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# Ruling Out Myocardial Infarction with Troponin T and Creatine Kinase MB Mass: Diagnostic and Prognostic Aspects

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***Objective***—To investigate the time window for ruling out myocardial infarction (MI) with troponin T (TnT) and creatine kinase isoenzyme MB mass (CK-MBm) and the prognosis of patients with ruled-out MI diagnosis.
***Design***—The study was based on 397 patients admitted with a suspected acute coronary syndrome but with relief of symptoms within 24 h.
***Results***—MI diagnosis was confirmed with elevated TnT (>0.10 μg/l) in 108 patients, in 91% within 12–24 h from the onset of symptoms, and in 99% within 12 h from admission. In 94 of these patients CK-MBm became elevated (>5.0 μg/l), in 95% within 10–12 h from the onset of symptoms, and in 99% within 6 h from admission. Among patients with ruled-out MI diagnosis, the 1-year incidence of recurrent coronary events was 29% in those with positive history of coronary heart disease (CHD) but only 7% in those without prior CHD ($p < 0.001$).
***Conclusion***—Using TnT or CK-MBm, MI can be ruled out within 12 h from admission in the majority of patients. Among patients with ruled-out MI diagnosis, positive history of CHD is an important determinant of prognosis.

**Key Words:** CK-MB mass, FINMONICA, myocardial infarction, troponin T

New biochemical markers of myocardial injury, such as troponin T (TnT) and creatine kinase isoenzyme MB mass (CK-MBm), recognize smaller myocardial infarctions (MIs) than conventional cardiac enzymes. Their specificity reduces the number of false positive MI diagnoses and unnecessary hospitalizations. The markers are particularly useful in confirming MI diagnosis in patients with normal or non-diagnostic electrocardiograms (ECGs) (1, 2).

The ruling out of the diagnosis of MI in patients admitted with acute coronary syndromes forms an important part of everyday work in emergency departments. The new sensitive markers of myocardial injury have proved to be useful in this decision-making (3). The time window for ruling out a MI with biochemical injury markers when chest pain symptoms are relieved depends on the rapidity of the release of the injury markers into the circulating blood. Usually the onset of ischaemic myocardial damage coincides with the beginning of chest pain symptoms. Thus, the blood sampling for the determination of injury markers should ideally be timed in relation to the onset of symptoms, as has been proposed by some investigators (4–7). This is, however, difficult to accomplish in busy emergency departments. We have studied the time window needed for ruling out the diagnosis of MI using TnT and CK-MBm in an unselected series of consecutive patients admitted with acute coronary syndromes to the Emergency Department, but with relief of symptoms within 24 h. The data were analysed by determining the time window in two ways: (i) from the onset of symptoms and (ii) from the hospital admission. We have also studied the prognosis of patients in whom MI was ruled out.

## PATIENTS AND METHODS

### *Patients*

During the period from 30 August 1995 until 29 February 1996, 559 patients with an index event of a suspected acute coronary syndrome were admitted to the Emergency Department of Kuopio University Hospital. In 482 (86%) of them the chest pain or equivalent symptoms were relieved within 24 h from hospital admission. In 399 (83%) of the 482 patients reliable time of onset of the symptoms was available. We excluded two patients, who died from acute MI at the Emergency Department soon after the first blood sample had been taken and within less than 2 h from the onset of symptoms. Both of them had TnT concentration of 0.08 μg/l. The final study population thus comprised 397 patients: 227 men and 170 women, aged 19–96 years (median age 69 years). The study was approved by the Ethics Committee of Kuopio University Hospital.

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### *Diagnosis of MI*

For the purposes of the present study, the diagnosis of MI in patients with chest pain attack or other symptoms compatible with an acute coronary syndrome was based on the elevation of serum TnT concentration to >0.10 μg/l within 24 h from hospital admission. An epidemiological diagnostic classification, modified FINMONICA criteria (8, 9), was used for the description of patient population. This classification is based on symptoms, ECG findings (using serial Minnesota coding), peak values of conventional enzyme activities (creatine kinase, its isoenzyme MB and lactate dehydrogenase isoenzyme 1), autopsy findings, and history of previous coronary heart disease (CHD).

