increased in the other 13 (mean, 14.5 μg/L; range, 6.9–24.8 μg/L). No correlation was found between cTnI and ST-segment changes. Electrocardiograms showed ST-segment alteration in two patients with echocardiographic signs of MC and in two patients without MC signs.

cTnI concentrations peaked between 6 and 12 h after chest trauma and disappeared 48–96 h after the trauma. Thus, the diagnostic window was narrower than it is during acute myocardial infarction, probably because of the lower peak serum concentration of cTnI.

We conclude that:

- The incidence of MC in our patients was 18%, as detected by TEE investigation.
- All of the MC patients had a positive cTnI test (>0.4 μg/L).
- The cTnI assay is more specific than CK-MB for MC after chest injury. The receiver operating characteristic curve shows the clinical performance of the two markers. Assuming that the cutoff concentrations for cTnI and CK-MB are 1.1 μg/L and 18 μg/L, respectively, these markers showed 100% (0.83–1.1 μg/L) and 80% (0.56–0.95 μg/L) specificity (Fig. 1).
- cTnI >1.1 μg/L indicates a cardiac lesion observable through TEE. Other authors have reported different cTnI cutoff concentrations that are >1.1 μg/L; the discrepancy is probably due to a different mode of echocardiographic investigation (6).
- Serum cTnI concentrations of 0.4–1.1 μg/L could be indicative of microlesions of cardiac tissue not detectable by echocardiography.

References


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Combined Use of Markers of Muscle Necrosis and Fibrinogen Conversion in the Early Differentiation of Myocardial Infarction and Unstable Angina

To the Editor:

Intracoronary formation of blood clots on ruptured arteriosclerotic plaques is considered the main cause of acute myocardial infarction (AMI) (1). After such ruptures, exposed tissue factor binds to factor VIIa from plasma, and the resulting tissue factor-factor VIIa complex activates factor X toward factor Va, the enzyme converting prothrombin to thrombin. By cleavage of fibrinopeptides A and B, thrombin produces desAABB-fibrin monomers that polymerize into still-soluble complexes called “thrombus precursor proteins” (TpPs). New antigens formed on these complexes were used for a TpP assay (2).

Because the acute thrombotic event precedes coronary occlusion and muscle necrosis, detection of activated coagulation potentially allows early detection of AMI. Until now, attempts in this field have focused on markers for factor Xa and thrombin activity, such as prothrombin fragment 1.2 and thrombin-antithrombin complexes. However, these markers are not necessarily closely related to the actual formation of fibrin clots (3), especially in chronically hypercoagulable patients, and TpP could perform better in this respect. We therefore studied plasma concentrations of TpP and fibrin monomers (FMs) in patients with suspected AMI. The results were compared with two small cytosolic cardiac marker proteins, myoglobin (Mb) and fatty acid-binding protein (FABP), that are early markers for necrosis (4, 5) and with a highly cardiосpecific marker, troponin I (TnI).

TpP was determined with a monoclonal sandwich ELISA provided by American Biogenetic Sciences (2). Intrassay imprecision, estimated on three different days by the 11-fold determination of three pools of citrated plasma with 2.9, 10.1, and 20.7 mg/L of TpP added, was 16%, 11%, and 12%, respectively (CVs). Interassay imprecision, estimated from duplicate measurements on 20 different days of citrated donor plasma and similar plasma with added TpP, was 23% and 30%, respectively, with mean values of 2.5 and 11.6 mg/L. FMs were determined with a sandwich ELISA (Boehringer Mannheim). The assay measures the free amino terminus of fibrin Aα-chains. Mb was determined with an immunoturbidimetric assay (Hoffmann-La Roche); FABP was determined with a monoclonal sandwich ELISA as described (6), creatine kinase MB isoenzyme (CK-MB) was determined with a microparticle immunoassay (Abbott), and TnI was determined with a one-step sandwich ELISA (Boehringer Mannheim). ROC curves were obtained from double logarithmic plots (7).
Twenty-five patients entering the University Hospital Maastricht with AMI or unstable angina pectoris (UAP) were studied. The final diagnosis of AMI required at least two of the following conditions: (a) typical chest pain, (b) electrocardiogram changes indicating AMI, or (c) a plasma CK-MB concentration exceeding the locally established cutoff value of 8 μg/L. Standard treatment included oral aspirin, intravenous heparin, and elective thrombolytic therapy or percutaneous transluminal coronary angioplasty. As of October 1, 1997, none of the patients had died, and no patient with UAP developed AMI, during the 16 y follow-up.

