

## Elevated heart-type fatty acid-binding protein predicts early myocardial injury and aids in the diagnosis of non-ST elevation myocardial infarction

心臟脂肪酸結合蛋白的升高可預測早期心肌受傷及幫助非ST段提升心肌梗塞的診斷

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**Background:** Biomarkers play an important role in the early diagnosis, risk stratification and management of patients with the acute coronary syndrome. **Objective:** The objective of this study was to evaluate the clinical reliability of heart-type fatty acid-binding protein (h-FABP) in identifying patients with the acute coronary syndrome in the early hours of chest pain. **Methods:** Creatine kinase (CK-MB) (in laboratory), troponin T (in laboratory) and h-FABP (with point-of-care test CardioDetect®) were performed on 791 patients who presented with chest pain with duration since onset ranging from 20 minutes to 12 hours. **Results:** Data of the 791 patients were analysed. h-FABP had a higher sensitivity of 75.76% and a specificity of 96.97% compared with 58.59% and 98.84% for troponin T and 68.69% and 97.54% for CK-MB respectively (in the first 6 hours). **Conclusion:** h-FABP was found to be a better biomarker of cardiac necrosis in the early hours in the diagnosis of non-conclusive ECG in patients with acute myocardial infarction. (*Hong Kong j.emerg.med.* 2009;16:141-147)

**背景：**在急性冠狀動脈綜合徵病人的早期診斷，風險排列及處理上，生物標誌扮演一個重要的角色。**目的：**本研究旨在評估心臟脂肪酸結合蛋白在胸痛早期識別出急性冠狀動脈綜合徵病人的臨床可靠性。**方法：**於791名呈現胸痛而開始時間由20分鐘至12小時的病人進行肌酸激酶(肌腦)(在化驗室測試)，肌鈣蛋白T(在化驗室測試)及心臟脂肪酸結合蛋白(用CardioDetect®護理點測試)。**結果：**分析791名病人的數據。在首6小時內，心臟脂肪酸結合蛋白的敏感性較高為75.76%而特異性為96.97%，肌鈣蛋白T分別為58.59%及98.84%，及肌酸激酶(肌腦)分別為68.69%及97.54%。**結論：**在急性心肌梗塞而心電圖未能確定診斷的病人中，心臟脂肪酸結合蛋白顯示為心肌壞死早期較好的生物標誌。

**Keywords:** Biological markers, coronary disease, creatine kinase, fatty acid-binding proteins, troponin T

**關鍵詞：**生物標誌、冠心病、肌酸激酶、脂肪酸結合蛋白、肌鈣蛋白T

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## Introduction

Cardiovascular disease is the most common cause of death in developed and developing countries. It accounts for 36% of the total deaths around the world and 25% of deaths in the United Arab Emirates (UAE) and the entire Gulf. Acute chest pain is one of the most common reasons for presentation to the emergency department. However, only 15-25% of patients with acute chest pain actually have acute coronary syndrome (ACS) after diagnostic evaluation. The difficulty is to differentiate patients with ACS from those with non-cardiac chest pain.<sup>1,2</sup> Several advances

in recent years have enhanced the accuracy and efficiency of the evaluation of patients with acute chest pain and include better blood markers for the detection of myocardial injury.<sup>3,4</sup> The early diagnosis of acute myocardial infarction (AMI) is however sometimes difficult due to:<sup>5</sup>

1. Equivocal electrocardiogram (ECG) changes and other conditions with ECG changes that mimic AMI.
2. AMI patients without ST-segment elevation.
3. Delayed liberation and detection of cardiac markers of myocardial necrosis such as troponin and creatine kinase (CK).

Cardiac troponin is frequently not detected until after 4-6 hours and in many cases, repeated measurement is needed 8-12 hours after admission. The importance of early risk stratification in the management of AMI is emphasized in the American Heart Association task force guidelines.<sup>6</sup> Risk stratification is an important objective in the evaluation of patients with ACS. The presence of positive biomarkers indicates higher risk and worse prognosis.<sup>7</sup> ST elevation myocardial infarction (STEMI) is diagnosed by the symptoms and the characteristic ST elevation on the ECG and is treated by immediate reperfusion, either fibrinolytic therapy or primary percutaneous coronary intervention. The other two variants of ACS, non-ST elevation myocardial infarction and unstable angina are differentiated from each other by the presence of positive cardiac biomarker in the former and the treatment varies accordingly.<sup>1-3</sup>

