Utility of Heart-Type Fatty Acid Binding Protein in Early Diagnosis of Acute Coronary Syndrome

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Abstract

Background: Early diagnosis of the patients presenting with suspected acute coronary syndrome using novel cardiac biomarkers, help to avoid delay in administering treatment, and to prevent inadvertent discharge of patients with acute myocardial infarction.

Objective: To determine the diagnostic accuracy of rapid Heart-type Fatty Acid-Binding Protein (H-FABP) test in patients suspected to have Acute Coronary Syndrome (ACS).

Patients and Methods: Ninety patients admitted with chest pain of possible or definite cardiac etiology (within 24 h duration), irrespective of (ECG) changes, were subjected to detailed and full history taking and thorough clinical examination, 12 lead ECG, and echocardiography, full laboratory investigation, including cardiac enzymes, troponin, and H-FABP. All patients underwent coronary angiography.

Results: Mean patient age was 56 years (SD 12), 88% was male, and 80 patients (89%) were diagnosed with ACS. The H-FABP test was performed within 24h after symptom onset. The positive predictive value (PPV) of H-FABP was 73.6%; the Negative Predictive Value (NPV) was 100% (95% CI 0.660-0.891). Sensitivity was 92.3% and specificity 56%. And the discriminatory power for H-FABP was higher as indicated by AUC 0.776 versus Troponin (0.675) within 4hrs after coronary occlusion and symptoms.

Conclusion: H-FABP is an early sensitive marker for diagnosis of myocardial infarction with higher sensitivity during the initial 4hrs from chest pain onset when compared with conventional troponin; therefore H-FABP can be used to rule out myocardial infarction during an early stage of chest pain presentation.

Key Words: Acute coronary syndrome (ACS) – Heart-type fatty acid – Binding protein (H-FABP).

Introduction

CHEST pain and other symptoms associated with ACS are among the most common presentation in the Emergency Department, with more than 5.5 million patients annually [1]. Patients with chest pain present a tremendous diagnostic challenge for many reasons, including a substantial overlap between characteristics of non-cardiac and cardiac pain, misinterpretations of ECG and cardiac biomarker levels, and the lack of a “typical” clinical presentation in approximately 20% to 25% of patients [2].

A single ECG cannot capture the entire dynamic process of ischemia. As a result, the initial ECG for acute MI patients can be normal or non-diagnostic in 20% to 25% of cases [3,4].

To date, cardiac troponin remains the most widely used assay in AMI diagnosis. Beside the delayed increased, conventional troponin lacks the ability to detect early phase ischemia in the absence of necrosis. Therefore patients who are at increased risk of cardiac adverse outcome remains undetected [5]. Novel biomarkers provide additional information to those already provided by troponin assay, which include early detection of myocardial ischemia, sign of unstable plaque and determine patients' prognosis [6].

H-FABP was first reported to be released from injured myocardium in 1988 [7]. The release kinetics of H-FABP following AMI mirror those of Myoglobin-typically it is detectable at 1-3 hours, peaks at around 4 hours and returns to baseline concentrations within 24 hours [8]. Much of the attention in the 1990s was focused on the utility of H-FABP as a superior early ACS diagnostic marker due to its favorable release kinetics following myocardial cell necrosis. H-FABP is superior to myoglobin in the early diagnosis of ACS, especially in the first 6 hours from onset of symptoms. This is probably because H-FABP is a slightly smaller molecule than myoglobin and the normal plasma value of H-FABP is much lower than that of myoglobin, both absolutely and relative to the magnitude of change seen in ACS [9].
Aim of the study:
To determine the diagnostic indices [sensitivity, specificity, positive predictive value, negative predictive value, Receiver Operating Characteristic (ROC) curve] of rapid Heart-type Fatty Acid-Binding Protein (H-FABP) test in patients suspected to have Acute Coronary Syndrome (ACS), and to compare it with conventional cardiac troponin test assay in diagnosing AMI according to the time of onset of chest pain.

