Equivalent Early Sensitivities of Myoglobin, Creatine Kinase MB Mass, Creatine Kinase Isoform Ratios, and Cardiac Troponins I and T for Acute Myocardial Infarction

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Early sensitivities of creatine kinase (CK), CKMB (activity and mass), CKMM and CKMB isoform ratios, myoglobin, cardiac troponin I (cTnI), and cardiac troponin T (cTnT) were compared to find the most sensitive serum marker for acute myocardial infarction (AMI) during the first hours after onset of chest pain. In a prospective study we investigated 37 consecutive patients with AMI who were admitted to the coronary care unit within 4 h after onset of chest pain. Blood samples were drawn every hour for the first 10 h after admission. CKMB mass concentrations, CKMM and CKMB isoform ratios, myoglobin, cTnI, and cTnT increased significantly (P ≤0.0067) earlier than CK and CKMB activity and were also significantly (P ≤0.046) and markedly more sensitive on admission. Differences in early sensitivities of myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT were small and not significant. Therefore, turnaround time and practicality for emergency determination of methods, specificities of markers, the required specificity in the individual patient, and costs mainly determine the choice among myoglobin, CKMB mass, CK isoforms, cTnI, and cTnT.

Indexing Terms: early diagnosis/enzyme markers/isoforms

Early identification and confirmation of acute myocardial infarction (AMI) are essential for correct patient care and disposition decisions (1). Approximately 5% of patients with AMI are released unintentionally from the emergency department, which places them at greater risk of morbidity and mortality from AMI complications (2). This occurs because as many as one-fourth of patients with AMI present with atypical signs and symptoms (1, 2). The goal is to treat patients with obvious AMI within 30 min after emergency department presentation and to treat all patients having AMI within 1 h (3). Although electrocardiography (ECG) is considered the simplest, most convenient, most reliable, and most reproducible method for early diagnosis of AMI, approximately half of all AMI patients have nondiagnostic ECGs at the time of presentation to the emergency department (1, 2). The conventional serum markers creatine kinase (CK) and CKMB activity are useful for retrospective confirmation of myocardial infarction in these patients, but neither is very helpful in the emergency department evaluation of the patient with chest discomfort (4).

The search for more sensitive biochemical markers for the early diagnosis of AMI (4, 5) reflects the need for an improved initial diagnostic accuracy of biochemical markers in patients with acute chest pain. Several biochemical markers (myoglobin, CKMB mass concentration, CK isoform ratios) have been proposed for the early diagnosis of AMI during recent years. All of them are markedly more sensitive than CK and CKMB activity during the early hours after the onset of infarct-related symptoms (6–8). Myoglobin and CKMB isoform ratio measurements are less heart-specific than CKMB isoenzyme and isoform ratio determination (5). However, CKMB is not an absolutely heart-specific marker either (5, 9). Therefore, because of their extraordinary high specificity for myocardial damage, cardiac troponins I and T (cTnI, cTnT) have gained particular interest (5, 9). Both exist in three different isoforms with an unique structure in striated muscles, one for slow-twitch, one for fast-twitch, and one for cardiac muscle (10, 11). The troponin complex consists of three subunits and is involved in the calcium-sensitive switch that regulates the interaction of actin and myosin in striated muscles. cTnT (Mr 37 000) binds the troponin complex to tropomyosin, and cTnI (Mr 22 500) is the inhibitory subunit of the troponin complex (5, 9). The clinical specificity of cTnT is limited by recent reports on discordances between serum cTnT and cTnI in renal disease (12, 13) and by the possibility of a reexpression of cTnT in chronically stressed skeletal muscle (14)—which has not, however, been demonstrated in humans so far. Increased cTnI concentrations have been found only after myocardial damage up to now (5, 9, 11).

