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# The Role of Cardiac Troponin T and Other New Biochemical Markers in Evaluation and Risk Stratification of Patients with Acute Chest Pain Syndromes

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**Summary**

*Background and hypothesis:* Increased serum creatinine kinase (CK) and CK-MB enzyme levels have been used for years to detect myocardial infarction (MI). However, serum myoglobin and CK-MB mass or protein levels may indicate MI earlier; cardiac troponin T is the most specific marker of myocardial injury and it can detect even minor myocardial necrosis. The diagnostic and prognostic utility of the traditional and new markers of cardiac injury in the emergency evaluation of patients with acute chest pain syndromes were therefore compared.

*Methods:* One hundred and fifteen consecutive patients with an acute coronary syndrome, and 64 controls recruited during the same period, were examined. The time elapsed from onset of symptoms to blood collection was recorded. Cardiac markers were measured in specimens collected upon arrival (0 h), and 2 and 5 –9 h, and later in cases of longer observation. The major cardiac events occurring up to 40 months after the index examination were recorded.

*Results:* cTnT levels provided unique information: they were the most specific indicators of myocardial damage and identified unstable angina patients at high risk of future major events. Up to 6 h after the onset of chest pain, the new markers were elevated more frequently than the traditional ones and permitted earlier MI recognition. The worst prognosis (nonfatal myocardial infarction or death) was noted in subjects with chest pain at rest within 48 h before the index examination and elevated cTnT levels.

*Conclusions:* The new markers, particularly cardiac troponin T, offer considerable advantages and they should be more widely used in the diagnosis and risk stratification of acute coronary syndromes.

**Key words:** cardiac troponin T, CK-HB mass, acute coronary syndromes, unstable angina, myocardial infarction

## Introduction

The combination of vasospasm, atherosclerosis, and nonocclusive or occlusive thrombosis of coronary arteries produces a spectrum of syndromes of increasing severity, including stable and unstable angina (SA, UA), as well as non-Q-wave and Q-wave myocardial infarction (MI). Increased serum activities of creatinine kinase (CK) and its MB isoenzyme have been used for many years to detect acute myocardial infarction (AMI).[1,2] However, these markers are neither cardiac specific, nor sensitive enough to identify minor myocardial necrosis. Newer markers, such as cardiac isoforms of troponins (T and I), are more specific and more sensitive indicators of myocardial damage; others, like the protein or mass of CK-MB and myoglobin, while less specific, are released faster than other constituents, permitting an earlier recognition or exclusion of myocardial necrosis.[2–4] Since the optimal use of these new markers in the emergency evaluation of patients with acute chest pain syndromes is not yet definitely established, we compared the diagnostic utility of cardiac troponin T (cTnT), CK-MB mass, and myoglobin with that of activities of CK and CK-MB. In addition, reviewing major cardiac events occurring up to 40 months thereafter, we also evaluated the contribution of cTnT to risk stratification of acute coronary syndromes. At the time of the index examination, only the cTnT test, not cardiac troponin I (cTnI), was available. Thus, we were unable to compare the relative utility of the two troponins in the present paper.

## Population and Methods

The population consisted of 179 patients (109 men, 70 women), seen in the emergency service of our hospital, a ter-

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tiary cardiac center, in the Spring of 1993. The main cohort consisted of 115 consecutive patients with an acute chest pain syndrome. Eleven patients with valvular disease, 21 patients with noncardiac chest pain, and 32 patients with chronic SA, recruited during the same period, served as controls. The clinical history of coronary artery disease, the results of complete physical examination and 12-lead electrocardiogram (ECG), the time elapsed from onset of symptoms to blood collection, as well as the conditions preceding chest pain (at rest; after physical exercise) were recorded.

Blood was collected upon arrival (0 h), and at 2 and 5–9 h (6.1 ± 1.2 h), as well as 12, 24, and 48 h later in patients who needed longer observation. Serum activity of CK (U/l) and of its MB isoenzyme (CK-MB U/l) was measured at 37°C, with reagents of Boehringer-Mannheim GmbH (Mannheim, Germany) on a Hitachi 717 analyzer (Tokyo, Japan). Cardiac troponin T levels were measured quantitatively with the first generation of Enzymun-test on an ES-300 analyzer, both from Boehringer-Mannheim. Creatine kinase-MB protein or mass, as well as myoglobin concentration were measured with reagents from Behring on an Opus II analyzer [Beckman Instruments (Canada) Inc., Montreal, QC]. The upper reference limits of normal were defined as follows: CK ≤200, CK-MB ≤ 30 U/l; CK-MB mass ≤ 5.0, myoglobin ≤ 100, and cTnT ≤ 0.10 μg/l. Results of CK and CK-MB activities were reported immediately and considered in medical decisions, but the results of the other cardiac markers were not revealed and did not affect treatments.

