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Rapid Detection of Myocardial Infarction With a Sensitive Troponin Test

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Key Words: Troponin; Acute coronary syndrome; Myocardial infarction

Abstract

Rapid identification and treatment of patients with a myocardial infarction (MI) is mandatory. We studied the diagnostic capacities of a sensitive troponin assay for detection of MI in emergency department patients within 2 hours after arrival.

The study included 157 patients suspected of having non–ST-elevation acute coronary syndrome. Blood was drawn on arrival (T0) and 2 (T2), 6, and 12 hours later. At T2, a troponin concentration above the MI cutoff is 87% sensitive and 100% specific for MI detection (positive predictive value [PPV], 100%; negative predictive value [NPV], 96%). If a difference of more than 30% between the troponin measurements at T0 and T2 in the absence of an absolute troponin increase above the 99th percentile of a reference population is also considered indicative of MI, the sensitivity increases to 100% and specificity decreases to 87% (PPV, 70%; NPV, 100%). Sensitivity and specificity of creatine kinase–MB and myoglobin are lower than those of troponin.

By using a sensitive troponin assay and simple algorithms, the diagnosis of MI can be determined within 2 hours after arrival at the emergency department. Measurement of myoglobin and creatine kinase–MB has no added value.

Acute coronary syndrome (ACS) describes a constellation of clinical symptoms and is caused by acute myocardial ischemia.1 Because of high morbidity and mortality and availability of specific treatments, patients with ACS need to be identified rapidly among all patients admitted with chest pain.

ACS is subdivided into 2 major categories according to presence of specific changes on a 12-lead electrocardiogram (ECG) on admission: ST-segment elevation myocardial infarction (STEMI) and other or no ECG changes. The second category is termed non–ST-elevation ACS and further categorized into non–ST-elevation MI (NSTEMI) and unstable angina pectoris (UAP). NSTEMI is distinguished from UAP by elevation of the levels of markers of myocyte necrosis.2 Troponin concentrations above the 99th percentile of a reference population measured with a 10% or less coefficient of variation (CV) are considered the most sensitive and specific markers for myocardial necrosis.2-4 Early after infarction, elevated concentrations of the creatine kinase–MB fraction (CK-MB) or myoglobin may be more sensitive in detecting myocardial necrosis.2 Current guidelines recommend serial blood sampling in patients with symptoms of ACS at hospital admission and 6 to 9 hours thereafter.4

As analytic performance of troponin assays has improved during recent years, the threshold for the diagnosis NSTEMI has continuously been lowered. Today, several commercially available troponin assays have CVs that lie well within the 99th percentile of a reference population, enabling detection of increases of troponin within the reference limits. One of these assays is the TnI-ultra kit (Siemens Healthcare Solutions Diagnostics, Breda, the Netherlands).5 Therefore, troponin might be a suitable early marker of myocardial necrosis, enabling triage of patients with chest pain in fewer than 6 hours.
after hospital admission. Rapid triage is indicated to prevent irreversible damage to the myocardium. Alternatively, ruling out MI early after admission speeds up passage of patients through the emergency department, thereby decreasing the use of scarce resources. Therefore, we evaluated the diagnostic capacity of a sensitive troponin test very early, i.e., 2 hours after admission of a patient to the emergency department.

Materials and Methods

Study Protocol and Patients

The study was conducted as a single-center, observational, prospective, longitudinal trial at Catharina Hospital, Eindhoven, the Netherlands, according to the declaration of Helsinki. The study was approved by the Medical Ethical commission of Catharina Ziekenhuis following Dutch law. The protocol was registered and published by the Dutch Central Committee on Research involving Human Subjects (http://www.ccmo-online.nl) as trial No. NL16413.060.07.

Every patient entering the emergency department with suspicion of non-ST-elevation ACS was eligible for inclusion. After giving informed consent, patients were enrolled. In the Eindhoven region, ambulance personnel take ECGs on the way to the hospital, and patients with ST elevations on the ECG are directly transferred to the catheterization laboratory for reperfusion therapy. Therefore, few patients with STEMI are included in this study, i.e., only patients in whom ST elevations developed after arrival at the hospital are included.

