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Original Article

Heart-type fatty acid-binding protein (H-FABP) as an early diagnostic biomarker in patients with acute chest pain

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ABSTRACT

Background: Heart-type fatty acid-binding protein (H-FABP) is an emerging biomarker, which was found to be sensitive for the early diagnosis of acute myocardial infarction (AMI). We prospectively investigated the usefulness of H-FABP determination for the evaluation of acute chest pain in patients arriving at the emergency department.

Methods: Fifty-four patients presenting with acute ischemic chest pain were evaluated. H-FABP was estimated at admission using latex-enhanced immunoturbidimetric assay. Serial cardiac troponin I (cTnI), creatinine kinase-MB (CK-MB) determination, ischemia workup with stress testing, and/or coronary angiogram (CAG) were performed according to standard protocols.

Results: The sensitivity and specificity of H-FABP was 89.7% and 68%, for cTnI it was 62.1% and 100%, and for CK-MB it was 44.8% and 92%, respectively for diagnosis of AMI. The sensitivity of H-FABP was found to be far superior to initial cTnI and CK-MB, for those seen within 6 h (100% vs. 46.1%, 33% respectively). On further evaluation of patients with positive H-FABP and negative cTnI, 71.4% of the patients had significant lesion on CAG, indicating ischemic cause of H-FABP elevation. Six patients with normal cTnI and CK-MB with high H-FABP had ST elevation on subsequent ECGs and were taken for primary angioplasty.

Conclusion: H-FABP is a highly sensitive biomarker for the early diagnosis of AMI. H-FABP as early marker and cTnI as late marker would be the ideal combination to cover the complete diagnostic window for AMI. Detection of myocardial injury by H-FABP may also be applied in patients with unstable angina. H-FABP can also be used as a marker for early detection of STEMI before the ECG changes become apparent.

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1. Introduction

The clinical evaluation, triage, and management of patients with possible acute coronary syndromes (ACS) present a substantial medical and fiscal challenge.

Cardiac troponin (cTn) is recommended as the preferred biomarker for early risk stratification.[1] cTn may not rise for the first 6 h after the onset of symptoms and, if negative, should be repeated within 8–12 h after the onset of pain.[1]

Application of an early biomarker potentially reduces diagnostic uncertainty in patients suspected of an ACS. This may lead to a reduction in unnecessary ICU admissions, patient's financial burden, hospital resources, and healthcare costs. Moreover, a diagnosis of ACS can be established much earlier than with troponin, which may result in earlier initiation of appropriate treatment, including revascularization procedures.

Heart-type fatty acid-binding protein (H-FABP) is a novel biomarker shown to be released from injured myocardium and detected in blood within 1 h after onset of ischemia.[2] Several studies have shown that it is a sensitive early marker of myocardial injury.[3–8]

This study was designed to evaluate the efficacy of serum H-FABP measurement for triaging of patients presenting to the emergency department with chest pain, in comparison to cardiac troponin I (cTnI) and creatinine kinase-MB (CK-MB).

2. Materials and methods

2.1. Study design

The study is a prospective observational study conducted in Amrita Institute of Medical Sciences, Kerala, India. The study was approved by the institutional ethical committee. From August 2013 to July 2014, 77 patients with acute chest pain presenting to the emergency department were enrolled and their data entered into a clinical database after obtaining informed, written consent. Inclusion criteria included men and women aged 18 years or older, with chest pain suggestive of cardiac ischemia at the discretion of the treating cardiologist. Patients with non-cardiac chest pain, renal insufficiency with an estimated glomerular filtration rate (eGFR) <60 ml/min, symptoms temporally related to direct local trauma of <3 days, ECG changes suggestive of STEMI at presentation, new onset dysrhythmia excluding sinus tachycardia, new onset congestive heart failure, acute pulmonary edema, recent cardiopulmonary resuscitation, liver disease, and sepsis were excluded from the study.

Important definitions related to inclusion and exclusion criteria are as follows: chest pain suggestive of coronary origin is defined, in accordance with ACC/AHA guidelines,[1] as chest or left arm pain as the chief symptom. Non-cardiac chest pain is defined at the discretion of the cardiologist after evaluation using radiography or other technical assessments. Acute myocardial infarction (AMI) was diagnosed if there is biochemical evidence of cardiac myocyte necrosis in the appropriate clinical setting as per the ESC/ACCF/AHA/WHF universal definition of myocardial infarction.[9] Patients with reduced renal clearance (eGFR <60 ml/min) were excluded due to higher pre-infarct baseline H-FABP levels.[4] Patients with a history of trauma less than 3 days were excluded due to potential elevation in H-FABP with muscle injury. Patients with ST elevation on ECG, heart failure, dysrhythmias, pulmonary edema, hypotension, or cardiopulmonary resuscitation were excluded due to potential early triaging and a potential inability to follow these patients throughout the study period.

