Diagnostic Efficiency of Troponin T Measurements in Acute Myocardial Infarction

Hugo A. Katus, MD; Andrew Remppis, MD; Franz J. Neumann; Thomas Scheffold, MD; Klaus W. Diederich, MD; Gabi Vinar, MD; Andreas Noe, MD; Gabi Matern, MD; and Wolfgang Kuebler, MD

Background. The present study was designed to evaluate the efficiency of a newly developed troponin T enzyme immunoassay for the detection of acute myocardial infarction.

Methods and Results. The study comprised 388 patients admitted with chest pain and suspected myocardial infarction and 101 patients with skeletal muscle damage and additional suspected myocardial cell damage. Troponin T was elevated to more than twice the analytical sensitivity of the assay (0.5 μg/l) in all patients with non-Q wave (range, 1.2–5 μg/l) and Q wave infarction (range, 3–220 μg/l). Troponin T appeared in serum as early as 3 hours after onset of pain in 50% of the patients and remained elevated in all patients for more than 130 hours, revealing release kinetics of both free cytosolic and structurally bound molecules. The diagnostic efficiency of troponin T was superior to that of creatine kinase-MB (98% versus 97%) and remained at 98% until 5.5 days after admission, if patients with unstable angina were excluded from analysis. In the 79 patients with unstable angina, troponin T was elevated (range, 0.55–3.1 μg/l) in at least one blood sample from each of 37 patients (56%). Circulating troponin T was correlated to the presence of reversible ST segment or T wave changes on the electrocardiogram (p<0.005) and to the frequency of in-hospital complications. In the 101 patients with skeletal muscle damage and suspected additional cardiac muscle damage, troponin T was the most useful test; its efficiency was 89% or 94% (depending on the discriminator value used) as compared with 63% for creatine kinase-MB.

Conclusions. Thus, the data of the study indicate that the newly developed troponin T test improves the efficiency of serodiagnostic tests for the detection of myocardial cell necrosis as compared with conventionally used cardiac enzymes. (Circulation 1991;83:902–912)

Among the many available serological tests for detecting acute myocardial infarction (AMI), the determinations of the MB isoenzyme of creatine kinase (CK, EC 2.7.3.2.) provide the highest diagnostic efficiency.1–5 Therefore, CK-MB determinations are generally regarded as the reference standard for diagnostic tests for AMI. Yet, variable normal serum levels of CK-MB,6 its presence in noncardiac muscular tissues,7–9 and its brief elevation in serum during the course of myocardial infarction10–12 limit the diagnostic value of CK-MB determinations. In practice, physicians are sometimes left with patients in whom a definitive diagnosis of myocardial infarction cannot be made by CK-MB measurements, and an alternative test of even greater sensitivity and specificity is needed.

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The contractile and regulative proteins of different muscle types exist as isoforms because of multiple gene expression and possible translational modifications.13–15 Troponin T belongs to the proteins of the contractile apparatus that are unique in their primary structure for cardiac muscle. Our investigative group developed an enzyme immunoassay for the cardiac troponin T isoform, which showed a cross-reactivity with troponin T extracted from mixed skeletal muscle of only 1–2%.16 With this assay, troponin T was found in serum samples of patients with AMI from 3.5 hours to more than 10 days after onset of pain.16 From these data, a higher sensitivity and specificity of troponin T compared with CK-MB measurements...
can be anticipated. Therefore, the diagnostic efficiency of troponin T measurements was analyzed in patients admitted to a general hospital with suspected AMI and in patients with skeletal and, possibly, additional cardiac muscle damage.

Methods

Troponin T Assay

A more detailed description of the assay development and of methods used for purification of troponin T, antibody selection, and purification has been published. Cardiac troponin T is measured by a newly developed immunometric one-step sandwich assay. In this assay, an affinity-purified, cardiospecific anti-troponin T fraction of polyclonal antibody is immobilized on polyvinylchloride test tubes. Troponin T standards or serum samples and peroxidase-labeled monoclonal anti-troponin T antibody is added to these antibody-coated test tubes. During the incubation period, the troponin T molecule is bound on different epitopes by both the solid-phase polyclonal antibody fraction and by the liquid-phase monoclonal antibody–enzyme complex. After the unbound peroxidase-labeled monoclonal antibodies were removed by washing, the antibody–enzyme complex adhering to the assay tubes corresponds to the amount of troponin T recognized by the polyclonal and monoclonal anti-troponin T antibodies. The amount of enzyme immobilized, as a direct measure of bound troponin T, is quantified in the spectrophotometer as peroxidase substrate conversion at a wavelength of 405 nm.

