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ORIGINAL ARTICLE

Heart-type fatty acid-binding protein detects more patients with non-ST segment elevation myocardial infarction compared to troponin-T

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KEYWORDS

Cardiac biomarker;
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Abstract *Objective:* To assess the value of using heart-type fatty acid-binding protein (H-FABP) as a marker of acute myocardial infarction (AMI) in patients presenting with non-ST segment elevation ACS (NSTE-ACS) in comparison with troponin-T (cTnT).

Methods: 122 consecutive patients presented with ischemic-type chest pain within the first 4 h of symptom onset with NSTE-ACS. Blood samples were obtained on arrival for H-FABP and cTnT. Patients with cTnT negative test on admission had a repeat analysis 6 h later. Patients with both H-FABP negative and admission cTnT positive had repeat analysis of H-FABP 6 h later.

Results: On admission, H-FABP was positive in 84 patients (68.9%) versus 36 patients (29.5%) with cTnT ($p = 0.032$). On repeat analysis after 6 h, total number of cTnT positive patients was 94 (77%) and cTnT negative was 28 (23%). All cTnT negative patients had negative H-FABP. Of cTnT positive patients, 84 (89.4%) had positive H-FABP test while the remaining 10 (10.6%) had "false" negative results.

Using the final results of cTnT positive as gold standard, early assessment of cTnT within 4 h of chest pain had sensitivity of 38.3% and specificity of 100% while H-FABP had sensitivity of 89.4% and specificity of 100%.

Conclusions: For patients presenting with suspected ACS within 4 h of onset of symptoms, H-FABP detects a significantly larger number of patients with NSTEMI compared to troponin-T.

1. Background

Chest pain accounts for a large proportion of adult emergency room (ER) attendances and hence the ability to rapidly identify ischemic chest pain is of importance.[1,2] Acute coronary syndromes (ACS), which include unstable angina and myocardial infarction (MI) with or without ST-segment elevation, are life-threatening disorders that remain a source of

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high morbidity and mortality despite advances in treatment.[3] Currently used biomarkers for cardiac ischemia are elevated in blood plasma after a delay of several hours and therefore unable to detect acute coronary syndrome (ACS) in a very early stage.[4]

Cardiac troponin (cTn) and creatine kinase MB isoenzyme (CK-MB) lack early sensitivity because their blood concentrations do not increase appreciably until 4–6 h after the onset of acute myocardial infarction (AMI), while most patients with symptoms suggestive of ACS present themselves to the ER between 1 and 3 h after onset of symptoms and optimal patient outcomes for those with AMI rely on the timely and effective implementation of proven therapies.[5]

Heart-type fatty acid-binding protein (H-FABP) is a novel biochemical marker found to be released early into the blood stream as early as 30 min after the onset of acute MI.[6] It is a small (15 kDa) cytoplasmic protein involved in lipid homeostasis, abundant in heart muscle. It is approximately 10-fold lower in skeletal muscle than in heart muscle, and the amounts in the kidney, liver, and small intestine are even lower.[7] H-FABP molecule is smaller than troponin and unbound within the cell, allowing its release into the blood stream earlier following restriction of oxygen to the heart.[8]

This study was done to assess the value of using H-FABP as a marker of AMI in patients presenting with non-ST segment elevation ACS (NSTE-ACS) in comparison with troponin-T.

2. Methods

This study included 122 consecutive patients presented to Ain Shams University hospitals with ischemic-type chest pain within the first 4 h of symptom onset who were admitted with the diagnosis of non-ST segment elevation acute coronary syndrome (NSTE-ACS).

