Cardiac Troponin T in Diagnosis of Acute Myocardial Infarction

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Troponin T is a structurally bound protein found in striated muscle cells. We tested concentrations of its cardiac-specific isotype in peripheral venous blood samples serially drawn from 72 patients with confirmed myocardial infarction. Fifty-nine patients received thrombolytic treatment with intravenous streptokinase, urokinase, or recombinant tissue-type plasminogen activator; because of contraindications, the remaining 13 patients did not. Concentrations of troponin T in plasma, measured by an enzyme-linked immunosorbent assay, started increasing within a few hours after the onset of symptoms (median, 4 h; range, 1–10 h). The sensitivity of troponin T for detecting myocardial infarction was 100% from 10 to 120 h after the onset of symptoms; sensitivity on the seventh day after admission was 84%. Concentrations were increased for up to three weeks in some patients with late or high peak values. Successful reperfusion in Q-wave infarction obviously influences the release of troponin T into plasma, with all such cases showing peak values ≤26 h (median, 14 h) after the onset of symptoms. Troponin T concentrations in these patients returned to within the reference interval more rapidly than in nonreperfused subjects. In the 13 patients without fibrinolytic therapy, troponin T tended to peak ~48 h (median) after the onset of chest pain. Troponin T concentrations in patients for whom thrombolysis was unsuccessful resembled those in patients without fibrinolytic therapy. The specificity of the assay was 96% as tested in samples of 96 emergency-room patients. The reference interval (<0.5 μg/L) was established from samples of 100 healthy blood donors. Troponin T measurements are a specific and sensitive method for the early and late diagnosis of acute myocardial infarction and could, therefore, provide a new criterion in laboratory diagnosis of its occurrence.

Additional Keyphrases: myoglobin · creatine kinase · enzyme-linked immunosorbent assay · thrombolytic reperfusion

The diagnosis of acute myocardial infarction (AMI) has traditionally been based on the triad of a characteristic clinical history, electrocardiographic abnormalities, and increased serum concentrations of cardiac enzymes. However, because the differential diagnostic value of chest pain is limited (1) and the electrocardiographic changes have various degrees of sensitivity and specificity (2–4), measurements of serum enzymes as a reflection of damage to myocardial muscle cells still play an important role in the diagnosis of AMI. Measurements of creatine kinase (CK), aspartate aminotransferase, and lactate dehydrogenase (LDH) are well-established methods for this. Considerable efforts have been made in recent years to improve the specificity and sensitivity of methods for diagnosing AMI. Myoglobin is an early and sensitive marker of cardiac cell damage but lacks specificity (5). The use of LDH isoenzyme 1 improves specificity in diagnosing AMI; however, these isoenzymes are not restricted to cardiac muscle tissue, and increases in their serum concentrations have been observed in noncardiac conditions (6). Clinicians would therefore benefit from the introduction of a new cardiac-specific marker of damage to myocardial muscle cells. The contractile and regulatory proteins of the myocardium provide such a useful diagnostic tool. Troponin T (TnT) is part of the troponin complex in striated muscles, where it binds the troponin complex to tropomyosin. Although cardiac and skeletal muscles both contain TnT, the amino acid sequence of the protein in the two types of muscle differs (7, 8), making it possible to raise antisera against cardiac-specific TnT. Here, we demonstrate the high specificity and sensitivity of cardiac TnT in diagnosing and monitoring AMI.

Materials and Methods

Patients

Subjects were divided into the following groups:

Group 1 (blood donors). We used 100 healthy blood donors (41 men and 59 women), ages 19 to 65 years (median, 44 years), with no history of cardiovascular disease, as controls to obtain a reference interval. The reference limits were calculated by nonparametric determination of percentiles.