Protocol of Troponin T Assay

The assay is manufactured as a test kit consisting of seven components: antibody-coated test tubes, monoclonal antibody–enzyme complex, incubation buffer, troponin T standard, control sera, substrate buffer, and the diammonium salt of 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS). For troponin T measurements, the antibody–enzyme complex, troponin T standards, and ABTS substrate are dissolved in the buffer solution provided in the test kit and thoroughly mixed by vortex. Troponin T standard or unknown patient serum (200 μl) is manually added to the test tubes while 1 ml antibody–enzyme complex (45 IU) and all the remaining solutions are added by a batch enzyme-linked immunosorbent assay analyzer (Enzymun-tests system ES 22, Boehringer Mannheim, Mannheim, FRG). Solid-phase antibody, troponin T–containing solutions, and antibody–enzyme complex are incubated at room temperature for 60 minutes. Thereafter, the tubes are emptied by suction and are washed twice with tap water. To each test tube, 1 ml substrate solution is then added, and the substrate conversion is measured as color formation after 30 minutes of incubation at room temperature. All measurements were performed in duplicate.

Specification of the Troponin T Assay

The measuring range of this assay extends from 0.5 to 25 μg/l with an interassay and intraday coefficient variation at 5 μg/l of 0.04% and 0.05%, respectively. There is a 1–2% cross-reactivity of the assay with troponin T extracted from human or bovine mixed skeletal muscle (quadriceps muscle), although the affinity-purified antibodies used are not cross-reactive in immunoblot analysis. This nonimmunologic cross-reactivity results from unspecific absorption of purified skeletal troponin T to the test tubes. Measurements performed in 5% bovine serum albumin, in human sera from 126 healthy subjects, and in a serum pool of blood donors indicate a substrate conversion corresponding to 0.17 μg/l, which is probably due to unspecific binding of the labeled antibody. The discriminating value between undetectable and elevated troponin T values was defined at 0.5 μg/l, which is 2.9 SD greater than mean unspecific color change of substrate solution (analytical sensitivity of the troponin T test).

Cardiac Enzyme Measurements

Total CK and lactate dehydrogenase (LDH, EC 1.1.1.27) activities were determined in a Chem 1 analyser (Technicon, Tarrytown, N.Y.) at 25°C. In these assays, the reagents and protocols of the manufacturers were used. The upper limit of normal for total CK activity was 75 IU/l and for LDH was 220 IU/l at 25°C. The CK-MB isoenzyme activity was measured with an immunoinhibition assay (CKMB-NAC aktiviert, Boehringer Mannheim). In this assay, activity of the CK-M subunit is inhibited by a goat anti-human CK-M antibody. The residual non-adenylate kinase activity in the serum samples then corresponds to CK-B activity. The CK-MB activity was expressed either as international units per liter or as percentage of total CK activity, with an upper limit of normal of 10 IU/l or 6%, respectively. If total CK activity exceeded 1,000 IU/l, the serum samples were diluted before CK-MB determinations.

Patient Evaluation

After admission, the patients were interviewed twice each day concerning their episodes of chest pain. A physical examination was routinely performed once each day. If there was an episode of chest pain, the patient was seen by the physician in charge and a 12-lead electrocardiogram was then recorded. A 12-lead electrocardiogram was routinely obtained twice on the first day and then once daily on the second, third, and seventh days and before hospital discharge. From the patients admitted to the coronary care unit with the clinical diagnosis of AMI or unstable angina, blood samples (5 ml) were obtained every 6 hours during the first day, every 8 hours on the second day, and then once daily until the seventh day. In patients with proven AMI, blood samples were then obtained every second day until the 20th hospital day. Blood samples were obtained
from patients admitted to general wards for exclusion of AMI on admission, 4 hours after admission, and 12–24 hours after admission. In patients with skeletal muscle damage, one blood sample was obtained on the subsequent 2 days after skeletal muscle damage had occurred.

