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A superior early myocardial infarction marker

Human heart-type fatty acid-binding protein

Ein überlegener Marker für die frühe Infarktdiagnostik: Humanes kardiales Fettsäurebindungsprotein (FABP)

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Zusammenfassung Aufgrund der höheren kardialen Spezifität scheint humanes kardiales FABP (Fettsäurebindungsprotein) im Vergleich zu Myoglobin ein vielversprechender Laborparameter zur frühen Herzinfarktdiagnostik zu sein. FABP ist ein niedermolekulares, zytoplasmatisches Protein (15 kDa) welches bereits sehr früh nach Einsetzen einer myokardialen Ischämie ins periphere Blut freigesetzt wird und daher zum biochemischen Nachweis oder Ausschluss eines akuten Myokardinfarktes (AMI) geeignet erscheint.

Bei n = 218 Patienten (Pat) mit akuten Thoraxschmerzen oder dem Verdacht auf einen AMI wurden in seriellen Messungen im peripheren Blut FABP und troponin I immunologisch sowie Kreatinkinase (CK) enzymatisch bestimmt. Bei n = 94 Patienten mit nachgewiesenem AMI erreichten die FABP-Konzentrationen innerhalb von drei Stunden nach Schmerzbeginn einen maximalen Level (577,6 ± 43,8 μg/L) und fielen innerhalb von 30 Stunden auf einen Normalwert ab. Die maximale FABP-Konzentration (peak) wurde im Mittel sieben bis neun Stunden früher erreicht, als bei der CK- oder Troponin-I-Bestimmung (2288 ± 131 U/L bzw. 357,1 ± 23,9 μg/L). Die CK-Werte normalisierten sich innerhalb von 50–70 Stunden während Troponin-I-Konzentrationen erst nach mehr als 70 Stunden die Nachweisgrenze unterschritten. Die Fläche unter der Receiver-Operating-Characteristics (ROC)-Kurve für FABP wurde zum Zeitpunkt der Aufnahme mit 0,871 und eine Stunde nach Aufnahme mit 0,995 errechnet, während die entsprechenden Flächen für CK 0,711 und 0,856 und für Troponin I 0,677 und 0,845 betrugen. Die diagnostische Trennschärfe zum Aufnahmezeitpunkt war für FABP am höchsten und wurde erst durch Troponin I acht Stunden nach Aufnahme (0,995) erreicht. Anhand der FABP-Messwerte konnte innerhalb einer Stunde nach Aufnahme eine Sensitivität von 100% als auch ein negativer Vorhersagewert von 100% erreicht werden.

Anhand von nur zwei Blutentnahmen zum Aufnahmezeitpunkt und nach Ablauf einer Stunde konnte mit der FABP-Bestimmung die Diagnose eines AMI sicher gestellt werden, umgekehrt konnte bei den übrigen Patienten mit 100% diagnostischer Sicherheit ein AMI ausgeschlossen werden, falsch negative Resultate wurden nicht gefunden. Die sogenannten späten Marker Troponin I und CK erbrachten eine vergleichbare diagnostische Sicherheit erst nach Ablauf von weiteren sieben Stunden. Somit scheint anhand der

Bestimmung von FABP im Blut der frühzeitige Nachweis oder Ausschluss eines AMI möglich zu sein.

Schlüsselwörter
Fettsäurebindungsprotein (FABP) – akuter Myokardinfarkt – Kreatinkinase – Troponin I

Summary Human heart-type fatty acid-binding protein (FABP) has a high potential as an early marker for myocardial infarction (MI) being more specific than myoglobin.

FABP is a low molecular mass cytoplasmic protein (15 kDa) that is released early after the onset of ischemia and it may be useful for rapid confirmation or exclusion of acute myocardial infarction (AMI).