Group 2 (AMI). Seventy-two patients (56 men and 16 women), ages 28 to 83 years (median, 60 years), were admitted to the coronary care unit within 6 h after the onset of symptoms, i.e., after the onset of the typical infarct-related symptoms, in particular, chest pain, generally accepted to indicate the onset of myocardial infarction. All participants gave informed consent for extra blood samples to be drawn. The median time to treatment was 120 min (range, 15–360 min). Subsequently, all patients proved to have sustained an AMI (65 Q-wave and seven non-Q-wave myocardial infarce-
tions consisting of 32 anterior- and 40 inferior-wall infarctions). A cardiologist diagnosed the myocardial infarction without recourse to TnT results, using only the World Health Organization criteria (9) of the patient's clinical history and symptoms, electrocardiographic findings, and increased serum concentrations of cardiac enzymes. Peripheral venous blood samples were collected with an indwelling forearm catheter (Venflon®) before the patients started therapy in the coronary care unit, and then hourly for the next 8 h, every 4 h until 24 h after starting therapy, again after 36 h, and then daily until the eighth day after admission. In a subgroup of 23 patients, blood samples were available for as long as 21 days after admission. Patient care requirements only occasionally prevented the taking of a sample.

Treatment varied, depending on clinical circumstances. Twenty-eight patients received intravenous streptokinase (1.5 × 10⁶ units for 60 min), 20 received intravenous urokinase (2 × 10⁶ units for 10 to 15 min), and 11 were given intravenous recombinant tissue-type plasminogen activator (rtPA) in a bolus of 10 mg, then 50 mg during the first hour and 20 mg each during the second and third hours after admission. Because of contraindications, 13 patients did not receive fibrinolytic treatment. Additionally, all patients received routine coronary care and were treated with intravenous heparin, acetylsalicylic acid, nitrates, and occasionally beta-blockers and antiarrhythmic agents as needed.

As has been shown recently (10), an invasive strategy in AMI of routine immediate coronary angiography (CAG) and percutaneous transluminal coronary angioplasty (PTCA) after thrombolytic therapy is not superior to a conservative strategy with selective CAG and PTCA on subsequent days. Thus, we used CAG and PTCA selectively only, usually several days after admission. This means that we could not observe reperfusion in Q-wave infarction directly by CAG, but had to infer reperfusion from noninvasive criteria (i.e., the combined analysis of CK and myoglobin release kinetics). As is well established, both clinically (11–14) and experimentally (15, 16), reperfusion in Q-wave infarction results in a more rapid increase in CK and myoglobin and early peaks of both proteins. We assumed that early reperfusion had occurred if there were both a myoglobin peak within 7 h and a CK peak within 16 h after the onset of chest pain (17).

Group 3 (severe skeletal muscle damage). In 13 polytraumatized patients without chest contusion, blood samples were obtained on admission to the intensive care unit and subsequently on the first and fourth days after admission.

Group 4 (emergency-room patients). We studied 96 emergency-room patients from the hospital's department of internal medicine. Subsequently, 23 patients proved to have sustained an AMI (15 Q-wave and eight non-Q-wave myocardial infarctions) as diagnosed by a cardiologist according to the above-mentioned criteria. Twenty-two patients presented with angina at rest; 19 presented with cardiovascular diseases other than coronary artery disease, including congestive heart failure and tachycardia. Another 32 patients suffered from miscellaneous diseases (e.g., infections, syncope, intoxications, decompensated diabetes mellitus, and gastrointestinal, pulmonary, and renal diseases). In these patients, a single blood sample was taken immediately after admission to the emergency room.

Laboratory Analysis

Blood collection. We collected blood in EDTA-coated tubes (Sarstedt, Nümbrecht, F.R.G.). CK and CK-MB were assayed without delay, and myoglobin within 24 h of collection. Blood samples for TnT measurements were centrifuged without delay and the plasma subsequently frozen and stored at −20°C until determination. In these conditions, TnT could be assayed for at least three months after collection without any decrease in concentrations.

Myoglobin. Myoglobin was determined by a commercially available radioimmunoassay (Byk-Sangtec, Dietzenbach, F.R.G.). The upper limit of the reference interval was 80 μg/L.

CK and CK-MB. We measured total CK and CK-MB activities at 25°C by means of an N-acetylcyesteine-activated, optimized ultraviolet test from Merck (Darmstadt, F.R.G.). CK-MB activities were determined by immunoinhibition, based on the presence of CK M-subunit antibodies. The upper limits of the normal reference interval of CK are 70 U/L for women and 80 U/L for men; the normal range of CK-MB activity is =10 U/L. In accordance with the manufacturer's instructions, CK-MB activities of >10 U/L and >6% of an increased total CK activity (both criteria were required) were assumed to indicate myocardial muscle cell damage.