Heart-type fatty acid-binding protein (h-FABP) is being evaluated as a rapid indicator for the assessment of myocardial damage in patients with typical cardiac chest pain and non-conclusive ECGs.<sup>8</sup> h-FABP is a low molecular mass cytoplasmic protein (15 kDa) available in abundance in myocardial tissue.<sup>8-10</sup> h-FABP is released from the heart during cell necrosis much quicker than any other marker. h-FABP serum level not only rises early but is normalised after 24 hours allowing for the detection of recurrent myocardial infarction. h-FABP's advantage is specifically dominant in the early phase of myocardial infarction. The combination of initial h-FABP release after symptom

onset, rapid kidney clearance from the circulation and high cardiac specificity suggests great potential for clinical use.<sup>8-10</sup> h-FABP has been researched since 1988, due to its high potential as an early marker for myocardial infarction. It bears considerable resemblance to myoglobin in terms of size, location within the cell, release and clearance kinetics, but is superior due to its higher specificity.<sup>11,12</sup> The only obstacle was finding a quick accurate tool to capture and measure the h-FABP without any further delay that accompanies ELISA tests.<sup>6,7</sup> This has been resolved by the innovative h-FABP point-of-care (POC) test (CardioDetect<sup>®</sup> med card by Rennesens GmbH, Berlin, Germany).<sup>11</sup>

This prospective study was undertaken to evaluate h-FABP as a rapid indicator for assessment of myocardial damage in patients with typical cardiac chest pain and non-conclusive ECG.

## Materials and methods

### *Study population*

Eligible patients with suspected AMI admitted to the Emergency and Trauma Center of Rashid Hospital, Dubai from September 2006 to September 2007 were included in the study, with the following criteria:

1. Time window of admission: onset of pain 20 minutes-12 hours.
2. Patients with typical cardiac chest pain.
3. Patients with no ST segment elevation in the ECG.

The exclusion criteria were:

1. ST elevation myocardial infarction.
2. Known renal disease.
3. Age less than 20 years.

### *Study design*

The study protocol was approved by the Dubai Medical Health Authority, Medical Ethics Committee and Medical Research Committee of Rashid Hospital. The Department of Health (Rashid Hospital) funded the study. All patients had a 12-lead ECG and biochemical markers which included troponin, CK, CK-MB and h-FABP.

After the initial assessment, a few drops of blood were taken (to measure h-FABP) from the same sample that were sent to the laboratory for assay of troponin, CK and CK-MB (informed consent was taken). These samples were taken blinded to clinical data and the CardioDetect® test was done by a trained nurse. h-FABP in the blood was qualitatively tested using the CardioDetect® POC test. It is an immunological rapid test with a detection threshold of 7 ng/ml. The concentration of troponin T (cTnT) was quantitatively measured in the laboratory using an electro-chemiluminescence immunoassay: (a) cut off value <0.03 ng/ml; (b) medium 0.3-0.9 ng/ml; (c) myocardial infarction  $\geq 1$  ng/ml. CK-MB was quantitatively measured in the laboratory using the Immunological UV SA; the baseline was 0-24 u/l.

The diagnostic performance of h-FABP was compared with that of cTnT, the standard test in clinical practice, in accordance with the American Heart Association task force guidelines. Serial troponin was repeated 6 to 12 hours after the initial sampling to establish a diagnosis. The diagnosis of myocardial infarction was confirmed with a positive troponin.

The patients who had negative cardiac biomarkers (at least 3 sets) and no sequential ECG changes were discharged from the Emergency Department, while those patients who turned out to have acute coronary syndrome were admitted by the cardiologist. Data were analysed based on the discharge diagnosis for clinical sensitivity, specificity and negative predictive value.

### *Study limitation*

h-FABP level is usually elevated in patients with renal insufficiency or renal failure, ending in false positive results despite the absence of AMI. This is due to the fact that h-FABP is cleared through the kidney and the clearance will be reduced in patients with renal problems. However, this limitation is not unique to h-FABP but also applies to cardiac troponins. In patients with renal impairment, quantitative analysis of h-FABP is required to see the rise and fall of the marker. Quantitative analysis was not available during the study period. Also, h-FABP was not repeated when the first test showed a negative result, as in the other

biochemical markers; another test should have been repeated after an hour if chest pain persisted.