NSTE-ACS was defined according to the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines as patients with acute chest pain but without persistent ST-segment elevation or new onset left bundle branch block (LBBB) (i.e. having rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves, or no ECG changes at presentation) based on the measurement of cardiac markers, they further qualify as non-ST-elevation MI (NSTEMI) or unstable angina.[9,10]

Ischemic-type chest pain was defined as prolonged (>20 min) anginal pain at rest; new onset angina (Class II or III of the Classification of the Canadian Cardiovascular Society (CCS))[11]; recent destabilization of previously stable angina with at least CCS Class III angina characteristics; or post-MI angina. Typical anginal pain was considered as retrosternal pressure or heaviness radiating to the left arm, neck, or jaw, which may be intermittent or persistent. It may be accompanied by diaphoresis, nausea, abdominal pain, dyspnea, and syncope.

Patients were excluded from the study, if they had chest pain lasting more than 4 h before medical contact; ST-segment elevation or new onset of LBBB on ECG; end stage renal disease or renal impairment; or chronic liver disease. Approval from institutional medical research ethical committee was obtained and an informed consent was obtained from all patients.

Detailed history was taken from all patients with thorough analysis of chest pain; time from pain to medical contact; risk factors for developing coronary artery disease (CAD) (smoking status, diabetes mellitus, hypertension, dyslipidemia, family history of premature CAD in first-degree relatives); history of renal disease (defined as end-stage renal disease on regular dialysis, or serum creatinine level more than 1.5 mg/dL).

2.1. Cardiac biomarkers analysis

Venous blood samples were obtained from all patients (Fig. 1) on arrival to the ER for heart-type fatty acid-binding protein (H-FABP), troponin-T, and serum creatinine. Patients found to have a troponin-T negative test on admission had a repeat analysis from another sample withdrawn 6 h later. Patients found to have both an H-FABP negative test and an admission troponin-T positive test had a repeat analysis from another sample withdrawn 6 h later for assessment of H-FABP to assess whether H-FABP had failed to diagnose those patients on admission or whether it was just delayed diagnosis.

2.2. Heart-type fatty acid-binding protein test

We used a rapid test card, qualitative, solid phase, two-site sandwich immuno-chromatographic assay for the detection of H-FABP in serum. Performing the test required extracting the test card from the pouch, applying the blood sample to the sample well then waiting for 15 min to obtain results.[12]

The membrane of the test card used was pre-coated with capture anti-H-FABP antibodies on the test band region and colloidal gold-labeled antibody on the control band region. The reaction was initiated by adding 100–120 μL of venous blood to the well with heparin used as an anticoagulant. The test result was considered positive when two red lines (control and result) were visible indicating that the concentration of H-FABP in the sample was above the threshold value of 7 μg/L. The test result was considered negative when only one red line was visible at control indicating that the concentration of H-FABP was equal to or below the threshold value. The test was considered invalid and discarded and immediately repeated if no lines were visible or if a line was visible only at result.[13] The result of each test was confirmed by both the ER physician and cardiologist on call.

2.3. Troponin-T assessment

Qualitative assessment was done using a one-step troponin-T test card device with membrane based immunoassay for the

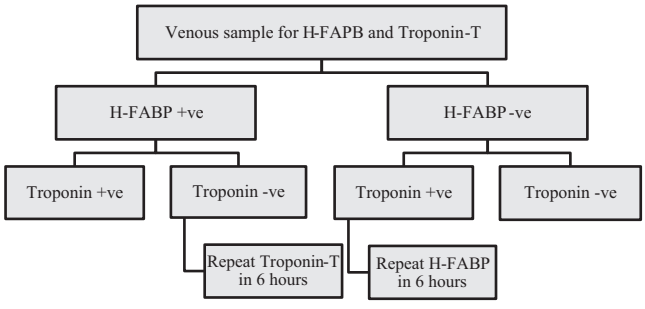

Figure 1 Sampling process for cardiac biomarkers.

Table 1 Baseline patient characteristics.