Myosin heavy chains (MHC). MHC were determined by a commercially available immunoradiometric assay (E.R.I.A. Diagnostics Pasteur, Marnes la Coquette, France). The upper limit of the reference interval is 300 micro-units/L.

Cardiac troponin T assay. An enzyme-linked immuno- sorbent assay (Boehringer Mannheim, Mannheim, F.R.G.) developed by Katus et al. (18) was used to detect cardiac TnT circulating in plasma. This test is a sandwich assay with cardiospecific polyclonal antibodies immobilized on poly(vinyl chloride) test tubes; peroxidase-labeled monoclonal antibodies are added to the antibody-coated test tubes after incubation with standard or unknown sample. The enzyme adhering to the assay tubes after washing corresponds to the amount of TnT bound and is indirectly quantified spectrophotometrically via substrate conversion ([di-ammonium-2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate)] at 405 nm. All measurements were performed in duplicate with a batch analyzer (Enzyme Test ES 22; Boehringer Mannheim). The measuring range of the assay extended from 0.05 to 15 μg/L. At <0.25 μg/L, the standard curve is too shallow to allow accurate determination of TnT. Therefore, for routine purposes the detection limit of the assay was defined as 0.25 μg/L (absorbance + 3 SD of the zero
Cross-reactivity with TnT from skeletal muscle was 1% (18). The intra-assay coefficient of variation (CV) was 5%; the interassay CV was 6%. The semiautomated assay procedure was completed within 90 min.

Statistical Procedures

We used nonparametric methods throughout. Medians, interquartile ranges, and percentiles were calculated to describe continuous variables. The association between variables was analyzed by the Spearman rank correlation test. Kruskal–Wallis one-way analysis of variance and Friedman's two-way analysis of variance were used for between-group comparison of more than two groups. Subsequently, we used the Mann–Whitney U-test and Wilcoxon signed rank test with Bonferroni adjustment of the P value to identify groups differing significantly from each other. Qualitative data were analyzed by contingency table analysis. P < 0.05 was considered significant. Sensitivity, specificity, efficiency, positive predictive value, negative predictive value, likelihood ratio, and Youden index (sensitivity + specificity – 1) were calculated to describe the performance of TnT in the diagnosis of AMI in emergency-room patients (19–21). Receiver-operating characteristics (ROC) curves were constructed to discriminate between AMI and non-AMI in these patients.

Results

Cardiac TnT in normal controls. The distribution of TnT concentrations in 100 healthy individuals is shown in Figure 1. The median cardiac TnT concentration in healthy blood donors was 0.2 μgL (interquartile range, 0.16–0.3 μgL; Table 1). The upper limit of the reference interval, calculated as the 99th percentile, was 0.5 μgL. TnT concentrations >0.5 μgL (upper cutoff value) were considered to indicate myocardial muscle cell damage. TnT concentrations were not influenced by age or sex. The correlation coefficient between TnT concentrations and age was 0.11 (P < 0.0001). The median concentrations of plasma TnT for healthy men (0.22 μgL) and women (0.19 μgL) did not differ significantly.

Cardiac TnT in polytraumatized patients without chest contusion. TnT peak concentrations in this group ranged from 0.2 to 0.69 μgL (median, 0.29 μgL; Table 1). Myoglobin concentrations measured in the same samples, however, were increased considerably, with peak concentrations ranging from 360 to 1060 μgL (median, 570 μgL). TnT concentrations were slightly increased (0.56, 0.59, and 0.69 μgL) in three samples from two patients. These borderline increases in TnT concentrations are probably attributable to the 1% cross-reactivity (18) of the assay with skeletal muscle TnT.

Cardiac TnT in AMI. All patients with confirmed AMI showed markedly increased peak concentrations (Table 1) and a typically time-dependent change in plasma concentrations of TnT. TnT concentrations showed a long plateau effect, with a plateau usually occurring from the second to fifth day after the onset of symptoms. In most cases, TnT showed a roughly biphasic release kinetics, with a peak during the first 24 h after the onset of symptoms and a second peak on or about the fourth day after admission (Figure 2). The median 31-fold increase (interquartile range, 19.6–45.4) of the upper cutoff value observed for cardiac TnT in AMI was significantly higher (P = 0.0001) than the median maximum/cutoff value ratios for both myoglobin (11.5; interquartile range, 9–15) and CK (11.0; interquartile range, 8.2–18.1). Even in patients with small myocardial infarctions, the time course of TnT concentration contrasted more strongly with the normal range than did myoglobin, CK, and CK-MB activity measured in the same patients.