### *Collection of follow-up data*

The coronary endpoints during the follow-up were: (i) CHD death, (ii) major CHD event (CHD death or non-fatal MI), and (iii) any CHD event (CHD death, non-fatal MI, hospitalization due to unstable angina or a prolonged attack of chest pain, or revascularization procedure). One patient could have several endpoints but only the first one was used in analyses. The follow-up time was 1 year. Methods used in the ascertainment of the endpoints have been described in detail elsewhere (10). Complete follow-up data were obtained on all the patients.

### *Laboratory methods*

The first blood sample for the measurement of conventional enzyme activities, and TnT and CK-MBm concentrations was drawn as soon as possible when the patient had arrived at the Emergency Department. Subsequent samples were drawn 2, 4 and 6 h after the first sample. During the 2nd and 3rd hospital day blood samples were drawn twice a day – between 7:00 and 8:00 and between 19:00 and 20:00. The last blood sample was taken in the morning of the 4th day, if the patient was still in the hospital. The results of TnT and CK-MBm determinations were used for study purposes only and they were not available to the physicians treating the patients. The laboratory personnel measuring the TnT and CK-MBm concentrations was blinded with regard to the results of the conventional enzyme determinations and clinical data.

Serum CK-MBm was measured using the immunochemical microparticle technique by Abbott IMx™ CK-MB assay (Abbott Laboratories, Abbott Park, Chicago, IL, USA). Elevated conventional enzyme activities and CK-MBm concentrations were regarded as non-specific in patients with any skeletal muscle injury. Cardiac TnT in serum was measured photometrically by an immunochemical ELISA method on plates of microtitre using reagents by Boehringer Mannheim (Mannheim, Germany) (11). Double monoclonal antibody technique was used to decrease the cross-reactivity with skeletal muscle TnT. In a series of 95 apparently healthy persons serum TnT concentration was $0.027 \pm 0.025$ μg/l by the second generation test used. Thus, the upper reference limit (corresponding to the upper limit of the 99% confidence interval) for the test was 0.10 μg/l. The coefficient of variation for TnT was 8.7% at 0.23 μg/l and 4.7% at 4.35 μg/l. The coefficient of variation for CK-MBm was 6.9% at 4.6 μg/l and 5.5% at 15.2 μg/l, respectively.

### *Statistical methods*

Data analyses were performed with SPSS for Windows Release 10.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the $\chi^2$ test. Statistical significance was based on the 0.05 level.

## RESULTS

### *Characteristics of the patients*

Characteristics of the patients with and without confirmed diagnosis of MI are shown in Table I. Of the 397 patients, 108 (27%) had MI. Thirty patients received thrombolysis: 19 (63%) in the hospital and 11 (37%) in a health centre before hospital admission. In two of them, however, the diagnosis of MI was not confirmed by conventional enzymes, ECG findings or TnT. In those patients who were at first admitted to the health centre, delays from the onset of symptoms to health centre admission were not available. Median delay from the onset of symptoms to thrombolysis was 2.7 h (range 0.6–25.3 h). None of the patients had a primary percutaneous coronary intervention.

### *Timeframe for the confirmation of or ruling out MI diagnosis*

The diagnosis of MI was mainly based on elevated TnT. However, all the patients with MI were not recognized with CK-MBm. The cut-off limit for TnT was 0.10 μg/l. Two different cut-off limits of 5.0 and 10.0 μg/l were used for CK-MBm, since mild elevations of CK-MBm due to skeletal muscle injury may lead to false positive MI diagnoses. Of the 289 patients in whom MI was ruled out on the basis of TnT ≤0.10 μg/l, CK-MBm was elevated to >5.0 μg/l in 30 (10.4%) patients and to >10.0 μg/l in 5 (1.7%) patients. On the other hand, of

Table I. *Characteristics of patients with confirmed diagnosis of MI and patients in whom the diagnosis of MI was ruled out (peak TnT ≤0.10 μg/l)*