Rapid and specific assays for measurement of myoglobin, CKMB mass, CKMB and CKMM isoforms,
cTnI, and cTnT have been or are being developed. At present it is not clear which of these serum markers is most sensitive and should be used for early diagnosis of AMI in clinical practice, because they have not yet been compared in the same cohort of AMI patients. This study compares the early sensitivities for AMI of CK and CKMB (activity and mass), CKMM and CKMB isoform ratios, myoglobin, cTnI, and cTnT from the onset of chest pain and addresses the questions of whether there are significant differences between these markers and, if so, whether these differences are clinically relevant.

Subjects and Methods

Subjects

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. We prospectively studied 37 consecutive patients with AMI (29 men, 8 women; median age 62, range 40–82 years; 23 anterior and 14 inferior wall myocardial infarctions; 25 with Q-wave and 12 with non-Q-wave infarction), who were all admitted within 4 h after the onset of chest pain (median 135, range 30–240 min) and who gave informed consent to extra blood sampling. Only patients with a well-defined onset of infarct-related chest pain were included. The diagnosis of definite myocardial infarction required at least two of the following three clinical criteria to be positive (15, 16): (a) typical prolonged severe chest pain and related symptoms of >20 min duration; (b) the evolution of abnormal Q waves or equivalents on serial ECGs in at least two leads of the same vascular territory; and (c) serial increases of CK and CKMB activity with an initial rise and a subsequent fall, and with peak values of twice the upper limit of the reference interval. An AMI was called Q-wave myocardial infarction if there was progression from no Q waves to definite Q waves (≥0.04 s, amplitude >1/4 R wave) or QS complexes, and non-Q-wave myocardial infarction if there were an ST-segment depression or increase of at least 0.1 mV (limb leads) and 0.2 mV (precordial leads), respectively, and a T-wave inversion in at least two leads of the same vascular territory of at least 24 h duration. All but two AMI patients received intravenous thrombolytic therapy with either streptokinase (n = 8), urokinase (n = 11), or alteplase (n = 16).

Thrombolytic therapy was immediately initiated after admission to the coronary care unit. The first blood sample was drawn just before administration of thrombolytic drugs. The decision for thrombolytic therapy was mainly based on ECG and clinical presentation; marker concentrations were usually not known at the time of this decision. No patient was treated with fibrinolytic drugs only because of an increased marker concentration. Acute coronary angiographies were not routinely performed after the end of thrombolytic treatment. Q-wave AMIs were divided into patients with (n = 19) and patients without (n = 6) early reperfusion according to their early rate of increase in myoglobin concentrations (cutoff value 150 μg/L per hour) (17). Eleven non-Q AMIs were “aborted” Q-wave AMIs (18), which means that they presented early after the onset of chest pain with typical ECG signs (regional ST increases), were given thrombolytic treatment, and did not develop new persistent abnormal Q waves later on. Blood samples were withdrawn immediately after admission before the start of thrombolysis, at every hour until 10 h, and at 12, 24, 36, 48, and 72 h after admission.

Laboratory Analysis

Blood collection. Venous blood for measurement of CK, CKMB activity and mass, myoglobin, and cTnT was collected in lithium heparin-containing tubes (final concentration ~20 KIU/L; Sarstedt, Nümbrecht, Germany), and for cTnI measurement in EDTA-coated tubes (final concentration 4 mmol/L; Sarstedt). Samples were immediately centrifuged at 2000g for 15 min. CK and CKMB activities were measured without delay, and plasma for measurement of the other variables was frozen and stored at −20 °C until analysis (performed within 4 weeks after collection). All blood samples for CK isoform determination were collected into evacuated tubes (CK isoform preservation tubes; Helena Labs., Beaumont, TX) pretreated with 2-mercaptoethanol (final concentration 10 mmol/L) and ethylene glycol bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA; final concentration 30 mmol/L). This combination inhibits carboxypeptidase N-mediated isoform conversion after sample collection (19). The samples were then centrifuged, and the plasma was removed for storage at −20 °C until analysis (within 2 weeks after collection).