Blood samples were obtained by indwelling catheters routinely placed in critically sick patients or by venipuncture. The blood samples were stored at room temperature for 30 minutes to allow clotting. After centrifugation at 5,000g for 10 minutes, the serum samples were stored frozen at −20°C as aliquots until troponin T measurements were performed. Neither storage at room temperature for less than 4 hours nor at −20°C for 3 months resulted in any loss in immunoreactivity of the serum samples.

**Diagnostic Criteria**

The following criteria were used for diagnosing Q wave AMI: 1) development of new Q waves (0.04 msec duration), R wave reduction (>25%), and ST segment changes suggestive of transmural ischemia in at least two leads of the standard 12-lead electrocardiogram; 2) time-dependent changes of total CK and LDH serum activities typical for AMI; 3) CK-MB activities exceeding 6% of total CK activities with typical time-dependent changes.

The following criteria were used for diagnosing non–Q wave AMI: anginal pain, elevated levels of cardiac enzymes showing typical time-dependent serum activity changes, and ST segment or T wave changes, or both, in at least two leads of the standard 12-lead electrocardiogram, persisting for at least 24 hours. The following criteria were used for diagnosing unstable angina: remittent anginal pain, each episode lasting 60 minutes or less, a 12-lead electrocardiogram that was unaltered or that revealed reversible ST or T wave changes, or both, and serum enzyme activities that did not exceed twice the upper limit of normal.

Myocardial infarction was excluded if the reported pain was not typical for angina and the 12-lead electrocardiogram remained unaltered. In this group of patients, cardiac enzymes did not reveal the pattern and time-dependent activity changes in serum typical of myocardial cell necrosis.

**Patients**

All patients gave written, informed consent to participate in the study after thorough explanation of the protocol. The study protocol was approved by the Ethics Committee of the University of Heidelberg. Patients were excluded from the present study who were admitted to the hospital later than 12 hours after the onset of pain or who had valvular heart disease, cardiomyopathy, or left bundle branch block.

The diagnostic value of troponin T measurements was analyzed in two groups of patients (Table 1). The first group consisted of 387 consecutive patients admitted to the hospital with suspected AMI. In 131 of these 387 patients, no evidence was found for myocardial cell necrosis on the 12-lead electrocardiogram or by sequential analysis of serum enzymes, and the complaints of the patients were not characteristic of anginal pain. In these 131 patients, the most frequent clinical diagnoses were: bone or joint disease in 49, gastrointestinal disease in 26, cancer in 15, and ethanol intoxication in nine.

Seventy-nine patients complained of unstable angina with the clinical classes being IIIA in two, IIIB in 23, IIIC in two, IIB in five, and IB in 23. In these patients, coronary angiography was performed on day 6±2.7 and revealed a significant obstruction (≥75% narrowing in vessel diameter) of a major coronary artery in 66 patients (84%). In two patients with symptoms of “unstable angina” but with normal coronary arteries, the clinical diagnosis was perimyocarditis. Acute interventions (bypass surgery or percutaneous transluminal coronary angioplasty) were performed in 29 patients during the initial hospital stay, whereas 25 patients were operated on electively. Six of the patients with unstable angina developed AMI during their hospital stay, of whom one died.

In 21 of the 56 patients with non–Q wave AMI and in 63 of the 121 patients with Q wave AMI who were admitted to the hospital earlier than 5 hours after onset of pain and who agreed to the planned therapeutic and diagnostic procedures, recanalization of an occluded coronary artery was attempted. Recan-

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**Table 1. Diagnostic Value of Troponin T Measurements in Two Groups of Patients**