## **Results**

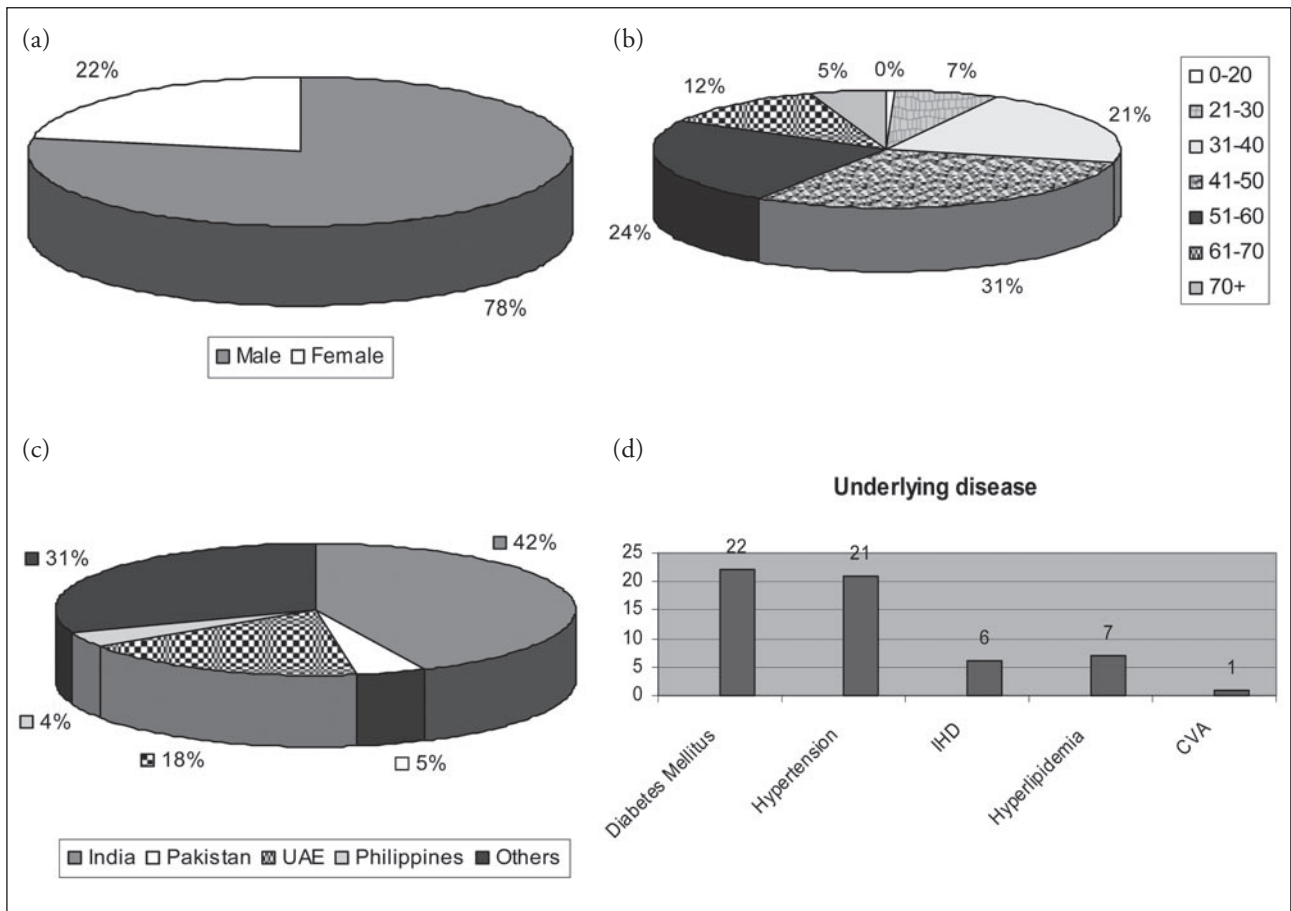
A total of 807 multi-ethnic cardiac chest pain patients with equivocal ECG findings were enrolled in the study. There were 627 males and 180 females, and 16 patients with incomplete data were excluded. Therefore the final analysis included the data of 791 patients. Patient demographics are shown in Figure 1; 42% were Indians as they constituted the major portion of UAE's workforce. Nationals comprised 18% of the study group which was quite a large number when compared to the UAE national population and it points to the increasing incidence of cardiovascular disease among our nationals.

Analysis of the data showed that h-FABP had a sensitivity of 75.76% and a specificity of 96.97% compared with 58.59% and 98.94% for cTnT and 68.69% and 97.54% for CK-MB in the initial 6 hours after the onset of chest pain (Figure 2 and Tables 1a & 1b). Altogether, 99 patients had acute myocardial infarction as confirmed by positive troponin levels (the gold standard test). Nine out of the 21 false positive patients tested by h-FABP had renal insufficiency with an abnormal creatinine level.