CK and CKMB activities. CK and CKMB activities were measured at 25 °C by means of an N-acetylcysteine-activated, optimized ultraviolet test from Merck (Darmstadt, Germany). The CKMB activity was determined by immunoinhibition (20). The upper reference limit (URL) of CK is 70 U/L for women and 80 U/L for men. The URL for CKMB activity is 10 U/L (20).

CKMB mass. CKMB mass concentration was measured by a microparticle enzyme immunoassay (Abbott, Abbott Park, IL) for use with the Abbott IMx™ automated analyzer. The URL is 5 μg/L (21).

Myoglobin. Myoglobin concentrations were determined by an immunoturbidimetric assay (Turbi-quant™ Myoglobin; Behringwerke, Marburg, Germany). The detection limit of this assay is 50 μg/L. The URL is 70 μg/L (7).

cTnT. cTnT was measured by an enzyme immunoassay (Boehringer Mannheim, Mannheim, Germany) specific for cTnT (22). The URL is 0.1 μg/L (21, 23).

cTnI. We measured cTnI by a highly specific enzyme immunoassay (Sanofi Diagnostics Pasteur, Marnes-la-Coquette, France). The URL is 0.1 μg/L (24), which was confirmed previously (25).

Creatine kinase isoforms. CKMM and CKMB isoform ratios were determined by high-voltage electrophoresis (REP, Helena Labs.). The isoforms were sep-
arated by high-resolution agarose gel electrophoresis and quantified by densitometric scanning (19). The URLs of the CKMM<sub>2</sub>/CKMM<sub>1</sub> and CKMB<sub>2</sub>/CKMB<sub>1</sub> isofrom ratios are 0.7 and 1.5, respectively (8, 19, 26–28). We measured the CK isofroms in a cohort of 27 apparently healthy individuals without a history of unaccustomed physical exercise or muscle soreness during the preceding days [17 men, 10 women, age 30 ± 10 (mean ± SD) years, range 18–63] to confirm previously reported URLs for CK isofrom ratios.

Data Analysis

Data are given as mean ± SD, median, quartiles, minimum, and maximum. Confidence intervals (95%) of sensitivities were calculated nonparametrically including population size. The URLs of markers were used as cutoff values for the calculation of sensitivities. Friedman test, Kruskal–Wallis test, Wilcoxon signed-rank test, Mann–Whitney U-test, and χ<sup>2</sup> test with Yates correction for continuity or Fisher’s exact test were used. Probability values <0.05 were considered significant.

Results

CK Isoform Ratios in Controls and Precision of CK Isoform Determination

Because we had not measured CK isofrom ratios previously in our laboratory, we first confirmed the URLs recommended by the manufacturer and other groups. The total CK activities in the control population were 40 ± 19 U/L (mean ± SD; median 40, 25th percentile 29, 75th percentile 50, minimum 14, maximum 85 U/L). The CKMM<sub>2</sub>/CKMM<sub>1</sub> isofrom ratios were 0.3 ± 0.2 (median 0.3, 25th percentile 0.1, 75th percentile 0.5, minimum 0.1, maximum 0.9). The calculated and used URL (97.5th percentile) was 0.7,

which is in good agreement with previous reports (26–28). Total CKMB activities were below the detection limit of the immuno inhibition method in all 27 subjects. The MB isoenzyme with its isofroms could not be detected by high-voltage electrophoresis either. We used 1.5 as the cutoff for the CKMB<sub>2</sub>/CKMB<sub>1</sub> isofrom ratio, which is recommended by the developers of the method and the manufacturer, and which was repeatedly confirmed previously (8, 19, 26–28). The precision of the CKMB isofrom separation was tested by using a plasma pool with a CKMB<sub>2</sub>/CKMB<sub>1</sub> ratio of 1.4. The intraassay and interassay CVs were 6.5% (n = 10) and 9.5% (n = 13), respectively. The precision of the CKMM isofrom separation was tested with a commercially available CK control serum (CK isoret; Sigma Diagnostics, St. Louis, MO) with a CKMM<sub>2</sub>/CKMM<sub>1</sub> ratio of 1.1. The intraassay and interassay CVs were 7.5% (n = 10) and 10.9% (n = 10), respectively.

