

# Rapid Assessment and Triaging of Acute Chest Pain Patients Using Human Fatty Acid Binding Protein (the RASTA study): Are we ready for prime time?

Mulugeta Z Fissha<sup>1\*</sup>, William R Maddox<sup>2</sup>, Almois Mohamad<sup>2</sup>, Stephen W Looney<sup>3</sup>, Bruce D Janiak<sup>4</sup>, Mahendra K Mandawat<sup>5</sup>, Sunita Dodani<sup>6</sup> and Vincent J B Robinson<sup>2</sup>

<sup>1</sup>Section of Cardiology, Newark Beth Israel Medical Center, Newark, NJ, USA

<sup>2</sup>Section of Cardiology, Medical College of Georgia, Augusta, GA, USA

<sup>3</sup>Department of Biostatistics, Medical College of Georgia, Augusta, GA, USA

<sup>4</sup>Department of Emergency Medicine, Medical College of Georgia, Augusta, GA, USA

<sup>5</sup>Department of Cardiology, Charlie Norwood VA Medical Center, Augusta, GA, USA

<sup>6</sup>Center for Outcome Research and Education, University of Kansas Medical center, Kansas City, Kansas, USA

## Abstract

**Background:** Triaging of patients with chest pain in the emergency department is costly and time consuming. Human fatty acid binding protein is an emerging biomarker which is known to be sensitive marker of early myocardial cell injury. We prospectively investigated the usefulness of serial Human Fatty Acid Binding Protein determination in the evaluation of acute chest pain in patients arriving at the emergency department.

**Methods:** In 47 consecutive patients who had acute chest pain for less than 12 hours without electrocardiographic changes and initial negative troponin elevation, serial human fatty acid binding protein was determined. Testing was performed at enrollment and 1 hour later using a point-of-care assay. Serial troponin determination and ischemia workup with stress testing was performed according to standard protocols.

**Results:** Human fatty acid binding protein was positive in 7/47 (14.9%) patients while troponin was positive in 4 (8.5%) patients. There were 2/47 (4.3%) patients with angiographically significant stenosis. The sensitivity and specificity of human fatty acid binding protein was 75% and 83.7%, respectively compared to serial troponin measurement. The positive and negative predictive value of human fatty acid binding protein was 30% and 93.3%, respectively. The diagnostic accuracy was 82.9%.

**Conclusion:** Point-of-care serial human fatty acid binding protein testing for early detection of myocardial cell injury has inferior diagnostic performance compared to serial troponin determination. The addition of human fatty acid binding protein measurement to troponin did not improve the diagnostic performance of troponin. Further assay validation and a larger study cohort is required to confirm these findings.

**Keywords:** Chest pain; Biochemical marker; Heart-type fatty acid binding protein; Point-of care assay

## Introduction

Chest pain is the second most common emergency department (ED) presenting complaint in the United States [1]. Approximately 5.6 million patients visit the ED each year for chest pain. (NCHS/CDC, March 2004). One half of these patients are found not to have an acute coronary syndrome. The cost for these negative inpatient cardiac evaluations has been estimated to be \$6 billion [1]. It is also well documented that 4% to 5% of patients with myocardial infarctions are inadvertently missed during the initial evaluation [2].

Cardiac troponin (cTn) is recommended as the preferred biomarker for early risk stratification [3]. cTn may not rise for the first 6 hours after the onset of symptoms and, if negative, should be repeated with in 8-12 hours after the onset of pain.<sup>3</sup> Human heart type fatty acid binding protein (H-FABP) is a novel biomarker shown to be released from injured myocardium and detected in blood within one hour after onset of ischemia [4]. Several studies have shown that it is a sensitive early marker of myocardial injury [5-10]. A study by Chan et al, of 218 patients with chest pain showed that H-FABP had better sensitivity and negative predictive value (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 hour after admission [11].

The primary objectives of this study were to (a) evaluate the efficacy of serial serum H-FABP measurement for early triaging of chest pain patients in the ED in comparison to cTn and to (b) evaluate the safety of serial serum H-FABP measurement in terms of 30-day all cause and cardiovascular adverse events.

