

# CHAPTER 7

Troponin I, Troponin T, CKMB-activity and CKMB-mass as markers for the detection of myocardial contusion in patients experiencing blunt trauma.

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## Summary

Myocardial contusion is an infrequent, but sometimes serious complication in patients experiencing deceleration (blunt) trauma. We investigated the assessment of the new cardiac markers Troponin I (cTnI) and Troponin T (cTnT) in relation to the conventional CKMB-activity, the CKMB-activity/CK-total ratio, CKMB-mass and the CKMB-mass/CK-total ratio for the detection of myocardial contusion in 89 patients with blunt trauma (38 patients with thoracic injuries and 51 patients without thoracic injuries). All parameters were analysed at admission ( $t_1$ ) and 24 hours after admission ( $t_2$ ). For the patients with thoracic injuries, at  $t_1$  cTnI was elevated in three and cTnT in four patients; at  $t_2$  both cTnI and cTnT were elevated in nine patients. At  $t_1$ , eighteen to thirty patients had increased levels of the conventional parameters; at  $t_2$  this was true for six to thirty-five patients. For the patients without thoracic injuries all cTnI and cTnT levels were within the reference ranges at  $t_1$ . At  $t_2$  one patient, who experienced an acute myocardial infarction, had elevated cTnI and cTnT levels. At  $t_1$ , five to thirty-five patients had increased levels of the conventional parameters; at  $t_2$  this was true for four to forty-two patients. From this study we conclude, that the conventional parameters are not useful for the detection of myocardial contusion in patients experiencing blunt trauma. The parameters cTnI and cTnT are equally accurate and more reliable for the selection of patients, who require intensive cardiac monitoring. If at admission the cTnI or the cTnT levels are within the reference ranges, a second analysis after admission is necessary to reach a reliable conclusion concerning myocardial contusion as a result of trauma on basis of the troponin levels.

## Introduction

Myocardial contusion can result from blunt thoracic trauma and is commonly suspected in deceleration injuries after a traffic accident or a fall from great height. Myocardial contusion has a patho-anatomical substrate that comprises subepicardial or subendocardial sharply-defined small areas of bleeding. Microscopically, disruption of myo(cardial)fibrils with leucocyte infiltration and oedema are found. Complications of myocardial contusion, such as arrhythmias, can potentially be life-threatening. However, not every patient with a blunt chest trauma has to be admitted to a hospital ward with cardiac monitoring facilities.

The reported incidence of myocardial contusion in patients with blunt chest injury varies among 0% (1-3) and 76% (4) and depends on the diagnostic criteria used and the severity of the blunt chest trauma (5,6). Biffi et al. (7) reported recently a 30% incidence in 359 patients with high-risk blunt chest trauma; complications (dysrhythmia and cardiogenic shock) requiring treatment occurred in 5% (8). Postmortem evidence of myocardial contusion was found in 14% of the immediate fatalities from blunt injuries (9).

Diagnosing myocardial damage as a result of trauma may be a problem. There is a lack of a 'gold standard' for establishing the diagnosis. It is generally accepted that patients with blunt thoracic injury are suspected of having myocardial contusion on basis of their complaints, ECG findings at admission, and an elevated creatine kinase (CK) MB-activity, whether or not expressed as a fraction of the CK-total activity (10,11). The measurement of CKMB-activity is complicated by artifacts as CK-macro-enzymes and CKBB in the blood. These artifacts do not influence the CKMB-mass measurements. However, CKMB-mass as well as CKMB-activity measurements are also elevated after severe skeletal muscle injuries.

The 12-lead ECG is another often performed diagnostic procedure. However, in the first few hours following a major injury ECG abnormality may simply reflect metabolic changes (12). In a review of twelve prospective studies, abnormal ECGs were reported in 33% of trauma patients (range 11-

81%), but in all these studies there was no uniform definition of what constituted an abnormal ECG (13). Another procedure is transthoracic echocardiography. This is a widely available bedside procedure that is used to assess the performance of the myocardium. Recent transthoracic studies have shown wall-motion abnormalities to occur in about 25% of blunt chest injury victims (14-16). However, sub-optimal examinations influence the reliability of this tool (17-19). So, there is much confusion as to how to diagnose myocardial contusion.