Blood samples were drawn, and troponin concentrations were analyzed on arrival at the hospital (T0) and 2 (T2), 6 (T6), and 12 (T12) hours later. CK-MB and myoglobin concentrations were measured at T0, T2, and T6. Venipunctures at T0, T6, and T12 (if the troponin concentration at T6 was less than 0.1 μg/L) are routine clinical practice; the venipunctures at T2 and, in some cases, at T12 are an extra burden for patients included in this study. Because a venipuncture at T12 was obligatory for all patients, a patient could be enrolled only if a bed in the cardiology ward was available for at least 12 hours. Only troponin concentrations at T0, T6, and T12 were reported to the clinic and used to make a clinical diagnosis; the troponin concentration at T2 and myoglobin and CK-MB mass concentrations were not reported but were entered into the study database.

During the observation period, patients were monitored by a 12-lead ECG. If a new episode of chest pain occurred, a 12-lead ECG was obtained and compared with a tracing obtained when symptoms had resolved spontaneously or after nitrates were given. When deemed necessary, an echocardiogram was recorded to assess left ventricular function and to eliminate other cardiovascular causes of chest pain.

After the observation period of 12 hours, a final clinical diagnosis was made by the attending cardiologist (clinical diagnosis) using all routinely acquired data, i.e., without knowledge of the CK-MB mass and myoglobin concentrations or troponin concentration at T2. Patients were divided into the following groups: ACS-STEMI (persistent ST wave elevation on ECG and troponin level >0.1 μg/L), ACS-NSTEMI (dynamic ECG changes without persistent ST elevation in combination with troponin level >0.1 μg/L), unstable angina (ACS-UAP, dynamic ECG changes with troponin ≥0.1 μg/L), and without acute myocardial necrosis (no ECG changes and troponin level <0.06 μg/L). After enrollment of subjects was complete, the diagnostic capacity of troponin, CK-MB mass, and myoglobin concentrations for confirmation and exclusion of the diagnosis of MI (NSTEMI, STEMI) were tested by use of 2 × 2 contingency tables.

Methods

CK-MB mass, myoglobin, and cardiac troponin I concentrations were measured on an Advia Centaur immunochemistry analyzer (Siemens Medical Solutions Diagnostics) using the manufacturer’s assay kits. The TnI-Ultra troponin kit is a second-generation, high-sensitivity test with a 10% CV at 0.05 μg/L and a troponin concentration of 0.06 μg/L at the 99th percentile of a reference population. The 99th percentile was established on 221 samples from 221 outpatients with no history of myocardial disease.5 Myoglobin concentrations of more than 110 μg/L (6.3 nmol/L) and CK-MB concentrations of more than 5 μg/L are indicative of myocardial damage.6,7 All biomarkers were measured in heparin plasma (Vacutainer, 4 mL, LH 68 IU Plus; Becton Dickinson, Erembodegen, Belgium).

Results

Patient Population

The study included 157 patients. During analysis, 20 patients were excluded because of violation of the study protocol (e.g., early discharge or no venipuncture at T2). Population data and medical history of the 137 patients who completed the study protocol are summarized in Table 1.

Clinical Diagnoses

Clinical diagnoses were made by the attending cardiologist as described in the “Study Protocol and Patients” section. Of 137 patients, 37 were diagnosed with ACS: 7 with UAP, 26 with NSTEMI, and 4 with STEMI. Thus, the prevalence of ACS in the study population is 27%, and the prevalence of MI is 22%.
Diagnostic Capacity of Troponin

The diagnostic capacity of the different biomarkers was assessed by using 2 × 2 contingency tables. The clinical diagnoses served as the “gold standard”: NSTEMI and STEMI were classified as MI; patients without evidence of MI were judged clinically negative. Table 3 gives an overview of the diagnostic capacity of a troponin concentration of more than 0.1 μg/L (the MI cutoff value) at arrival in the emergency department and 2, 6, and 12 hours later. In the study population, the positive predictive value (PPV) of a troponin concentration at T0 and T2 above the MI cutoff was 100% at all points in time. The negative predictive value (NPV) increased from 92% at T0 to 96% at T2 and up to 99% at T6 and T12.