Early Sensitivities and Time Courses of Markers after Myocardial Infarction

On admission before the start of thrombolytic treatment (0–4 h period after the onset of chest pain), CK and CKMB activities were significantly (P ≤0.046) less frequently increased than the other markers, and there were no significant differences in the frequencies of increased values of myoglobin, CKMB mass, CK isofrom ratios, cTnI, and cTnT. The sensitivities of the latter two were roughly identical (Table 1). CK was increased in 8, CKMB activity in 1, CKMB mass in 20, CKMM<sub>2</sub>/CKMM<sub>1</sub> isofrom ratio in 17, CKMB<sub>2</sub>/CKMB<sub>1</sub> isofrom ratio in 18, myoglobin in 20, cTnI in 18, and cTnT in 17 of the 37 investigated patients. Subgroup analysis of the early sensitivities of biochemical markers before thrombolytic therapy in Q-wave and non-Q-wave AMIs revealed similar results. In Q-wave as well as non-Q-wave AMIs, CKMB activity was significantly (P ≤0.046) less sensitive than CKMB mass, CK isofrom ratios, myoglobin, and the troponins, without a statistically significant difference among the latter (see Table 1). The sensitivities of markers did not differ significantly between Q-wave and non-Q-wave AMIs except for CK activity.

Sensitivities before thrombolytic therapy of all markers with their 95% confidence intervals according to the time from onset of chest pain are listed in Table 2. During the 0–2 h period CK and CKMB activity were significantly (P <0.05) less sensitive than CKMB mass, CK isofrom ratios, myoglobin, cTnI, and cTnT. There were no statistically significant differences between

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**Table 1. Early sensitivities (95% confidence intervals) of biochemical markers for AMI during the 0–4 h period after the onset of chest pain.**

<table>
<thead>
<tr>
<th>Time from onset of chest pain, h</th>
<th>CK activity</th>
<th>CKMB activity</th>
<th>CKMM&lt;sub&gt;2&lt;/sub&gt;/CKMM&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CKMB&lt;sub&gt;2&lt;/sub&gt;/CKMB&lt;sub&gt;1&lt;/sub&gt;</th>
<th>MM&lt;sub&gt;2&lt;/sub&gt;/MM&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Myoglobin</th>
<th>cTnI</th>
<th>cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>0.02(0.10-0.38)</td>
<td>0.25(0.15-0.54)</td>
<td>0.0(0.0-0.26)</td>
<td>0.0(0.0-0.26)</td>
<td>0.04(0.01-0.20)</td>
<td>0.0(0.0-0.26)</td>
<td>0.04(0.01-0.20)</td>
<td>0.0(0.0-0.26)</td>
</tr>
<tr>
<td>2–4</td>
<td>0.49(0.32-0.66)</td>
<td>0.40(0.21-0.61)</td>
<td>0.67(0.35-0.90)</td>
<td>0.35(0.21-0.72)</td>
<td>0.50(0.35-0.76)</td>
<td>0.42(0.15-0.72)</td>
<td>0.42(0.15-0.72)</td>
<td>0.42(0.15-0.72)</td>
</tr>
</tbody>
</table>

* *In 37 AMI patients before thrombolytic therapy.*

**Table 2. Early sensitivities (95% confidence intervals) of biochemical markers in 37 patients with AMI on admission before thrombolytic therapy.**