<table>
<thead>
<tr>
<th>Study group</th>
<th>n</th>
<th>M</th>
<th>F</th>
<th>Age (yr)</th>
<th>CK (IU/l)</th>
<th>TnT (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected AMI in a general hospital population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI excluded</td>
<td>131</td>
<td>86</td>
<td>45</td>
<td>40±15</td>
<td>40</td>
<td>0.16</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>79</td>
<td>66</td>
<td>13</td>
<td>56±9</td>
<td>34</td>
<td>0.59</td>
</tr>
<tr>
<td>Non–Q wave AMI</td>
<td>56</td>
<td>43</td>
<td>13</td>
<td>59±10</td>
<td>310</td>
<td>5.50</td>
</tr>
<tr>
<td>Q wave AMI</td>
<td>121</td>
<td>103</td>
<td>18</td>
<td>62±13</td>
<td>950</td>
<td>15.50</td>
</tr>
<tr>
<td>Suspected CM damage in patients with SM damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM damage</td>
<td>73</td>
<td>49</td>
<td>24</td>
<td>43±19</td>
<td>400</td>
<td>0.18</td>
</tr>
<tr>
<td>SM+CM damage</td>
<td>28</td>
<td>23</td>
<td>5</td>
<td>55±14</td>
<td>2,400</td>
<td>11.50</td>
</tr>
</tbody>
</table>

CK, median peak value of total serum creatine kinase activity; TnT, median value of total serum troponin T concentration on day 4; AMI, acute myocardial infarction; CM, cardiac muscle; SM, skeletal muscle.
alization was achieved by thrombolysis or percutaneous transluminal coronary angioplasty in 17 and 52 patients, respectively.

The second study group consisted of 101 patients with skeletal muscle damage in whom additional cardiac muscle damage was suspected. In 73 of these patients, electrocardiograms were normal. Skeletal muscle damage was most frequently due to blunt trauma in 19 patients, abdominal or orthopedic surgery in 15, seizures in 13, ethanol intoxication in 12, arterial gangrene in four, septic shock in three, and heavy physical exercise in three patients. In the remaining 28 patients of this group, there was clear evidence of both skeletal and additional cardiac muscle damage. This was due to AMI with repetitive ventricular fibrillation and resuscitation in 18 patients; cardiogenic shock in four; myocarditis, repetitive ventricular tachycardias, and direct current shocks in three; septic shock with pathologically documented subendocardial infarction in two; and systemic lupus erythematoses in one.

Data Analysis

The history of the patients, 12-lead electrocardiograms, and coronary angiograms were evaluated by experienced cardiologists (F.J.N. and K.W.D.), who were unaware of the serological test results. The results are expressed in terms of sensitivity (number of true positive test results in all patients with AMI), specificity (number of true negative test results in all persons without AMI), positive predictive value (number of true positive test results of all positive test results observed), negative predictive value (number of true negative test results of all negative test results observed), and efficiency (number of true positive and negative test results of all positive and negative test results observed). Fisher's exact test (two tailed) was used to analyze the validity of troponin T measurements in the patients with unstable angina.

Results

Diagnostic Efficiency of Troponin T Measurements in a General Hospital Population

Figure 1 shows the distribution of the peak troponin T levels during the first day after hospital admission in 387 patients with chest pain and suspected AMI. Troponin T levels are expressed as a relative troponin T increase, which is defined as the ratio of the patient's troponin T blood level to the analytical sensitivity of the troponin T test (0.5 μg/l). With the analytical sensitivity of the troponin T test as a discriminator between normal and elevated values, troponin T was found in 48 of the 210 patients in whom AMI was excluded (11 patients with atypical chest pain and 37 patients with unstable angina; specificity, 78%; Table 2 and Figure 1) and in all patients with AMI (sensitivity, 100%), which resulted in a diagnostic efficiency of 88%. Because of the persistent elevation of troponin T serum concentrations, sensitivity of troponin T measurements for detection of AMI remained at 100% until the sixth hospital day. At that time, release of troponin T was still detectable in 15 of the 37 patients (41%) with symptoms of unstable angina and elevated troponin T levels on day 1. Four of these 15 patients with persistently elevated troponin T levels and unstable angina had progressed to AMI as indicated by the electrocardiogram and cardiac enzyme measurements. Specificity and efficiency of the troponin T test on the first day after hospital admission improved to 93% and 95%, respectively, with only
minimal loss in sensitivity (Table 2) when 1 μg/l troponin T was used as discriminator value. Four patients in the control group did not have unstable angina but had serum troponin T levels exceeding 1 μg/l. The clinical diagnoses were cirrhosis of the liver in two and rheumatoid arthritis in two, with significantly elevated serum immunoglobulin levels in all four patients.