The sensitivity of TnT for the diagnosis of AMI is time dependent. Cardiac TnT started increasing from the first hour after the onset of symptoms. The diagnostic sensitivity of TnT was 50% after 4 h (interquartile range, 2.1–5 h) and 100% by 10 h after the onset of pain. The diagnostic sensitivities of myoglobin, CK, and CK-MB activity, calculated from measurements in the same patients, were 50% at 3 h (myoglobin: interquartile range, 2.6–4 h), 4.5 h (CK: interquartile range, 3.25–5 h), and 5 h (CK-MB activity: interquartile range, 3.6–6 h) after the onset of symptoms. Figure 3 shows the sensitivity of TnT in the diagnosis of AMI compared

Table 1. Cardiac Troponin T in AMI, Polytraumatized Patients without Chest Contusion, and Controls

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td>100</td>
<td>0.2</td>
<td>0.16–0.3</td>
</tr>
<tr>
<td>AMI (peak concn)</td>
<td>72</td>
<td>15.3</td>
<td>9.6–22.7</td>
</tr>
<tr>
<td>Polytraumatized without chest contusion (peak concn)</td>
<td>13</td>
<td>0.29</td>
<td>0.23–0.43</td>
</tr>
</tbody>
</table>
observed significantly earlier than those of CK ($P = 0.0013$) and CK-MB activity ($P = 0.0006$). However, the differences between the first appearances of TnT and myoglobin activity ($P = 0.18$) and between TnT and CK activity ($P = 0.026$) were not significant according to the Bonferroni adjustment. Increased CK-MB activities were observed significantly later ($P = 0.0051$) than increased TnT concentrations in the same patients. The sensitivity of TnT in the diagnosis of AMI was 100% between 10 and 120 h after the onset of symptoms. On the seventh day after admission, 84% of all AMI patients had increased TnT concentrations (sensitivity 84%). In the subgroup of 23 patients for whom blood samples could be obtained beyond the seventh day after admission, TnT concentrations usually returned to within the normal range by about the 12th to 14th day after admission. Figure 4 demonstrates the differences in the time courses of myoglobin, CK activity, MHC, and cardiac TnT in a single AMI patient. In another patient, who did not sustain a reinfarction during this time, the TnT concentration was still increased (1.5 μg/L) 21 days after admission to the hospital.

The correlation ($r$) in AMI patients between maximal

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**Fig. 2.** Cardiac troponin T release profile in Q-wave myocardial infarction: (A) 33 reperfused patients receiving fibrinolytic therapy; (B) 21 patients receiving fibrinolytic therapy without subsequent early reperfusion; and (C) 13 patients without fibrinolytic treatment. Data given as median (solid lines) and interquartile range (broken lines representing 25th and 75th percentiles). From 48 h after admission, concentrations in A were significantly less than in either B or C. There was no significant difference between concentrations in B and C.

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**Fig. 3.** Diagnostic sensitivity of cardiac troponin T, myoglobin, CK, and CK-MB activity during the first 12 h after the onset of AMI symptoms ($n = 72$). The lowest value for each interval was included in the calculation of the cumulative frequency of increased values.
concentrations of TnT and maximal activity of total CK was 0.86 ($P < 0.0001$); between TnT maxima and CK-MB activity maxima, 0.89 ($P < 0.0001$); and between cardiac TnT maxima and LDH activity maxima, 0.85 ($P < 0.0001$). TnT concentrations were not affected by the agent used in thrombolysis (e.g., streptokinase, urokinase, or rtPA; $P > 0.15$), by the site of the myocardial infarction ($P > 0.1$), or by the age (−0.07 < r < 0.41) or sex ($P > 0.13$) of patients (data not shown).