Immunochemically assayed FABP, cardiac troponin I (cTnI) and enzymatically assayed creatine phosphokinase (CPK) were determined serially in plasma and serum samples from 218 patients presenting with chest pain and suspected MI. In the 94 patients with confirmed MI, FABP rose to a maximum level (577.6 ± 43.8 µg/L) 3 hours after the onset of symptoms and returned to normal within 30 hours. The FABP level peaked 7–9 hours earlier than CPK (2288 ± 131 U/L) and cTnI (357.1 ± 23.9 µg/L). CPK took 50–70 hours to return to normal level and cTnI returned to normal level over 70 hours. The areas under the receiver operating characteristic (ROC) curves for FABP were calculated as 0.871 at admission and 0.995 one hour after admission, whereas for CPK the areas were 0.711 and 0.856 and for cTnI the areas were 0.677 and 0.845, indicating that the FABP test gave a better diagnostic classification at the early stage being reached by cTnI (0.995) only 8 hours after admission. For FABP, both sensitivity and negative predictive value (NPV) increased quickly to 100% for samples monitored just one hour after admission.

By using only two samples, one at admission and one 1 hour post admission, sequential FABP monitoring can reliably diagnose AMI patients 1 hour after admission and 100% of non-AMI patients can be excluded with no false negative results. The late markers cTnI and CPK have the similar diagnostic performance only 7 hours later. Thus measurement of FABP in plasma or serum allows the earliest immunochemical confirmation or exclusion of AMI.

Key words
Fatty acid-binding protein – acute myocardial infarction – cardiac troponin I – creatine phosphokinase – receiver operating characteristic

Introduction

Rapid triaging of patients admitted to the hospital with chest pain suggestive of acute myocardial infarction (AMI) is needed to facilitate early installment of appropriate therapy in patients with AMI and to exclude low-risk patients who can be safely sent home. Biochemical markers of myocardial injury, specifically the cardiac troponins, are now universally accepted as important determinants for the diagnosis of those patients. However, the early diagnosis of AMI is still problematic in those patients without obvious ST-segment elevation because cardiac troponins are not detected frequently until after 6 hours and a repeated measurement is necessary at 8–12 hours after admission [4]. At present attention is focused on defining those cardiac marker proteins (or combinations) that show a high sensitivity as well as specificity for AMI detection especially in the early hours after admission.

Heart-type FABP, a small cardiac protein (15 kDa), has been proposed as an early biochemical marker for AMI [5, 7, 8, 14–16, 22]. This heart-type cytoplasmic protein is distinct from other types of FABP such as those found in the liver and intestine [10, 25]. FABP shows release characteristics from injured myocardium and elimination rates from plasma that are similar to those of myoglobin. An elevation is detectable as early as 1–3 hours after AMI onset, peak values are reached at 6–8 hours, and the plasma level returns to normal within 24–30 hours [14, 21, 23, 24]. This resemblance relates to the similar molecular masses of FABP and myoglobin (17.6 kD). Several clinical studies have revealed a superior performance of FABP over myoglobin for early AMI detection as well as early estimation of infarct size [20, 24, 26]. This finding most likely relates to marked differences in tissue contents of FABP and myoglobin in cardiac and skeletal muscles that result in a relatively low upper reference concentration in plasma for FABP compared with that for myoglobin. Due to its early elevation and rapid kidney clearance from the circulation, FABP analysis may be a practical and useful tool to confirm or exclude AMI at an early stage.

The aim of the present study was to investigate the performance of FABP analysis by serial measurement in patients presenting with chest pain and suspected myocardial infarction. In order to make an early definite diagnosis in chest pain patients, FABP and cTnI concentrations and CPK activities were analyzed using frequently taken samples.

Patient population

The present study involved 218 patients admitted to the Coronary Care Unit (CCU) and Chest Pain Unit of the Prince of Wales Hospital (PWH) in Hong Kong from 1997 to 2001. The study protocol was approved by the Clinical Research Ethical Committee of the Faculty of Medicine, the Chinese University of Hong Kong. The protocol was thoroughly explained to the patients, and signed consent was obtained.

As shown in Table 1, a total of 94 patients (75 male and 19 female) with an average age of 63.1 ± 11.9 (mean ± SD) years were diagnosed with AMI. 72 patients (52 male and 20 female) were diagnosed as other heart disease (OHD) with a mean age of 66.8 ± 12.0 years and 52 patients (28 male and 24 female) were diagnosed as non-heart disease (NHD) with a mean age of 57.3 ± 12.2 years. Both OHD and NHD were defined as non-AMI patients.

