Office Cardiologists Cooperative Study on Whole Blood Rapid Panel Tests in Patients With Suspicious Acute Myocardial Infarction

— Comparison Between Heart-Type Fatty Acid-Binding Protein and Troponin T Tests —

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Background  The whole blood rapid troponin T test, used to determine the early diagnosis of acute myocardial infarction (AMI), is effective only for 3–4 h after onset.

Methods and Results  The present office cardiologists cooperative study compared the diagnostic efficacy of a newly developed whole blood rapid panel test for heart-type fatty acid-binding protein (H-FABP) with that of the rapid troponin T test in 129 consecutive patients with suspicious AMI according to certain time-frames from onset to presentation. Thirty-one patients (24.0%) had a final diagnosis of AMI. The respective sensitivities of the rapid H-FABP and troponin T tests were 100% vs 50% (p<0.05) for patients presenting within 3 h of onset; 75% vs 0% for those between 3 and 6 h; 100% vs 60% for those between 6 and 12 h; and 100% vs 100% for those presenting later than 12 h. The respective specificities were 63% vs 96.3% (p<0.05); 93.8% vs 93.8%; 72.7% vs 100%; and 75.0% vs 87.5%. Negative predictive value was 100% vs 86.7%; 93.8% vs 78.9%; 100% vs 84.6%; and 100% vs 100%, respectively. Patients with non-AMI myocardial damage associated with unstable angina or severe heart failure showed positive H-FABP test results and blunted the specificity.

Conclusions  When using the novel rapid H-FABP test, cardiac emergency triage to exclude non-AMI patients should be effectively organized within 3 h of onset. (Circ J 2004; 68: 144–148)

Key Words: Acute coronary syndrome; Fatty acid-binding protein; Myocardial infarction; Point of care; Troponin T; Unstable angina

Cardiac emergency triage and the therapeutic decision are the crucial issues in the effective management of acute myocardial infarction (AMI). Detection of an early phase biochemical marker specific for myocardial damage would provide better diagnostic and therapeutic decisions for patients with suspicious AMI. The currently available simple and rapid whole blood assay for cardiac troponins fulfills, at least in part, such a need1–3 but as we have reported, the rapid troponin T (TnT) test is not always effective for diagnosing AMI in the early acute phase4,5.

Heart-type fatty acid-binding protein (H-FABP) is a low molecular weight protein that is abundant in the cytosol and is rapidly released from the cytosol into the circulating blood after myocardial damage. Consequently, quantitative measurement of serum H-FABP concentration is a novel sensitive marker for the early diagnosis of AMI6–8. We have recently reported the diagnostic efficacy of a newly developed whole blood rapid panel test for H-FABP in the Multicenter Emergency Triage by Rapid H-FABP Test (MET-HFABP) study. The present office cardiologists cooperative study compared the diagnostic efficacy of the newly developed rapid H-FABP test with that of rapid TnT test in routine clinic practice.

Methods

Patients and Sample Collection

The present study enrolled 129 consecutive patients

<table>
<thead>
<tr>
<th>Table 1 Clinical Background of the Patients</th>
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<tbody>
<tr>
<td>Age (years), mean (standard deviation)</td>
</tr>
<tr>
<td>Male n, (%)</td>
</tr>
<tr>
<td>Risk factors and past history n, (%)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
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<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Smoking</td>
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<td>ECG findings</td>
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<tr>
<td>ST elevation</td>
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<tr>
<td>ST depression</td>
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<tr>
<td>Bundle branch block</td>
</tr>
<tr>
<td>T wave inversion</td>
</tr>
<tr>
<td>Arrhythmia or pacing</td>
</tr>
<tr>
<td>No abnormal findings</td>
</tr>
</tbody>
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Circ J 2004; 68: 144–148
Tokyo-ROC Study on Rapid Panel Tests for AMI

Table 2 Electrocardiographic Findings According to the Specified Time-Frame From the Onset to Presentation

<table>
<thead>
<tr>
<th></th>
<th>Within 3h</th>
<th>3 to &lt;6h</th>
<th>6 to &lt;12h</th>
<th>≥12h</th>
<th>Unclear</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST elevation</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>20</td>
<td>6</td>
<td>61 (48.0)</td>
</tr>
<tr>
<td>ST depression</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>25 (9.7)</td>
</tr>
<tr>
<td>T inversion</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td></td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
<td>5</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>No specific change</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>No abnormal findings</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>11 (8.7)</td>
</tr>
</tbody>
</table>

Results

Final Diagnoses of the Patients

The final diagnosis for 31 patients (24.0%) was AMI according to the WHO criteria, 50 (38.8%) were diagnosed as non-AMI cardiovascular disease, such as unstable angina (n=17), stable angina pectoris (n=8) or other cardiovascular diseases (n=25), and 48 patients (37.2%) were diagnosed as having non-cardiovascular etiology, such as reflux esophagitis, gastric ulcer, upper respiratory infection, cholecystitis, or other diseases.