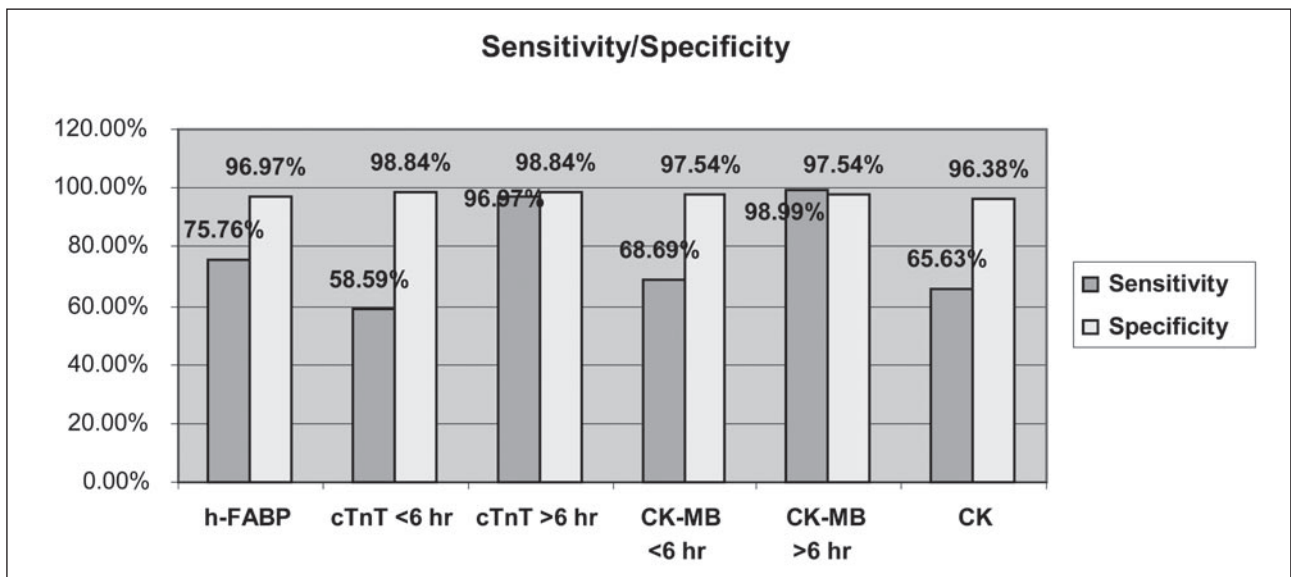
Repeated troponin testing 6 hours after the onset of chest pain showed positive results in 38 patients out of the 41 false negative patients, thus increasing the sensitivity of troponin to 96.97% and the specificity to 98.84% (6 hours after the onset of chest pain).

The sensitivity and specificity of CK-MB was 98.99% and 97.54% respectively after 6 hours. h-FABP diagnosed 75 AMI patients as compared to 58 patients by cTnT in the initial 6-hour period; i.e. 17 more patients were diagnosed by h-FABP. Sensitivity could have been higher if h-FABP was repeated as the other biochemical markers if the first test was negative.

h-FABP was found to have a higher negative predictive value when compared with that of cTnT and CK-MB.



**Figure 1.** Patient demographics (a) gender; (b) age; (c) nationality; (d) underlying disease. CVA=cerebrovascular accident; IHD=ischaeamic heart disease; UAE=United Arab Emirates.



**Figure 2.** Sensitivity and specificity of cardiac markers. CK=creatinine kinase; CK-MB=creatinine kinase MB fraction; cTnT=cardiac troponin T; h-FAPB=heart-type fatty acid binding protein.

The negative predictive values of h-FABP, cTnT and CK-MB were 96.55%, 94.34% and 95.61% respectively (Table 1c).