| | MI confirmed ($n$ = 108) | MI ruled out ($n$ = 289) |
|---|---|---|
| Men/women (%) | 63/45 (41.7%) | 164/125 (43.3%) |
| Age (years): median (range) | 72 (19–96) | 68 (29–91) |
| Positive history of CHD | 65 (60.2%) | 189 (65.4%) |
| Delay from the onset of symptoms to hospital admission | | |
| 0–2 h | 30 (27.8%) | 67 (23.2%) |
| >2–4 h | 26 (24.1%) | 65 (22.5%) |
| >4–6 h | 20 (18.5%) | 44 (15.2%) |
| >6–8 h | 6 (5.6%) | 29 (10.0%) |
| >8–10 h | 7 (6.5%) | 13 (4.5%) |
| >10–12 h | 3 (2.8%) | 19 (6.6%) |
| >12–24 h | 11 (10.2%) | 28 (9.7%) |
| >24 h | 5 (4.6%) | 24 (8.3%) |
| Thrombolytic treatment | 28 (25.9%) | 2 (0.7%) |
| Epidemiological diagnosis | | |
| Definite MI | 54 (50.0%) | 0 (0%) |
| Probable MI | 22 (20.4%) | 12 (4.2%) |
| No MI | 32 (29.6%) | 277 (95.8%) |
| Chest pain symptoms | | |
| Typical | 78 (72.2%) | 143 (49.5%) |
| Atypical or inadequately described | 18 (16.7%) | 49 (17.0%) |
| Other | 12 (11.1%) | 97 (33.5%) |
| ECG abnormalities | | |
| Q-/QS-wave evolution | 13 (12.0%) | 0 (0%) |
| ST-/T-wave abnormalities | 56 (51.9%) | 41 (14.2%) |
| Unchanged ischaemic | 23 (21.3%) | 136 (47.1%) |
| Uncodable | 9 (8.3%) | 37 (12.8%) |
| Normal | 7 (6.5%) | 75 (26.0%) |
| Conventional enzymes | | |
| >2 × URL | 56 (51.9%) | 0 (0%) |
| >1 × URL, ≤2 × URL | 21 (19.4%) | 33 (11.4%) |
| ≤1 × URL | 22 (20.4%) | 244 (84.4%) |
| Non-specific | 9 (8.3%) | 12 (4.2%) |

CHD = coronary heart disease; ECG = electrocardiogram; MI = myocardial infarction; TnT = troponin T; URL = upper reference limit.

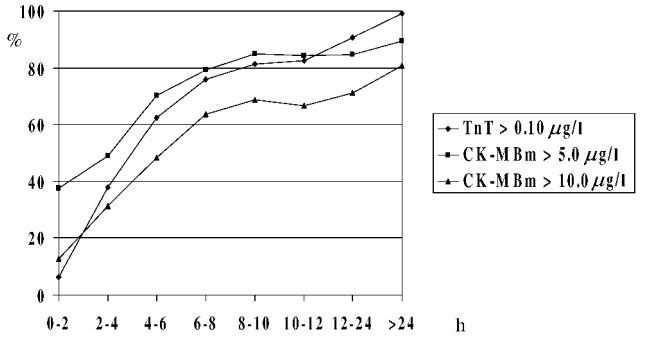


*Fig. 1.* Time for elevation of biochemical markers from the onset of symptoms in 108 patients with myocardial infarction. TnT = troponin T; CK-MBm = creatine kinase isoenzyme MB mass.

the 108 patients with MI on the basis of TnT >0.10 μg/l, CK-MBm was ≤5.0 μg/l in 14 (13.0%) patients and ≤10.0 μg/l in 26 (24.1%) patients.

Figure 1 shows the time from the onset of symptoms to the elevation of TnT and CK-MBm in 108 patients with MI. With TnT the diagnosis of MI was confirmed in 91% of the patients 12–24 h from the onset of symptoms and with CK-MBm (with the cut-off limit of 5.0 μg/l) in 85% during the same time. Among the 94 patients in whom CK-MBm became elevated to >5.0 μg/l, the diagnosis of MI was confirmed 10–12 h from the onset of symptoms in 95%. Thus, CK-MBm with the cut-off limit of 5.0 μg/l was found to be an earlier indicator of MI than TnT. When the cut-off limit of 10.0 μg/l was used for CK-MBm the diagnosis of MI was confirmed in 81% of the 108 patients 24 h from the onset of symptoms. Consequently, MI was ruled out with a high probability if the concentration of TnT remained within normal limits up to 12–24 h or CK-MBm up to 10–12 h from the onset of symptoms.