2.2. Study protocol

Information regarding patient demographics and relevant clinical data, such as that concerning the patient's cardiac history and contact address, was recorded on a data collection sheet. Blood samples were taken upon arrival to the Casualty. All blood tubes for biomarker determination were obtained using clot activator tubes, centrifuged immediately at 3000 rpm for 5 min, and the serum was analyzed.

2.3. Tests

A latex-enhanced immunoturbidimetric assay via Olympus AU2700 for H-FABP was used, with an upper limit of normal of 6.4 ng/L as recommended by the manufacturer (Randox Laboratories, UK). H-FABP was estimated only at admission. cTnI was measured using Abbott Architect-Chemiluminescence method on admission, and at 6th and 12th hours post-admission as part of the standard chest pain protocol, and a cut-off value of 0.14 ng/ml was taken with a 99th percentile reference range as recommended by ACC/AHA.[1] A diagnosis of myocardial infarction was made if cTnI measured 12 h after admission was greater than the upper limit of normal. Serum CK-MB was estimated by photometric method on admission, and at 6th and 12th hours post-admission as part of the standard chest pain protocol along with cTnI.

Possible myocardial ischemia was evaluated with myocardial stress imaging and/or coronary angiography. Stress test was performed in conjunction with ECHO imaging. Coronary angiography was carried out in those patients with positive stress testing or those patients deemed to have a high-pretest probability for coronary artery disease (CAD) based on subsequent cTnI results. All angiographic images were reviewed by experienced cardiologists. A positive coronary angiography is defined as stenosis resulting in ≥50% diameter reduction in any major epicardial vessel. Final diagnosis was based on the discharge diagnosis documented on discharge summaries.

2.4. Statistics

Continuous variables were presented as mean ± SD, and categorical variables as frequencies (percentages). Comparisons for categorical variables were performed using McNemer test. The sensitivity, specificity, and positive and negative predictive values were calculated to assess the diagnostic accuracy of H-FABP, cTnI, and CK-MB in the exclusion of ACS on admission and at 6th and 12th hours post-admission for cTnI and CK-MB. Sensitivity of H-FABP, cTnI1, and CK-MB1 was compared using Z-test statistic for proportion. All statistical

Table 1 – Risk factors ($n = 54$).

Risk factors	n	%
Severe angina	8	14.8
Family history of CAD	7	13.0
Hypertension	34	63.0
Dyslipidemia	31	57.4
Type 2 DM	34	63.0
Current smoker	2	3.7
Known case of CAD	25	46.3
Aspirin use with in last 24 h	24	44.4
ST deviation	23	42.6
Increased markers (standard markers)	29	53.7

analyses were performed using the IBM SPSS version 20.0 software package (IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY: IBM Corp).

3. Results

Seventy-seven patients were evaluated in the casualty and H-FABP was estimated. 23 patients were excluded from the study after further evaluation because of the various causes (renal failure, liver disease, sepsis, etc.). The mean age was 63.4 ± 11.5 years and 68.5% were men. The risk factors are summarized in Table 1. Hypertension, type 2 diabetes, and history of CAD account for 63%, 63%, and 46.3%, respectively. TIMI risk score for unstable angina/NSTEMI was calculated based on the risk factors on presentation. 25.9% of patients had TIMI risk score of 2. Majority of the patients had TIMI risk score between 2 and 4. 53.7% of patients presented within 6 h of onset of chest pain. Though majority of patients were clear about the history of duration of pain, few patients gave history of vague pain, which had started few days previously and increased gradually. In such patients, the time from onset of initial chest discomfort was taken as duration of chest pain. 15 (27.8%) patients had regional wall motion abnormality on echocardiography. Coronary angiogram (CAG) was done in 40 (74.1%) patients.

Only patients with NSTEMI, positive stress test, or patients with high-clinical suspicion underwent CAG. Out of the 40 patients who underwent CAG, 32 (59.3%) patients had significant disease. Table 2 summarizes the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of H-FABP, cTnI, and CK-MB on admission with relation to duration of chest pain.

The sensitivity of H-FABP was found to be superior to initial cTnI (89.7% vs. 62.1%, $Z = 4.61$, $p < 0.01$) and CK-MB (89.7% vs. 44.8%, $Z = 6.90$, $p < 0.01$). In patients presenting within 6 h after onset of chest pain, the sensitivity of H-FABP was found to be far superior to initial cTnI (100% vs. 46.1%, $Z = 8.93$, $p < 0.01$), and CK-MB (100% vs. 33.3%, $Z = 10.40$, $p < 0.01$), but the specificity of H-FABP for AMI was poor (68%). Table 3 summarizes sensitivity and specificity of various markers serially done after admission.