Reperfusion-dependent release kinetics of cardiac TnT in Q-wave myocardial infarction. Reperfusion of the infarct-related artery, which was achieved early in 33 of 54 patients undergoing thrombolytic therapy, obviously influences the release of TnT into plasma in cases of Q-wave infarction (see Figure 2). All such cases showed TnT peaks no later than 26 h (median; interquartile range, 12–18 h) after the onset of symptoms with a subsequent rapid decrease. Concentrations of TnT in these patients peaked significantly earlier ($P = 0.0001$) and returned to within the normal range more rapidly than in the nonreperfused patients. The sensitivity of TnT on the seventh day after admission was 68%, significantly less ($P = 0.036$) than that observed for both other groups. In patients without thrombolytic therapy, TnT tended to peak ~48 h (median; interquartile range, 23–96; mode, 96 h) after the onset of pain. Concentrations on the seventh day were still markedly increased (sensitivity on the seventh day, 100%). TnT concentrations of patients for whom thrombolysis was unsuccessful resembled those of patients without fibrinolytic therapy (see Figure 2). The median time to peak was 24 h (interquartile range, 16–40 h), which was not significantly different from patients without thrombolytic treatment ($P = 0.11$). The sensitivity of TnT on the seventh day after admission was 84% (not significantly different from patients without fibrinolytic therapy, $P = 0.09$). Peak concentrations of TnT did not differ significantly between all three groups ($P = 0.55$). From 48 h after admission onwards, TnT concentrations in successfully reperfused patients were significantly less ($P < 0.0028$) than the concentrations in either of the other groups.

Cardiac TnT in non-Q-wave myocardial infarction. The time course of TnT after non-Q-wave myocardial infarction is of special interest to the clinician. Non-Q-wave AMI is more difficult to diagnose than Q-wave AMI, because electrocardiographic findings in non-Q-wave AMI are nonspecific and must be correlated with the clinical setting. Table 2 summarizes the TnT- and CK-release kinetics of seven patients with non-Q-wave AMI. All seven patients received thrombolytic therapy. The median delay from the onset of symptoms to the first increased concentrations of TnT in plasma was 4 h (range, 2–8 h). In six patients, TnT concentrations showed a biphasic time course, with a peak during the first 24 h after the onset of pain and a second increase at about the fourth day after admission. Another patient showed only one peak on the second day. TnT concentrations showed a median 25-fold increase (range, 8–71-fold) above the upper cutoff value in non-Q-wave infarction. Six patients had increased TnT concentrations on the seventh day after admission. Four of eight emergency-room patients studied, who were subsequently diagnosed as having sustained a non-Q-wave AMI, had increased TnT concentrations on admission, whereas only three had increased CK activity in the same blood samples.

Diagnostic performance of cardiac TnT for AMI in emergency-room patients. The prevalence of AMI was 24% (pretest odds = 0.31). Figure 5 shows the distribution of TnT concentrations and values of CK activity in the emergency-room patients studied. The median TnT concentrations were 0.58 μg/L (range, 0.12–3.86) in AMI patients, 0.2 μg/L (range, 0.05–0.54) in patients with cardiac diseases other than coronary artery disease, and 0.18 μg/L (range, 0.03–1.05) in patients with miscellaneous diseases. The median values of CK activity (measured in the same blood samples) were 65 U/L (range 20–696) in AMI patients, 37 U/L (range, 11–165) in patients with angina at rest, 27 U/L (range, 12–158) in patients with cardiac diseases other than coronary artery disease, and 24 U/L (range, 11–175) in patients with miscellaneous diseases. ROC curves for the discrimination between AMI and non-AMI in emergency-room patients were constructed (Figure 6). The discriminative power of TnT—reflected by the area under the ROC curve—was found to be greater than that of CK activity. The maximum Youden Index of TnT (0.53) was