Figure 2 shows the time from hospital admission to the elevation of TnT and CK-MBm in 108 patients with MI. The diagnosis of MI was confirmed with TnT in 99% of the patients within 12 h and in all of them within 24 h from hospital admission. With CK-MBm and cut-off limit of 5.0 μg/l the diagnosis of MI was confirmed in 88% of the patients within 12 h from hospital admission. However, CK-MBm was elevated to >5.0 μg/l by 6 h from hospital admission in 93 (99%) of the 94 patients in whom CK-MBm became elevated within 72 h. When the cut-off limit of 10.0 μg/l was used for CK-MBm the diagnosis of MI was confirmed in 76% of the 108 patients within 12 h and in 81% of the patients within 24 h from hospital admission. MI was ruled out with a high probability if the concentration of TnT remained within normal limits up to 12 h or CK-MBm up to 6 h from hospital admission.

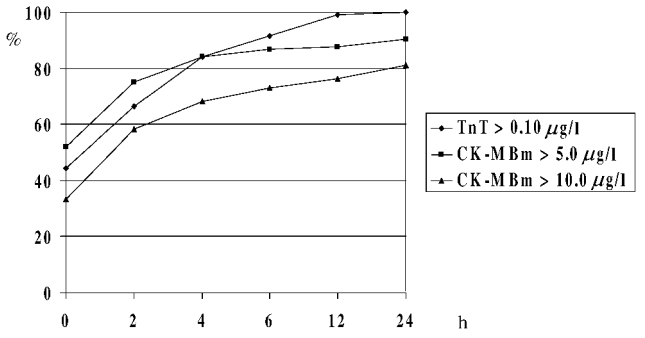


*Fig. 2.* Time for elevation of biochemical markers from hospital admission in 108 patients with myocardial infarction. TnT = troponin T; CK-MBm = creatine kinase isoenzyme MB mass.

Since the elevation rate of the biochemical marker concentrations is affected by thrombolysis and reperfusion, the 80 patients who did not receive thrombolysis were analysed separately. The curves for elevated biochemical marker concentrations remained virtually unchanged (data not shown).

*Prognosis of the patients in whom MI was ruled out*

Table II shows the incidence of major and all CHD events during the follow-up of 1, 3 and 6 months and 1 year in 289 patients in whom MI was ruled out. However, 65% of them had a history of CHD and a worse prognosis than the patients with no or unknown history of CHD. Only one (0.5%) patient with a history of CHD died from CHD within 1 month. Within 3 months five (2.6%) patients and within 6 months nine (4.8%) patients with CHD died from CHD, but none of the patients without history of CHD. Within 1 year 11 (5.8%) patients with and 1 (1.0%) patient without history of CHD died from CHD ($p$ = NS).

Six (2.1%) of the 289 patients without MI died within 1 month after hospital admission. As mentioned above, one of them died from CHD. The remaining five patients died from various reasons, e.g. pneumonia,

Table II. *Incidence of major and all CHD events during the follow-up of 1, 3 and 6 months and 1 year in patients without MI as an index event*

| Events | Positive history of CHD ($n$ = 189) | No or unknown[a] history of CHD ($n$ = 100) | All patients ($n$ = 289) |
|---|---|---|---|
| Major CHD event | | | |
| 1 month | 2 (1.1%) | 2 (2.0%) | 4 (1.4%) |
| 3 months | 7 (3.7%) | 2 (2.0%) | 9 (3.1%) |
| 6 months | 13 (6.9%) | 2 (2.0%) | 15 (5.2%) |
| 1 year | 18 (9.5%)* | 3 (3.0%) | 21 (7.3%) |
| Any CHD event | | | |
| 1 month | 11 (5.8%) | 3 (3.0%) | 14 (4.8%) |
| 3 months | 26 (13.8%)* | 4 (4.0%) | 30 (10.4%) |
| 6 months | 42 (22.2%)*** | 5 (5.0%) | 47 (16.3%) |
| 1 year | 54 (28.6%)*** | 7 (7.0%) | 61 (21.1%) |

[a] Information on the history of CHD not available.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as compared with the incidence in patients with no or with unknown history of CHD.

CHD = coronary heart disease; MI = myocardial infarction.

cardiac failure after valvular operation, or ruptured aortic aneurysm. All of these patients died in hospital during the index hospitalization.