Number	122
Age (years)	54.6 ± 9.8
Male gender, *n* (%)	96 (78.7%)
Diabetes mellitus (type II), *n* (%)	76 (62.3%)
Hypertension, *n* (%)	80 (65.6%)
Current Smoker, *n* (%)	74 (60.7%)
Dyslipidemia, *n* (%)	62 (50.8%)
Family history of premature CAD, *n* (%)	52 (42.6%)
Time from onset of chest pain to medical contact (minutes)	187.2 ± 48
Admission ECG, *n* (%)	
–Normal	22 (18%)
–ST-segment changes	46 (37.7%)
–T-wave changes	34 (27.9%)
–Pathological Q waves	20 (16.4%)

Continuous variables are expressed as mean and standard deviation, whereas categorical variables are expressed as numbers (percentage).
CAD indicates atherosclerotic coronary artery disease.

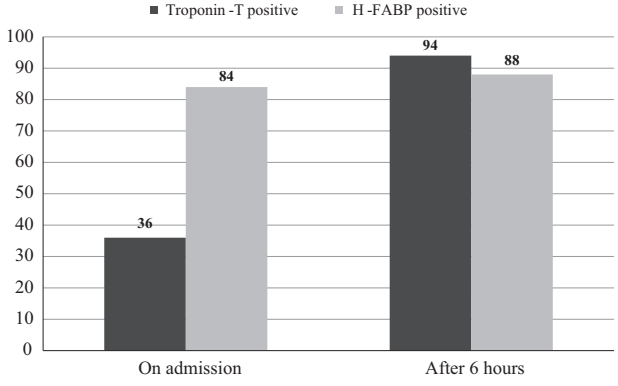

Figure 2 Comparing number of patients with troponin-T and H-FABP positive results on admission and after 6 h.

detection of cTnT. The membrane of the test used was pre-coated with capture reagent on the test line region of the test card. During testing, the whole blood specimen reacted with the particle coated with anti-cTnT antibodies. The presence of a colored line in the test line region indicated a positive result, while its absence indicated a negative result. To serve as a procedural control, a colored line must always have appeared in the control line region. If the control line did not appear, the test result was considered invalid and was immediately repeated. The result of each test was confirmed by both the ER physician and cardiologist on call.

2.4. Statistical analysis

Data were statistically analyzed using SPSS statistical package version 17 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as number and percentage. Continuous variables were expressed as mean ± SD. Tests used were Student's *t*-test for continuous variables and chi-square test or Fisher's exact test when the expected count was less than 5 for categorical variables. Correlations were done using Pearson's correlation coefficient. A probability value $p < 0.05$ was considered statistically significant and a p value < 0.0001 was considered highly significant.

3. Results

3.1. Baseline characteristics

This study included 122 consecutive patients in the period from March 2014 to January 2015. The mean patient age was 54.6 ± 9.8 years with 96 males (78.7%). Seventy-six patients (62.3%) had diabetes mellitus (all type II), 80 patients (65.6%) were hypertensive, 74 patients (60.7%) were current smokers, 62 patients (50.8%) had dyslipidemia, and 52 patients (42.6%) had a positive history of premature CAD. The time from onset of chest pain to medical contact ranged from 45 to 240 min with an average of 187.2 ± 48 min.

Admission ECG was normal in 22 patients (18%), 46 patients (37.7%) had significant ST-segment depression, 34 patients (27.9%) had T-wave changes, and 20 patients (16.4%) had pathological Q waves of old myocardial infarction (Table 1).

3.2. Cardiac biomarkers on admission

A larger number of patients had H-FABP positive on admission 84 patients (68.9%) versus 36 patients (29.5%) with cTnT ($p = 0.032$). Of the H-FABP positive patients 30 (35.7%) had admission cTnT test positive while 54 (64.3%) had a negative test (Fig. 2).

3.3. Repeat analysis for admission troponin-T negative patients

The 86 patients (70.5%) with a cTnT negative test on admission had a second assessment after 6 h. Of them 58 patients (67.4%) had cTnT positive results on repeat testing and 28 patients (32.6%) still had negative results.