Unstable angina was diagnosed in patients having chest pain while resting, or for the first time, as well as if the frequency and severity of chest pain increased, accompanied by CK and CK-MB activities within the reference range. These patients were also classified according to Braunwald's criteria.[5] Acute MI was diagnosed in the presence of two of the three entities: (1) prolonged chest pain; (2) gradual increase of serum CK-MB activities above normal reference range; and (3) ischemic ECG changes, with or without new Q waves. In September 1996, the medical records were reviewed for the following subgroups: (1) nonischemic chest pain (n = 21); (2) SA (n = 32); (3a) UA with normal serum cTnT concentration (n = 74; Braunwald class I = 14, class II = 1, class III = 59); (3b) UA with increased cTnT concentration (n = 13; all in Braunwald class III); (4) AMI ( n= 28). The frequency of major coronary events [emergency observation for > 24 h or hospitalization for cardiac reasons; thrombolysis, coronary angioplasty (PTCA), aortocoronary or mammarocoronary bypass graft surgery (CABG, MCBG); nonfatal MI; cardiac death] occurring before, during, or after the index examinations of 1993 was recorded. The date of follow-up nonfatal MI or death was identified.

### Statistical Analysis

The Stat View (ABACUS) program was used for statistical evaluations. The differences between the results of continuous variables of various subgroups were compared by the ANOVA procedure and those in the nominal variables by Pearson chi-square test or the Fisher's exact test. The cumulative hazard curve of cardiac death or nonfatal MI as first event was examined by the Kaplan-Meier method and the differences were judged by log rank statistics.

## Results

### Baseline Clinical Characteristics

Table I shows the baseline clinical characteristics, including the initial ECG changes and the frequency of major previous cardiac events of selected subgroups. As expected, the frequency of previous MI and of prior hospitalization was lower in the subgroup of nonischemic chest pain than in other subgroups. In both the cTnT negative and positive subgroups of UA, the frequency of prior hospitalization was higher than in the AMI group. The frequency of prior PTCA was also higher in the subgroup of cTnT negative UA than in the subgroup of AMI. Table II shows the frequency of past cardiac events/patient. The figures indicate that, in general, the patients with cTnT positive UA had more previous cardiac events (hospitalization, PTCA, AMI) than the other subgroups.

### Biochemical Characteristics

*Patients with valvular disease, atypical chest pain, or chronic stable angina (n = 64):* Eleven patients had valvular disease or arrhythmias of nonischemic origin (Table IIIA). Atypical chest pain occurred in 21 patients, and 32 patients (Table IIIB) had chronic stable angina (Table IIIC). All mean values of the three groups were within reference range and similar at 0, +2, and +5–7 h. Regarding the individual results, 7 of 64 patients (11%) had elevated but stable CK activity and 1 of 64 (1.6%) elevated, stable CK-MB activity. Nevertheless, in these patients the normal CK-MB mass and myoglobin concentrations did not indicate recent skeletal muscle lesions and the normal cTnT values excluded recent myocardial damage.

*Patients with acute coronary syndromes (n = 115):* There were three categories of patients with acute coronary syndromes:

(a) CK-MB activity and cTnT serum level within reference range:

In all, 74 patients had UA with < 0.1 μg/l cTnT values (Table IV), and 58 of these had severe chest pain at rest within 48 h (Braunwald class III). The mean values of markers did not differ from those shown in Table III. Five patients (6.8%) had elevated, stable CK but normal CK-MB activities. However, in these patients, the CK-MB mass and the myoglobin values were within reference range and the normal cTnT concentration excluded recent myocardial damage.

(b) CK-MB activity within reference range or stable and cTnT levels elevated: Thirteen patients had UA with elevated cTnT values (Table IVB). During the 48 h preceding the examination, all patients had chest pain at rest. The means of nonspecific cardiac markers were within reference limits,

TABLE I Baseline clinical characteristics

| | (1) | (2) | Acute coronary syndrome (3) Unstable angina | | (4) MI |
|---|---|---|---|---|---|
| Characteristics | Non-ischemic chest pain | Chronic stable angina | (a) CK-MB normal cTn T normal | (b) CK-MB normal cTn T elevated | CK-MB elevated |
| Number of patients | 21 | 32 | 74 | 13 | 28 |
| Age (mean ± SD) | 57.3 ± 13.2 | 61.3 ± 13.2 | 60.8 ± 10.9 | 65.7 ± 9.9 | 62.2 ± 11.1 |
| Female gender | 10 (47.6%) | 15 (46.9%) | 26 (35.1%) | 7 (53.8%) | 7 (25%) |
| History of MI | 2 (9.5%) | 13 (41%)[a] | 38 (51.4%)[b] | 9 (69.2%)[c] | 12 (43%)[d] |
| Prior hopsitalization | 8 (38.1%) | 26 (81%)[a] | 63 (85.1%)[b] | 11 (84.6%)[c] | 12 (43%)[g, h, i] |
| Prior CABG | 4 (19%) | 8 (25%) | 14 (18.9%) | 3 (23.1%) | 4 (14%) |
| Prior PTCA | 1 (4.8%) | 8 (25%) | 41 (55.4%)[b] | 5 (38.5%)[c] | 3 (11%)[h] |
| Thrombolysis | 1 (4.8%) | 2 (6%) | 3 (4.1%) | 0 | 2 (7%) |
| Time from chest pain onset to blood collection (h) | 5.0 ± 4.4 | 4.2 ± 4.6 | 6 ± 6.5 | 4 ± 4.8 | 5.8 ± 5.8 |
| ECG changes at arrival | | | | | |
| None | 7 (33.3%) | 9 (28%) | 8 (10.8%)[b, e] | 0[c, f] | 1 (3.6%)[d, g] |
| Nonspecific | 4 (19%) | 5 (16%) | 48 (64.9%)[b, e] | 6 (46.2%) | 7 (25%)[h] |
| New ST-T changes | 0 | 8 (25%)[a] | 15 (20.3%)[b] | 7 (55.8%)[c] | 8 (29%)[d] |
| New Q waves | 0 | 0 (0%) | 0 | 0 | 9 (32%)[d, h] |
| Other | 10 (47.6%) | 10 (31%) | 3 (4.1%)[b, e] | 0[c, f] | 3 (10.7%)[d] |