Total serum CK activity was frequently elevated in the patients complaining of chest pain (38 false-positive test results in the 131 patients) and less frequently in patients with unstable angina (14 of 79 patients), which reduced specificity to 75% (Table 2). Measurement of CK-MB improved specificity to 92% (six false-positive results in the patients with atypical chest pain and 11 positive results in patients with unstable angina). In two patients in whom recanalization of the occluded coronary artery was achieved within 1 hour, CK and CK-MB serum activity changes did not exceed the upper limit of normal, whereas peak troponin T levels reached 1.0 and 1.2 μg/l, and the electrocardiogram revealed transmural myocardial ischemia (sensitivity of CK and CK-MB, 99% and 98%, respectively).

When the patients with unstable angina, some of whom may have had microinfarcts not detected by the electrocardiogram or by cardiac enzyme measurements, are excluded from evaluation of the troponin T test (Table 3), specificity of the troponin T was 95% or 97%, respectively, depending on the discriminator value of 0.5 or 1 μg/l troponin T, and sensitivity was 100% or 99%, respectively. In this group, the diagnostic efficiency of troponin T measurements was 98% or 99%, respectively, whereas the efficiency of CK and CK-MB was 87% and 97%, respectively.

**Time-Dependent Diagnostic Sensitivity of Troponin T Measurements**

Figure 2 shows the median and interquartile range of troponin T and cardiac enzymes in 121 patients with Q wave AMI. The test results are expressed as ratios of the patients' serum activities to the upper limit of normal in the case of CK and LDH or to the analytical sensitivity of the assay (0.5 μg/l) in the case of troponin T. Troponin T appears in circulation slightly earlier than CK activity, and it increases to a first peak value of 40 times the detection limit during the first day. By contrast to CK levels, troponin T levels remain elevated until 12 days or more after onset of pain, revealing a second peak value of 30 times the detection limit on about the fourth day. Serum CK and LDH activity only increase to nine and three times the upper limit of normal, respectively. The prolonged serum elevation of troponin T results in a diagnostic window of 10.5–140 hours after onset of pain, during which troponin T was detectable in all serum samples of all patients (Table 4). This time interval of absolute diagnostic sensitivity of troponin T measurements is six times that of CK and nearly twice that of LDH.

The changes of troponin T serum concentrations in patients with non–Q wave AMI reveal kinetics similar to those in patients with Q wave AMI (Figure 3). Again, a persistent increase of troponin T serum concentrations is found, with a poorly defined peak value on about the fourth day after onset of pain. The time interval of absolute diagnostic sensitivity of troponin T measurements was 10–131 hours after onset of pain (Table 4). Serum LDH levels were not elevated in all patients with Q wave AMI; thus, for this enzyme, absolute diagnostic sensitivity is not attained.

Figure 4 shows the changes in serum concentrations in the 37 of the 66 patients with unstable angina, coronary artery disease, and elevated levels of troponin T. Because in this group there were several episodes of anginal pain of different intensity at various times before and after admission, the changes in serum concentrations are related to the time of admission. In these patients with unstable angina and elevated levels of troponin T, a median increase of troponin T to twice the analytical sensitivity of the test is found on days 1 and 2. Median
troponin T levels remain elevated until the sixth hospital day, whereas median serum CK and LDH activities are not elevated.

Validity of Troponin T Measurements in Patients With Unstable Angina

Troponin T levels were elevated from 0.55 to 3.1 μg/l in at least one blood sample in 37 of the 66 patients with unstable angina and with 75% or more obstruction of a major coronary artery and in two of the 13 patients with symptoms of unstable angina but with 75% or less obstruction of a major coronary artery. These latter two patients suffered from acute perimyocarditis. Thus, elevated levels of troponin T were found only in patients with cardiac disease, for example, severe coronary artery narrowing or perimyocarditis (specificity, 100%). Yet in 31 of the 66 patients with symptoms of unstable angina and severe coronary artery disease, circulating troponin T was not found. Thus, in patients with less-severe ischemia, troponin T measurements may not be an effective diagnostic tool. As a consequence, the troponin T test cannot be used to screen for the presence of severe coronary artery disease (predictive value of a negative test, 0.26 and 0.2) (Table 5). On the other hand, when elevated levels of troponin T are found, the test indicates severe coronary artery narrowing with high specificity (85% and 95%) (Table 5).