On examining results of the repeat troponin-T test with the admission H-FABP test results, we found that of the 58 patients with repeat cTnT positive test 54 patients (93.1%) had a positive admission H-FABP test, while the 28 patients with negative repeat cTnT test all (100%) had negative admission H-FABP test.

3.4. Comparing biomarkers at 6 h from admission for all patients

After repeat testing 6 h from admission, the total number of cTnT positive patients was 94 (77%) and that with cTnT negative was 28 (23%). All troponin-T negative patients had negative H-FABP results. Of the troponin-T positive patients, 84 (89.4%) had positive H-FABP test while the remaining 10 (10.6%) had "false" negative results (H-FABP negative and cTnT positive). For those with false negative results, we did a repeat assessment of H-FABP after 6 h and found 4 patients to have a positive result while 6 patients had the same negative results.

So the final total number of H-FABP positive patients was 88 (72.1%) and that with H-FAPB negative was 34 (27.9%) (Fig. 2).

3.5. Sensitivity and specificity of troponin-T within 4 h of chest pain onset

Using the final results of cTnT positive patients after 6 h from admission as the gold standard, we found that early assessment of cTnT within 4 h of chest pain onset had a sensitivity of 38.3%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 32.5%.

3.6. Sensitivity and specificity of H-FABP

Using the final results of cTnT positive patients after 6 h from admission as the gold standard, we found that H-FABP within 4 h of chest pain onset had a sensitivity of 89.4%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 73.7%, and an accuracy of 91.8%.

4. Discussion

The burden of acute coronary syndromes is increasing exponentially, making the rapid and accurate diagnosis of utmost importance.[14,15] Early diagnosis of NSTEMI leads to a reduction of morbidity and mortality in such patients as the patients will be risk stratified sooner, hence receiving the necessary pharmacological and/or interventional management in a timely manner.[16]

Having point-of-care tests available such as troponin-T readily available in the ER helps to identify such patients who are at increased risk of major adverse cardiac events. Despite the exhaustive evidence on the value of cTn in early detection of myocardial damage to the point that it is an integral recommendation of all guidelines of practice for acute coronary syndromes,[9,10] the short time from onset of ischemic chest pain till the rise of cTn has been proven valuable and there is increasing demand for novel biomarkers that may be able to detect myocardial damage at an earlier stage.

Human-type fatty acid-binding protein (H-FABP) has shown promise in several studies and has been proven to detect myocardial damage as early as 30 min after the onset of ischemic chest pain reaching a peak in 6 h and returning to normal within 24 h.[12] This rapid return to number is valuable in the detection of re-infarction.[17]

This study has demonstrated that a significantly larger number of patients were detected by point-of-care H-FABP test available in the ER compared to cTnT for patients presenting in the very early hours (less than 4 h) after the onset of chest pain and accordingly it can be used to rapidly rule out acute myocardial infarction especially in those presenting early after the onset of chest pain. We have also demonstrated that point-of-care H-FABP test has a high sensitivity and specificity when used in the first 4 h after symptom onset. Other studies have shown that H-FABP improves the diagnostic performance when combined with other cardiac markers[18,19] and that it is more sensitive than Troponin I within 6 h of chest pain.[20]

4.1. H-FABP in other studies

We performed a comparison between sensitivity and specificity of H-FABP and cTnT at presentation in patients in the current study and several other studies (Table 2). Ruzgar et al. studied 40 consecutive patients presenting with suspected ACS; they were divided into two groups; the first group ($n = 26$) seen within 6 h of onset of chest pain and the other ($n = 14$) seen within 6–24 h. They concluded that within 6 h of ACS, H-FABP is a more sensitive biochemical marker than troponin-T in the early detection of ischemic myocardial necrosis; but after that the sensitivity of H-FABP decreases, and it should not be used alone in patients admitted 24 h after the onset of chest pain.[21] Cavus et al. compared the efficacy of H-FABP compared to CK-MB and troponin-T in early diagnosis of ACS in 67 patients presenting less than 1 h after onset of chest pain. They examined the biomarkers at 4 h from admission and concluded that point-of-care assays of H-FABP in patients presenting within 20 h of symptom onset may lead to an earlier diagnosis of ACS.[22]