<table>
<thead>
<tr>
<th>Time from onset of chest pain, h</th>
<th>CK activity</th>
<th>CKMB activity</th>
<th>CKMM&lt;sub&gt;2&lt;/sub&gt;/CKMM&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CKMB&lt;sub&gt;2&lt;/sub&gt;/CKMB&lt;sub&gt;1&lt;/sub&gt;</th>
<th>MM&lt;sub&gt;2&lt;/sub&gt;/MM&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Myoglobin</th>
<th>cTnI</th>
<th>cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>0.19(0.04-0.40)</td>
<td>0.00(0.00-0.22)</td>
<td>0.47(0.21-0.73)</td>
<td>0.47(0.21-0.73)</td>
<td>0.47(0.21-0.73)</td>
<td>0.47(0.21-0.73)</td>
<td>0.47(0.21-0.73)</td>
<td>0.47(0.21-0.73)</td>
</tr>
<tr>
<td>2–4</td>
<td>0.32(0.14-0.55)</td>
<td>0.05(0.00-0.23)</td>
<td>0.64(0.41-0.83)</td>
<td>0.59(0.36-0.79)</td>
<td>0.55(0.32-0.76)</td>
<td>0.59(0.36-0.79)</td>
<td>0.59(0.36-0.79)</td>
<td>0.59(0.36-0.79)</td>
</tr>
</tbody>
</table>

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1288  CLINICAL CHEMISTRY, Vol. 41, No. 9, 1995
the latter two. During the 2–4-h period all other markers were significantly \( P < 0.045 \) more sensitive than CKMB activity. Differences between CK activity and CKMB mass, CKMB isofrom ratio, myoglobin, and cTnI were also significant \( P < 0.05 \) during this time interval.

In these 37 patients the first increased marker values were found at 5 (median; range 1–14) h after onset of chest pain for CKMB activity, 4 (1–14) h for CK activity, 3 (0.5–7) h for CKMM isofrom ratio, 3 (0.5–12) h for CKMB isofrom ratio, 3 (0.5–7.75) h for cTnT, 3 (0.5–6.25) h for cTnI, 3 (1–7) h for myoglobin, and 3 (0.5–5) h for CKMB mass (Tables 3 and 4). The differences in times to first increases were statistically significant (Friedman test, \( P = 0.0001 \)). Myoglobin, CKMB mass, CK isofrom ratios, cTnI, and cTnT all increased markedly and significantly (Wilcoxon signed-rank test, \( P \leq 0.0067 \)) earlier than CK and CKMB activity (Tables 3 and 4). However, there were no significant differences in times to first increases above URL between myoglobin, CKMB mass, CK isofrom ratios, cTnI, and cTnT (Friedman test, \( P = 0.21 \)). The early sensitivities of markers according to time from the onset of chest pain in these 37 patients are listed in Table 3. Myoglobin, CK isofrom ratios, CKMB mass, cTnI, and cTnT were significantly \( P < 0.025 \) and markedly more sensitive than CKMB activity during the 2–6-h period after the onset of chest pain. All were significantly \( P < 0.05 \) and markedly more sensitive than CK activity during the 3–4-h period (see Table 3). Up to 3 h from the onset of chest pain the sensitivities of myoglobin, CK isofrom ratios, CKMB mass, cTnI, and cTnT were almost identical; during the 3–6-h period CKMB mass and myoglobin tended to be more sensitive than the others. CKMB mass was the tendenously most sensitive marker of all tested. The sensitivities of myoglobin, CK isofrom ratios, cTnI, and cTnT were mostly within the 95% confidence interval of CKMB mass (see Table 3). We found small, significant \( P < 0.05 \) differences between CKMB mass and CKMM isofrom ratios at 4, 5, and 6 h, and between CKMB mass and CKMB isofrom ratios as well as the troponins at 4 and 6 h after the onset of chest pain.

Comparing the sensitivities of all markers during the 0–4-h period after the onset of chest pain before thrombolytic therapy with the sensitivities of markers during the same period when samples drawn after thrombolytic therapy were not excluded revealed that the sensitivities of all tested markers were significantly \( P \leq 0.04 \) and markedly higher after thrombolytic therapy (Tables 1 and 3). However, in both groups the sensitivities of CK and CKMB activities were

### Table 3. Early sensitivities (and 95% confidence intervals) in 37 patients with AMI including samples drawn after thrombolytic therapy.