$p < 0.05$.
[a] 2 vs. 1.
[b] 3a vs. 1.
[c] 3b vs. 1.
[d] 4 vs. 1.
[e] 3a vs. 2.
[f] 3b vs. 2.
[g] 4 vs. 2.
[h] 4 vs. 3a.
[i] 4 vs. 3b.

*Abbreviations:* MI = myocardial infarction, CK = creatine kinase, cTn T = cardiac troponin T, SD = standard deviation, CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty, ECG = electrocardiogram.

without significant change with time; by definition, the cTnT values were elevated. The range of the peak values was between 0.11–1.14 μg/l. The cTnT values were elevated in all specimens of seven patients. One patient (7.7%) had stable, elevated CK and CK-MB activity and four patients (31%) had modestly increased CK-MB mass concentration. None of the patients had elevated myoglobin values.

(c) Consecutive increases of CK-MB activity and cTnT levels: Twenty-eight patients were in this group and had fulfilled the diagnostic criteria of AMI, 9 of 28 (32%) of them with and 19 of 28 (68%) without new Q waves. The means ± standard deviations of old and new cardiac markers, observed at different time intervals, as well as the delays from beginning of symptoms to blood collection are indicated in Tables V A–C. At arrival (0 h), CK and CK-MB activities were elevated in nine (32%) patients, in whom the time elapsed between the beginning of symptoms and arrival was the longest. In all patients, chest pain occurred at rest. Seven of these patients had Q-wave and two had non-Q-wave infarction. Two hours after arrival, five (18% of AMI) additional patients had elevated CK and CK-MB activities; in two of these the chest pain started at rest. All of the patients had non-Q-wave infarction. By 5 to 9 h after arrival, 14 (50% of AMI) additional patients had elevated CK and CK-MB activities. In nine patients, the chest pain started at rest. Two patients had Q-wave and 12 had non-Q-wave infarction.

Table VI shows the relative frequency, in terms of numbers of patients, with which AMI could be diagnosed by increased values of various cardiac markers, together with the other manifestations, at arrival, at + 2 hours, or later (6.1 ± 1.2 h). Increased CK or CK-MB activity permitted confirmation of the diagnosis of AMI in 32% of patients at arrival, in 50% 2 h later, and in all 5–9 h after arrival. Replacement of these tests with CK-MB mass determination would probably permit earlier recognition of AMI: 2 h after arrival, 75% of patients had increased values; when compared with the frequency of elevat-

TABLE II Mean number of past caridac events/patient in subgroups of coronary artery disease (mean ± standard deviation)

| | (A) Stable angina (n = 32) | (B) Unstable angina cTnT negative (n = 74) | (C) Unstable angina cTnT positive (n = 13) | (D) Myocardial infarction (n = 28) |
|---|---|---|---|---|
| Age | 61.3 ± 13.2 | 59.1 ± 12.8 | 65.7 ± 9.9 | 62.6 ± 11.0 |
| Hospitalization | 2.2 ± 1.7 | 2.9 ± 2.6 | 4.1 ± 3.9 | 0.9 ± 1.2 [a, b] |
| Myocardial infarction | 0.44 ± 0.56 | 0.57 ± 0.62 | 1.15 ± 1.07 [c, d] | 0.25 ± 0.44 [e] |
| PTCA | 0.41 ± 0.80 | 0.63 ± 1.03 | 0.85 ± 1.57 | 0.14 ± 0.45 [f] |
| PAC | 0.25 ± 0.44 | 0.20 ± 0.44 | 0.39 ± 0.87 | 0.14 ± 0.36 |
| Thrombolysis | 0.06 ± 0.25 | 0.04 ± 0.20 | 0 | 0.07 ± 0.26 |
| All events | 3.37 ± 2.41 | 4.34 ± 3.58 | 6.69 ± 5.74 [g] | 1.50 ± 2.19 [h, i] |

[a] D vs. B p = 0.0024.
[b] D vs. C p = 0.0013.
[c] C vs. A p = 0.0116.
[d] C vs. B p = 0.0307.
[e] D vs. C p = 0.0016.
[f] D vs. C p = 0.0462.
[g] C vs. A p = 0.0352.
[h] D vs. B p = 0.0035.
[i] D vs. C p = 0.0002.

*Abbreviations:* PAC = premature atrial contraction. Other abbreviations as in Table I.

ed results for CK-MB activity, the higher frequency of elevated results of CK-MB mass or myoglobin approached the level of significance (p = 0.055). Five to 9 h after arrival, all patients had elevated values for all markers, except for myoglobin, which disappears faster from blood than the other markers.