Comparison of Diagnostic Tests

The respective sensitivities of the rapid H-FABP and TnT tests were 100% vs 50% (p<0.05) for patients presenting within 3 h of onset; 75% vs 0% between 3 and 6h; 100% vs 60% between 6 and 12h; and 100% vs 100% for later than 12h (Table 3, Fig 1). The respective specificities were 63% vs 96.3% (p<0.05); 93.8% vs 93.8%; 72.7% vs 100%; and 75.0% vs 87.5%. Thus, the sensitivity of the rapid H-FABP test was significantly higher in the early acute phase within 3 h of onset. Conversely, the specificity of the rapid TnT test was significantly higher in the early acute phase. Positive predictive values showed a tendency to be higher for the rapid TnT test and the respective negative predictive values were 100% vs 86.7%; 93.8% vs 78.9%; 100% vs 84.6%, and 100% vs 100%. Overall, the sensitivity of the rapid H-FABP test was greatest in the early acute phase, whereas that of the rapid TnT test came into line with the rapid H-FABP test at 12 h after onset.
Rapid H-FABP Test Results and Patient Outcome

Of 56 patients who were judged as H-FABP test positive, 49 (87.5%) were hospitalized and 28 patients (50%) were finally diagnosed as AMI and 4 as unstable angina (7.1%). None of the remaining 7 patients who were not hospitalized were diagnosed as AMI, but 4 (5.5%) were diagnosed as unstable angina.

False-Negative or -Positive Results of the Rapid H-FABP Test

False-negative results of the rapid H-FABP test were obtained in 3 patients and there were 20 false-positive test results (5 patients had unstable angina, 1 had angina pectoris, 1 had a previous myocardial infarction, 6 had congestive heart failure, 2 had hypertensive heart disease, and 5 had non-cardiovascular etiology).
Discussion

H-FABP Quantitative Assay and Rapid Panel Test

Although H-FABP is present in both the heart and skeletal muscle tissue, its concentration in skeletal muscle is 10-fold lower than that in the myocardium, compared with myoglobin, which is 2-fold higher in skeletal muscle than in myocardium\textsuperscript{12,13}. Comparative studies for the diagnosing of AMI have demonstrated that quantitative measurement of H-FABP is more sensitive than both myoglobin and CK-MB measurements, and more specific than myoglobin\textsuperscript{14,15}. Clinical investigations of the release kinetics of H-FABP and other biochemical markers have revealed that H-FABP is elevated above the cut-off level within 3 h of onset, reaching a peak value at 4 h, and its release into the blood is approximately 24–36 h after onset of AMI\textsuperscript{16,17}. However, a quantitative assay using the sandwich-ELISA method requires an analysis time of 90 min or more and requires the use of laboratory equipment, so whole blood rapid panel tests have been developed for use in emergency situations. The rapid H-FABP test detects concentrations of H-FABP >6.2 ng/ml, the cut-off level for diagnosing AMI, in whole blood samples within 15 min. In the MET-HFABP study we found that the concordance rate of the rapid H-FABP test and simultaneously obtained quantitative measurements was 84.6\%\textsuperscript{9}.

Diagnostic Efficacy of Rapid H-FABP Test

The introduction of the rapid TnT test for cardiac emergencies was revolutionary because it facilitated rapid bedside evaluation and risk stratification in patients with suspected acute coronary syndrome\textsuperscript{1,2}. However, our previous study, the Tokyo TnT Trial, which evaluated the diagnostic efficacy of the rapid TnT test, revealed that positive test results could only be obtained more than 3–4 h after onset because of the time-lag in the release kinetics of TnT, and therefore the diagnostic sensitivity was temporally limited for patients assessed in the early acute phase\textsuperscript{1,3}. The present study again showed this limitation in the diagnostic sensitivity of the rapid TnT test in the early acute phase. Its sensitivity was 50\% for patients visiting within 3 h of onset, which is the most beneficial time-frame for performing coronary reperfusion therapy to salvage the myocardial infarct and thus improve long-term prognosis\textsuperscript{18,19}. The present comparative study clearly demonstrated a markedly higher sensitivity of the rapid H-FABP test (100\%) for diagnosing AMI in this early acute phase and its use should therefore assist in the making of earlier and appropriate therapeutic decisions.

Another advantage of the rapid H-FABP test is its superior negative predictive value, which reached almost 100\% for patients of all time-frames. In contrast, the rapid TnT test displayed significantly higher specificity than the rapid H-FABP test. A multicenter study of cardiac emergency in the United States, the Chest Pain Evaluation in the Emergency Room (CHEER), reported that approximately 50\% of patients hospitalized with suspected AMI were non-cardiac cases, and 2–5\% of patients with AMI were overlooked in emergency rooms. The authors of the CHEER Institute a chest pain observation unit to establish the differential diagnosis of chest pain on 6 h of serial monitoring of ECG and CK isoenzyme measurements, and demonstrated an effective and cost-saving means of cardiac primary care for patients with suspected AMI\textsuperscript{20}. Although they did not use rapid panel tests in their study, their results and our data taken together emphasize the clinical utility of rapid panel tests in cardiac emergencies. When using the rapid H-FABP test, however, cardiac emergency triage to exclude non-AMI patients should be organized to take effect within 3 h of onset. McCord et al\textsuperscript{21} recently reported the efficacy of 90 min exclusion of AMI by using quantitative point-of-care testing of troponin I and myoglobin: the sensitivity and negative predictive value were both more than 95\% for the combination of troponin I and myoglobin at 90 min after the initial visit. However, they did not analyze the diagnostic efficacy according to time-frames from onset to presentation, which we have done and thereby demonstrated the greater diagnostic efficacy of the rapid H-FABP test in the early acute phase without the necessity of repeated assessments.