## Materials and Methods

### Study design

The RASTA study is a prospective observational pilot study conducted at the Medical College of Georgia (MCG) hospital. The

**\*Corresponding authors:** Mulugeta Z Fissha, Newark Beth Israel Medical Center, Newark, NJ 07112, USA, Tel: 973-926-7828; Fax 973-926-8216; E-mail: [mfissha@gmail.com](mailto:mfissha@gmail.com)

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study was approved by the local institutional review board. From July 2009-April 2010, 47 patients with acute chest pain presenting to the ED were enrolled and their data entered into a clinical database after informed, written consent was obtained. All patients had negative initial cTn and no electrocardiographic (ECG) changes suggestive of ischemia on admission. Inclusion criteria included; (a) men and women age 18 years old or older, (b) chest pain suggestive of coronary origin at the discretion of an ED physician's assessment, (c) and onset of chest pain less than 12 hours prior to enrollment. Exclusion criteria included; (a) Non-cardiac chest pain, (b) renal insufficiency with an estimated glomerular filtration rate (eGFR) less than 60ml/min, (c) symptoms temporally related to direct local trauma of less than 3 days, (d) ECG changes suggestive of ischemia, (e) new onset dysrhythmia excluding sinus tachycardia, (f) new onset congestive heart failure, (g) acute pulmonary edema, (h) cardiopulmonary resuscitation or (i) hypotension with systolic blood pressure less than 90 mmHg.

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. ECG changes suggestive of ischemia are defined as pathologic Q waves of more than 40msec, ST-segment elevation or depression of more than 1mm or abnormal T wave morphology. Non ST-elevation myocardial infarction is defined as initial point-of-care cTn elevation of >0.04ng/ml in addition to ECG changes. Non-cardiac chest pain is defined at the discretion of the ED physician after evaluation using radiography or other technical assessments. Patients with reduced renal clearance (eGFR <60ml/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 ECG changes suggestive of ischemia, 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.

### Study protocol

All eligible subjects were given a unique study number according to identity-unlinked technique [12]. Information regarding patient demographics and relevant clinical data such as that concerning the patient's cardiac history and contact address were recorded on a data collection sheet. Blood samples were taken upon arrival to the ED and at 1st hour post admission. The study scheme is depicted in Figure 1. All blood tubes for H-FABP determination were labeled with the patient's study code only. Two 5 ml blood samples (collected twice at one hour apart) were obtained using clot activator tubes, centrifuged

immediately at 3000 rpm for 5 minutes and the serum stored at -80°F for analysis at a later date. Data for cTn were collected from the MCG patient database. The identity-unlinked technique was used to avoid the perceived ethical and medico legal implications of discovering a positive marker test result for patients who had already been discharged home from the ED. Accordingly, after all clinical data were recorded, all patient identifiers were removed from the data sheets. Clinical and serologic data were linked after removing these identifiers and after a master list linking patients to their study codes was destroyed.

### Tests

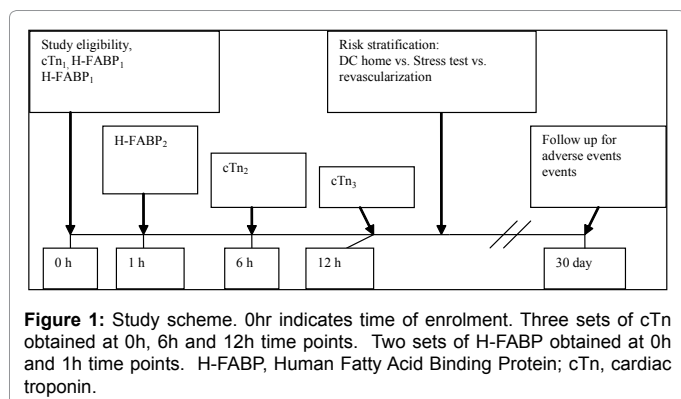
A rapid chromatographic immunoassay (point-of-care assay) for H-FABP was used with an upper limit of normal of 7.0µg/L as recommended by the manufacturer (Cardio Detect®, R&C Biogenius Limited, Hong Kong). From each sample, three drops of serum (equivalent to 100-120µl of serum) was applied to the test field of a Cardio Detect® card assay and analyzed by inspection 15 mins after application. Whenever bands appear at both the result and control zones, the result was considered positive. When only the control band registered, the result was considered negative. cTn was measured using Access® AccuTni assay (Beckman Coulter, Inc. Fullerton, Ca, USA) on admission, and at 6<sup>th</sup> and 12<sup>th</sup> hours post admission as part of the standard chest pain protocol. A cut off value of 0.04ng/ml was taken with a 99<sup>th</sup> percentile reference range as recommended by ACC/AHA [3]. A positive cTn was defined as presence of one or more cTn determinations greater than the upper limit of normal.

Possible myocardial ischemia was evaluated with myocardial stress imaging and/or coronary angiography. Stress test was performed in conjunction with either nuclear or ECHO imaging at the discretion of the ED physician. 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 based on subsequent cTn results. All angiographic images were reviewed by an experienced cardiologist. A positive coronary angiography was defined as stenosis resulting in ≥50% diameter reduction in any major epi cardiac vessel. Final diagnosis was based on the discharge diagnosis documented on ED and hospital admission forms.