## DISCUSSION

We studied a consecutive series of 397 patients who were admitted with a suspected acute coronary syndrome, in whom the time of onset of the symptoms was available, and whose symptoms were relieved within 24 h from admission. In earlier studies, the blood samples for biochemical markers were collected by a schedule relative to either the onset of symptoms or to hospital admission. In this study the biochemical marker measurements were assessed in relation to both points of time. In this series of patients MI was ruled out with a high probability if the concentration of TnT remained within normal limits until 12–24 h from the onset of symptoms. MI was ruled out with a relatively high probability if the concentration of CK-MBm remained $\leq$5.0 $\mu$g/l until 10–12 h from the onset of symptoms. Our results are concordant with earlier studies by de Winter et al. (4, 6), and by Zimmerman et al. (7). During the first hours of an acute event, elevation of CK-MBm up to >5.0 $\mu$g/l was an earlier indicator of MI than elevation of TnT. However, the results were rather sensitive to the cut-off limit used for CK-MBm.

In clinical practice, the time of onset of the symptoms cannot always be defined reliably. Additionally, patients may have recurrent attacks of chest pain. Individual timing of blood samples for biochemical markers in relation to the onset of symptoms is problematic. However, in our series of patients TnT was elevated to >0.10 $\mu$g/l in 92% of patients with MI by 6 h and in 99% by 12 h from the hospital admission. CK-MBm was elevated to >5.0 $\mu$g/l by 6 h from the hospital admission in 99% of the patients in whom CK-MBm became elevated at all. Practically, the timing of biochemical marker measurements in relation to hospital admission is sufficient. MI may be ruled out with a high probability if concentrations of TnT and CK-MBm, or either of them if only one marker is used, remain within normal limits up to 12 h after hospital admission. However, the different diagnostic time windows of these markers must be kept in mind (12, 13). In patients who have had MI several days before admission to hospital, CK-MBm may already have returned to the normal level but TnT may still be elevated. Moreover, potentially life-threatening non-cardiac diseases must be excluded in patients with biochemical markers of myocardial injury within normal limits.

We have earlier studied the difference between TnT-based and epidemiological diagnosis in a larger patient group (14). In that study we found that the number of MIs would increase by 23%, if the diagnosis was based on elevated TnT instead of the epidemiological criteria. In the population of the present study TnT-based diagnosis of MI was compared to epidemiological diagnoses in Table I. In another previous study (9) we have shown that epidemiological diagnosis of definite MI did not change, if TnT was used as the basis of MI diagnosis instead of conventional enzyme activities. However, TnT was not elevated in one-third of the patients with epidemiological diagnosis of probable MI, whereas, TnT was elevated in 13% of the patients without any epidemiological diagnosis of MI.

In this study, the first sample was drawn as soon as possible after arrival at the Emergency Department. Subsequent samples were drawn 2, 4 and 6 h thereafter, and on the next morning (approximately 12 h after the first sample). The schedule was influenced by laboratory resources and other practical reasons. The diagnosis of MI would probably have been confirmed earlier by TnT in an even larger proportion of the patients, if the blood samples had been drawn more frequently between 6 and 12 h from hospital admission. According to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee (15), blood samples for biochemical marker measurements should be obtained on hospital admission, at 6–9 h and again at 12–24 h if earlier samples are negative and there is a strong suspicion of MI. Our results are in accordance with this recommendation.

Our own experience (16), in accordance with others (17, 18), is that concordance between the results of quantitative analyses and rapid bedside tests for the biochemical markers is good. Thus, bedside tests are useful in ruling out MIs in hospitals or health centres which have adequate possibilities to observe and retest the patients with initially negative tests but in which 24-h quantitative determinations are not available.

Earlier studies on ruling out MI with TnT either have not examined prognosis of patients with ruled-out MI (4, 7) or have reported results only for short-term prognosis (18). We found that among the patients in whom MI was ruled out the 1-year risk of CHD events was strongly influenced by a positive history of CHD. The 1-year incidence of CHD events was 25% in patients with and only 7% in those without prior CHD. de Winter et al. (5) also found that in patients in whom MI had been ruled out using WHO criteria, a documented history of CHD was the best predictor of coronary events within 6 months. In Finland, in age groups comparable to our patient population, all-cause mortality in 1998 was 1% and CHD mortality 0.2% (19). In our patients in whom MI was ruled out and who had no history of CHD the 1-year CHD mortality was 1%.

It is practical to observe the patients, who are candidates for discharge within 12–24 h after admission, in chest pain observation units attached to emergency departments (20). After an adequate observation time, patients with chest pain relieved, repeatedly normal levels of biochemical markers, and no significant ECG changes may be discharged or undergo an exercise ECG testing for further risk stratification (21). Thus, unnecessary hospitalizations and costs for hospital care will be reduced.

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