Patients and Methods
Between October 2007 to July 2009, it is a prospective, randomized clinical trial which included ninety patients admitted to the Critical Care Department with acute coronary syndrome after exclusion of the following:

Patient’s selection: It is a prospective, randomized clinical trial which included ninety patients admitted to the Critical Care Department with chest pain of possible or definite cardiac etiology, irrespective of (ECG) changes after exclusion of the following patients:
1- Those less than 18 years old.
2- Those with complaints lasting more than 24 hours, as H-FABP levels usually return to normal 24 hours after onset of myocardial ischemia [8].
3- Who are admitted with an identified noncardiac cause of chest pain on presentation (such as pneumonia or pulmonary embolism).
4- Subjects with chest trauma causing suspected myocardial contusion.
5- Those with Renal failure requiring dialysis; it has been shown that the mean plasma concentration of H-FABP in the patients with chronic renal failure requiring dialysis is 21 to 25 times higher than in normal adults [10].
6- Pregnancy, heart failure.
7- Patients with a history of recent muscle injury (<3 days), including intramuscular injection, and those with acute or chronic skeletal muscle damage or disorders including rhabdomyolysis, dermatomyositis, muscular dystrophy, and polymyositis [11].
8- Critically ill patients, including those with cardiogenic shock, septic, intubated and ventilated patients.
9- Patients who had had a recent myocardial infarction or received fibrinolytic therapy or angioplasty within the last 14 days prior to presentation to the ED.

All patients were subjected to detailed and full history taking and thorough clinical examination, 12 lead ECG, an echocardiography, and coronary angiography was done for all patients.

Laboratory investigations: Blood samples withdrawn from the patients on admission for the routine tests which includes: Compete blood count (EDTA blood), coagulation profile (citrated blood), and Liver and kidney functions (whole blood). Cardiac biomarkers including: CPK, CPK (MB), and troponin measured for all patients on admission (serum samples) to be repeated every 4-6 hours for up to 3 sets in –ve troponin patients. Also Heart-fatty acid binding protein as a specific cardiac biomarker.

Principle of the H-FABP assay: The test contains two different specific monoclonal antibodies for H-FABP, one of which is gold-labelled and the other one biotinylated. The sample liquid releases the gold-labelled and the biotinylated anti-H-FABP antibodies out of their matrices. If the sample to be examined contains H-FABP, the antibodies form a sandwich complex with the analyte (anti-H-FABP-antibody (gold-labelled) <-> h-FABP <-> anti-h-FABP-antibody (biotinylated), this complex flows over the test strip.

Depending on the concentration of h-FABP in the sample, a red/purple line becomes visible at the T-marking, hence the intensity of the test line increases proportionally to the concentration of H-FABP. If the sample does not contain H-FABP, no complex can be formed and therefore no test line will appear. The excess gold-labelled antibodies bind unspecific on the control line (C) and indicate that the test has worked properly.

Performing the test: By applying 120ul serum in the sample reservoir, the test result become ready after 15 minutes.

Interpretation of the test result: The red/purple control line (C) indicates the test has worked properly, if the control line does not appear, the test should be repeated, the test also should be repeated if the test line (T) appear, but the control line does not.

Negative test: <5.4ng/ml: A red/purple line appears in the upper section of the panel (control line C) indicating that the test worked properly, however, no test line appear, this indicates that the concentration of H-FABP in the sample was <5.4 ng/ml.

Positive test: >5.4ng/ml: A red/purple line appears in the upper section of the panel (control
Infarction not likely or outside the diagnostic window

Infarction likely

Invalid result perform a new test

Invalid result perform a new test

Statistical analysis: Data were prospectively collected and coded prior to analysis using the professional Package for Social Sciences (SPSS version 16.0). Continuous variables were expressed as mean and Standard Deviation (SD). Categorical variables were expressed as frequency and proportion. Student- \( t \) Test (\( t \)) was used for comparison between two groups as regards normally distributed (parametric) quantitative data. Chi-Square Test (\( \chi^2 \)) was used for comparison between two groups as regard qualitative data. A Receiver Operating Characteristic (ROC) analysis was performed to define a cutoff value of different markers. patients divided into three groups according to the onset of chest pain as: (Group 1) in whom the onset of pain 4hrs or less, (Group 2) had pain more than 4hrs and less than or equal 12hrs while (Group 3) had chest pain more than 12hrs but less than 24hrs. Diagnostic indices for (H-FABP and troponin) were determined for each group. Results were considered statistically significant if \( p<0.05 \).