Patients were contacted by telephone 30 days after initial presentation to the ED. Patients were asked about the occurrence of any symptoms since the enrollment visit and whether contact with a physician or any other health care provider occurred during the follow-up period. For those patients who could not be reached by telephone after 3 attempts, all available inpatient and outpatient medical records were reviewed. A patient was defined as having sufficient follow-up information for analysis if either a current medical record was obtained for review that accounted for the 30 day follow-up period or the patient was interviewed by phone. Adverse events recorded include all-cause death, myocardial infarction, recurrent angina, cardiac arrhythmias, and unanticipated ED or clinic visit for a cardiac cause.

### Statistics

Continuous variables are presented as mean ± SD, and categorical variables as frequencies (percentages). Comparisons for categorical variables were performed using chi-square test. The sensitivity, specificity, positive and negative predictive values were calculated to assess the diagnostic accuracy of H-FABP in the exclusion of ACS on admission, and at 6th and 12th hours post admission. Inter-test correlation between H-FABP and cTn was assessed using Cohen's Kappa. All statistical analysis was performed using the NCSST/ PASS 007 software package (NCSST.com, Kaysville, Utah, USA).



## Results

### Patient demographics

The demographic characteristics are listed in Table 1. The mean age was  $49.4 \pm 9.7$  years and 42% were males. Hypertension, type 2 diabetes and history of coronary artery disease (CAD) account for 77.8%, 28.9% and 13.3%, respectively. Forty-four percent of the patients experienced chest pain for less than 6 hours. The average ED stay was 27 hours. Ninety-six percent of patients had a follow up interview at 30 days. There was 1 patient who reported visiting the ED for chest pain. Four patients had a positive cTn on repeat evaluation and all of them were positive at the 6<sup>th</sup> and 12<sup>th</sup> hour post admission. Seven patients were H-FABP positive and all of them were positive in the first and second sample. A stress test was performed in 74.5% of patients. Overall, an ischemia workup with either stress testing or cardiac catheterization was performed in 80.9% of patients. Six patients underwent cardiac catheterization of whom two were found to have significant CAD.

### Diagnostic performance of H-FABP

Table 2 depicts the diagnostic performance of H-FABP. The overall sensitivity and specificity were 75% and 83.7%, respectively. The positive and negative predictive values were 30% and 93.3%, respectively. The diagnostic accuracy was 82.9%. Patients who had chest pain less than 6 hours had a higher trend towards positive H-FABP but did not reach statistical significance, OR=3.75 (95% confidence interval 0.70-20.1, p=0.12; Figure 2). Use of serial H-FABP measurements did not improve the test performance of cTn. The inter-test agreement between cTn and H-FABP was modest. ( $\kappa=0.49$ )

### Adverse events

One patient reported visiting the ED for chest pain 24 days after initial visit. The patient underwent further stress testing with nuclear imaging which was negative. One patient, classified as negative by H-FABP, was found to have three vessels CAD including 90% stenosis of ostial left anterior descending artery, 100% stenosis of left circumflex artery and 80% of right coronary artery subsequently requiring coronary artery bypass surgery. This patient arrived at the ED within 6-12 hours of symptom onset. Two patients were unable to be contacted by phone. No visit could be identified from the MCG database during the follow up period for those lost to follow up.

## Discussion

The main findings of this pilot study indicate that H-FABP demonstrated poorer diagnostic performance when compared to cTn for the diagnosis of significant CAD. H-FABP showed lower sensitivity and higher diagnostic misclassification. The time from symptom onset to determination of H-FABP (<6 hours vs.  $\geq 6$  hours) did not have significant effect on the sensitivity. Serial determinations of H-FABP one hour apart did not improve the sensitivity of the test. (Figure 2) Furthermore, combining H-FABP with cTn did not improve overall sensitivity.

Our findings raise questions concerning the role of H-FABP as an early marker for the detection of myocardial ischemia. Several factors including varying H-FABP assay characteristics may have influenced our findings. In a number of studies, H-FABP was reported to be a sensitive marker of myocardial injury, particularly within a few hours of symptom onset [4,5,13,14]. This assertion stems from its low molecular weight (15kDa) and its abundance in the cytoplasm [15]. It was shown to have characteristics similar to that of myoglobin, with typical rise

within 2 hours of symptom onset, a characteristic peak at 6 hours and a return to baseline concentration within 24 hours [11,16]. In a study by Nakata et al, in 113 patients presenting to an emergency room with suspected acute coronary syndrome H-FABP had the highest area under the receiver operating curve for detecting ACS and acute myocardial infarction when compared to myoglobin, troponin T and CK-MB [5]. However, a study by Lefevre G et al. [17] compared the diagnostic accuracy of H-FABP using a semi-quantitative assay (CardioDetect<sup>®</sup>) and a cTn assay found that H-FABP was not better than cTn in terms of diagnostic efficiency [17]. These mixed results raise the question of assay reliability. The lack of a standardized assay for H-FABP further limits comparison of different studies. As Jafe et al. noted there is no U.S. Food and Drug Administration approved assay for H-FABP [18].

