S-Troponin T in Suspected Ischemic Myocardial Injury Compared with Mass and Catalytic Concentrations of S-Creatine Kinase Isoenzyme MB

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In a multicenter study we compared three tests for ischemic myocardial injury (IMI): a new, automated enzyme immunoassay for S-troponin T (S-TNT; Boehringer Mannheim) and two S-creatine kinase (CK) isoenzyme MB assays (mass and catalytic concentrations). For critical evaluation of clinical sensitivity, we studied 243 cases with an IMI prevalence of 43% and an 18% prevalence of cases with unstable angina. Relative peak values of S-TNT and S-CK-MB (mass) after onset of pain were four-to fivefold higher than S-CK-MB (catalytic) results. Increases of S-TNT and S-CK-MB (mass), even though still within their reference ranges, indicated minor myocardial damage in about one-third of the cases primarily classified as unstable angina. The diagnostic window for S-TNT ranged from hours to weeks after the acute episode. The time courses were frequently biphasic, with the initial S-TNT peak closely paralleling that of the mass concentrations of S-CK-MB. With a biological half-life for S-TNT of 2 h, the prolonged increases in S-TNT indicate a continuous release of S-TNT from necrotizing cells. Clinical specificities of S-TNT and S-CK-MB (mass) were greater than that of S-CK-MB (catalytic), even in the presence of 30% to 40% severe skeletal muscle injuries. The combination of S-TNT and S-CK-MB (mass) is excellent for detection of acute IMI, including minor myocardial damage.

Additional Keyphrases: myocardial infarction · angina pectoris

Cardiac troponin T is a 37-kDa polypeptide subunit of the myofibrillar regulatory troponin complex (1, 2). Because the amino acid sequence is unique to cardiac muscle, one can immunologically differentiate skeletal muscle and cardiac protein isoforms (3, 4). In the cardiomyocyte, troponin T is compartmentalized into a minor cytosolic (5%) and a major myofibrillar bound (95%) fraction (5). A previous enzyme immunoassay with sheep polyclonal antibodies indicated that, after an ischemic myocardial injury (IMI), both troponin T pools were released from necrotizing myocytes (6). During the evolution of an acute myocardial infarction (AMI), the kinetics of concentration changes in blood depend on time elapsed until reperfusion and on the degree of reperfusion of the infarcted zone (6). A specific, automated enzyme immunoassay of troponin T, based on use of monoclonal antibodies with <2% cross-reactivity with skeletal muscle troponin T, has recently been developed by Boehringer Mannheim (Mannheim, F.R.G.) for routine use (7).

The purpose of this multicenter study was to evaluate this assay and compare the diagnostic performance of S-troponin T (S-TNT) with that of S-creatine kinase (CK; EC 2.7.3.2) isoenzyme MB (catalytic and mass concentrations) in suspected cases of IMI. Five hospitals cooperated in collecting timed serial samples after onset of acute symptoms in patients in their coronary care units who were thought to have had IMI. Further, we included samples from stable angina patients and some nonischemic heart disease patients from medical departments because it is not realistic to evaluate clinical sensitivity and specificity with only definite AMI vs non-AMI patients. Consequently, we decided to compare test performances under "worst-case" conditions by including relatively large numbers of borderline cases such as unstable angina in the IMI group and severe skeletal muscle injuries in the reference group. S-TNT and S-CK-MB (cat) were determined on all samples and S-CK-MB (mass) on all samples from three of the hospitals (1, 3, 5).

Materials and Methods

Subjects

The IMI group (AMI + MMD) comprised 87 cases of AMI, classified according to the World Health Organization criteria (8) by characteristic chest pain, unequivocal changes in the electrocardiogram, and increased S-CK (cat) and S-CK-MB (cat). Forty-three cases were primarily classified as unstable angina pectoris (UAP) on the basis of chest pain at rest or provoked by minimal exertion, a new pattern of chest pain in a previously chronic angina, or both, with or without ST-depression

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Received October 23, 1990; accepted May 31, 1991.