A more sensitive approach for detection of MI is summarized in Table 4. A troponin concentration at T0 or T2 above the 99th percentile of a reference population (0.06 μg/L) or an increase of 30% in the troponin concentrations between T0 and T2 with absolute concentrations less than 0.06 μg/L was considered biochemical evidence of MI. With this definition, the sensitivity of troponin for the clinical diagnosis of MI increases to 100%, while specificity decreases to 87%. The NPV is 100%, while the PPV declines to 70%.

Table 3
Diagnostic Capacity of Troponin Concentrations More Than the Myocardial Infarction Cutoff (>0.1 μg/L) to Detect Myocardial Infarction*

<table>
<thead>
<tr>
<th>T0</th>
<th>T2</th>
<th>T6</th>
<th>T12</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>1.00 (0.81-1.00)</td>
<td>1.00 (0.84-1.00)</td>
<td>1.00 (0.85-1.00)</td>
</tr>
<tr>
<td>NPV</td>
<td>0.92 (0.84-0.96)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.99 (0.94-1.00)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.70 (0.68-0.93)</td>
<td>0.97 (0.90-1.00)</td>
<td>0.99 (0.94-1.00)</td>
</tr>
<tr>
<td>Specificity</td>
<td>1.00 (0.95-1.00)</td>
<td>1.00 (0.95-1.00)</td>
<td>1.00 (0.95-1.00)</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.

* Test characteristics are shown for time of arrival at the emergency department (T0) and 2 (T2), 6 (T6), and 12 (T12) hours later; 95% confidence intervals are in parentheses.

Diagnostic Efficiency of Troponin

By using the sensitive approach outlined, measurement of troponin concentrations at T0 and T2 has a diagnostic efficiency ([30 True-Positive + 87 True-Negative Patients]/137 Patients) of 85%. Because there are no false-negative troponin results (Table 4), the putative diagnosis of MI can be ruled out for patients whose troponin values remain negative after 2 hours. In the population studied, this was 68.6% of patients ([87 Without Necrosis + 7 UAP]/137 Patients). Of the 137 patients, 31.4% (43 patients) needed to be observed further. Of the 43 patients, 70% (30 patients) were finally diagnosed with MI.
Myoglobin and CK-MB in the Detection of MI

To assess potential added value of myoglobin and CK-MB in the early detection of MI, myoglobin and CK-MB were measured on arrival of patients in the emergency room and 2 and 6 hours later. As shown in **Table 5**, the sensitivity and specificity of CK-MB and myoglobin are lower than those of troponin. Thus, when using a sensitive troponin assay, measurement of myoglobin or CK-MB mass does not aid in early detection of MI.

### Discussion

This study investigated the performance of a sensitive troponin assay early after arrival in the emergency department. Only patients with chest pain but without ST segment elevation on ECG were included. The study was thus performed in the patient group that benefits most from the diagnostic information of troponin: patients with non-ST-elevation ACS. In this patient group, a negative troponin level on repeated measurements rules out acute myocardial necrosis and a positive test result warrants further investigation into its origin. NSTE-MI then is a likely diagnosis, although nonischemic causes must be excluded.8

Two decision thresholds were tested in this study to predict MI. The first is a peak troponin concentration of more than 0.1 μg/L. The second is a troponin concentration above the 99th percentile but less than 0.1 μg/L or a 30% difference between 2 troponin measurements within the 99th percentile. We chose 2 cutoffs for 2 reasons. First, it is known that the 99th percentile of a reference population for a sensitive troponin test is strongly dependent on the reference population. For the test used here, 99th percentiles from 0.04 to 0.08 μg/L have been described.5,9,10 Second, a recent report on intraindividual variation indicated that owing to the low index of individuality for troponin (a low index of individuality indicates that reference values may be of less value), the relative change in troponin concentration may be the preferred strategy to identify myocardial necrosis.11

The National Academy of Clinical Biochemistry guideline12 arbitrarily states that a 20% change in troponin concentration should be applied to detect a rise and fall in troponin levels. We chose a 30% change because Wu and coworkers11 reported a 10% intraindividual within-day variation and the between-day analytic precision of the Advia Centaur ultra troponin analyzer used in this study is 6.6% at 0.1 μg/L (n = 350; 240 days; data not shown). Therefore, a 30% change in troponin concentrations within 2 hours signifies acute myocardial necrosis (2 × the combined CVs). With this approach, all patients with the final diagnosis of MI are identified within 2 hours after arrival in the emergency department (NPV, 1; 95% confidence interval [CI], 0.95-1.00). As expected, applying a higher cutoff of 0.1 μg/L yields a lower NPV (~95%) in combination with a PPV of 1 (95% CI, 0.81-1.00).