Results

I- Baseline patients characteristics:

Patient's characteristics are presented in table below, as shown in this table the majority of the patients were admitted within four hours of chest pain onset, and STEMI was final diagnosis in half of these patients.

II- Receiver operating characteristic curves:

ROC analysis was done to demonstrate H-FABP levels in patients with myocardial infarction (using 2nd set of troponin and coronary angiography as gold standard for diagnosis of MI), from the ROC the optimum cut-off value above which H-FABP can be considered positive was found to be 5.4ng/ml. The area under the ROC was observed to be 0.776 with 95% CI (0.660-0.891) \( (p<0.001) \). At the optimum cut-off value, sensitivity and specificity were found to be 92.3% and 56% respectively, with PPV 73.6, and NPV was 100, comparison of ROC of H-FABP with troponin showed marked significance for H-FABP with the area under the curve 0.675, sensitivity and specificity was 37% and 100% respectively (cut-off value 0.15ng/ml).

III- Diagnostic indices of H-FABP and troponin in relation to chest pain onset:

As shown in the table below the sensitivity of H-FABP for detection of myocardial infarction is highest in Group 1 and Group 2 patients (those presented by chest pain less than 12hrs) with NPV of 100%, on the other hand the sensitivity of conventional cardiac troponin for early detection of myocardial infarction was only 13% with 23% NPV, however for patient with late presentation (Group 3) the sensitivity of H-FABP only 37%, with NPV of 28.6%, on contrary to troponin which has higher sensitivity and higher NPV for those
with late presentation. Also there was a higher specificity for conventional cardiac troponin than H-FABP for diagnosis of myocardial infarction with PPV 100%.

IV- H-FABP and myocardial ischemia:

H-FABP was found to be a sensitive marker for myocardial infarction where a highly positive statistically significant relation was found between the value of H-FABP and acute myocardial infarction (H-FABP was 24.2±16.9ng/ml in patients with myocardial infarction compared to <5.4ng/ml in patients without acute myocardial infarction) (p<0.001), also H-FABP was found to be a sensitive marker in patients with acute myocardial ischemia without infarction (unstable angina) where (H-FABP was 18.7±12.3ng/ml in patients with unstable angina compared to <5.4ng/ml in those without ischemic heart disease) (p<0.001), however H-FABP alone can't differentiate between acute myocardial infarction and unstable angina (H-FABP was 24.2±16.9ng/ml in patients with myocardial infarction, compared to 18.7±12.3ng/ml in those with unstable angina (p=0.302).

<table>
<thead>
<tr>
<th>Age (yrs) (mean ± std)</th>
<th>55.53±11.72 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male %</td>
<td>87.8%</td>
</tr>
<tr>
<td>Female %</td>
<td>12.2%</td>
</tr>
<tr>
<td>Risk factors:</td>
<td></td>
</tr>
<tr>
<td>Current smoker %</td>
<td>40%</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>60%</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>45.6%</td>
</tr>
<tr>
<td>Dyslipidemia %</td>
<td>22.2%</td>
</tr>
<tr>
<td>Previous IHD %</td>
<td>26.7%</td>
</tr>
<tr>
<td>Chest pain onset:</td>
<td></td>
</tr>
<tr>
<td>≤4hrs%</td>
<td>64.4%</td>
</tr>
<tr>
<td>4-12hrs%</td>
<td>24.4%</td>
</tr>
<tr>
<td>≥12hrs%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

| Laboratory data:       |                   |
| +ve 1st cardiac enzymes % | 26.7%         |
| +ve 2nd cardiac enzymes %  | 72.2%         |
| +ve H-FABP (>5.4μg/ml) %   | 78.9%         |

| Echocardiography:       |                   |
| EF>45%                 | 92.2%             |
| EF<45%                 | 7.8%              |

| Final diagnosis:        |                   |
| STEMI %                | 50%               |
| Non-STEMI %            | 38.9%             |
| Non cardiac            | 11.1%             |

| Chest pain onset:      |                   |
| ≤4hrs%                 | 64.4%             |
| 4-12hrs%               | 24.4%             |
| ≥12hrs%                | 11.1%             |

Table (2): Sensitivity, specificity, PPV, and NPV of H-FABP and troponin in relation to chest pain onset.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>NPV %</th>
<th>PPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>H-FABP 100</td>
<td>Troponin 13</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Group 2</td>
<td>H-FABP 100</td>
<td>Troponin 91</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>Group 3</td>
<td>H-FABP 37.5</td>
<td>Troponin 100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Fig. (2): ROC analysis for H-FABP, and myocardial infarction.