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6 Nonstandard abbreviations: IMI, ischemic myocardial injury; AMI, acute myocardial infarction; MMD, minor myocardial damage; UAP, unstable angina pectoris; SAP, stable angina pectoris; post-AMI, patients with an AMI older than 48 h; S-CK-MB (cat), creatine kinase isoenzyme MB in serum, catalytic activity concentration; S-CK-MB (mass), creatine kinase isoenzyme MB in serum, mass concentration; S-TNT, cardiac troponin T in serum; and IHD, ischemic heart disease.
or T-wave inversion in the electrocardiogram (9). None had signs of an AMI within the last 24 h. Maximal S-CK (cat) and S-CK-MB (cat) values within the diagnostic time window (10–12) remained below their respective discrimination limits. However, 16 of the 43 UAP patients were subsequently reclassified as minor myocardial damage (MMD) by unambiguous S-CK-MB (mass) changes as described in reclassification (see Results). This gave a total number of 103 IMI = 87 AMI + 16 MMD cases.

The reference group comprised 74 cases of stable angina pectoris (SAP), as characterized by typical attacks of chest pain provoked by physical exertion and pain relief by nitroglycerine, and 39 cases of non-ischemic heart disease (IHD; no history of chest pain and no electrocardiographic signs of ischemia). None of these patients had skeletal muscle injuries. This gave a total of 140 reference cases: 27 UAP without S-CK-MB (mass) change + 74 SAP + 39 non-IHD.

To compare the clinical specificities of the tests, we collected 55 samples from patients with extensive skeletal muscle injuries, e.g., multiple traumas, minor and major surgery, and from chronic alcoholics.

**Blood Sampling**

In all IMI-suspected patients, the onset of acute symptoms was established as accurately as possible, and samples were taken from a few hours after admission to weeks after the acute episode (see Figure 1). One blood sample each was drawn from patients with non-IHD, with SAP (without an angina pectoris attack), or with skeletal injury. Serum samples were stored at -70 °C for a maximum of two months until analysis. Preliminary experiments showed no considerable losses of S-CK-MB (cat) (12), S-CK-MB (mass), and S-TNT under these conditions.

**Methods**

**S-troponin T.** The troponin T immunoassay (ELISA Troponin(e) T; Boehringer Mannheim) was performed on all samples from all patients studied at each of the five participating centers. This new enzyme immunoassay was carried out in coated tubes by using the microprocessor-controlled Boehringer Mannheim ES 22 photometer. The method is based on a single-step sandwich principle, with streptavidin-coated tubes as the solid phase and two monoclonal anti-human cardiac troponin T antibodies (7). Troponin T is bound on different epitopes by the capture and signal antibodies. The capture antibody is biotinylated, binds completely and reproducibly to the streptavidin-coated tube, and is 99% specific for cardiac troponin T (7). The second antibody is labeled with horseradish peroxidase (EC 1.11.1.7) and has about 20% cross-reactivity with skeletal muscle troponin T. Because of the capture antibody's high specificity, the assay is immunologically specific for cardiac troponin T. However, in samples with high concentrations of skeletal muscle troponin T, unspecific binding to the tube wall may result in increased S-TNT values.

![Graph](image_url)

**Fig. 1.** Individual time series with relative concentrations of all analytes (ordinate, discriminator set at 1.0) plotted as a function of time in hours after onset of acute symptoms (abscissa).