<table>
<thead>
<tr>
<th>Time from onset of chest pain, h</th>
<th>n</th>
<th>CKMB activity</th>
<th>CK activity</th>
<th>CKMB mass</th>
<th>MB2/MB1 ratio</th>
<th>MM2/MM1 ratio</th>
<th>Myoglobin</th>
<th>cTnI</th>
<th>cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(0.0-0.5)</td>
<td>(0.0-0.3)</td>
<td>(0.08-0.76)</td>
<td>(0.08-0.76)</td>
<td>(0.03-0.65)</td>
<td>(0.08-0.76)</td>
<td>(0.03-0.65)</td>
<td>(0.08-0.76)</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>0.13</td>
<td>0.13</td>
<td>0.38</td>
<td>0.38</td>
<td>0.25</td>
<td>0.38</td>
<td>0.25</td>
<td>0.38</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>0.13</td>
<td>0.40</td>
<td>0.67</td>
<td>0.73</td>
<td>0.67</td>
<td>0.73</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>0.37</td>
<td>0.48</td>
<td>0.78</td>
<td>0.78</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.74</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>0.43</td>
<td>0.51</td>
<td>0.95</td>
<td>0.81</td>
<td>0.73</td>
<td>0.89</td>
<td>0.84</td>
<td>0.81</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>0.54</td>
<td>0.70</td>
<td>1.0</td>
<td>0.89</td>
<td>0.84</td>
<td>0.97</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>0.68</td>
<td>0.84</td>
<td>1.0</td>
<td>0.95</td>
<td>0.89</td>
<td>1.0</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>0.86</td>
<td>0.89</td>
<td>1.0</td>
<td>0.97</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.97</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>0.89</td>
<td>0.92</td>
<td>1.0</td>
<td>0.97</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>0.95</td>
<td>0.95</td>
<td>1.0</td>
<td>0.97</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Table 4. Times to first increase of marker concentrations to above the URL after AMI.

<table>
<thead>
<tr>
<th>Marker</th>
<th>All AMI</th>
<th>Non-Q-wave AMI</th>
<th>With early reperfusion</th>
<th>Without early reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKMB activity</td>
<td>5.0* (4.0-6.5)</td>
<td>4.5 (4.0-6.7)</td>
<td>4.0 (4.0-6.1)</td>
<td>6.0 (5.0-7.0)</td>
</tr>
<tr>
<td>CK activity</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>CKMB mass</td>
<td>3.0 (3.0-6.0)</td>
<td>2.5 (3.0-5.0)</td>
<td>2.5 (3.0-5.1)</td>
<td>4.0 (4.0-6.0)</td>
</tr>
<tr>
<td>MB2/MB1 ratio</td>
<td>3.0 (2.0-3.5)</td>
<td>2.5 (2.0-3.0)</td>
<td>2.1 (3.0-3.2)</td>
<td>3.25 (3.25-4.0)</td>
</tr>
<tr>
<td>MM2/MM1 ratio</td>
<td>3.0 (2.0-4.0)</td>
<td>2.75 (2.0-4.5)</td>
<td>2.0 (2.0-4.0)</td>
<td>3.75 (3.75-5.25)</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>3.0</td>
<td>2.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Cardiac troponin I</td>
<td>3.0 (2.0-3.5)</td>
<td>2.75 (2.0-3.0)</td>
<td>3.0 (2.0-3.5)</td>
<td>3.0 (2.0-3.5)</td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

* Data are hours from onset of chest pain as median (25th and 75th percentiles).
significant (P ≤ 0.046) and markedly lower than those of the other investigated markers; no significant differences were seen among CKMB isoform ratios, CKMB mass, myoglobin, and the troponins.