Recently, the cardiac markers troponin I (cTnI) and troponin T (cTnT) have become available. Troponin I, C and T form a complex that regulates the calcium-modulated interaction of actin and myosin in striated muscle. Troponin I from cardiac muscle and slow- and fast-twitch skeletal muscle are products of different genes with unique amino acid sequences (20-22). Skeletal muscle in animals and in humans does not express cTnI at any developmental stage or in response to any pathological stimuli (23,24). In contrast, cTnT is expressed in fetal and neonatal skeletal muscle in humans and experimental animals, but is suppressed in healthy adult skeletal muscle (25-27).

We investigated the assessment of the new biochemical parameters cTnI and cTnT, in relation to the more conventional CKMB-activity, the CKMB-activity/CK-total ratio, CKMB-mass and the CKMB-mass/CK-total ratio for the detection of myocardial contusion in patients who have experienced blunt trauma.

## **Patients and methods**

### **Patients and Controls**

Between July and December 1996 we investigated the value of CKMB-activity, CKMB-activity/CK-total ratio, CKMB-mass, CKMB-mass/CK-total ratio, cTnI and cTnT in 89 consecutive patients experiencing blunt trauma. At admission an ECG and chest X-ray were performed on these patients according to the hospital trauma protocol. When myocardial damage was suspected, a cardiologist was consulted. The patients were divided into two groups: patients with and without thoracic injuries. The group with thoracic injuries consisted of 38 patients. If thoracic injury was excluded (normal ECG, normal X-ray, no obvious external chest injury and no complaints of chest pain) patients were categorised in the group patients without thoracic injuries (n=51). Some of this group (17) were patients with injuries of the extremities only.

The reference ranges of the biochemical parameters were confirmed with sera from 69 healthy control persons (45 male, mean age 38 years; 24 female, mean age 37 years).

### **Methods**

Blood was taken at admission ( $t_1$ ) and 24 hours after admission ( $t_2$ ) for analysis of the biochemical parameters. After centrifugation at 1000 g at 20 EC the serum was separated. CK-total and CKMB-activities were analysed immediately. If the CKMB-activity/CK-total ratio was more than 3%, a CK-isoenzyme electrophoresis was carried out to exclude CK-macro-enzymes and CKBB. For retrospective analysis of cTnI, cTnT and CKMB-mass, serum was stored at -20 EC. These measurements were performed in one batch on the same day after the inclusion of patients was finished.

CK-total and CKMB-activity (immune-inhibition) were measured with a Vitros 750C analyser (Ortho Clinical Diagnostics, Beerse, Belgium).

For cTnI measurements an Access analyser (Sanofi Diagnostics Pasteur, Vlaardingen, The Netherlands) was used. After separation of the bound and unbound fractions, a dioxetane chemiluminescent substrate provides a long-lasting signal which is proportional to the cTnI concentration (28).

cTnT measurements were performed on an Elecsys 2010 analyser (Boehringer Mannheim, Almere, The Netherlands) using the more cardiac specific 'second generation' cTnT antibodies (29). After the forming of a 'sandwich'-complex, in which ruthenium is incorporated, the application of a voltage induces chemiluminescent emission which is measured by a photomultiplier (30).

CKMB-mass was measured with a MAGIA 7000 analyser (Merck, Amsterdam, The Netherlands). The principle of separation after the one step competition reaction is based on magnetising of 'paramagnetic microparticles'. Substrate is added after this procedure for the chemical reaction catalysed by alkaline phosphatase (31).

CK-isoenzyme analyses were performed electrophoretically with a Cardio Rep analyser (Helena Laboratories, Beaumont, TX, USA) (32).

To compare the various parameters the test results were normalised by dividing the result of the analysis by the cut off value (cov) of the parameter. The covs are the upper limits of reference ranges of the biochemical parameters. The parameters CKMB-mass, cTnI and cTnT are not in common use in our hospital. For these parameters the reference ranges recommended by the manufacturers are used.

## **Results**

The patient and trauma characteristics are summarized in Table 1. The levels of the biochemical parameters in the sera of the control persons were all below the upper limits of the reference ranges. On basis of the trauma protocol used in this study, three patients with thoracic injuries were suspected for myocardial contusion.