**Analytical procedure:** In a first step, duplicate 200-μL samples and labeled antibodies are incubated for 1 h. After two washing steps, the peroxidase substrate 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate), diammonium salt, is added and color develops for 30 min. Absorption at 405 nm is directly correlated to troponin T concentration in the sample ≤15 μg/L. The mean troponin T concentration is calculated from the duplicate samples by a microprocessor by comparison with the calibration curve constructed from six calibration standards (range 0 to 15 μg/L), which consist of purified bovine cardiac troponin T in a human serum matrix. The calibration procedure for assay of human troponin T is described elsewhere (7).
**Pre-trial familiarization period.** Imprecision for the five laboratories was established by 10 determinations on three different days of each of four quality-assessment materials with nominal S-TNT values of 2.0, 4.0, 5.7, and 8.0 μg/L. Within-series imprecision (CV) was 2.7%, 2.5%, 2.3%, and 1.9%, respectively. At the same respective concentrations, between-laboratory imprecision was 4.0%, 3.6%, 2.9, and 3.2%. The imprecision of the current assay increased considerably at concentrations <0.20 μg/L. S-TNT in healthy individuals is below the detection limit of the evaluation assay used in this study.

**CK-MB, catalytic activity concentration (U/L).** This analysis was performed on all samples from all patients in the study. We determined S-CK-MB (cat) as residual activity by using the European Committee for Clinical and Laboratory Standards–Scandinavian Committee on Enzymes standard method at 37 °C (13, 14) after immunoinhibition of all S-CK M-subunit activity with reagents from Merck, Darmstadt, F.R.G., and from Boehringer Mannheim (15, 16). The results were multiplied by 2 to be expressed as S-CK-MB (12–15). The current discrimination limit for AMI by conventional criteria is 24 U/L (10–12, 16). S-total CK (cat) and S-CK-MB (cat) were systematically determined in all samples from all cases except for 20 persons with low total S-CK (cat) in the reference group.

**CK-MB, mass concentration.** The NovoClone™ CK-MB mass concentration assay (Novo Biolabs, Cambridge, U.K.) was performed on all samples from hospitals 1, 3, and 5. This two-site enzyme immunometric sandwich method with two monoclonal antibodies is carried out in 96-well microtiter plates coated with specific anti-CK-B antibody. Technical details, imprecision, and the reference range for healthy individuals, 0–6 μg/L, have been published recently (17, 18). The discrimination limit in this report is 6 μg/L (see below).

For test evaluation quantities, definitions, and terminology, see Appendix.

**Results**

Time series were plotted for all patients thought to have possible IMI. Figure 1 shows the time courses of S-CK-MB (cat), S-CK-MB (mass), and S-TNT in three illustrative cases. Relative concentrations, with the discriminator value set at 1.0 on the ordinate, were plotted as a function of time after onset of acute symptoms. Figure 1A shows the pattern for a non-Q-wave AMI in a 69-year-old man. The relative peak value of S-CK-MB (mass) was nearly fivefold that of S-CK-MB (cat). S-TNT showed a typical biphasic course: an initial, continued increase exceeding that of S-CK-MB (mass), and then a prolonged plateau, remaining increased 10-fold at 100 h after onset of symptoms. The diagnostic time window was thus far wider than that of S-CK-MB (cat and mass).

Figure 1B shows the pattern for a 66-year-old man (case 1.34, Table 1) admitted with unstable angina, syncope, and severe hypotension after vasodilatation treatment. The parallel increases of S-CK-MB (mass) and of S-TNT indicated MMD. The relative peak value of S-CK-MB (mass) was about fourfold greater than that of S-CK-MB (cat). Note that relative to the 100- to 140-h baseline values, peak S-TNT and S-CK-MB (mass) were 2.5- and twofold increased, respectively. The patient died five days later in an AMI.

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### Table 1. Sixteen Cases of MMD, Biochemically Classified by Changes of S-CK-MB (Mass) in Individual Time Series

