the parameters CKMB-act, CKMB-mass, troponin I and troponin T in sixty patients undergoing major non-cardiac surgery, from who two experienced an AMI.

Parameter	Url	Specificity (95% CI)	PPV (95% CI)
CKMB-act	10 U/l	0.67 (.52-.79)	0.05 (.01-.25)
CKMB-mass	5.0 µg/l	0.47 (.34-.61)	0.06 (.01-.21)
troponin I	2.0 µg/l	0.95 (.85-.99)[a]	0.40 (.05-.85)
troponin T	0.1 µg/l	0.98 (.91-1.00)[a]	0.67 (.09-.99)

Url: upper limit of the reference range;
PPV: positive predictive value;
CI: confidence interval;
[a] $p<0.01$ compared to CKMB-act and CKMB-mass.

In table 2 the specificities and the PPV's with their corresponding 95% confidence intervals are depicted for the parameters CKMB-act, CKMB-mass, troponin I and troponin T. From this table it can be seen, that the new biochemical markers troponin I and troponin T show statistically significant higher specificities and higher PPV's than the conventional markers CKMB-act. and CKMB-mass.
The two groups of patients do not differ regarding the prevalence of myocardial infarction (either group contains one AMI patient).

Discussion

Patients planned for extensive surgery are at risk for the development of myocardial ischemia and infarction (1). The risk for the development of cardiac ischemia or infarction is related to age, preexisting cardiovascular morbidity, the type and length of operation and anaesthesia (1,17). The establishment of myocardial infarction after surgery may be complicated. The patient experiences tissue and muscle damage from other than myocardial origin as a result of the surgical procedure. Furthermore, the patient may not always be able to complain about chest pain. The mainly used parameters for the diagnosis of cardiac ischemia and myocardial infarction in these patients are ECG changes and elevation of biochemical markers. Conventionally, the biochemical marker CKMB is still the gold standard to evaluate the prevalence and extent of myocardial damage (3). Recently, it has been reported, that troponin I and troponin T have been a more sensitive and more specific biochemical marker for the detection of myocardial damage in ischemic patients (18,19) and in patients with combined myocardial and skeletal muscle damage (20). The troponin I measurement has been complicated, because troponin I is released in circulation after tissue necrosis in several forms. These forms include free as well as various forms of complex-bound troponin I (21). Consequently, several different troponin I measurements have been possible and commercially available (22). On the other hand, only one troponin T measurement has been

commercially available, because the use of the troponin T antibody has been patented. But the troponin T measurement has also been complicated. This applies, especially, for the first generation of the troponin T reagent, which has been characterised by cross-reactivity of the label-antibody with skeletal muscle troponin T (14). This cross-reactivity may happen, if there has been a massive skeletal muscle damage.

Therefore, in our study, we have investigated the performance of both the troponin I and the troponin T parameters in relation to the conventional CKMB-markers and ECG changes for the detection of myocardial injury in patients undergoing major non-cardiac surgery. The conventional marker CKMB-activity has been elevated in twenty different patients, although for only two patients the diagnosis AMI could be established by the WHO-criteria. CKMB-mass, which has been known to be more sensitive for minor myocardial tissue damage than CKMB-act., has even been elevated in thirty-two different patients. The use of the non heart specific CKMB-activity as parameter for the detection of AMI has initially been resulted for one patient (patient C) in the unjustified diagnosis non Q-wave AMI, and, subsequently, in an unnecessarily prolonged stay of this patient at the ICU. The diagnosis AMI has been established because of 1. ECG changes, 2. history of coronary artery disease of this patient and 3. elevation of CK-total and CKMB-act. However, the CKMB-act measurement in the serum of this patient has been resulted in falsely elevated activities by the presence of the CKBB isoenzyme. This CKBB isoenzyme was caused by the bowel surgery. In contrast, all troponin I and troponin T concentrations of this patient C were below the url's at any time point.

The new markers troponin I and troponin T have been elevated in three and five different patients, respectively. This is more in agreement with the number of patients for who an AMI was diagnosed. As can be seen from table 2, this results also in significantly higher specificities and higher PPV's of the troponin I and troponin T parameters than those of the CKMB-act and CKMB-mass. As the number of AMI patients is (too) small compared to the number of non-AMI patients, it has no sense to calculate sensitivities and negative predictive values.

Two patients (D and E) have had ECG changes without elevations of the troponin I and troponin T concentrations. For these patients it should be considered, that changes of the 12-lead ECG do not necessarily have to be a result of AMI. Especially, in the first few hours following major injury, there is metabolic chaos and any ECG abnormality may reflect this (23). On the other hand, one patient (G) has had elevated troponin I and troponin T concentrations at three succeeding timepoints (t_2-t_4) without notification of ECG changes. The findings of the biochemical parameters strongly suggest that this patient experienced myocardial injury, although all routine ECG's were normal. The findings of these three patients are examples, from which it appears that ECG changes are not 100% specific for the detection of AMI.

The influence of the haemodynamic optimisation on the incidence of AMI after major non-cardiac surgery can not be statistically considered in this study. For this purpose much larger populations are needed. A sample size of 769 patients in the control group and 769 patients in the protocol group will be needed to detect a significant difference of 2% on the incidence of AMI. These sample sizes are based on a normal incidence of 3% AMI after major noncardiac surgery achieving a power of 80% given an alpha of 0.05. Unfortunately, it will take too much time to get such large populations.

From this study we conclude that troponin I and troponin T are more specific and reliable for the detection of myocardial injury after major noncardiac surgery than the conventional biochemical

markers CKMB-act. and CKMB-mass; furthermore, the measurement of troponin I or troponin T looks like to be more accurate than (discontinuous) ECG monitoring for the detection of myocardial injury after major noncardiac surgery.

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