In Figure 1, the normalised results (for reasons of clarity only the range 0 - 10) are depicted of the

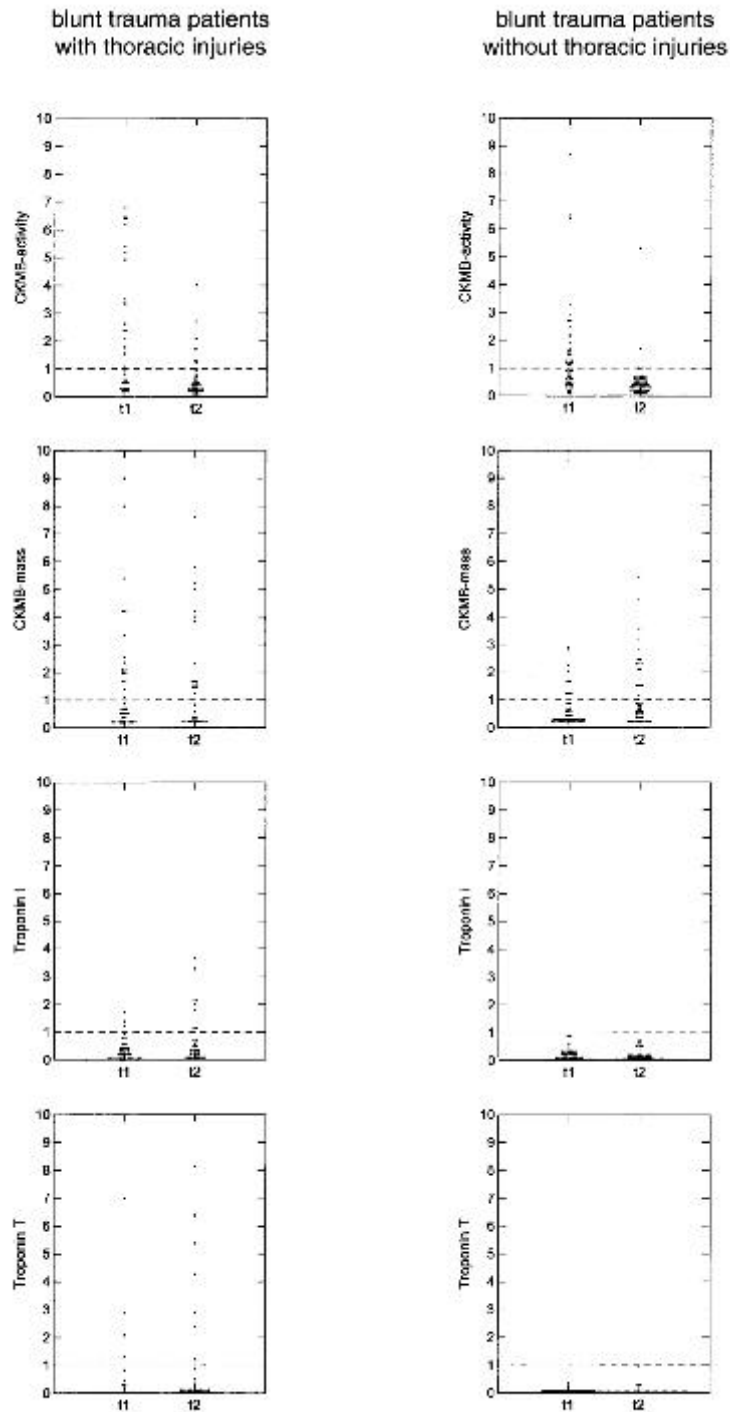


Figure 1. Normalised results of biochemical markers are shown for 38 blunt trauma patients with thoracic injuries and 51 blunt trauma patients without thoracic injuries at admission ( $t_1$ ) and 24 h after admission ( $t_2$ ). For reasons of clarity, only the results out of the range 0-10 are shown. The dashed lines indicate the upper limits of the reference ranges. Patients with thoracic injuries, who have increased troponin results at  $t_1$ , have also increased results at  $t_2$ .

biochemical markers CKMB-activity, CKMB-mass, cTnI and cTnT at admission ( $t_1$ ) and 24 hours

after admission ( $t_2$ ) for both groups of patients. As the patterns for the CKMB-activity/CK-total ratios and the CKMB-mass/CK-total ratios are similar to those of CKMB-activity and CKMB-mass, these pictures are not shown for reasons of clarity.