Table VII indicates the relative frequency of elevated serum concentration of various biochemical markers above the reference range, obtained at various time intervals after the beginning of clinical symptoms leading to AMI. The significant differences are indicated. The prevalence of elevated markers

TABLE III Serum concentration of cardiac markers in patients without acute coronary syndromes (means ± SD)

| | 0 h | +2 h | +5–7 h | p Value |
|---|---|---|---|---|
| A. Patients without coronary heart disease (n = 11) | | | | |
| CK (U/l) | 82 ± 18 | 77 ± 13 | 74 ± 12 | NS [a] |
| CK-MB (U/l) | 11 ± 4 | 10 ± 6 | 10 ± 4 | NS [a] |
| CK-MB mass (μg/l) | 1.6 ± 0.6 | 2.1 ± 1.6 | 1.7 ± 0.6 | NS [a] |
| Myoglobin (μg/l) | 19 ± 6 | 19 ± 8 | 19 ± 6 | NS [a] |
| cTroponin T (μg/l) | 0.007 ± 0.006 | 0.005 ± 0.007 | 0.008 ± 0.009 | NS [a] |
| B. Patients with atypical chest pain (n = 21) | | | | |
| CK (U/l) | 102 ± 59 | 94 ± 53 | 91 ± 47 | NS [a] |
| CK-MB (U/l) | 11 ± 5 | 11 ± 6 | 12 ± 5 | NS [a] |
| CK-MB mass (μg/l) | 1.6 ± 1.0 | 1.5 ± 0.8 | 1.7 ± 0.8 | NS [a] |
| Myoglobin (μg/l) | 19 ± 13 | 20 ± 16 | 21 ± 17 | NS [a] |
| cTroponin T (μg/l) | 0.002 ± 0.004 | 0.006 ± 0.007 | 0.005 ± 0.007 | NS [a] |
| C. Patients with chronic stable angina ( n = 32) | | | | |
| CK (U/l) | 113 ± 75 | 106 ± 69 | 104 ± 64 | NS [a, b] |
| CK-MB (U/l) | 14 ± 6 | 12 ± 5 | 14 ± 7 | NS [a, b] |
| CK-MB mass (μg/l) | 1.8 ± 1.2 | 1.8 ± 1.1 | 1.9 ± 1.3 | NS [a, b] |
| Myoglobin (μg/l) | 20 ± 13 | 20 ± 13 | 22 ± 14 | NS [a, b] |
| cTroponin T (μg/l) | 0.012 ± 0.013 | 0.014 ± 0.019 | 0.015 ± 0.020 | NS [a, b] |

[a] Compared with 0 h, no significant changes at +2 or +5–7 h.
[b] Compared with A or B, there are no significant changes for any of the parameters.

*Abbreviations:* SD = standard deviations, h = hour, NS = not significant. Other abbreviations as in Table I.

TABLE IV Serum concentration of cardiac markers in patients with unstable angina

| | 0 h | +2 h | +5–7 h | p Value |
|---|---|---|---|---|
| A. Normal troponin T vales (n = 74) | | | | |
| CK (U/l) | 101 ± 64 | 93 ± 62 | 91 ± 58 | NS |
| CK-MB (U/l) | 14 ± 9 | 14 ± 10 | 14 ± 10 | NS |
| CK-MB mass (μg/l) | 1.6 ± 1.1 | 1.7 ± 1.1 | 1.7 ± 1.2 | NS |
| Myoglobin (μg/l) | 21 ± 18 | 21 ± 17 | 21 ± 16 | NS |
| cTroponin T (μg/l) | 0.012 ± 0.016 | 0.015 ± 0.017 | 0.017 ± 0.020 | NS |
| B. Elevated troponin T values (n = 13) | | | | |
| CK (U/l) | 102 ± 91 | 87 ± 66 | 85 ± 57 | NS |
| CK-MB (U/l) | 19 ± 19 | 16 ± 7 | 13 ± 4 | NS |
| CK-MB mass (μg/l) | 2.8 ± 2.1[a] | 3.3 ± 2.5[a] | 4.0 ± 2.5[a] | NS |
| Myoglobin (μg/l) | 30 ± 30 | 32 ± 23 | 31 ± 25 | NS |
| cTroponin T (μg/l) | 0.222 ± 0.298[a] | 0.277 ± 0.304[a] | 0.292 ± 0.263[a] | NS |

[a] $p < 0.001$ compared with Group A.
NS = compared with 0 h, no significant changes at +2 or +5–7 h.
Abbreviations as in Table III.

was quite low in patients examined within 3 h. Up to 6 h after the beginning of chest pain, serum myoglobin concentration was the most frequently increased cardiac marker, followed by CK-MB mass. In samples obtained at 6.1–9 h, these two markers were always positive, followed closely by the other markers. At 9.1–12 h all markers except myoglobin were positive. At that time all markers except myoglobin were more frequently above the reference range than earlier, and myoglobin was more frequently above reference range than at 0–3 h. At > 12 h, CK activity and cTnT concentration were always elevated, followed closely by CK-MB measured either as activity or as protein mass.