These results are comparable to what others have reported on the performance of the Advia troponin ultra test.13,14 Both studies assessed the predictive power of a single troponin measurement within 3 hours after arrival at the emergency department and included all patients with chest pain (including STEMI). A troponin concentration of 0.04 μg/L was used as cutoff. The studies found sensitivities and specificities of about 90%. The NPVs were close to 100% in combination with PPVs of about 65%.

Because sensitive troponin assays are able to detect minimal myocyte damage from any cause, the serial measurement of troponin to detect a rise and fall is important to differentiate acute damage from other causes of myocyte necrosis. Therefore, in accordance with clinical and laboratory guidelines,12,15 we advocate the use of serial measurements as compared with a single measurement to detect myocyte necrosis.

In parallel with troponin measurement, we tested the value of CK-MB mass and myoglobin as early markers of MI. Our results confirm an earlier report that a sensitive troponin assay alleviates the need for the use of CK-MB and myoglobin testing.16

A clear limitation of this study is the relatively low number of patients included. Therefore, subgroup analysis was not possible, and the 95% CIs of several predictive values are broader than one would want. On the other hand, the performance of the Centaur troponin assay in the current study is very comparable to what others have reported before.13,14 What this study adds is the notion that the lack of a troponin change of 30% or more is sufficient to exclude MI as the cause of chest pain. To our knowledge, this study is the first to demonstrate that troponin can be used to rule out MI within 2 hours after admission of the patient.

**Table 5**

| Diagnostic Capacity of CK-MB Mass and Myoglobin to Detect Myocardial Infarction* |
|-------------------------|----------------|----------------|
|                         | T0             | T2             | T6             |
| CK-MB mass              | 0.92 (0.92-1.00) | 0.82 (0.56-0.95) | 0.91 (0.69-0.98) |
| PPV                     | 0.85 (0.77-0.91) | 0.84 (0.75-0.91) | 0.91 (0.84-0.96) |
| Sensitivity             | 0.42 (0.25-0.63) | 0.48 (0.30-0.67) | 0.69 (0.49-0.89) |
| Specificity             | 0.99 (0.93-1.00) | 0.96 (0.89-0.99) | 0.98 (0.92-0.99) |
| Myoglobin               | 0.75 (0.43-0.93) | 0.67 (0.42-0.85) | 0.96 (0.56-0.97) |
| PPV                     | 0.83 (0.74-0.91) | 0.86 (0.76-0.91) | 0.85 (0.76-0.91) |
| Sensitivity             | 0.32 (0.17-0.52) | 0.50 (0.31-0.69) | 0.41 (0.24-0.61) |
| Specificity             | 0.97 (0.90-0.99) | 0.92 (0.84-0.96) | 0.98 (0.92-1.00) |

CK-MB, creatine kinase–MB fraction; PPV, negative predictive value; PPV, positive predictive value.

* Test characteristics are shown for time of arrival at the emergency department (T0) and 2 (T2) and 6 (T6) hours later; 95% confidence intervals are in parentheses.
This study suggests that MI can be ruled out safely within 2 hours after admission if a sensitive troponin assay is used and a sensitive algorithm is applied. Other markers of myocyte damage have no added value in the diagnosis of MI. With this approach, MI is dismissed as the cause of chest pain in 68% of the patients arriving at the emergency department. About two thirds of the remaining patients are finally diagnosed with MI. If these results are confirmed in a larger cohort, a clinical protocol can be introduced that substantially speeds up early diagnosis of MI. Thereby, time to diagnosis and length of hospitalization may be shortened and cost efficiency increased.

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References