Subgroup analysis in patients with Q-wave AMI (divided into patients with and without early reperfusion) and non-Q-wave AMI revealed similar results (Table 4). In early reperfused Q-wave AMI and non-Q-wave AMI patients, first increased values of all markers were observed earlier than in Q-wave AMI patients without early reperfusion of the infarct-related coronary artery. The differences did not yield statistical significance because of the relatively small group of AMI patients without early reperfusion (n = 6). Times to first increases in non-Q-wave AMI and Q-wave AMI with early reperfusion were almost identical. Within each subgroup CK and CKMB activity increased later than the other markers. The differences between myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT were small (Table 4).

Every tested marker was increased above URL in all investigated AMI patients. Marker concentration time courses of early reperfused Q-wave AMI patients (largest subgroup, n = 19) during the first 24 h after the onset of chest pain are shown in Fig. 1. In every patient of this subgroup all markers showed a pattern with a rise and fall except for four patients with only a falling pattern of CKMB isoform ratio. Myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT increased parallel to each other (see Fig. 1 and Table 4). Peak values of markers were found at 9.25 (median; interquartile range 8–12) h after onset of chest pain for CKMB activity, 9.5 (7.4–10.1) h for CK activity, 6 (5–7.75) h for CKMM isoform ratio, 4 (3–7) h for CKMB isoform ratio, 12 (9.25–12) h for cTnT, 8 (6.1–10) h for cTnI, 4 (3.5–6) h for myoglobin, and 8.5 (7–10) h for CKMB mass (Fig. 1). Almost all individual marker time courses of these 19 patients had only one peak during the first 24 h after the onset of chest pain (time period shown in Fig. 1). Two peak values were found in two patients for the CK isoform ratios and in one patient for CK, CKMB activity, and CKMB mass. In contrast to the other markers, myoglobin (median time to peak 24, interquartile range 16.5–36 h) and the CK isoform ratios (MB ratio: median 16.9, interquartile range 12–24 h; MM ratio: median 20, interquartile range 16.1–24 h) frequently returned to normal within 24 h after the onset of infarction (see Fig. 1).

Discussion

In contrast to previous studies on early sensitivities of biochemical markers for AMI, we tested in this study the same cohort of AMI patients for myoglobin, CK isoforms, CKMB mass and activity, CK activity, cTnI, and cTnT. These markers are already or will be soon commercially available. Testing the same patients is a prerequisite to address the question of which marker to use for the early diagnosis of AMI and to compare early sensitivities of different markers, because it reduces the effects of possible biases distorting results (i.e., delay between attack and treatment, different therapies, size and site of infarction, blood flow in the infarct-related coronary artery). The heterogeneity of patients concerning reperfusion status of the infarct-related coronary artery does not upset our results, because all biochemical markers tested are affected in a similar manner (17, 29, 30). This is highlighted by the fact that we obtained equal results in blood samples withdrawn before and after thrombolytic treatment. In both circumstances CK and CKMB activity were markedly less sensitive than myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT, and there were no significant differences among the latter five. The comparison of sensitivities within 4 h after the onset of chest pain in samples drawn before thrombolytic treatment and samples collected after the start of thrombolysis revealed that the sensitivities of all markers were markedly higher in the latter group, which is in accordance with previous reports (17, 29, 30). The chronological order of increases in markers was the same regardless of whether reperfusion had occurred or not. However, first increases in all markers were observed later in patients without early recanalization. Therefore, the very high sensitivities of markers > 4 h after the onset of chest pain, shown in Table 3, are related to the high proportion of early reperfused AMI patients. Sensitivities of 100% are
expected to be achieved later in patients without thrombolytic therapy. In general, our results are in accordance with previous studies on early sensitivities of different biochemical markers, and the sensitivities of markers that we report in this study are in the range of previously published values. We confirm that myoglobin, CKMB mass, and CK isoform ratios are more sensitive during the first hours after onset of AMI than are CK and CKMB activity (4, 6–8, 19, 27, 28). Similar to earlier reports, the early sensitivities of myoglobin, CKMB mass, and cTnI were in the same range (9, 21, 31), and the early sensitivities of CKMB mass and CK isoform ratios were equivalent (28). We could also confirm the recently published observation of Adams et al. of a parallel increase in CKMB mass and cTnI after AMI (32). CK isoform ratio sensitivities of our investigation may be compared with previous reports (8, 27, 28), because in all these studies the same technology (REP system) was applied. However, since we carried out this study, Helena Labs. upgraded their system (Cardio-REP), which is claimed to improve analytical sensitivity for CK isoforms.