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, years</th>
<th>History</th>
<th>Follow-up</th>
<th>S-TNT (0.20 μg/L)*</th>
<th>Mass (μg/L)*</th>
<th>Cat (24 U/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.15</td>
<td>63</td>
<td>AMI + unstable angina</td>
<td>Bypass</td>
<td>0.13</td>
<td>6.6</td>
<td>6</td>
</tr>
<tr>
<td>1.34</td>
<td>66</td>
<td>AMI</td>
<td></td>
<td>0.30</td>
<td>7.0</td>
<td>6</td>
</tr>
<tr>
<td>1.57</td>
<td>83</td>
<td>AMI</td>
<td>Bradycardia syncope</td>
<td>0.20</td>
<td>7.2</td>
<td>23</td>
</tr>
<tr>
<td>1.03</td>
<td>81</td>
<td>AMI + angina</td>
<td>Died in AMI six months later</td>
<td>0.29</td>
<td>8.1</td>
<td>16</td>
</tr>
<tr>
<td>2.10</td>
<td>74</td>
<td>Unstable angina</td>
<td>Angina</td>
<td>0.08</td>
<td>8.3</td>
<td>16</td>
</tr>
<tr>
<td>1.99</td>
<td>63</td>
<td>AMI</td>
<td>Angina</td>
<td>0.05</td>
<td>9.3</td>
<td>1</td>
</tr>
<tr>
<td>1.95</td>
<td>59</td>
<td>AMI</td>
<td>Angina</td>
<td>0.20</td>
<td>9.5</td>
<td>10</td>
</tr>
<tr>
<td>1.01</td>
<td>71</td>
<td>AMI + angina</td>
<td>Angina</td>
<td>0.07</td>
<td>9.7</td>
<td>8</td>
</tr>
<tr>
<td>1.81</td>
<td>73</td>
<td>Angina</td>
<td>Angina</td>
<td>0.37</td>
<td>12.4</td>
<td>16</td>
</tr>
<tr>
<td>1.28</td>
<td>65</td>
<td>AMI + angina</td>
<td>Bypass</td>
<td>0.20</td>
<td>13.6</td>
<td>7</td>
</tr>
<tr>
<td>1.47</td>
<td>75</td>
<td>Angina</td>
<td>Angina</td>
<td>0.40</td>
<td>19.1</td>
<td>12</td>
</tr>
<tr>
<td>2.02</td>
<td>49</td>
<td>AMI + unstable angina</td>
<td>Angina</td>
<td>0.37</td>
<td>19.3</td>
<td>22</td>
</tr>
<tr>
<td>1.05</td>
<td>76</td>
<td>Angina</td>
<td>Angina</td>
<td>0.24</td>
<td>27.4</td>
<td>22</td>
</tr>
<tr>
<td>1.94</td>
<td>68</td>
<td>Intermittent auricular fibrillation</td>
<td>Respiratory insufficiency</td>
<td>0.43</td>
<td>29.8</td>
<td>20</td>
</tr>
<tr>
<td>1.98</td>
<td>72</td>
<td>AMI + thrombolysis</td>
<td>Angina</td>
<td>0.44</td>
<td>31.7</td>
<td>20</td>
</tr>
<tr>
<td>1.96</td>
<td>61</td>
<td>Mitral stenosis</td>
<td>Angina</td>
<td>0.29</td>
<td>37.9</td>
<td>23</td>
</tr>
</tbody>
</table>

*a Discriminator value for each test.

b Female.

Shown are the maximal values of each assay. Cases are arranged in order of increasing S-CK-MB (mass). All showed changes of S-TNT. All patients had severe ischemic heart disease; electrocardiographic series showed transitory ischemic changes but were not conclusive for AMI. Fourteen were admitted with UAP, one with syncope, one with auricular fibrillation.
Figure 1C presents data for a 49-year-old man (case 2.02, Table 1) with a previous AMI who was admitted with UAP. The patient had two acute episodes, at time zero and at around 80 h, causing the increases of S-CK-MB (mass) and S-TNT that indicate an initial MMD (17, 18) followed by an AMI, as determined by conventional criteria. The initial peak for S-CK-MB (mass) was considerably higher than that of S-CK-MB (cat), with the latter remaining just below the discriminator value. During subsequent months, this patient had three myocardial infarctions.

Reclassification of 16 cases of UAP as MMD. Time series (e.g., Figure 1) were plotted for all IMI-suspected patients. Unambiguous time curves of S-CK-MB (mass) and of S-TNT, as in Figures 1B, C, indicated IMIs in 16 (36%) of the 43 patients primarily classified as UAP. Consequently, these 16 cases (data in Table 1) were reassessed as MMD (17, 18). All of these showed changes of S-TNT as well.

