The role of heart-type fatty acid-binding protein in the diagnosis of acute coronary syndrome

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J Rosman, G Kavala, K Obunai, SR Bergmann. The role of heart-type fatty acid-binding protein in the diagnosis of acute coronary syndrome. *Int J Angiol* 2009;18(2):79-81.

BACKGROUND: Heart-type fatty acid-binding protein (H-FABP) is a membrane-bound protein that facilitates transport of fatty acids from the blood into the heart. It is currently being used outside the United States for the early diagnosis of myocardial infarction (MI). However, previous studies have shown inconsistent correlation of H-FABP with standard cardiac biomarkers.

METHODS: Fifty patients admitted with ST segment elevation MI (n=25), non-ST segment elevation MI (n=15) or unstable angina (n=10) were evaluated. The CardioDetect med cardiac infarction test (rennesens GmbH, Germany) was used to measure both qualitative and quantitative H-FABP.

In conjunction with clinical symptoms and electrocardiogram (ECG) changes, cardiac troponins I and T are currently the gold standard for the biochemical diagnosis of acute myocardial infarction (MI) (1,2). Troponins are large proteins located predominately within the structure of myocardial fibers. Because of the large size and location of troponin, it can take several hours to detect serum levels of troponin in patients presenting with an acute MI (3). This can lead to a delay in diagnosis and treatment in patients with acute coronary syndrome (ACS).

Heart-type fatty acid-binding protein (H-FABP) is a low molecular weight cytoplasmic protein. Because of its small size and location, it is released rapidly into the blood following myocardial damage (4,5). It is currently used to diagnose MI outside the United States in patients presenting shortly after chest pain onset. However, the accuracy and utility of H-FABP for diagnosing MI and unstable angina is not well established (4-10). We therefore evaluated the sensitivity and specificity of H-FABP in patients presenting with ACS.

METHODS

Patient selection

The study population consisted of 50 patients admitted to Beth Israel Medical Center (New York, New York, USA) within 24 h of chest pain onset. A standard 12-lead ECG was obtained to evaluate for ST segment elevation MI (STEMI). Serum values for troponin I were obtained on presentation. Serial blood samples were drawn every 6 h to obtain peak level of cardiac enzymes. After written, informed consent was obtained, serum drawn from blood venipuncture was used to measure qualitative and quantitative levels of H-FABP using a rapid H-FABP assay (CardioDetect med; rennesens GmbH, Germany).

RESULTS: Of the 40 patients with acute MI, the initial troponin assay was positive in 35 patients (88%), the qualitative H-FABP assay was positive in 23 patients (58%) and the quantitative H-FABP assay was positive in 15 patients (38%) ($P=0.001$). No patient with MI had a positive H-FABP assay with a negative initial troponin assay.

CONCLUSION: In the present study, the results of both the qualitative and quantitative H-FABP assays neither appeared earlier nor provided increased sensitivity compared with troponin in diagnosing acute MI. Accordingly, the use of H-FABP as a diagnostic tool for MI is limited.

Key Words: Acute coronary syndrome; Cardiac biomarkers; Fatty acid-binding protein; Myocardial infarction; Troponin

Methods

The diagnosis of MI and unstable angina was determined based on medical history, clinical presentation, ECG findings and results of cardiac biomarkers (1). All patients with a history of ACS, who presented within 24 h of chest pain onset, were divided into three groups based on ECG findings and standard cardiac enzymes: STEMI (patients with standard cardiac enzymes greater than two times the upper limit of normal, a clinical history consistent with acute MI and greater than 0.2 mV ST segment elevation in two or more contiguous precordial leads, or greater than 0.1 mV ST segment elevation in two or more contiguous limb leads); non-STEMI (cardiac enzymes greater than two times the upper limit of normal and a clinical history consistent with MI but without ECG criteria for STEMI); and unstable angina (patients without elevated cardiac enzymes and without ECG criteria for STEMI, but with clinical history and ECG changes suggestive of unstable angina). Both qualitative and quantitative assessment of H-FABP levels were compared with initial troponin I levels to evaluate the clinical efficacy of H-FABP in diagnosing acute MI.

A rapid H-FABP assay (CardioDetect med) was used for the qualitative and quantitative analysis of H-FABP (11). For the qualitative assay, two shaded lines (control and H-FABP) on the H-FABP assay kit indicate positive results for MI. The H-FABP line detects serum H-FABP concentrations greater than 3×10^{-6} g/L. For the quantitative assay, the CardioDetect quant system measures the intensity of the results line on the CardioDetect med cards. A value of 7×10^{-6} g/L or greater was considered to indicate myocardial injury (11). An Investigational Device Exemption was obtained for the CardioDetect assays. The present study protocol was approved

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TABLE 1
Baseline characteristics (n=50)

Men, %	74
Age, years, mean $\pm$ SD	65 $\pm$ 17
History of coronary artery disease, %	47
Diabetes, %	31
Hypertension, %	64
Dyslipidemia, %	39
Smoking, %	41
Creatinine, μ mol/L, mean $\pm$ SD	141 $\pm$ 141

TABLE 2
Sensitivity and specificity of quantitative heart-type fatty acid-binding protein (H-FABP) for acute coronary syndrome

H-FABP positive, g/L	Sensitivity (n=40 patients with STEMI and NSTEMI)	95% CI	Specificity (n=10 patients with unstable angina)	95% CI
$\geq 3 \times 10^{-6}$	0.64	0.47–0.79	0.80	0.44–0.97
$\geq 4 \times 10^{-6}$	0.56	0.40–0.72	0.90	0.56–1.00
$\geq 5 \times 10^{-6}$	0.51	0.35–0.68	1.00	0.69–1.00
$\geq 6 \times 10^{-6}$	0.44	0.28–0.60	1.00	0.69–1.00
$\geq 7 \times 10^{-6}$	0.38	0.23–0.55	1.00	0.69–1.00

NSTEMI Non-ST elevation myocardial infarction; STEMI ST elevation myocardial infarction

by the Beth Israel Medical Center's Institutional Review Board.