## Discussion

Despite the advent of cardiac centres and the development of assays for highly sensitive and specific biochemical markers of myocardial necrosis, emergency department evaluation and triage of patients with chest pain of unclear origin remain a challenge.<sup>12</sup> Studies have suggested that from 2% to 4% of patients with chest pain presenting to the emergency department who are released after initial evaluation is ultimately found to have had a myocardial infarction.<sup>13</sup> A sensitive and specific earlier marker of myocardial cell injury might be helpful in making triage and treatment decisions.<sup>13</sup> The principal characteristics that would make an ideal marker for early detection of myocardial injury include:

1. Small size: a small size molecular marker is more rapidly released into the circulation allowing early detection of myocardial damage.
2. Absence in the circulation under physiological conditions, thus its detection will be abnormal with even minimal increase of the marker in the plasma.
3. Absolute specificity for the myocardium.<sup>14</sup>

h-FABP's advantage is dominant in the early phase of myocardial infarction due to: (1) its size and weight, (2) abundance in the heart tissue, and (3) release and clearance kinetic.<sup>15</sup> The combination of a sensitive marker such as h-FABP for early detection, with a cardiospecific marker such as troponin for later confirmation can be recommended to provide optimal diagnostic performance, specifically non-STEMI, to minimise the risk of false exclusions of patients with AMI.<sup>16</sup>

With increasing health awareness, more people present earlier to the emergency department, especially chest pain patients. A single biomarker assay in the

**Table 1.** (a) Sensitivity, (b) specificity and (c) negative predictive value of cardiac markers

<b>(a) Sensitivity</b>					
Cardiac marker	h-FABP	cTnT (<6 hr)	cTnT (>6 hr)	CK-MB (<6 hr)	CK-MB (>6 hr)
True positive	75	58	96	68	98
AMI patient	99	99	99	99	99
False negative	24	41	3	31	1
<b>Sensitivity %</b>	<b>75.76%</b>	<b>58.59%</b>	<b>96.97%</b>	<b>68.69%</b>	<b>98.99%</b>
<b>(b) Specificity</b>					
Cardiac marker	h-FABP	cTnT (<6 hr)	cTnT (>6 hr)	CK-MB (<6 hr)	CK-MB (>6 hr)
True negative	671	684	684	675	675
Non-AMI patient	692	692	692	692	692
False positive	21	8	8	17	17
<b>Specificity %</b>	<b>96.97%</b>	<b>98.84%</b>	<b>98.84%</b>	<b>97.54%</b>	<b>97.54%</b>
<b>(c) Negative predictive value</b>					
Cardiac marker	h-FABP	cTnT	CK-MB		
True negative	671	684	675		
False negative	24	41	31		
<b>Negative predictive value</b>	<b>96.55%</b>	<b>94.34%</b>	<b>95.61%</b>		

AMI=acute myocardial infarction; CK=creatinine kinase; CK-MB=creatinine kinase MB fraction; cTnT=cardiac troponin T; h-FABP=heart-type fatty acid binding protein

emergency department has inadequate sensitivity to exclude AMI or adverse outcomes. Rashid hospital's experience with h-FABP demonstrates that the sensitivity of h-FABP is higher when compared to other biochemical markers (troponin by approximately 15%) and around the same specificity in comparison with other biomarkers in the early hours.

We included patients with chest pain durations of 20 minutes to 12 hours when h-FABP was compared with troponin which usually elevates 4-6 hours after the onset of chest pain. Patients with known renal disease were not included in the study. However most of the patients were newly diagnosed to have renal impairment in the hospital and these patients were also included in the study. The results of laboratory investigations including renal function test took around half an hour and h-FABP had already been done on all patients with cardiac chest pain at the time of presentation to our emergency department.

The cost of performing h-FABP was higher than that of cTnT and CK-MB (\$6 for cTnT or CK-MB; \$12 for h-FABP); as at Rashid Hospital. New tests, like new drugs, are usually more expensive than the ones they replace, and budgetary constraints frequently hamper introducing new tests even when there is abundant evidence. h-FABP supplies diagnostic safety in the first and decisive hours, closing the diagnostic gap. Once myocardial infarction is excluded at an early stage, considerable cost to the public and private healthcare sectors can be saved.

h-FABP was found to be a superior biomarker of cardiac necrosis in the diagnosis of myocardial infarction in patients with non-conclusive ECG. POC testing of h-FABP and cTnT can be used as diagnostic tool for early triage. h-FABP can be performed in serial measurement and usage of CardioDetect® quant (a device that can interpret h-FABP results quantitatively) may further improve the diagnostic value of h-FABP. A broader multicentre study needs to be conducted for further evaluation.

## Conclusion

h-FABP is a superior biomarker of cardiac necrosis in the diagnosis of AMI in patients with non-conclusive ECG in the early hours due to higher sensitivity and higher negative predictive value in comparison with other biomarkers, namely cTnT and CK-MB.

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