Graphic test evaluation of diagnostic performances. The double histograms, Figures 2-4, compare the frequency distributions of peak S-TNT, S-CK-MB (mass), and S-CK-MB (cat) of the IMI cases (upper field) with those of the reference cases (lower field), all plotted as a function of test value (abscissa) (19, 20). We compared test performances in the absence and presence of skeletal muscle injuries.

S-Troponin T. We compared the IMI group (103 cases = 87 AMI + 16 MMD) with the reference group (140 cases = 39 non-IHD + 74 SAP + 27 UAP). However, seven apparent reference cases showed increased S-TNT values (range 0.20-0.78 µg/L). The patients’ records showed that these patients had had an AMI two days to four weeks previously. The increased S-TNT values thus correctly indicated a recent IMI. Consequently, these seven cases were allocated to the IMI group as post-AMI.

In Figure 2A (upper field) we plotted all 110 IMI cases (87 AMI cases + 16 MMD + 7 post-AMI cases) as a function of S-TNT values (abscissa) in 40 test classes, from 0 to 4 µg/L. The frequency distribution extended over a wide range, with >40% of the IMI cases having peak values >4 µg/L, i.e., 20-fold the discriminator value. The lower field shows the distribution of the 133 remaining reference cases [21 UAP patients without increases of S-CK-MB (mass) and S-TNT + 39 non-IHD cases + 73 SAP]. The sensitivity and specificity curves were plotted as a function of test value (19, 20) and reflect the different distributions. The reader can estimate sensitivity and specificity for different discriminator values directly off the scale on the right ordinate of the graph (19, 20). Based on these curves, a discriminator value of 0.20 µg/L yielded a sensitivity of 96% and a specificity of 98% (Table 2).

In Figure 2B we replotted the S-TNT data on an expanded abscissa scale to show the distribution of the 16 MMD cases among the IMI cases (upper field) and of 55 cases of severe skeletal muscle injuries added to the reference group (lower field) for critical evaluation of specificity under worst-case conditions. Of the MMD cases, 75% had peak S-TNT values exceeding the discriminator value of 0.20 µg/L; 80% of the severe skeletal muscle injuries remained S-TNT negative. The clinical specificity in the presence of 29% skeletal muscle injury cases in the reference group decreased to 94%.

S-CK-MB (cat). S-CK-MB (cat) is routinely used as an early marker for AMI with a discriminator of 24 U/L
(10–12). As expected, S-CK-MB (cat) values in the seven post-AMI cases of Figure 2 had returned to normal. For this test we considered it most correct to plot these seven cases in the reference group.

In Figure 3A (upper field), we plotted the frequency distribution of the same 103 IMI cases as in Figure 2, in 40 test classes from 0 to 480 U/L, i.e., to 20-fold the routine discriminator value of 24 U/L (12). Compared with S-TNT, the frequency distribution of peak S-CK-MB (cat) in the same cases was concentrated to the lower range, tailing toward the higher values. Only about 1% of the IMI cases were increased 20-fold. Relative to a discriminator of 24 U/L, clinical sensitivity was 94%, specificity 98%.

The expanded plot, Figure 3B, shows that all 16 MMD cases in the IMI group (upper field) had peak S-CK-MB (cat) values below the discriminator value of 24 U/L (Table 1). The lower field shows the distribution of 55 skeletal muscle injury cases added to the reference group: 75% of the skeletal muscle injuries remained S-CK-MB (cat) negative. Clinical specificity in the presence of 31% of skeletal muscle injury cases in the reference group decreased to 91%.