Fig. (3): ROC analysis for troponin, and myocardial infarction.
Discussion

To date, cardiac troponin remains the most widely used assay in AMI diagnosis. Beside the delayed increased, conventional troponin lacks the ability to detect early phase ischemia in the absence of necrosis. Therefore patients who are at increased risk of cardiac adverse outcome remains undetected [5]. Novel biomarkers provide additional information to those already provided by troponin assay, which include early detection of myocardial ischemia, sign of unstable plaque and determine patients’ prognosis [6].

In a number of studies [9,12-15] H-FABP has been reported to be particularly sensitive within the first few hours after the onset of coronary occlusion and symptoms, the present study showed that H-FABP was found to be a reliable biomarker for early detection of myocardial infarction with higher sensitivity (92.3%) and NPV (100%) with 95% CI (0.660-0.891) when compared with Troponin (sensitivity was 37%, and NPV 37.8%, with 95% CI (0.568-0.782). This sensitivity may be explained by the high concentration of H-FABP in myocardium compared to other tissues; the stability and solubility of H-FABP; its low molecular weight; 15 kDa compared to 37 kDa for cardiac Troponin [8,16] its rapid release into plasma after myocardial injury (60 minutes following an ischemic episode) [8,12]. These results are similar to study published by Body et al., evaluating the ability of 8 biomarkers to rapidly exclude AMI. [8]. In their 705 patients heart fatty acid binding protein (H-FABP) had an AUC of 0.86 (95% CI 0.82-0.90), which was significantly higher than any other biomarker including cTnI [13].

The present study showed that sensitivity of H-FABP as a marker of myocardial infarction was higher in Group 1 and Group 2 patients (those admitted within 12hrs from the onset of coronary occlusion and symptoms), compared to Group 3 patients (those admitted more than 12hrs). Also the sensitivity of H-FABP was higher when compared with troponin in Group 1 patients (those admitted within first 4hrs from symptoms onset). This could be explained by the release kinetics of H-FABP following AMI-typically it is detectable at 1-3 hours, peaks at around 4 hours and returns to baseline concentrations within 24 hours, making H-FABP an early sensitive marker of myocardial infarction [8]. On the other hand cardiac troponins (cTns) appear in the blood 3-4 hours of the acute episode and remain elevated for 4-14 days [17]. Confirmary to this study; that published McCann’s et al., at the European Heart Journal in 2008, they prospectively evaluated 664 chest pain patients presenting to two coronary units in the UK, where They demonstrated that assessment of H-FABP within the first 4 hours of symptom onset was superior to TnT (4th gen) for the detection of AMI [18].

The present study showed that H-FABP was found to be a sensitive marker in patients with unstable angina (p<0.001), however it couldn’t differentiates myocardial infarction from unstable angina (p=0.302), making the specificity of H-FABP for myocardial infarction only 56%. This explained by the fact that H-FABP is released not only during myocardial necrosis but also during acute myocardial ischemia [19]. This fact was confirmed by: Meng et al., who demonstrated that H-FABP concentration in peripheral blood in rats rose four-fold from the baseline concentration after just 15 minutes of induced myocardial ischemia [19]. Secondly, in human autopsy cases, it was found that H-FABP myocardial depletion in patients dying suddenly after the onset of chest pain despite the absence of myocyte necrosis on electron microscopy [20].

Study limitation: In addition to the small sample size, the subjective nature reports from the patients about the exact onset of their ischemic symptoms may potentially overestimate or underestimate the duration of their ischemic symptoms. This may have influenced the grouping of patients according to the predetermined time frame and eventually affect the diagnostic indices of the group studied.