In five out of the seven patients with positive H-FABP and negative cTnI, CAG was done based on either positive stress test or high-clinical suspicion of CAD. All the 5 patients had significant lesion on CAG indicating ischemic cause of H-FABP elevation. Rest of the 2 patients had a negative stress test.

Table 2 – Comparison of admission cardiac markers with relation to duration of chest pain ($n = 54$).

	Duration of chest pain								
	≤6 h ($n = 29$)			>6 h ($n = 25$)			Total ($n = 54$)		
	H-FABP	cTnI	CK-MB	H-FABP	cTnI	CK-MB	H-FABP	cTnI	CK-MB
Sensitivity	100%	46.1%	33.3%	78.6%	78.6%	57.1%	89.7%	62.1%	44.8%
Specificity	85.7%	100%	92.9%	45.5%	100%	90.9%	68%	100%	92.0%
Accuracy	93.1%	72.4%	62.1%	64%	88%	72%	79.6%	79.6%	66.7%
PPV	88.2%	100%	83.3%	64.7%	100%	88.9%	76.5%	100%	86.7%
NPV	100%	63.6%	56.5%	62.5%	78.6%	62.5%	85%	69.4%	59%

H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; CK-MB, creatinine kinase-MB; PPV, positive predictive value; NPV, negative predictive value.

Table 3 – Comparison of cardiac markers serially done after admission ($n = 54$).

	On hospital admission ($n = 54$)			6 h after hospital admission ($n = 54$)		12 h after hospital admission ($n = 54$)	
	H-FABP	cTnI	CK-MB	cTnI	CK-MB	cTnI	CK-MB
Sensitivity	89.7%	62%	44.8%	96.6%	75.9%	100%	79.3%
Specificity	68%	100%	92%	100%	96%	100%	92%
Accuracy	79.6%	79.6%	66.7%	98.1%	85.2%	100%	85.2%
PPV	76.5%	100%	86.7%	100%	95.7%	100%	92%
NPV	85%	69.4%	59%	96.2%	77.4%	100%	79.3%

H-FABP was estimated only on admission and was not repeated thereafter. cTnI estimated 12 h after hospital admission was assumed to be the gold standard and hence the 100% accuracy. H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; CK-MB, creatinine kinase-MB; PPV, positive predictive value; NPV, negative predictive value.

4. Discussion

Early diagnosis of AMI facilitates rapid and appropriate triage of patients within the Accident and Emergency department, helping to prevent inadvertent discharge of patients with AMI. It also avoids delay in administering treatment for AMI, and reduces the possibility of patients without AMI given treatments from which they will not benefit, and which have the potential to cause significant harm. The 12-lead ECG is an important tool for early detection of AMI, but it has significant limitations, e.g., LBBB or a permanent pacemaker may make interpretation impossible and ECG changes may not be apparent early in the course of the disease. Another significant factor is that interpretation of the 12-lead ECG is dependent on the experience of the physician.[10]

AMI is diagnosed if there is biochemical evidence of cardiac myocyte necrosis in the appropriate clinical setting.[9] Cardiac troponins have assumed an important role in modern cardiology practice, both in diagnosis of AMI and in risk stratification of patients with acute chest pain. A major drawback with cardiac troponins is that they are released relatively slowly from damaged myocytes.[11] This study confirms the limitation of sampling cardiac troponin at the time of admission for patients presenting with acute ischemic-type chest pain. The sensitivity of initial cTnI on admission was 62%. The sensitivity of initial troponin was at its lowest for patients who presented within 6 h of symptom onset (46.1%) (Table 2). It increased with increasing time from symptom onset to admission, with a sensitivity of 78.6% for patients who presented after 6 h of onset of chest pain. This leaves a false negative rate of 21.4% for the initial cTnI even in patients who presented 6 h after the onset of chest pain (i.e., subsequent cTnI sampled later from admission becoming positive) (Table 3). These findings were similar to a study by McCann et al. where the sensitivity of initial cardiac troponin T (cTnT) for AMI was found to be 75%. The sensitivity of initial cTnT for patients who presented within 4 h of symptom onset was 55%.[14]

This study has demonstrated that, of all the investigational biomarkers, H-FABP has a potential role in the very early diagnosis of AMI. There has been interest in H-FABP as a biochemical marker of myocardial injury since 1988, when it was demonstrated to be released from injured myocardium.[12] The release characteristics of H-FABP after AMI show that a rise is detectable as early as 1 h after symptom onset, a peak level is reached after 2–4 h, and due to rapid renal clearance, the level returns to baseline within 16–24 h.[2,13] Several studies reporting the usefulness of H-FABP as an early marker of AMI pre-dated the widespread use of cardiac troponins.[3–8] Data for the diagnostic performance of admission of H-FABP using the modern definition of AMI are limited.