S-CK-MB (mass). As described above, the individual time curves with this assay were used to identify the 16 MMD cases described in Table 1. Figure 4A (upper field) shows the frequency distribution of peak S-CK-MB (mass) in 67 IMI cases plotted in 40 test classes within the range of 0 to 140 µg/L, i.e., up to 20-fold the discriminator value of 8 µg/L. The frequency distributions of the S-CK-MB (mass) and S-TNT values of the IMI cases were quite similar and shifted toward higher values than did S-CK-MB (cat); 24% of all IMI cases had
Table 2. Summary of Test Performances

<table>
<thead>
<tr>
<th></th>
<th>S-CK-MB (cat)</th>
<th>S-CK-MB (mass)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-troponin T</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>Specificity</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Specificity at 30–40%</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>severe skeletal muscles injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVpos at 50% IMI*</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>PVneg at 50% IMI*</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

*To allow comparison, we recalculated predictive values (in the absence of skeletal muscle injuries) to have one and the same prevalence of 50% of IMI cases by using the found sensitivity and specificity values (19, 20). PVpos, PVneg as defined in Appendix.

20-fold increased values of S-CK-MB (mass).

The reference group comprised 67 of the same cases as in the previous figures. Relative to a discriminator value of 8 μg/L, sensitivity was 96% and specificity 100%.

The expanded plot, Figure 4B, shows that about 75% of the MMD cases (upper field) had S-CK-MB (mass) values exceeding the discriminator value of 8 μg/L; 95% of the added skeletal muscle injury cases (lower field) remained S-CK-MB (mass) negative. The clinical specificity in the presence of 40% severe skeletal muscle injury cases in the reference group decreased to 95%.

Table 2 summarizes the various test performances. To allow comparison of predictive values, we have recalculated all of these to one and the same IMI prevalence of 50% (19, 20).

Discussion

We compared the diagnostic performances of S-TNT, S-CK-MB (mass), and S-CK-MB (cat) under similar difficult conditions, including a relatively large fraction of UAP cases. If, instead, we had added a larger number of definite AMI to our IMI group, we could have reached any high (and completely irrelevant) clinical sensitivity. The distribution of subgroups and the prevalence of about 40% IMI corresponds well to the situation in a European coronary care unit with a relatively high fraction of borderline cases.

Current diagnostic tests for AMI by conventional criteria are quite adequate. Evaluation of new and more-sensitive tests that can detect MMD (17, 18, 21) poses a new problem. The classical procedures of comparing the findings of new diagnostic tests, on the one hand, with "true," conventional, clinical classification on the other, are no longer adequate. In fact, the new tests may be the only possible means of detecting MMD (17, 18, 21).

Diagnostic test data may be evaluated in three different modes: (a) relative to a conventional discriminator value (the position of the discriminator depends on the borderline cases; all our 16 MMD cases were included in all three tests); (b) relative to individual baselines, e.g., convalescence values (see Figure 1B); and (c) by unambiguous changes even with values below the discriminator value (e.g., Figure 1B, C). Our 16 MMD cases were classified by changes in S-CK-MB (mass) values in the time series (17, 18), although their peak S-CK-MB (cat) values remained below the discriminator, 24 U/L. In contrast, peak S-CK-MB (mass) values of 13 of these 16 MMD cases were higher than the discriminator of 8 μg/L (Table 1), and sensitivity for S-CK-MB (mass) was 96% (Figure 4). All 16 MMD cases showed changes of S-TNT (Figure 1B, C).

In individual time series, the relative peak S-CK-MB (mass) values were four- to fivefold greater than those of S-CK-MB (cat), and those of S-TNT were frequently even higher. Relative to individual baseline values in convalescence samples (e.g., Figure 1B), increases were even greater.