Statistical analysis

Exact 95% CIs were calculated for the sensitivity and specificity estimates. Patients with unstable angina, who by definition did not have elevated levels of the standard biomarkers, served as the 'control' group. The Cochran-Armitage test was used to detect an upward trend in sensitivity estimates with increasing peak troponin level.

RESULTS

Of the 50 patients (Table 1), 29 (58%) presented within 6 h of chest pain onset and 21 (42%) presented after 6 h of chest pain. Twenty-five patients (50%) were diagnosed with STEMI, 15 (30%) with non-STEMI and 10 (20%) with unstable angina. Seventy-four per cent (n=37) of patients were men. The mean ($\pm$ SD) age of the cohort was 65 $\pm$ 16 years. Of the 40 patients with acute MI, the initial troponin was positive in 35 patients (88%); qualitative H-FABP was positive in 23 patients (58%) and quantitative H-FABP was positive in 15 patients (38%) ($P<0.001$). No patient had a positive H-FABP with a negative initial troponin.

The sensitivity and specificity of the qualitative H-FABP assay for detecting MI were 0.57 (95% CI 0.41 to 0.73) and 0.8 (95% CI 0.44 to 0.97), respectively. The sensitivity and specificity of the quantitative H-FABP assay for detecting MI were 0.38 (95% CI 0.23 to 0.55) and 1.0 (95% CI 0.69 to 1.00), respectively. Various levels of quantitative H-FABP were evaluated to determine the optimum cut-off value for best sensitivity and specificity (Table 2).

In the 40 patients with an MI, peak troponin level correlated with qualitative and quantitative H-FABP. As the peak level of troponin increased, there was a significant increase in

Figure 1) Percentage of heart-type fatty acid-binding protein (H-FABP) positive assay results based on peak troponin levels

TABLE 3
Accuracy of initial troponin and heart-type fatty acid-binding protein (H-FABP) obtained on presentation in acute coronary syndrome patients presenting <6 h after chest pain onset (n=29)

	Sensitivity	95% CI	Specificity	95% CI
Initial troponin	0.78	0.56–0.93	0.83	0.36–1.00
H-FABP qualitative	0.57	0.34–0.77	0.67	0.22–0.96
H-FABP quantitative	0.50	0.28–0.72	1.00	0.54–1.00

the percentage of positive, qualitative H-FABP assay results (Cochran-Armitage test for trend, $P<0.05$) and quantitative H-FABP values (Cochran-Armitage test for trend, $P<0.001$) (Figure 1). Patients who presented within 6 h of chest pain onset were evaluated to compare the accuracy of initial troponin and H-FABP in the early diagnosis of acute MI. Initial troponin was more sensitive than either qualitative or quantitative H-FABP (Table 3).

DISCUSSION

The present study showed that the predictive accuracy of H-FABP in diagnosing acute MI is inferior to troponin. The sensitivity of H-FABP, even in the first 6 h, was poor and significantly worse than troponin. The specificity of H-FABP was good and comparable with initial troponin levels.

Recent studies have correlated elevated levels of H-FABP with poor prognosis following ACS (12–14). However, studies evaluating the diagnostic accuracy of H-FABP have reported variable sensitivities and specificities (4–10). Okamoto et al (5) evaluated H-FABP in patients presenting within 12 h of chest pain onset. H-FABP had a sensitivity of over 90% and a specificity of 67%. Tanaka et al (6) evaluated H-FABP in 83 patients presenting within 12 h of chest pain onset. H-FABP had a sensitivity of 93% and a specificity of 64%. Seino et al (7) evaluated 371 patients with chest pain and suspected MI. H-FABP had a sensitivity of over 90% and a specificity of 50%. More recently, Mad et al (9) evaluated H-FABP levels in 280 patients presenting within 24 h of chest pain. H-FABP had a sensitivity of 69% and specificity of 74%. Valle et al (10) evaluated 419 patients presenting within 3 h of chest pain. H-FABP had a sensitivity of 60% and specificity of 88%. The results of the present study are more consistent with Mad et al (9) and Valle et al (10), with low sensitivity and high

specificity. This is in contrast to earlier studies that reported high sensitivities but low specificities (5-8). Taken together, the disparity and variability observed for H-FABP sensitivities and specificities suggests that H-FABP is not a reliable early marker for detecting myocardial damage.

CONCLUSION

The results of the present study demonstrate that H-FABP is not a sensitive marker for the early diagnosis of acute MI. Troponin, even in the initial hours after symptom onset, had a higher diagnostic yield than H-FABP. Accordingly, its use as a biomarker for ACS is limited.

Limitations

The major limitation of the present study was the small sample size. However, when diagnosing acute MI, the sensitivity of an assay should be as high as possible, ideally 100%, so that therapy is not mistakenly withheld in a life-threatening situation. Despite the small cohort, it is unlikely that more patients would have yielded results needed to justify the use of H-FABP for the early detection of MI. A second limitation of the study was the assay used for detection of H-FABP. Because there is no standardization of H-FABP assays, the various studies may have yielded different results because of the different assays used.

ACKNOWLEDGEMENTS: We thank Theresa Perlis PhD for her assistance with the statistical analysis. The authors have no conflict of interest and there was no financial support for this research project. This material is original and has not been published previously.

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