On the basis of extended and frequent blood sampling, we found that the sensitivities of all tested biochemical markers were poor (<50–60%) during the first 3 h after the onset of chest pain. This corroborates our earlier observation that CK, CKMB (activity and mass), myoglobin, and cTnT could not provide additional information to the ECG during this time interval, whereas thereafter CKMB mass was superior to the ECG and all other tested markers for the diagnosis of AMI (33). Myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT did not achieve 100% sensitivity for myocardial infarction before 6–10 h after the onset of chest pain. Consequently, a negative test result during this time period is of limited value for clinical decision making. The sufficiently high early sensitivities of new markers, however, allow the recommendation of the determination of CKMB mass, CK isoform ratios, myoglobin, cTnI, and cTnT from 3–4 h after the onset of AMI onwards; within the first 3–4 h after the onset of chest pain the sensitivities of all tested markers are too low to justify their measurement. The therapeutic and prognostic consequences of early diagnosis of AMI in patients with nondiagnostic-presenting ECG are not yet clearly delineated (34), because the inclusion criteria of major intervention trials were mainly based on clinical history and electrocardiographic findings. Therefore, at present the decision for or against fibrinolysis is usually made clinically and electrocardiographically and will only in rare instances rely upon the demonstration of increased myocardial markers. There are currently no biochemical guidelines for commencing thrombolytic therapy, and our reported sensitivities of markers before thrombolytic therapy during the 0–4 h period after the onset of chest pain are too low to make it very likely that myoglobin, CKMB mass, CK isoform ratios, cTnI, or cTnT will play a major role for the decision to administer thrombolytic therapy in the future as well. Serum markers are, however, important to confirm a suspected myocardial infarction, may decide the diagnosis in difficult cases, and may be useful for more rapid and accurate triaging of chest-pain patients, a procedure for which demand is increasing (35).

We found that early sensitivities of myoglobin, CKMB mass, CK isoform ratios, cTnI, and cTnT are roughly equivalent. The differences were small and are not deemed to be clinically relevant. Therefore, the debate on the choice of markers will focus on their specificities. In this respect, the clinical specificities of myoglobin and CKMB on admission to the emergency department are comparable in nontraumatic chest-pain patients (7, 36), which we also expect for CKMM isoform ratio and CKMB in this preselected population. On the other hand, in a patient with concomitant skeletal muscle damage, even CKMB determination may not be very helpful, and cTnI or cTnT are required (5, 9); in patients with renal diseases and suspected myocardial injury, only cTnI measurement will allow definitive diagnosis (12, 13). In addition, differences in cross-reactivities of troponin assays with their skeletal muscle isoforms, which affect clinical specificity of test results, have to be considered in patients with concomitant skeletal muscle injury.

In summary, we could demonstrate by frequent blood sampling that it is often possible to diagnose an AMI on the basis of positive test results of new biochemical markers even at a time when CK and CKMB activities are still within the reference interval. Therefore, myoglobin, CKMB mass, CK isoform ratios, cTnI, or cTnT should replace CK and CKMB activity measurements for ruling in AMI during the early period after its onset. The differences in early sensitivities of new markers were small and are hardly of clinical relevance. Consequently, apart from early sensitivity, the choice among myoglobin, CKMB mass, CK isoforms, cTnI, and cTnT should be mainly based on turnaround time and practicality for emergency determination of methods, specificity of markers, required clinical specificity in the individual patient, laboratory equipment, and finally costs of determination.

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References