Figiel and his colleagues studied 100 patients admitted with chest pain lasting less than 24 h from admission and strong suspicion of NSTE-ACS and measured H-FABP, troponin-T, and CK-MB on admission, at 3 and 6 h. Data from admission results are shown in Table 2, and they also showed that the positive predictive values were 100%, 92.6% and 100% and the negative predictive values were 93.4%, 67.8% and 68.2% for H-FABP, CK-MB and troponin-T respectively.[23]

Another study assessing the value of early measurement of H-FABP, CK-MB, and troponin-I examined 705 patients presented with ACS without persistent ST-segment elevation with onset of chest pain less than 24 h. They concluded after evaluating eight biomarkers for their potential to rapidly exclude AMI at the time of presentation that while none of the biomarkers alone were able to exclude AMI, multivariate analysis identified that the optimal multi-marker strategy incorporated H-FABP and troponin-I. Combined with clinical risk stratification, this strategy could rapidly exclude AMI in 44.7% of all patients and suggested that H-FABP may play an important role for enabling rapid exclusion of AMI in the emergency room.[8] Further results from other studies are shown in Table 2.[24–26]

4.2. Use of novel biomarkers in practice

Although this was not examined in the current study, it is of note that studies have shown the prognostic value of elevated H-FABP in predicting long-term mortality and re-infarction in

Table 2 Sensitivity and specificity of H-FABP and admission troponin in this and other studies.

Study	H-FABP		Troponin	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Ruzgar et al.[21]	95.2	100	38.1	100
Cavus et al.[22]	97.6	88.5	100	88.5
Figiel et al.[23]	94.7	100	64.9	100
Body et al.[8]	75	89	42	96
Naroo et al.[24]	75.8	97	58.6	98.8
Gururajan et al.[25]	92	93	54	95
Xie et al.[26]	81.8	100	40.9	100
This study	89.4	100	38.3	100

troponin-negative patients with acute coronary syndrome[27] as well as identifying high-risk patients.[28] Other studies have shown H-FABP only to improve diagnostic accuracy while not adding any diagnostic value when high sensitivity troponin-T is available.[29,30] It is therefore generally recommended to combine H-FABP to cTn which is more specific to confirm or exclude AMI.

According to recent ACC/AHA guidelines for the management of patients with NSTE-ACS, the use of selected newer biomarkers may be reasonable to provide additional prognostic information for patients with NSTE-ACS (Class IIb, level of evidence: B).[9] Similarly, ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation state that early diagnosis of ACS may be improved by measurements of fatty acid-binding protein.[10]

4.3. Study limitations

Limitations of the current study are that it comes from a single medical center with a relatively limited number of patients. We relied mainly on qualitative results as we meant to examine point-of-care tests. Comparing to quantitative high sensitivity troponin might be of added value but we aimed to assess point-of-care tests. Follow-up of patients to show whether those detected and managed early by the H-FABP test had better outcomes in comparison with those detected later by troponin-T was not done so we cannot identify the actual effect on mortality and morbidity. Finally, the use of cardiac Troponin-T as the gold standard to identify non-ST segment elevation myocardial infarction might not have been appropriate and it could have been more appropriate to use coronary angiography; however, this was not feasible in our study due to logistic and financial considerations.

5. Conclusion

For patients presenting with suspected ACS within 4 h of onset of symptoms, H-FABP detects a significantly larger number of patients with NSTEMI compared to troponin-T. Qualitative H-FABP test has good sensitivity and specificity and thus plays an important role in diagnosing or ruling out NSTEMI in the emergency room.

Conflict of interest

All authors have no conflict of interest and no financial disclosures regarding the topic at hand.

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