Our study used a point-of-care (POCT) qualitative H-FABP test to compare with a quantitatively measured cTn assay. This may also have affected the overall strength of our results. A study by Hiura M et al. [19] showed that the diagnostic accuracy of a POCT H-FABP is lower (80% concordance) than a quantitatively measured H-FABP [19]. Similarly, a study by Tanaka T et al. [20] demonstrated poor diagnostic accuracy of a POCT H-FABP (64%) compared to troponin T [20].

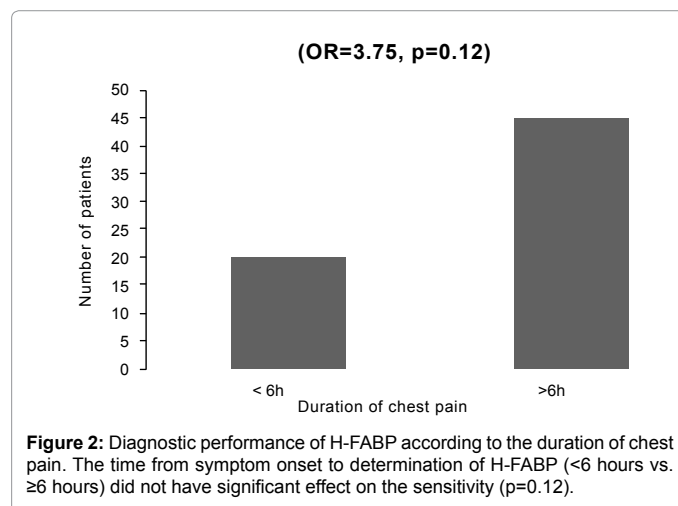
The current study is also limited by the small sample size and low

VARIABLE	N	%
Age mean (SD)	49.4 (9.7)	
Male	20	42.6
History of CAD	6	12.8
Hypertension	36	76.6
Diabetes	14	29.8
Chest pain <6Hr	20	42.6
ED stay,Hr (SD)	27 (11.2)	
30-Day follow up	45	96
Adverse event	1	2.1
cTn positive	4	8.5
H-FABP positive	7	14.9
Stress test	35	74.5
Cardiac cath	6	12.8
Stress or cath	38	80.9
Significant CAD ( $\geq 50\%$ stenosis)	2	4.3

**Table 1:** Demographic data and diagnostic workup. (n = 47) CAD, coronary artery disease; cath, cardiac catheterization; ED stay, mean emergency department stay.

	cTn+	cTn-	Total
H-FABP +	3	4	7
H-FABP -	1	39	40
Total	4	43	47

**Table 2:** diagnostic performance of H-FABP compared to troponin. The overall sensitivity and specificity of H-FABP was 75% and 83.7%, respectively, compared to serial cTn determination.



**Figure 2:** Diagnostic performance of H-FABP according to the duration of chest pain. The time from symptom onset to determination of H-FABP (<6 hours vs.  $\geq 6$  hours) did not have significant effect on the sensitivity (p=0.12).

risk population with very few adverse events. Most studies included unselected patients with a higher prevalence of CAD. Nevertheless, not all of these studies showed consistent results. For example, the study by Lefevre G et al. [17] was done on a high-risk patient population (61 out of 100 ACS cases) but showed no added benefit of H-FABP [17]. Several studies have also indicated that a multimarker strategy with serial measurement may improve the test performance of cTn [21,22]. Accordingly, an early marker of myocardial injury (e.g. myoglobin) in conjunction with a late marker (e.g. cTn) has been recommended as an alternative to the traditional serial cTn measurement [3]. H-FABP is one of the markers considered in this strategy [23]. However, our data do not support this assertion. We also found no increase in the overall sensitivity by combining H-FABP with cTn.

## Conclusion

Point-of-care serial human fatty acid binding protein testing for early detection of myocardial cell injury has inferior diagnostic performance compared to serial troponin determination. Further validation analysis followed by a large scale randomized study would need to be performed to confirm our findings.

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