Release of troponin T was more frequent in patients with signs of myocardial ischemia on the 12-lead electrocardiogram (Figure 5 and Table 5). In 27 of the 49 patients (55%) with reversible ST segment changes or T wave inversion, or both, circulating troponin T was found, whereas troponin T was detectable in only 10 of 30 patients (33%) with normal electrocardiograms. The correlation between troponin T release and signs of ischemia on the electrocardiogram was improved when only ST segment depression was used as an indicator of ischemia ($p<0.005$).

In five of six patients with unstable angina who developed AMI during their hospital stay, elevated levels of troponin T were found at least 12 hours before the diagnosis of AMI could be established by

**Table 4. Time Interval of Absolute Diagnostic Sensitivity in Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>AMI</th>
<th>Q wave AMI</th>
<th>Non-Q wave AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interval (hr)</td>
<td>Duration (hr)</td>
</tr>
<tr>
<td>CK</td>
<td>9.0–31</td>
<td>22</td>
</tr>
<tr>
<td>LDH</td>
<td>20.0–90</td>
<td>70</td>
</tr>
<tr>
<td>TnT 0.5</td>
<td>10.5–140</td>
<td>129</td>
</tr>
<tr>
<td>TnT 1.0</td>
<td>12.5–130</td>
<td>117</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; Interval, beginning and ending of marker protein elevations in all serum samples of all patients related to the time after onset of pain; Duration, duration of marker protein elevation; CK, total serum CK activity >75 IU/l; LDH, total serum lactate dehydrogenase activity >220 IU/l; –, 100% diagnostic sensitivity is not reached because LDH activities are <220 IU/l in four patients; TnT 0.5, troponin T concentrations ≥0.5 μg/l; TnT 1.0, troponin T concentrations ≥1 μg/l.
electrocardiography or serum enzyme analysis. Thus, complications mostly occurred in the patients with increased levels of troponin T (sensitivity, 83%; Table 5) and were rare in patients without elevated levels of troponin T (predictive value of a negative test, 0.98).

**Diagnostic Efficiency of Troponin T Measurements in Patients With Skeletal Muscle Damage**

In 73 of the 101 patients (72%) with skeletal muscle damage, electrocardiograms were normal. In this group, the CK and CK-MB serum activities were 110--49,400 and 4--740 IU/l, respectively (Figure 6). CK-MB activity was higher than 10 IU/l in 37 of the 73 patients (51%), whereas the CK-MB/CK ratio was greater than 6% in 11 (15%). Cardiac troponin T was found in 11 patients (15%) and was greater than 1 µg/l in six (8%).

In 28 patients with skeletal and cardiac muscle damage, the serum CK activity was 380--14,000 IU/l. In this group, serum CK-MB activity was elevated in all patients (range, 10--440 IU/l). The ratio of CK-MB/CK activity was less than 6% in 23 of 28 patients despite clear evidence of myocardial cell necrosis in all patients. Troponin T serum concentrations were elevated in all patients to at least twice the detection limit of the assay.

As shown in Table 6, CK-MB measurements in these patients allow the detection of myocardial cell necrosis with high sensitivity (100%) but with a low specificity (49%). The specificity of CK-MB measurements can be improved greatly by relating the CK-MB activity to total CK. Yet, relating CK-MB to total CK activity is of little clinical value because of its low sensitivity. Troponin T measurements were the most useful test to assess presence or absence of cardiac injury in these patients (sensitivity, 100%; specificity, 84%; efficiency, 89%). The diagnostic efficiency of troponin T measurements could be improved to 94% when 1 µg/l troponin T is accepted as discriminator value.

**Discussion**

In patients with chest pain and signs of AMI on the electrocardiogram, measurements of cardiac enzymes, if timed properly, are highly accurate, but the test results are only complementary to the diagnosis already made. If, however, small AMIs have to be excluded from the diagnosis in patients with equivocal or normal electrocardiograms, more precise tests are then needed because of the low prevalence of disease and only minor elevations of myocardial cell constituents in serum. Measurements of CK-MB isoenzyme concentrations with immunologic techniques improved the sensitivity of serological testing in patients with suspected AMI but the variable normal serum levels of CK-MB and the brief elevation of CK-MB in serum after onset of necrosis limit the diagnostic value of this marker protein. In trauma victims or in patients with multiple organ damage, a third group of patients in whom serological testing for AMI is ordered, the distribution of CK-MB in skeletal...
Efficiency