**Table 1.** Patient and trauma characteristics.

	total patients	patients with thoracic injury	patients without thoracic injury
Number	89	38	51
Mean age in years (range)	36 (5-84)	37 (8-82)	33 (5-84)
Cause of the accident (freq.):			
Traffic	62	31	31
Fall from height	22	5	17
Other	5	2	3
Accompanying injuries*			
Trauma capitis	48	23	25
Abdomen	23	15	8
Pelvis	4	4	0
Extremity	51	19	32
Back	6	2	4
Other	1	0	1

\* Patients could have more than one injury.

In Table 2 the percentages of elevated results of all the examined biochemical parameters at  $t_1$  and at  $t_2$  for both groups of patients are shown.

In the thoracic injury group, three patients had elevated cTnI and four patients had elevated cTnT results at  $t_1$ . For nine patients out of this group both cTnI and cTnT results were above the cov at  $t_2$ . None of the conventional markers was elevated in these nine patients at  $t_1$  and at  $t_2$ . On the other hand, there were elevated levels of CKMB-activity (five patients), CKMB-activity/CK-total ratio (four patients), CKMB-mass (fifteen patients) and CKMB-mass/CK-total ratio (seven patients) in the twenty-nine patients with thoracic injuries for whom the cTnI and cTnT results were not elevated and for whom myocardial damage was also not suspected clinically.

Although in the group consisting of patients without thoracic injuries none could have myocardial damage resulting from trauma, a number of them had elevated results at  $t_1$  and  $t_2$  for the markers CKMB-activity (twenty-nine and four patients, respectively), the CKMB-activity/CK-total ratio (forty-six and ten patients, resp.), CKMB-mass (ten and twenty patients, resp.) and the CKMB-mass/CK-total ratio (nineteen and eleven patients, resp.). Even in the subpopulation of seventeen patients with only trauma of the extremities, 50% of the results of these biochemical parameters were elevated. All patients without thoracic injuries had cTnI and cTnT results within the reference ranges at  $t_1$ . At  $t_2$  one patient had elevated cTnI and cTnT results after experiencing an acute myocardial infarction (AMI) 7 hours after admission, not as a direct result of trauma.

The CKMB-activity/CK-total ratios above 15% (normalised ratio 5) from 37 out of the total 89 patients were all shown to be influenced by an increased concentration of CKBB by performing a CK-isoenzyme analysis. The phenomenon of elevated CKBB was seen for all patients only at  $t_1$ .

**Table 2.** Cut off values and the percentages of elevated results of all examined biochemical parameters at admission and 24 h later for blunt trauma patients with thoracic injuries and for blunt trauma patients without thoracic injuries.

Parameter	% Elevated results of 38 blunt trauma patients with thoracic injuries		%Elevated results of 51 blunt trauma patients without thoracic injuries		Cov <sup>a</sup>
	$t_1$	$t_2$	$t_1$	$t_2$	
	CKMB-activity	63	24	57	
Ratio <sup>b</sup>	79	13	90	20	3.0 %
CKMB-mass	47	61	20	39	5.0 µg/L
Ratio <sup>c</sup>	55	32	38	22	3.0 %
Troponin I	8	24	0	2	0.1 µg/L
Troponin T	10	24	0	2	0.1 µg/L

$t_1$ : admission;  $t_2$ : 24 hours after admission;

<sup>a</sup>Cov: cut off value (upper limit of reference range);

<sup>b</sup>Ratio: CKMB-activity/CK-total;

<sup>c</sup>Ratio: CKMB-mass/CK-total.

## Discussion

It is often very difficult to establish the diagnosis of myocardial contusion. The seriously injured trauma patient usually cannot provide adequate information about injury mechanism and often cannot complain about chest pain. Clinicians use a variety of tools for this diagnosis. To date, blood analyses (conventional and recent markers) are the most-often used tools to determine myocardial contusion.