Background of the False-Negative or Positive Test Results

Three false-negative results for the rapid H-FABP test were obtained. Two of the patients had not had the time onset of symptoms clarified and the reason for the false negative test results in those 2 patients seems to be the short diagnostic time-frame of the rapid H-FABP test, which is associated with the relatively short time release kinetics of H-FABP in AMI in which serum H-FABP concentrations normalize within 48–72 h of onset. Therefore, we believe that the onset of AMI in the 2 patients was not within the diagnostic time-frame of rapid H-FABP test. Another patient was entered into the time-frame of between 3 and 6 h of onset of chest pain and this patient had negative test results for not only the rapid H-FABP test, but also for the TnT test. Although both tests were negative, the treating physician recommended hospitalization because of the ST elevation in anterior leads, which strongly suggested acute or previous myocardial infarction. The reason for the false test results in this case seems to be inadequate judgment of the time of onset, which can be difficult to determine in a cardiac emergency.

On the other hand, false-positive results for the rapid H-FABP test were obtained in 15 patients with non-AMI cardiovascular diseases, such as unstable angina or severe congestive heart failure, and in 5 patients with non-cardiovascular diseases. However, the non-AMI cardiovascular group should be interpreted as true positive because presumably there was myocardial damage. We have shown that H-FABP and TnT are markers of ongoing myocardial damage and are associated with subsequent cardiac events in patients with chronic heart failure\textsuperscript{22}. The present study cannot exactly explain why there were more than a few patients with non-cardiovascular etiology who showed positive test results, but it may be related to contamination by skeletal muscle damage or diminished renal clearance, as we recently reported\textsuperscript{9,22}.

Study Limitations and Clinical Implications

Recently, the Joint Committee of the European Society of Cardiology and American College of Cardiology presented a redefinition of AMI and recommended that troponins should be measured as the AMI marker because of their almost absolute myocardial tissue specificity and high sensitivity, reflecting myocardial necrosis at even the microscopic level\textsuperscript{23}. In the present study, the diagnosis of AMI was based on the ECG and measurement of CK and CKMB according to the WHO criteria because of the universal distribution of those criteria in Japan. Thus the diagnostic values of the 2 rapid tests would be underesti-
ized compared with the newly redefined criteria. From the viewpoint of more effective emergency triage, further investigation to definitively establish the diagnostic cut-off level of H-FABP is necessary so that AMI according to the new definitions is not misdiagnosed. However, it may not be easy to distinguish AMI from unstable angina by H-FABP measurement because the distinctive merit of TnT, the essential marker in the redefinition of AMI, is that any release of TnT into the circulating reflects the development of myocardial damage itself and TnT is never detected (or below the detection limit of assay) in normals. Another issue would be the prognostic value of the rapid H-FABP test. Although many studies have shown the prognostic value of TnT measurements in patients with acute coronary syndrome, there are as yet few reports regarding the prognostic value of either H-FABP measurement or the rapid H-FABP test in patients with acute coronary syndrome. Further investigation of whether the rapid H-FABP test is valuable for prognostic assessment compared with the TnT test is necessary. The results of the present study suggest that the newly developed rapid H-FABP test compensates for the limitations of the rapid TnT test; namely, its ability to exclude non-AMI patients in the early acute phase.

References

Appendix 1

The following office cardiologists enrolled the patients with suspicious AMI from their clinic practice according to the protocol for the present Tokyo Rapid-test Office Cardiologists (Tokyo-ROC) study. Takashi Nakamura, MD, Kunio Tanaka, MD, Yoshio Katoh, MD, Akiko Nomura, MD, Yoshikuni Osamura, MD, Kanji Ohbayashi, MD, Mitsuko Katoh, MD, Kaoru Katoh, MD, Hisatake Aoki, MD, Shin-ichiro Shimai, MD, Hiroshi Kikuchi, MD, Kengo Suzuki, MD, Keiko Itoh, MD, Kyonono Koike, MD, Terumitsu Kohda, MD, Hirokazu Saitoh, MD, Masahiro Akaie, MD, Kaname Kuchii, MD, Noriko Isogane, MD, Yoshimi Tomita, MD, Yoshio Yoshida, MD, Seihiro Ono, MD, Hiromu Hamamoto, MD, Shin-ichi Ohkuni, MD, Takeshi Ino, MD, Norikatsu Mori, MD, Hanuyuki Nakagawa, MD.