The histograms indicate that S-CK-MB (mass) and S-CK-MB (cat) do not measure quite the same component: compared with the IMI frequency distributions of S-CK-MB (cat), those of S-CK-MB (mass) and also of S-TNT were shifted toward considerably greater values. IMI peak values were more than 20-fold the discriminator value in 40% of the cases with S-TNT, and in 24% of the cases with S-CK-MB (mass), compared with only 1% with S-CK-MB (cat). This was also apparent from the much steeper decrease of the sensitivity curve of S-CK-MB (cat) with increasing values (see Figure 3A). The clinical sensitivities and specificities of S-TNT and S-CK-MB (mass) were greater than those of S-CK-MB (cat). Clinical sensitivity of S-CK-MB (cat) in this study was lower than previously reported (10–12) because the older evaluations had to be based on AMI as classified by conventional criteria. MMD cases could not be so identified and were consequently allocated to the reference groups.

Despite a biological half-life of S-TNT of 2 h (6), the diagnostic time window of S-TNT is unusually wide, ranging from a few hours to several weeks after the acute episode. The biphasic serum changes of S-TNT may be explained by an initial leakage of the minor cytosolic fraction, followed by the prolonged release of the much larger structurally bound troponin T pool from the necrotizing cells (5, 6, 22–24). When the myocytes have been depleted of CK-MB, and serum values have returned to normal, release of troponin T continues. In cases of late admission after onset of the acute episode, a finding of increased S-TNT and normal S-CK-MB (mass) in a sample indicates an IMI of >48 h previously, which should be monitored.

Recent data indicate that the biphasic time course of S-TNT is found only in patients with reperfused AMI and that the ratio between the initial peak and the subsequent plateau at 80–90 h correlates with the duration of ischemia before recanalization and the degree of subsequent reperfusion (5, 6, 25).

In routine use, the clinical specificities of each of the three tests will depend on the prevalence and degree of skeletal muscle injury cases in the requesting department. This will be low in a coronary care unit and
considerably greater in a surgical intensive care unit. For comparison of clinical specificities under similar worst-case conditions, we included 30–40% cases of severe skeletal muscle injuries such as multiple trauma and major surgery in the respective reference groups. The decreases of clinical specificities were less for S-TNT and S-CK-MB (mass) than for S-CK-MB (cat). We conclude that the combination of S-TNT and mass concentration S-CK-MB is excellent for the detection of ischemic myocardial injury, including minor myocardial damage. Time will show whether S-TNT alone may replace current IMI markers.

Appendix

Test evaluation quantities, definitions, and terminology. Discriminator: clinically selected numeric boundary between two adjoining test classes (26). Test class: numerical subset of a scale separated by numeric class boundaries (27). Negative, positive test classes: numerical subsets with respectively lower or higher values than the discriminator value (19, 20, 26). Prevalence of IMI: fraction (%) of IMI cases of all cases in the study (19, 20). Clinical sensitivity: fraction (%) of all IMI cases with a positive test result (19, 20, 26). Clinical specificity: the fraction (%) of all reference cases with a negative test result (19, 20, 26). PVpo: fraction (%) of all test-positive patients who have an IMI (19, 20, 26). PVneg: fraction (%) of all test-negative patients who do not have an IMI (19, 20, 26).

Graphic computer support: Comparative graphic test evaluation by double histograms with overlaid sensitivity and specificity curves were produced by a PC program, TEST EVALUATION, developed for IBM-compatible PCs with a minimum RAM of 640 kilobytes, a Hercules or VGA graphic card, MS DOS 3.2 or higher, and a diskette drive capable of reading 1.2 or 1.4 megabyte HD diskettes (available by request from the first author). The database was stored in Excel and exported as ASCII files to TEST EVALUATION.

This multicenter study was made possible by support from Boehringer Mannheim GmbH, Mannheim, F.R.G. We thank Dr. W. Rüdinger and D. Banuach (Boehringer Mannheim) for their intensive and dedicated participation and organization efforts; the authors from laboratories 1, 3, and 5 thank Novo BioLabs, Denmark, for generously supplying instruments and CK-MB reagents; and the authors from Lasaretet, Halingborg, Sweden, thank Thelma Zoegas Fond for generous support of part of this project and Ann-Katrin Herbert and Laila Petersen for excellent technical assistance.

References

CLINICAL CHEMISTRY, Vol. 37, No. 8, 1991 1411