Of the 218 patients, 132 (61.1%) patients were admitted to the CCU or the Chest Pain Unit of the hospital within the first three hours (Fig. 1) after the onset of symptoms. Of the patients, 87.2% were admitted to the hospital within the first six hours following the onset of chest pain.

Cardiac markers analysis

Blood samples were taken upon admission to the CCU and at 1, 3, 8, 12, 28, 48 and 72 hours thereafter. The blood samples were collected in either heparin containing tubes or clot activator tubes (co-

Table 1 Patient population and classification

Diagnosis	Patient n	Age		
		Range	Mean	SD
Acute Myocardial Infarction (AMI)				
Male	75	36–85	61.4	11.7
Female	19	46–83	69.8	10.4
Total	94	36–85	63.1	11.9
Other Heart Disease (OHD)				
Male	52	37–87	64.3	12.5
Female	20	54–84	72.8	7.0
Total	72	37–87	66.8	12.0
Non-Heart Disease (NHD)				
Male	28	33–82	54.9	12.7
Female	24	40–74	60.2	11.2
Total	52	33–82	57.3	12.2

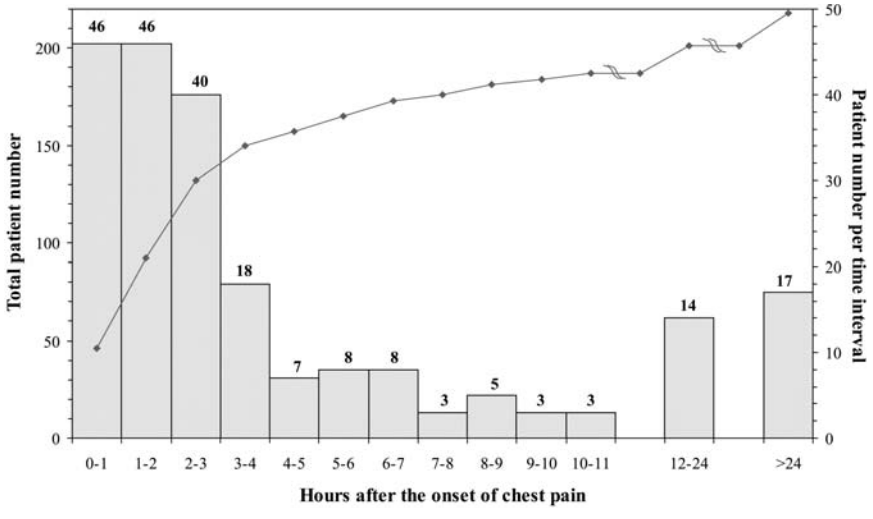

Fig. 1 Distribution on the time delay of patients presenting to hospital after the onset of chest pain

agulation period 20 minutes). The plasma or serum samples were then centrifuged at 3000 rpm for 15 minutes to remove the blood cells. Aliquots were stored at –80 °C for subsequent analysis.

Sandwich FABP ELISA

FABP was determined in the plasma and serum samples using a modified one-step enzyme linked immunosorbent assay of the antigen capture type (sandwich ELISA) as described by Wodzig et al. [27], which also mentions that FABP concentrations measured in serum do not differ from those measured in heparinated plasma. Both catcher and detector monoclonal antibodies were produced in-house. Catcher antibodies directed to FABP were coated on 96-well microtiter plates (Immulon 2 HB Flat Bottom, 3455, Dynex Technologies Inc.) in 0.1 mol/l carbonate buffer, pH 9.6 at 4 °C overnight. All further steps were performed at room temperature in PBT (10 mM phosphate-buffered saline, pH 7.4, supplemented with 0.1% (wt/vol) bovine serum albumin (BSA) and 0.05% (vol/vol) Tween-20). Between each step, the plate was washed 5 times with PBT. After coating and washing, 50 µL of sample or standard and 50 µL of detector antibodies conjugated with horseradish peroxidase (peroxidase labeling kit, 129 696, Boehringer Mannheim) were mixed and incubated for 2 hours, allowing the FABP to bind to the antibodies attached to the plates and forming sandwiches with the conjugated antibodies. Then 100 µL of substrate mixture (peroxidase EIA substrate kit, 172–1067, BIO-RAD) containing 3,3′, 5,5′-tetramethylbenzidine (TMB) and hydrogen peroxide (H_2O_2) was added to each well. The enzyme reaction was stopped within 10 minutes with 50 µL of 2 M sulphuric acid (H_2SO_4), and the absorbance at 450 nm was measured using a micro plate reader (Dynatech Medical Products Limited, Guernsey). The detection limit of the assay was 0.2 µg/L and yielded a coefficient of variation of less than 10% in inter- and intra-assay verifications.