**Follow-Up Clinical Events**

Figures 1 to 3 represent, for selected subgroups, the cumulative hazard curves of cardiac death or nonfatal MI as first event, occurring up to 40 months after the index examination. Figure 1 shows the curves of patients in the cTnT negative and positive UA groups, as well as of those with AMI. The hazard curves of patients in the cTnT positive versus negative UA group were significantly different. In the cTnT positive group, 5 of 13 (38.5%) patients had cardiac events and 4 of 13 (30.5%) died; on the other hand, in the negative group, 10 of 74 (13.5%) patients had cardiac events and 8 of 74 (10.8%)

TABLE V Serum concentration of cardiac markers in patients with acute myocardial infarction (mean ± SD)

| | 0 h | +2 h | +5–7 h | p Value |
|---|---|---|---|---|
| Diagnostic of AMI at arrival or 0 h (n = 9). Delay between beginning of clinical symptoms and 0 h: 12.3 ± 5.9 h | | | | |
| CK (U/l) | 1005 ± 1040 | 1013 ± 907 | 1265 ± 983 | > 0.10 |
| CK-MB (U/l) | 142 ± 148 | 133 ± 112 | 153 ± 103 | > 0.10 |
| CK-MB mass (μg/l) | 82.8 ± 92.5 | 79.7 ± 77.6 | 96.9 ± 72.7 | > 0.10 |
| Myoglobin (μg/l) | 347 ± 400 | 430 ± 449 | 521 ± 800 | > 0.10 |
| cTroponin T (μg/l) | 3.548 ± 5.383 | 4.349 ± 6.109 | 6.139 ± 6.353 | 0.0012 |
| Diagnostic of AMI at +2 h (n = 5). Delay between beginning of clinical symptoms and 0 h: 2.5 ± 2 h | | | | |
| CK (U/l) | 139 ± 59 | 414 ± 250 | 1072 ± 1152 | 0.1007 |
| CK-MB (U/l) | 20 ± 3.8 | 51 ± 28 | 129 ± 115 | 0.0692 |
| CK-MB mass (μg/l) | 3.7 ± 1.9 | 25.4 ± 14.2 | 30.2 ± 17.0 | 0.0091 |
| Myoglobin (μg/l) | 67 ± 50 | 659 ± 763 | 509 ± 564 | > 0.10 |
| cTroponin T (μg/l) | 0.21 ± 0.42 | 0.870 ± 0.850 | 2.112 ± 1.906 | 0.0613 |
| Diagnostic of AMI at +5–9 h (6.1 ± 1.2) (n = 14). Delay between beginning of clinical symptoms and 0 h: 2.4 ± 1.6 h | | | | |
| CK (U/l) | 112 ± 44 | 144 ± 61 | 424 ± 237 | < 0.0001 |
| CK-MB (U/l) | 12 ± 3 | 19 ± 11 | 58 ± 31 | < 0.0001 |
| CK-MB mass (μg/l) | 2.3 ± 1.1 | 5.2 ± 3.2 | 29.0 ± 20.0 | < 0.0001 |
| Myoglobin (μg/l) | 50 ± 73 | 177 ± 144 | 229 ± 131 | < 0.0001 |
| cTroponin T (μg/l) | 0.024 ± 0.042 | 0.062 ± 0.064 | 0.520 ± 0.430 | < 0.0001 |

*Abbreviation:* AMI = acute myocardial infarction. Other abbreviations as in Table III.

TABLE VI Relative frequency ( in terms of number of patients) with which AMI could be diagnosed by increased concentration of a biochemical marker at arrival or later

| | At arrival | | +2 h | | +5–9 h | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| CK > 200 U/l | 9 | 32.1 | 14 | 50 | 28 | 100[b,c] |
| CK-MB > 30 U/l | 9 | 32.1 | 13 | 46.4 | 28 | 100[b,c] |
| CK-MB mass > 5 µg/l | 11 | 39.3 | 21 | 75[a] | 28 | 100[b,c] |
| Myoglobin > 100 µg/l | 10 | 35.7 | 21 | 75[a] | 23 | 82.1[b] |
| cTroponinT > 0.1 µg/l | 11 | 39.3 | 17 | 60.7 | 28 | 100[b,c] |

$p < 0.05$.
[a] 2 vs. 0 h.
[b] 5–9 vs. 0 h.
[c] 5–9 vs. 2 h.
*Abbreviations:* AMI = acute myocardial infarction, CK = creatine kinase, h = hour.

died. The frequency of future MI/patient was also significantly higher in cTnT positive UA population than in negative subgroup ($1.15 \pm 1.07$ vs. $0.57 \pm 0.62$; $p = 0.031$). The future risk hazard curve of patients in the cTnT positive UA group did not differ significantly from AMI patients; 7 of 28 (25%) patients with AMI had cardiac events and 6 of 28 (21.4%) died. However, in the cTnT positive UA group, the number of future hospitalizations/patient for cardiac events was higher than that in the MI subgroup ($2.9 \pm 2.6$ vs. $0.9 \pm 1.2$; $p = 0.021$). Figure 2 shows that the cumulative hazard curve of all patients with elevated cTnT levels (cTnT positive UA as well as AMI) also differed significantly from those with cTnT levels within the reference range. In the group with elevated cTnT levels, 12 of 41 (29.3%) patients had future events and 10 of 41 (24.4%) died; in the group with normal cTnT levels, 10 of 106 (9.4%) patients had cardiac events and 8 of 106 (7.5%) died. Figure 3 compares the cumulative hazard curves of all patients with UA+AMI belonging to Braunwald class I with those of class III. Not considering the AMI observed within the first 8 h after arrival, the risk of future AMI or of cardiac death was significantly higher in the second group: only 1 of 40 (2.5%) patients in Braunwald class I had a cardiac event and died, but 21 of 104 (20.2%) class III patients had future cardiac events and 9 of 104 (8.7%) died. It is evident from these figures that the identification of patients in the cTnT positive UA group selects the group with highest risk of future cardiac events or mortality; most of these events occurred during the first year after index examination.