*Conventional markers.* Although CKMB-isoenzyme measurement is currently a recommended biochemical test for the detection of myocardial damage (11), it is less accurate in patients with chest trauma. As CKMB is present in myocardial muscle and in skeletal muscle, CKMB from both types of tissue is released and causes blood values to be elevated in response to the injury (33,34). Also in our study population many patients without thoracic injuries had elevated levels of CKMB-activity, CKMB-activity/CK-total ratio, CKMB-mass and CKMB-mass/CK-total ratio. Even in the 17 patients who only had trauma of the extremities, 50% of the results for these biochemical parameters were elevated. If these variables had been used as criterium for myocardial damage, these patients could have been incorrectly classified. Subsequently, since patients with myocardial damage should



be monitored for 48 h (12), they could have been unnecessarily exposed to an expensive intensive care unit.

The false positive finding of CKMB-activity/CK-total-ratios over 15% (for 37 out of the total 89 patients) is related to the CKBB-isoenzyme. The CKBB-isoenzyme is normally not detectable in the blood. CKBB is present not only in brain tissue, but also in other tissues such as stomach, intestine, kidney, bladder, prostate and uterus (35). Thus, after an accident with involvement of these tissues the CKMB-activity/CK-total ratio may be elevated.

Because the CKMB-mass measurement is not influenced by the CKBB-isoenzyme, the CKMB-mass/CK-total ratio is also used as index for myocardial damage (36), despite the fact that CKMB-mass and CK-total are expressed in different units. If we compare the results of these ratios with those of the CKMB-activity/CK-total ratios for patients without thoracic injury, the CKMB-mass/CK-total ratios are more reliable. However, there are still eight patients for whom at  $t_1$  both the CKMB-mass and the CKMB-mass/CK-total ratio are elevated and at  $t_2$  this is true for five patients. Thus, the CKMB-mass/CK-total ratio is also not specific for the detection of myocardial damage in patients after blunt trauma.

*Recent markers.* Adams et al. (36) reported that measurement of troponin is more sensitive than the conventional diagnostic tools for the detection of myocardial damage in patients after trauma. Moreover, it is also easier and less costly than using echocardiography as a routine screening test to detect cardiac injury after blunt chest trauma (36). The determination of troponin is more specific, as has been reported by Bodor et al. (37). They showed by histological experiments on biopsies of skeletal and myocardial muscle tissues, that cTnI was only detectable in myocardial tissue. For cTnT they show cross reactions with skeletal muscle biopsy specimens. However, they used their own produced antibodies, and these are different from those used by the manufacturer of the commercially available reagent. This may explain why we did not find elevated cTnT results in the patients without thoracic injuries. Moreover, we used the 'second generation' reagent for the cTnT measurements. As has recently been reported (29), the antibody used in this reagent is more specific for myocardial tissue and shows less cross-reactivity with skeletal muscle tissue.

As we did not find elevated troponin results in the group of patients without thoracic injuries and for reasons of reported sensitivity and specificity (36-39), we prefer the troponin results as criteria for the detection of traumatic myocardial damage and for the selection of patients, who require intensive cardiac monitoring. However, as can be concluded from Table 2, measurement of cTnI and cTnT at admission can be too early for a definite conclusion: the cTnI and cTnT levels were still within the reference ranges at  $t_1$  for most patients with thoracic injuries who have elevated cTnI and cTnT results at  $t_2$ . This phenomenon is similar to that of patients experiencing an AMI. For these patients it takes several hours for the troponins to be elevated after AMI. Further studies should be carried out to determine the clearance characteristic curves of cTnI and cTnT in circulation after myocardial damage caused by trauma. From such studies the earliest reliable time after trauma can be determined, at which traumatic myocardial damage can be detected.

We conclude from this study, that CKMB activity, the CKMB-activity/CK-total ratio, CKMB-mass and the CKMB-mass/CK-total ratio are not useful for the detection of myocardial damage in patients experiencing blunt chest trauma. The parameters cTnI and cTnT are equally accurate and more reliable than the other biochemical markers for the detection of myocardial damage and for the selection of patients, who require intensive cardiac monitoring. If at admission the cTnI or the cTnT results are still within the reference ranges, a second analysis after admission is necessary to reach a reliable conclusion concerning myocardial contusion as a result of trauma on basis of the troponin results.

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