Sandwich troponin I ELISA

The concentration of cTnI was quantitatively measured using CARD-i-KIT®ELISA Troponin I test (AboaTech Ltd, Finland) in human serum or plasma. Microtiter wells were coated with anti-human cTnI monoclonal antibody. 50 µL of standards and specimens were added into appropriate wells. The frame was then incubated for 30 minutes at room temperature with slow shaking. After washing, 50 µL of anti-human cTnI monoclonal antibody conjugated with horseradish peroxidase was added and incubated for 30 minutes at room temperature with slow shaking. After washing, 50 µL of substrate solution containing both TMB and H_2O_2 was added and incubated for 15 minutes. The enzyme reaction was stopped with 50 µL of 5% H_2SO_4. The absorbance was measured in the micro plate reader (Dynatech Medical Products Limited, Guernsey) at 450 nm within 10 minutes. The analytical sensitivity of cTnI ELISA was calculated to be 0.17 µg/L and yielded a coefficient of variation of less than 10% in inter- and intra-assay verifications.

Creatine phosphokinase activity

The activity of creatine phosphokinase was measured spectrophotometrically at 37 °C in the Pathology Laboratory of the Prince of Wales Hospital using a Dade Behring kit (Cat. No. DF29A).

Statistical analysis

The data are expressed as mean ± SD. Release curves of proteins into plasma or serum are presented as mean ± SEM for the sake of clarity. A t-test for independent samples was used to assess statistically significant differences. The level of significance was set at $p < 0.05$.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to assess the performance of the main biochemical markers CPK, cTnI and FABP in the exclusion of AMI at admission and 1, 3, 8, 12 hours after admission, respectively. Using receiver operating characteristic (ROC) curves, the interplay between sensitivity and specificity at different diagnostic decision thresholds was elucidated.

Results

The FABP concentration remained below the cut-off value in all non-AMI patients. On the other hand, there was a significant elevation in FABP concentration in patients who were diagnosed as AMI cases. Large differences up to 30 times were detected.

Typical cases of AMI patients

Figure 2 presents four typical AMI cases. Patients A and B came to the hospital soon after the onset of chest pain with either minor or severe infarction.