## Discussion

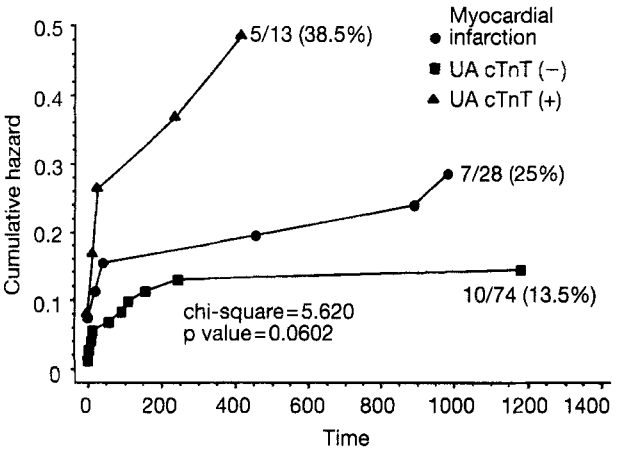
### The Importance of Cardiac Troponin T in the Diagnostic Workup and Risk Stratification of Unstable Angina

Recent publications[6–17] demonstrated an increased risk of future cardiac events for patients whose acute coronary syndrome was associated with elevated serum cTnT levels. However, the conditions of these studies varied considerably. In most, the population consisted of patients with UA, but some included all acute coronary syndromes. Only three used

TABLE VII Relative frequency of increased values of cardiac markers at various time intervals after onset of clinical symptoms of acute myocardial infarction

| | 0–3 h (%) (n = 20) | 3.1–6.0 h (%) (n = 17) | 6.1–9.0 h (%) (n = 19) | 9.1–12.0 h (%) (n = 10) | >12 h (%) (n = 18) |
|---|---|---|---|---|---|
| CK > 200 U/l | 10 | 35.3 | 94.7[b,e] | 100[c,f] | 100[d,g] |
| CK-MB > 30 U/l | 10 | 29.4 | 89.5[b,e] | 100[c,f] | 94.4[d,g] |
| CK-MB mass > 5 µg/l | 20 | 52.9 | 100[b,e] | 100[c,f] | 94[d,g] |
| Myoglobin > 100 µg/l | 30 | 70.6[a,i] | 100[b,c] | 90[c] | 55.5[h,k,j] |
| cTroponin T > 0.1 µg/l | 15 | 47.0 | 89.5[i] | 100[c,f] | 100[d,g,l] |

$p < 0.05$.
[a] 3.1–6 h vs. 0–3 h.
[b] 6.1–9 h vs. 0–3 h.
[c] 9.1–12 h vs. 0–3 h.
[d] > 12 h vs. 0–3 h.
[e] 6.1–9 h vs. 3.1–6 h.
[f] 9.1–12 h vs. 3.1–6 h.
[g] > 12 h vs. 3.1–6 h.
[h] > 12 h vs. 6.1–9 h.
[i] CK-MB vs. myoglobin at 3.1–6 h.
[j] CK-MB vs. myoglobin at > 12 h.
[k] CK-MB mass vs. myoglobin at > 12 h.
[l] c Troponin T vs. myoglobin at > 12 h.
Abbreviations as in Table VI.




UA cTnT (−) vs. UA cTnT (+): chi-square=5.215; p value=0.024
UA cTnT (+) vs. AMI: chi-square=0.926; p value=0.336

FIG. 1 Cumulative hazard curves of cardiac death or nonfatal myocardial infarction as first event in patients with acute coronary syndrome. UA = unstable angina, cTnT = cardiac troponin T, AMI = acute myocardial infarction.

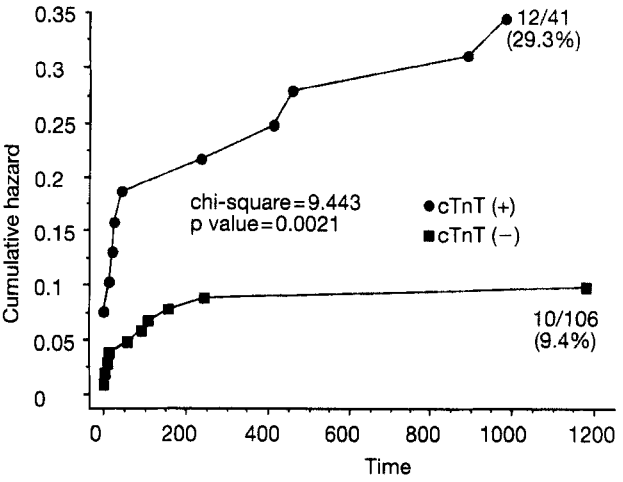



FIG. 2 Cumulative hazard curves of cardiac death or nonfatal myocardial infarction as first event in patients with positive or negative troponin.