### Table 2. Release Kinetics of TnT and CK Activity In Seven Cases of Non-Q-Wave Infarction

<table>
<thead>
<tr>
<th>Patient</th>
<th>First increased values*</th>
<th>To peak values</th>
<th>Conc, μg/L (U/L)</th>
<th>Maximum</th>
<th>On day 7</th>
<th>No. of peaks</th>
<th>Maximum/cutoff-value ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (5)</td>
<td>18 (15)</td>
<td>35.6 (849)</td>
<td>7.0 (42)</td>
<td>2 (1)</td>
<td>71.2 (10.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (6)</td>
<td>20 (20)</td>
<td>28 (658)</td>
<td>4.6 (50)</td>
<td>2 (1)</td>
<td>56.0 (8.2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (4)</td>
<td>24 (12)</td>
<td>35.3 (769)</td>
<td>5.7 (40)</td>
<td>2 (1)</td>
<td>70.6 (9.6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (4)</td>
<td>48 (13)</td>
<td>4.1 (246)</td>
<td>0.43 (26)</td>
<td>1 (1)</td>
<td>8.2 (3.1)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8 (9)</td>
<td>96 (23)</td>
<td>5.3 (289)</td>
<td>0.7 (51)</td>
<td>2 (1)</td>
<td>10.6 (3.6)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (5)</td>
<td>15 (13)</td>
<td>5.0 (270)</td>
<td>1.56 (24)</td>
<td>2 (1)</td>
<td>10.0 (3.4)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4 (4)</td>
<td>17 (17)</td>
<td>12.6 (444)</td>
<td>2.0 (35)</td>
<td>2 (1)</td>
<td>25.2 (5.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated at the onset of symptoms.
found at a cutoff value of 0.5 μg/L. Thus, this cutoff value, which was first defined in healthy blood donors, could be confirmed in patients admitted to the emergency room. Although a slightly higher Youden index (0.37) was found at 50 U/L, the cutoff value of CK activity recommended by the assay’s manufacturer (70 U/L for men, 80 U/L for women) should be used to achieve an acceptable rate of false-positive results. Various parameters describing the diagnostic ability of a test are given in Table 3 (TnT cutoff value, 0.5 μg/L; CK cutoff value, 80 U/L; prevalence, 24%). Because the sensitivities of TnT and CK activity are time dependent, the sensitivities of 57% (TnT) and 35% (CK) observed for the patients investigated reflect the average delay from the onset of symptoms to emergency-room admission. Only three false-positive TnT results (specificity 96%) were found, in samples from a patient with angina at rest (0.84 μg/L), a patient with fever of unknown origin (1.05 μg/L), and a patient sustaining pulmonary embolism (0.94 μg/L). The Youden Index, which does not depend on the prevalence of a disease in the population investigated, and the diagnostic efficiency of TnT were greater than those of CK activity. Thus, measurement of TnT turned out to be diagnostically superior to measurement of CK activity, even in the diagnosis of evolving myocardial infarction.

**Discussion**

Although TnT is a contractile protein, structurally bound in cardiac muscle cells, TnT concentrations increased within 4 h (median) after infarction, which is not significantly different from the earliest detectable increase in cytoplasmic myoglobin and CK activity. TnT reached a plateau from the second to the fifth day after the onset of pain. In most patients, TnT release was roughly biphasic. In patients without thrombolytic treatment, maximal TnT concentrations were observed several days after admission. A plateau existed for several days before and after the occurrence of peak concentrations of TnT. Some of these patients showed a second, usually much smaller, increase during the first 24 h after admission. In successfully reperfused patients, TnT peaked within 24 h of admission (median, 14 h after onset of symptoms). A second, much smaller peak was observed at about the fourth day after admission to the hospital. TnT time courses of patients receiving thrombolytic therapy not leading to early reperfusion resembled those of patients without thrombolytic treatment.

The rapid decrease in TnT concentrations and the significantly decreased concentrations from the second day onwards after successful reperfusion may reflect a reduced size of myocardial infarction. It remains to be shown whether cumulative TnT release provides a more useful tool in noninvasive estimation of infarct size than the commonly used cumulative measurements of CK-MB or LDH1 release. The occurrence of reperfusion in Q-wave infarction could not be observed directly by CAG, but had to be inferred from combined analysis of CK and myoglobin kinetics (time to peak values). Patients with early reperfusion after thrombolytic treatment can be identified with a 95% probability of correct classification by the discriminatory time limits we used (27). A limitation of noninvasive detection of reperfusion is that the exact time of clot resolution and the

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**Table 3. Comparison of the Diagnostic Ability of TnT and CK for AMI in 96 Emergency-Room Patients**

<table>
<thead>
<tr>
<th>Cutoff value</th>
<th>TnT (μg/L)</th>
<th>CK (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>96</td>
<td>89</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>Efficiency, %</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>Youden index</td>
<td>0.53</td>
<td>0.24</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>14.25</td>
<td>3.2</td>
</tr>
<tr>
<td>Positive test odds*</td>
<td>4.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Prevalence of AMI was 24% (pretest odds, 0.31).
amount of blood flow to the infarcting zone cannot be assessed. Thus, the data on perfusion-dependent release of TnT should be confirmed additionally in a series of patients who have undergone intracoronary thrombolytic treatment or early CAG to assess therapeutic success immediately after stopping thrombolytic therapy.