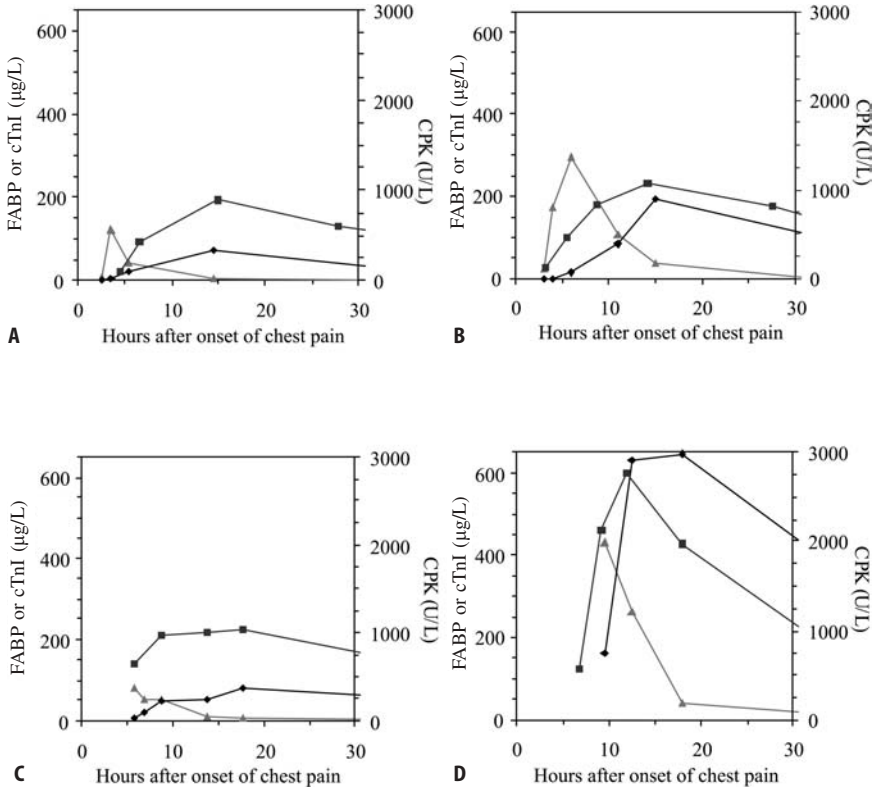

Fig. 2 Plots show the FABP concentrations (▲), cTnI concentrations (◆) and CPK (■) activities in four typical AMI patients after the onset of chest pain: one patient with early and minor infarction (**A**), one patient with early and severe infarction (**B**), one patient with late and minor infarction (**C**) and one patient with late and severe infarction (**D**). The cutoff value for FABP is 10 μg/L, cTnI is 2 μg/L and CPK is 229 U/L

The release curves of FABP, cTnI and CPK clearly show the rapid elevation of FABP in plasma after myocardial damage. However, for patients C and D with either minor or severe infarction who came to the hospital later after the onset of chest pain, only part of the release pattern of FABP can be observed with no significant difference for cTnI and CPK. For patients coming to the hospital even later, there was no elevation of FABP.

Release kinetics of biochemical markers

Among the 94 AMI patients investigated, the mean concentrations or activities of the proteins examined as a function of time in the first 72 hours after the onset of chest pain did indeed show a clear difference between the kinetics of FABP, cTnI and CPK (Fig. 3). The peak concentration of FABP (577.6 ± 43.8 μg/L) was reached 3 hours after the onset of chest pain, whereas those of CPK (2288 ± 131 U/L) and cTnI (357.1 ± 23.9 μg/L) were reached only 10 and 12 hours after the onset of AMI (mean ± SEM). Within 30 hours, the plasma concentration of FABP had returned to normal, whereas CPK took 50–70 hours and cTnI took more than 70 hours (Fig. 3).

In one patient, a recurrent myocardial infarction developed soon (< 10 hours) after the initial AMI [24, 26]. The appearance of this recurrent infarction is reflected clearly in the plasma curve for FABP but is less apparent in the cTnI and CPK curves (Fig. 4).

Early diagnosis and exclusion of AMI

Figure 5 A presents ROC curves for FABP, cTnI and CPK at admission time and one hour after admission. The areas under the curves (AUC) for FABP were 0.871 and 0.995 (1.00 being 100% sensitivity and 100% specificity), while for cTnI the areas were 0.677 and 0.845 and for CPK the areas were 0.711 and 0.856, demonstrating that the FABP test has better diagnostic properties at the early stage and reaches that of cTnI (0.995) 8 hours after admission.

Patients admitted 0–3 hours after the onset of symptoms showed the AUC of 0.826 for FABP, 0.500 for cTnI and 0.610 for CPK; while patients admitted 3–6 hours after the onset of symptoms showed the AUC of 0.945 for FABP, 0.828 for cTnI and 0.864 for CPK (Fig. 5 B). The AUC for FABP was significantly greater than those of cTnI and CPK within 6 hours after the onset of symptoms. Thus, FABP has great potential as an excellent biochemical cardiac marker for the diagnosis of AMI in the early phase.

Using the ROC-Galen and Gambino analysis [19], cut-off values of 10 μg/L for FABP, 2.0 μg/L for cTnI