the Braunwald classification of UA. The timing of blood collection differed considerably; in some only one specimen was measured, in others specimens were collected for up to 2 days. The first studies used 0.2 μg/l, the most recent ones 0.1 μg/l, as discriminatory level of cTnT. In most studies, the period of follow-up extended only for a few weeks, whereas in two studies it lasted for 5 or 6 months and in two for up to 28–36 months. Hamm *et al.*,[6] during the relatively short period of hospitalization, noted a higher risk of future events in patients with UA having μ0.2 μg/l cTnT values. With similar discriminatory values, and following patients with UA for up to 28–36 months, Ravkilde *et al.*[10] and Stubbs *et al.*[14] presented similar observations. Lindahl *et al.*[15] observed patients with UA for up to 5 months and noted a low risk of cardiac events among those who had < 0.06 μg/l cTnT levels, an intermediate risk with 0.06–0.18 μg/l, and a high risk with greater serum concentrations. Recently, Ohman *et al.*[16] noted a higher mortality rate within 30 days among patients seen with AMI who had > 0.1 μg/l cTnT values. Antman *et al.*[18] obtained similar data measuring cTn I.

In our study, during a follow-up of 40 months, the patients with UA who had ≥ 0.1 μg/l serum cTnT values had a tendency for more future nonfatal MI ($p = 0.0667$) and had a significantly higher cardiac mortality ($p = 0.0394$) than patients with SA. The cumulative hazard curve for these events was significantly higher among patients with cTnT positive UA than in those with cTnT negative UA. Most of the events occurred within the first year (Fig. 1). We would have missed patients with cTnT positive UA if we had measured cTnT only at arrival, but the relative frequency of cTnT positive UA might have been higher if we had collected blood in all patients with UA not only for up to 9 h, but up to 24 h.

Increased cTnT levels indicate myocardial damage, and as in other studies, the cumulative hazard curve of our patients with cTnT positive UA did not differ significantly from that of patients with AMI (Fig. 1). Comparing all patients with positive versus negative cTnT, as in recent studies,[16] a significantly higher risk of future events was noted in the cTnT positive than in the cTnT negative group (Fig. 2). Thus, cTnT positive UA patients seem to be in the same pathologic and clinical entities as AMI patients, and cTnT positive UA could be viewed as a small non-Q-wave AMI.

Apparently onset of chest pain at rest projects a much higher risk for later cardiac events for all acute coronary syndromes. All of our patients with cTnT positive UA had this characteristic. Even in the cTnT negative UA subgroup, only those in Braunwald class III had future cardiac events. While AMI was observed after considerable physical exercise in eight patients, even these patients had a much lower risk for

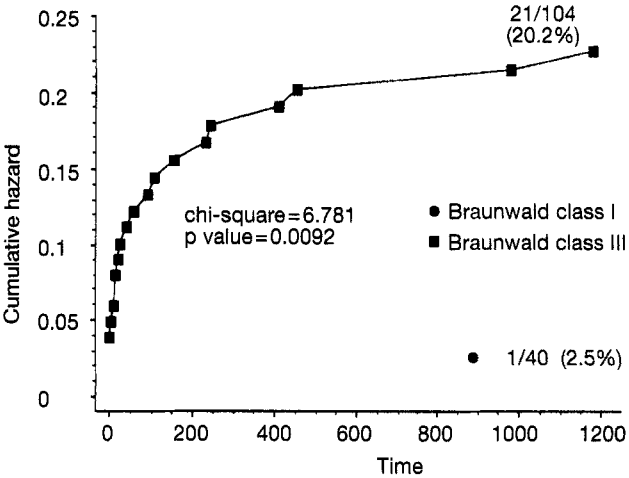



FIG. 3 Cumulative hazard curves of cardiac death or nonfatal myocardial infarction as first event in patients with Braunwald class I or III.

later future cardiac events than those in whom the chest pain occurred at rest. Thus, comparing the late future risk in all Braunwald III versus I patients, cumulative hazard curves differed significantly (Fig. 3).

Our study is the first to indicate that patients with cTnT positive UA had more frequent previous cardiac hospitalizations than patients with cTnT negative UA or those who had AMI at index examination. In more detail, they had more previous AMI than patients with SA, with cTnT negative UA, or patients with AMI at index examination. They also had more previous PTCA than the patients with AMI at index examination. Thus, patients with cTnT positive UA had more cardiac events not only in the future but also in the past, than the other groups. It is reasonable to assume that these patients have unstable atherosclerotic plaques, producing several episodes of minor myocardial necroses.

All these data indicate that one should measure cTnT in all patients with UA, preferably in more than one specimen. Future prospective studies are needed to evaluate which of the various treatments (plaque stabilization, anticoagulation, PTCA, CABG) could best diminish the high risk of future cardiac events among patients with cTnT positive UA. Compared with SA, even the cTnT negative, but Braunwald class III patients with UA are at higher risk of future cardiac events and should be followed carefully. In our population, two such patients had AMI 24 h after the index examination.