Conclusion: H-FABP is an early sensitive marker for diagnosis of myocardial infarction with higher sensitivity during the initial 4hrs from chest pain onset when compared with conventional troponin, therefore H-FABP can be used to rule out myocardial infarction during an early stage of chest
Utility of H-FABP in Early Diagnosis of ACS

pain presentation. On contrary to troponin, H-FABP can be detected in the blood in the setting of acute myocardial ischemia without infarction, making it sensitive for diagnosis of unstable angina.

References


الملخص العربي

لعبة الدلالات البيوكيميائية للقلب دوراً مترابعاً في تشخيص متلازمة السكريّة التاجية الحادة (ACS) منذ تطور استبارات الأكينية (AST) في عام 1955. وتتيح الآن، لا يزال التبرسيون الستيسيم أكثر استخداماً في تشخيص الإحتشاء الحاد للقلب. وذلك بالرغم من إتفاق التبرسيون التقليدي على أن المضاعفات على الكشف المبكر للأعراض الناجية نتيجة التورم في الدم، مما يقلل من خصائص الكشف المبكر للمرضى قصور السكريّة التاجية الحادة. مما يجعل من هؤلاء المرضى عرضة لحدوث مضاعفات.

أما الآن فقد ظهرت دلالات البيوكيميائية حديثة تتضمن نقص الدم الذي يؤدي التبرسيون بالإضافة إلى نقصه على الكشف المبكر عن نقص تروية عضلة القلب، والتبني القذري القلبية غير مستقرة.

ومن هذه الدلالات التبرسيون المرتبط بالملامس الدموية القلبية حيث تم نشأة في عام 1988 بحيث أن يتميز بالظهور المبكر بالدم بعد ساعة من حدوث نقص بروتين عضلة القلب مما أدى إلى نتائج إستثنائية في استخدامه في التشخيص المبكر للمرضى الحاد للسكريّة التاجية وذلك في عام 1990، وذلك أيضاً مؤشرات لإستخدامه في حالات التبني البدني القذري غير مستقرة وذلك يتفوق على التبرسيون في اكتشاف القصور الحاد للسكريّة التاجية في عدم وجود جلطة السكريّة التاجية في حالة أخرى فإن الدراسات التي تشير بين عام 2005 و2007 ركزت على استخدام القيمة التشخيصية للترويد المرتبط بالмиامي الدموية القلبية في مرضى متلازمة السكريّة التاجية الحادة.

الهدف من هذا البحث هو إثبات نقص قوة التبرسيون المرتبط بالملامس الدموية القلبية في التشخيص المبكر لأعراض السكريّة التاجية الحادة، حيث يمكن إكتشاف مبكر وذلك قبل ارتفاع نسبة إنزيمات القلب والتبرسيون، مما يجعله أكثر حساسية في التشخيص المبكر، والتدخل المبكر عن طريق الأدوية، والقسطرة القلبية.

تضمنت الدراسة:

* جمعيّة من المرضى وعددهم تسعة مرضى قد تم حجزهم بصورة الدراسة في مركز السكريّة التاجية بالقاهرة العيني، نتيجة إشتباه قصور بالسكريّة التاجي.

* تطبيق شروط الدراسة.

* تم التقييم الكليبيكي والأختبارات العشوائية التبرسيونية وبعض الاختبارات الخاصة بالدراسة (من ضمنها قياس إنزيمات القلب والتبرسيون والترويد)

* المرتبط بالملامس الدموية القلبية.

* تم عمل موجات صوتية على القلب، بعمل قسطرة قلبية لجميع المرضى.

* وكانت النتائج إيجابية بطرق ملحوظة من حيث:

  - الالتباس المرتبط بالملامس الدموية القلبية أكثر حساسية في التشخيص المبكر لإحالة عضلة القلب حيث وصلت إلى 35% وكان هذا أعلى بالمقارنة مع التبرسيون، خاصة في المرضى الذين يتأثرون في خلال أربعة ساعات بعد نقص الترويد في عضلة القلب.

  - الالتباس المرتبط بالملامس الدموية القلبية يمكن الاستفادة منه في المرضى الذين يعانون من نقص الترويد الحاد دون احشتها بعضة القلب.

وتوصي الدراسة بالأكينية:

* استخدام الالتباس المرتبط بالملامس الدموية القلبية في التشخيص المبكر للمرضى الحاد للسكريّة التاجية.