Patients With dehydrogenase (LDH) activity comparable was

TABLE 5. Validity of Troponin T Measurements in Unstable Angina

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PV positive test</th>
<th>PV negative test</th>
<th>Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TnT 0.5</td>
<td>TnT 1</td>
<td>TnT 0.5</td>
<td>TnT 1</td>
</tr>
<tr>
<td>Significant CAD</td>
<td>0.35</td>
<td>0.26</td>
<td>0.85</td>
<td>0.92</td>
</tr>
<tr>
<td>Ischemia on ECG</td>
<td>0.76</td>
<td>0.48</td>
<td>0.64</td>
<td>0.86</td>
</tr>
<tr>
<td>Complications</td>
<td>0.83</td>
<td>0.83</td>
<td>0.56</td>
<td>0.82</td>
</tr>
</tbody>
</table>

PV, predictive value; TnT 0.5, serum troponin T >0.5 μg/l; TnT 1, serum troponin T >1 μg/l; significant CAD, ≥75% obstruction of a coronary artery; ischemia on ECG, reversible ST segment alteration or T wave inversion, or both, on the electrocardiogram; Complications, acute myocardial infarction or death.

FIGURE 4. Plot of median and 25th–75th percentile range of relative increase of serum creatine kinase (CK) and lactate dehydrogenase (LDH) activity and troponin T (TnT) concentrations in 37 patients with unstable angina, coronary artery disease, and elevated troponin T levels. Relative increase of marker protein in serum corresponds to the ratio of patients' serum activity to the upper limit of normal for CK and LDH and the ratio of patients' serum concentration to the analytical sensitivity of the test for troponin T.
In addition to the relative increase in serum concentration, the duration of marker protein elevation in serum critically affects sensitivity of a diagnostic test. Cardiac troponin T is largely compartmented in the contractile apparatus and has to be dissociated in a time-consuming process from the troponin complex of the thin filament before it can gain access to the serum. This leads to a long-lasting release despite the short serum half-life of troponin T of 120 minutes. Elevated troponin T levels were, therefore, found in all patients with Q wave and non-Q wave AMI during a time period of 124 hours, which is a period more than four times longer than that for total serum CK activity. The prolonged period of elevated serum levels of troponin T increases the likelihood of a troponin T test with a positive result, particularly in the late period of AMI when CK activity has already returned to normal.

As a consequence of the high sensitivity of the troponin T test, elevated troponin T levels were found in all patients with non-Q wave AMI and in many patients with angina at rest even though cardiac enzyme changes exceeded the upper limit of normal in only a few of these latter patients. According to the present data, it cannot be determined whether elevated troponin T in patients with unstable angina indicates "microinfarcts" not detected by the electrocardiogram or cardiac enzyme measurements or whether it only reveals reversible ischemic myocardial damage. Yet, within the spectrum from stable angina to AMI detected by conventional electrocardiographic and enzyme criteria, the results indicate that some patients with more severe ischemic damage can be identified by increased levels of cardiac troponin T and that these patients are at higher risk for complications during the hospital stay. As pointed out, troponin T release is caused by severe ischemic cell damage. Thus, a normal troponin test result in a patient with unstable angina does not preclude the presence of severe coronary artery disease and a poor prognosis for the patient.

**FIGURE 5.** Bar graph of circulating cardiac troponin T and signs of ischemia on the electrocardiogram in 79 patients with symptoms of unstable angina.

**FIGURE 6.** Plot of median and total range of peak values of total serum creatine kinase activity (CK), CK–MB isoenzyme activity (CKMB), CKMB/CK ratio and cardiac troponin T (TnT) concentration in patients with skeletal muscle damage but with normal electrocardiograms (SM) and in patients with skeletal and concomitant cardiac muscle damage (SM+CM). Normal range of the respective marker protein is indicated by hatched columns. ● Elevated levels of troponin T and of the respective CK and CKMB activities as well as CKMB/CK ratios of these patients with elevated levels of troponin T. ○, Results of marker protein measurements in patients without elevated levels of troponin T. △ and ◢, Serological test results in two patients with very high CK activities.