After patients gave informed consent, a blood sample was obtained before medication was given. Clotting was prevented with sodium citrate, and plasma was stored at −80 °C. The median delay between the first symptoms and acquisition of the blood sample was 3 (range, 0.8–5) h in 15 patients with AMI (9 men and 6 women) and 2.6 (0.5–6) h in 10 patients with UAP (6 men and 4 women). The median ages were 71 (35–87) years and 64 (51–78) years, respectively. A tendency toward higher TpP values when delays in hospitalization were shorter (4 mg·L⁻¹·h⁻¹) was noted, but that tendency did not hold for FM. As shown in Fig. 1, the assay for TnT did not discriminate between AMI and UAP in patients who were hospitalized early. Median TnT values, with first and third quartiles, were 0.12 (0.08–0.14) μg/L in patients with AMI and 0.13 (0.05–0.25) μg/L in patients with UAP. Better discrimination was observed for FM and for TpP, and even better discrimination was observed for Mb and FABP. For clinical application of the low cutoff values shown in Fig. 1, day-to-day imprecision of the TpP and FABP assays should be reduced.

In the AMI group, FABP and Mb concentrations were highly correlated (r = 0.90), whereas the correlation between TpP and FM was much weaker (r = 0.49). Interestingly, FABP and TpP were not significantly correlated (r = 0.01). Apparently the two markers identified different patients; this suggests a potential for clinical utility in the combined use of these markers. Indeed, 87% sensitivity with 80% specificity was obtained when either FABP > 6 μg/L or TpP > 7 mg/L was considered as diagnostic for AMI. Moreover, the performance of both a combined test will be relatively insensitive to delays in hospitalization because the TpP assay will perform better in patients hospitalized earlier, whereas the FABP assay will perform better in patients admitted later (4, 5).

Low TpP values were found in patients with UAP, with the TpP concentration exceeding 6 mg/L (8.1 mg/L) in only one patient. Moreover, this patient was the only one showing a slight CK-MB increase (to 6 μg/L) over the next day, suggesting minor necrosis. Such lack of coagulation activation in UAP patients contrasts with data in the literature (8, 9) and may be explained by two factors: Prothrombin fragment 1.2 and thrombin-antithrombin complexes, as measured in these studies, may correlate poorly with fibrin generation in spite of a hypercoagulable state (3, 9) and minimal myocardial necrosis, as reflected by borderline increases of TnT or of CK-MB, identified UAP patients with no better prognosis than patients with AMI (10). Our use of a CK-MB cutoff of 8 μg/L shifted such patients to the AMI group, which could explain the lack of TpP and FM in the remaining UAP patients.

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More on Interference of N-Acetylcysteine in Measurement of Acetaminophen

To the Editor:

Acetaminophen (ACET) is a common analgesic and antipyretic drug that in excessive concentrations may cause acute liver damage and acute renal failure (1). Although the normal elimination of ACET seems to involve conjugation of a toxic alkylating metabolite with liver glutathione to yield a detoxified conjugation product, excessive doses of ACET deplete liver glutathione stores, causing accumulation of the toxic metabolite N-acetyl-imidoquinone (1–3).

Acetylcysteine (NAC, N-acetyl-3-mercaptoalanine) is the drug of choice for the treatment of an ACET overdose. Although the mechanism responsible for the ability of NAC to serve as an effective antidote in vivo has not been fully elucidated, a major route of detoxification seems to depend on the ability of NAC to serve as a potent sulfhydryl donor that restores depleted hepatic reduced glutathione (3).

A 28-year-old woman was recently admitted to the emergency room of our hospital after a confirmed (suicidal) ACET overdose. One hour after treatment with NAC was initiated (150 mg/kg of body weight, infused i.v. for 15 min), a blood sample was withdrawn for ACET assay in our laboratory. We routinely assay ACET by an enzymatic assay (GDS enzymatic acetaminophen, GDS Diagnostics) based on the hydrolysis of ACET by acylamidase to yield p-aminophenol and acetate. The p-aminophenol is measured colorimetrically by its conversion to indophenol in the presence of o-cresol, using periodate as a catalyst. Unexpectedly, no ACET was found in the serum despite the patient’s ingestion of a toxic dose of the drug. A similar enzymatic assay (acetaminophen assay, cat. no. 503–10, Diagnostic Chemical) that uses acyl amidohydrolase to cleave the amide bond in ACET but in which the formed p-aminophenol reacts with 8-hydroxyquinoline in the presence of manganese ions to form the colored compound 5-(4-iminophenol)-8-quinolone, also failed to detect ACET in the sample.

In contrast to the two enzyme-based assays that failed to demonstrate ACET intoxication, the TDx assay (Abbott Laboratories) confirmed high, toxic concentrations of the drug in the same blood sample. The TDx assay is based on the competition between ACET in the sample and tracer-labeled ACET for a specific antibody and measures the change in the polarization of fluorescent radiation emitted by the fluorescein-labeled tracer.

These conflicting results and a recent report on false negative results for urinary ACET screening in the presence of NAC (4) raised the possibility that NAC interferes with the

Fig. 1. Comparison of enzymatic and TDx assays for ACET determination.
(A) Enzymatic assays; (B) TDx assay.