The release profile of TnT after AMI is similar to that of troponin I and tropomyosin reported by Cummins et al. (22, 23), although there are, so far, no data on the perfusion-dependent release of troponin I and tropomyosin. Both proteins started to increase parallel to CK-MB, peaked at ~18 h (mean) after the onset of infarction, and had increased concentrations in serum for several days. Troponin I usually showed a second, but smaller, peak between 60–80 h after infarction. The release profiles of the proteins of the troponin–tropomyosin complex are different from the time-dependent changes in serum concentrations of myosin light chains (MLC) and MHC after AMI (24, 25). MLC also started to increase within 6 h of the onset of pain. We observed peak values on the fourth or fifth days, regardless of reperfusion (26). MHC concentrations, by contrast, started to increase from 24 h after infarction onwards and remained greater than normal for at least eight to 10 days. MHC peak values occurred at about the fifth day after admission (Figure 4). The different concentrations of these proteins, present as soluble cytoplasmic pools of protein precursors, could be one reason for the contrasting release profiles. The biggest cytoplasmic pool must be postulated for the proteins of the troponin–tropomyosin complex. Evidence of a small cytoplasmic pool of MLC is available (27, 28). Obviously, such a pool does not exist for MHC because of their late appearance in serum after AMI. Consequently, the biphasic release profile of TnT is probably the result of a rapid loss of a cytoplasmic pool superimposed on the prolonged myofibrillar degradation that results in a long plateau effect several days after the onset of pain.

The important clinical implications of the present study are the high specificity (96%) and sensitivity of cardiac troponin T in the early and late diagnosis of AMI. There were no false-negative TnT results (sensitivity 100%) in blood samples from AMI patients at 10–120 h after the onset of pain. In many patients, increased concentrations of plasma TnT beyond the seventh day allowed a diagnosis based on this biochemical marker even during the second week after admission. Cardiac TnT showed a median 31-fold increase above the upper cutoff value in AMI, significantly greater than both myoglobin and CK, which partly explains the high diagnostic sensitivity of cardiac TnT. TnT also provides reliable diagnosis of non-Q-wave myocardial infarction. Even in patients with small myocardial infarctions, the time course of TnT concentration contrasted more strongly with the normal range than did myoglobin, CK, and CK-MB activity measured in the same patients.

TnT is an early marker of myocardial injury. The sensitivity was 50% at 4 h after the onset of AMI. The clinical implication of this finding is of limited value until rapid determination of TnT is available. Although the TnT assay used can be performed in 90 min, even a brief delay in thrombolytic therapy for patients in whom there is considerable clinical suspicion of AMI is unwarranted. However, negative TnT assay results (<0.5 μg/L) in samples obtained >10 h after the onset of symptoms exclude the diagnosis of an AMI. Accurate diagnosis of AMI would facilitate the choice of appropriate therapy and the degree of care, resulting in more efficient and economic use of the critical care facility. We tested the specificity of the TnT assay in patients presenting to an emergency room in a department of internal medicine, a population that did not include postoperative patients or patients with trauma or burns. We also tested TnT concentrations serially in samples of 13 polytraumatized patients without chest contusion. Borderline increases in concentrations of TnT, found in three samples from two patients, are probably due to slight cross-reactivity (1%) of the assay with skeletal muscle TnT (18). Finally, because of extremely high sensitivity and specificity, cardiac TnT could provide a new criterion in laboratory diagnosis and monitoring of AMI.

We dedicate this paper to Prof. Dr. Erich Kaiser of Vienna, Austria, on the occasion of his 65th birthday.

We gratefully acknowledge the help of the nursing staff from the coronary care unit of the University Hospital of Innsbruck in carrying out this study.

References