**Diagnostic Efficiency of Troponin T Measurements in Patients With Cardiac and Skeletal Muscle Damage**

Cardiac troponin T is a unique myocardial antigen that in the present assay was differentiated from its skeletal muscle isofoms by cardiospecific affinity, that is, purified polyclonal antisera. The remaining minor cross-reactivity of the assay with purified skeletal troponin T of 1–2% is due to unspecific absorption of the purified troponin T antigen to the wall of the test tubes. This unspecific binding may result from an increased "stickiness" of the troponin T molecule due to structural changes during protein purification.

Clinically, skeletal muscle damage can be differentiated from cardiac muscle damage with greater specificity by determinations of cardiospecific troponin T in serum than by measurements of CK-MB (84% versus 49%). Specificity of the troponin T test
TABLE 6. Diagnostic Efficiency in Patients With Skeletal and Suspected Cardiac Muscle Damage

<table>
<thead>
<tr>
<th>Suspected CM and SM</th>
<th>Without</th>
<th>With</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>CK-MB</td>
<td>TnT 0.5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.00</td>
<td>0.49</td>
</tr>
<tr>
<td>PV</td>
<td>-</td>
<td>0.28</td>
</tr>
<tr>
<td>positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Efficiency</td>
<td>0.28</td>
<td>0.63</td>
</tr>
</tbody>
</table>

n=101 for patients with suspected cardiac and skeletal muscle damage: n=73 without and n=28 with.

CM and SM cardiac and skeletal muscle damage; CK, total serum creatine kinase >75 IU/l; CK-MB, creatine kinase-MB isoenzyme activity >10 IU/l; TnT 0.5, peak serum troponin T level ≥0.5 μg/l; TnT 1, peak serum troponin T level ≥1 μg/l; PV positive, predictive value of a positive test result; PV negative, predictive value of a negative test result.

was further improved to 95% without loss in sensitivity when a discriminator of troponin T of 1 μg/l was used. The diagnostic efficiency of troponin T measurements was 94%. The high specificity of troponin T measurements is also evident in a patient (△, Figure 6) with major skeletal muscle damage and CK and CK-MB serum activities of 660 and 18 times the upper limit of normal. In this patient, troponin T levels were just above the analytical sensitivity of the assay. These data show that the cross-reactivity of 1–2% measured with purified skeletal troponin T may not be a relevant problem in clinical practice.

Minor increases in troponin T levels were found, however, in 15% of the patients who were classified as having skeletal muscle damage. In 8% of these patients, troponin T levels exceeded 1 μg/l. The difficulties in excluding additional cardiac muscle damage in these patients can be exemplified in a patient with the diagnosis of rhabdomyolysis after gastroenteritis in whom 5 μg/l troponin T was found (▲, Figure 6). The CK- and CK-MB activity measurements in this patient of 255 and 740 times, respectively, the upper limit of normal and the relatively high CK-MB/CK ratio of 3.9% indicates that, most probably, additional cardiac muscle damage not detected on the electrocardiogram was present in this patient. Thus, although false-positive results of the troponin T test may occur, the coexistence of major skeletal and minor cardiac muscle damage may be a more frequent cause of elevated levels of troponin T. The enhanced sensitivity of troponin T measurements, compared with the CK-MB/CK ratio, was particularly evident in this subgroup of patients with cardiac and skeletal muscle damage.

In summary, the determination of troponin T, compared with conventionally applied analysis of cardiac enzymes, offers several distinct advantages for the diagnosis of AMI: Troponin T is normally not detectable in serum; it is a cardiospecific antigen; and as a subcellularly compartmented protein, its release in serum lasts long after AMI. As shown, the characteristics of this marker protein lead to improved efficiency of serological testing of AMI. In particular, this results in improved detection of minor myocardial cell necrosis and myocardial damage in patients with skeletal muscle damage and results in a larger diagnostic window that allows serological detection of subacute myocardial infarction.

References


Key Words: acute myocardial infarction, enzyme immunoassay, troponin T, creatine kinase–MB, creatine kinase
Diagnostic efficiency of troponin T measurements in acute myocardial infarction.
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_Circulation_. 1991;83:902-912
doi: 10.1161/01.CIR.83.3.902

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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