Our study has demonstrated that measurement of H-FABP in patients with acute ischemic-type chest pain at the time of admission is useful and complements the subsequent measurement of cardiac troponin. The sensitivity and specificity of H-FABP in our study were 89.7% and 68%, respectively. The sensitivity of H-FABP is superior to initial cTnI for those seen within 6 h (100% vs. 46.1%%, $Z = 8.93$, $p < 0.01$), but the specificity of H-FABP for AMI was poor (68%) (Table 2). The specificity of H-FABP for AMI reported in previous studies varies from 49% to 86%.[3–8,14,15] In a study by Chan et al., H-FABP had better sensitivity and NPV on admission (72% and 67%, respectively) than cTn (51% and 51%, respectively). Furthermore, the sensitivity and NPV of H-FABP increased to 100% for samples taken 1 h after admission.[15] A study by Ruzgar et al.[4] showed 38% sensitivity with troponin, 76% sensitivity with CK-MB, and 95% sensitivity with H-FABP in patients admitted within 6 h of chest pain onset. Within 6–24 h, sensitivity of troponin and CK-MB increased to 100 and 90% respectively, while that of H-FABP was 91%.

The sensitivity of H-FABP was also found to be superior to CK-MB in the early diagnosis of AMI in the present study. The sensitivity of CK-MB in our study was found to be 44.8%. In patients who presented within 6 h, the sensitivity was even lower (33.3%), whereas the specificity of CK-MB was higher compared to H-FABP (92% vs. 68%) (Table 2). Recently, a high-sensitivity troponin T (hsTnT) assay has been developed, permitting measurement of concentrations that are 10-fold lower than those measurable with conventional assays.[16,17] Though hsTnT assay offers excellent diagnostic performance to rule out ACS, a recent study by Inoue et al. showed that it is prone to more false-positive results compared to H-FABP with similar overall diagnostic performance.[18]

The reason for the relatively poor specificity of H-FABP in the current study may relate to a number of factors. Firstly, H-FABP was estimated in all the patients regardless of the duration of chest pain. As the level returns to base-line within 20 h due to rapid renal clearance, it is unlikely to be positive in patients presenting after 20 h of chest pain onset unless they had a re-infarct. Though the overall specificity was only 68%, the specificity in patients presenting within 6 h of chest pain was 85.7%, indicating that the low specificity is due to plasma kinetics (Table 2). Secondly, H-FABP may be released from ischemic myocardium, as well as infarcted myocardium. In our study on further evaluation, five out of the seven patients with positive H-FABP and negative cTnI had significant lesion on CAG indicating ischemic cause of H-FABP elevation. Thirdly, H-FABP is present, albeit at lower concentrations, in skeletal muscle. In this study, no data were collected on recent physical exercise, recent injury, or recent intramuscular injections.

Out of the 54 patients included in the study, 6 patients with normal cTnI and CK-MB with high H-FABP at presentation had new onset ST elevation, 1–2 h after hospital admission, and underwent primary angioplasty. These results indicate the potential for H-FABP for early diagnosis of STEMI even before the ECG changes develop. All these patients had very high H-FABP values (>100) with normal troponin and CK-MB.

4.1. *Limitations*

A limitation of this study is that recruitment took place at the time of admission from casualty of a tertiary care hospital with cardiology specialization. This is reflected in the relatively high incidence of AMI (53.7%). As a consequence, the results presented may not necessarily be applicable to lower risk populations, such as all patients with chest pain presenting to the Accident and Emergency department. Another limitation is that this study only assessed the potential benefit from a

single measurement of H-FABP at the time of admission. Sequential measurements were not investigated. Myoglobin was not measured for comparison purposes. Unlike myoglobin, the concentration of H-FABP in cardiac muscle is higher than in skeletal muscle.[10] This may mean that H-FABP is potentially more suitable than myoglobin as an early marker of myocyte injury. This study was designed taking cTnI done after 12 h of admission as a gold standard for diagnosis of AMI though it is not 100% specific.

4.2. Conclusions

H-FABP is one of the promising new biomarkers for myocardial tissue injury detection. H-FABP is a highly sensitive biomarker for acute ischemia and infarction. Measurement of H-FABP in patients with acute ischemic-type chest pain at the time of admission will assist in the early diagnosis of AMI. For patients presenting within 6 h of symptom onset, the sensitivity of H-FABP is significantly higher than cTnI and CK-MB. Cardiac troponins are specific but rather late markers for detection of AMI. H-FABP as early marker and cTnI as late marker would be the ideal combination to cover the complete diagnostic window for AMI. However, the specificity of H-FABP alone for diagnosis of acute MI is poor. H-FABP elevation was also found in patients with chest pain and significant stenosis on CAG without myocardial infarction. This sensitive detection of myocardial ischemia by H-FABP may also be applied in patients with unstable angina though further studies are required. H-FABP can also be used as a marker for early detection of STEMI before the ECG changes become apparent.

Conflicts of interest

The authors have none to declare.

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