### The Importance of Creatine Kinase-MB Mass, of Myoglobin, and of Cardiac Troponin T in the Diagnostic Workup of Acute Myocardial Infarction

Several recent studies analyzed the role of various biochemical markers in the diagnosis of AMI.[2, 3, 19–25] It is generally accepted that ischemic damage of cardiomyocytes increases the permeability of their cellular membranes and those of cellular organelles, and facilitates the release of cellular constituents into the circulation. The greater the cellular damage and thus the permeability, the larger are the molecules that can be released. The best marker of myocardial damage would be a specific constituent, the molecular weight, dimensions, and intracellular localization of which leads to its earliest release and for which there is a precise, reliable non-time-consuming technique for its detection in serum. To assure the earliest detection of MI, the consecutive specimens should be collected within a shorter time interval than previously suggested (e.g., at arrival, + 2 h, etc.). Among the new markers examined, cTnT isoform is a specific constituent of cardiomyocytes; however, in rare conditions, it can also be expressed in skeletal muscle.[26–29] Normally, it is not detectable in the serum in the majority of patients. Thus, a small increase of its concentration indicates myocardial damage with great sensitivity and specificity. The available data suggest that cTnT I level could provide the same advantages.[18] Use of either marker is suggested by the American Heart Association.[25]

In general, our results are in agreement with those of recent studies. Evidently, in a patient arriving with clinical manifestations suggesting AMI, the moment when an increased cardiac marker supports the diagnosis depends on the delay between the onset of clinical manifestations and patient arrival. In our population, within 3 h after the beginning of chest pain, most of the markers were within the reference range. At 3.1–6 h, serum myoglobin was significantly more frequently elevated than CK–MB activity. At 6.1–9 h most, and at 9.1–12 h all of the markers except myoglobin were elevated. At arrival, not considering the delay between onset of chest pain and arrival, only 32% of patients had elevated CK and CK-MB activities; cTnT, CK-MB mass, and myoglobin were elevated in a somewhat greater number of patients. Two h after arrival, 75% of patients had elevated CK-MB mass and myoglobin levels, followed in frequency of positive results by cTnT, and activities of CK and CK-MB. At 5–9 h post arrival, all the markers except myoglobin were positive (Table VI). The differences between markers at the three time intervals were not significant. It can be suggested that normal values of myoglobin up to 2 h after arrival are useful for excluding AMI in patients arriving relatively soon after the beginning of chest pain. However, in our series, 5 of 28 (18%) patients with proven AMI had stable myoglobin values within reference range, some of these observed shortly after beginning of chest pain. The advantage of cTnT was not in its fastest increase, but in its greatest specificity as marker of myocardial injury. In addition, elevated cTnT could identify the MI developed 4–10 days earlier, when the other markers would give negative results.

## Conclusions

1. For the proper selection of biochemical markers for earliest indication of AMI, one should evaluate, whenever possible, the time of delay between the beginning of clinical symptoms and the examination of patients. With 0–3 h delay few, but with >9 h delay all of the markers provide evidence of AMI. The use of the new markers is most advantageous in patients examined with 3–9 h delay after the onset of symptoms. The chronological order of increase of various markers is myoglobin, CK-MB mass, cTnT, CK, and CK-MB activities.

2. The classification of UA according to Braunwald provides more homogeneous subgrouping of patients. Our results also indicate that chest pain at rest within the last 48 h is associated in itself with increased risk of future cardiac events for patients with both UA and MI.

3. In patients without ECG evidence of AMI at arrival, who represent the majority, the biochemical markers provide the most important diagnostic and prognostic information. In each patient with an acute coronary syndrome, one should measure cTnT, CK, and CK-MB mass values, the latter particularly in those arriving within 3–6 h of the beginning of symptoms or in those having reinfarction within 4–10 days.

4. To exploit the advantages of aggressive treatment of AMI, all the initial (0 h) negative or positive results need rapid reevaluation 2 and 5–8 h later, thus within a shorter time frame than practiced earlier.

(a) Consecutively increasing values of cTnT, CK-MB mass, and CK confirm the diagnosis of AMI.

(b) Because serum CK-MB mass normalizes faster after AMI than does cTnT, CK-MB mass determination is recommended for the confirmation of reinfarction within 10 days.

(c) Moderately elevated, relatively stable cTnT results, accompanied by stable CK that is within reference range, will identify patients with UA with highest risk of future cardiac events.

(d) Normal cTnT and CK-MB mass values up to 8 h after arrival can exclude with high probability both actual AMI and high-risk UA. Nevertheless, patients with cTnT negative UA in Braunwald class III also have moderately increased risk of future cardiac events and need attentive follow-up and an additional measurement of cTnT and CK-MB mass 16–24 h after the index examination.

5. Certainly, cardiac troponin tests (a fast quantitative cTnT technique, or the actual test of cTnI) and CK-MB mass determinations will gain importance in the diagnostic workup of acute coronary syndromes. While such a change will generate somewhat greater expenses in the laboratory, the earlier and more correct identification and suitable treatment of high-risk patients will probably save money in the long term.

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