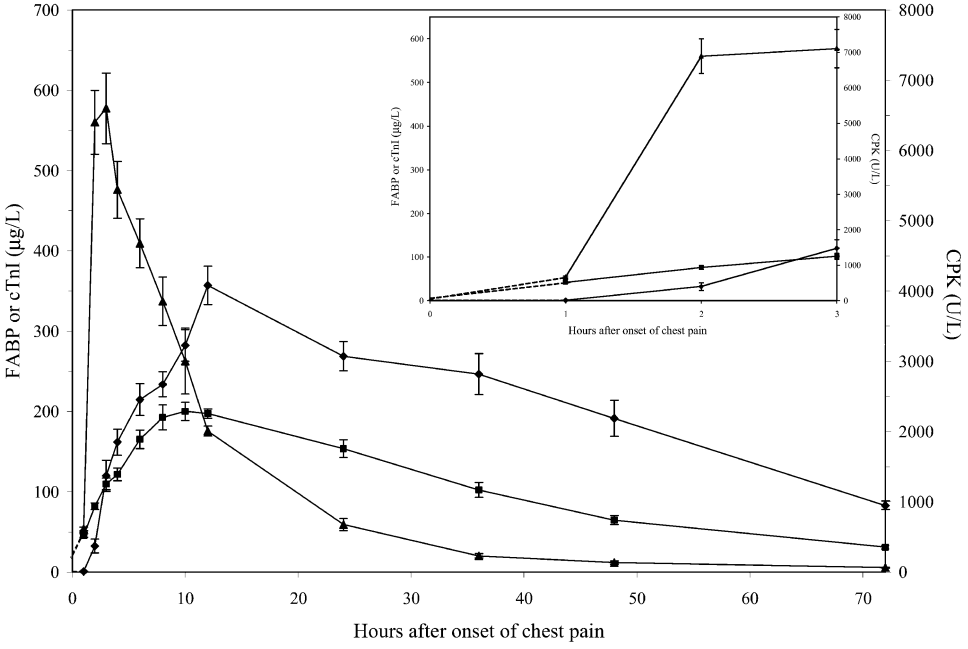

Fig. 3 Plot shows the mean FABP (▲) concentrations, cTnI (◆) concentrations and CPK activities (■) in 94 AMI patients after the onset of chest pain. The inset plot shows the amplified kinetic curves of FABP, cTnI and CPK from 0–3 hours after the onset of chest pain. The cutoff value for FABP is 10 μg/L, cTnI is 2 μg/L and CPK is 229 U/L

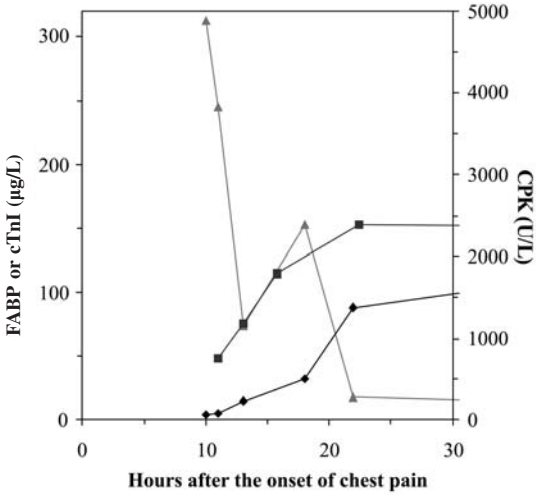

Fig. 4 Plot shows FABP concentrations (▲), cTnI concentrations (◆) and CPK activities (■) after the onset of chest pain in a patient who developed a recurrent AMI. The cutoff value for FABP is 10 μg/L, cTnI is 2 μg/L and CPK is 229 U/L

and 229 U/L for CPK were calculated to give the best specificity and diagnostic performance possible for the test (Table 2).

As shown in Table 2, the sensitivity and NPV for FABP of the patient samples taken at admission were 72% and 67%, respectively. Both increased to 100% at 1 hour after admission that would be allowed for exclusion. Therefore, 100% of non-AMI patients were excluded without false negative results. On the other hand, the sensitivity and NPV for the late marker CPK were 54% and 55% at admission, and for cTnI 51% and 51%, respectively. Both values of these two cardiac markers increased to optimum percentages only 8 hours after admission, 7 hours later than for FABP. However, the sensitivity and NPV for FABP decreased to 79% and 51% 12 hours after admission.

Discussion

FABP as an early cardiac marker for AMI

Early and correct diagnosis of AMI patients enabling interventions to reduce the mortality rate is of paramount importance. Furthermore, it is important to identify patients who are not suffering from AMI and who can be sent home safely early after admission, thus contributing considerable economic gains for both patients and hospitals. Among 218 patients who presented to the CCU and the Chest Pain Unit, 43.1% were clinically diagnosed as AMI. The average FABP levels in AMI patients were approximately 30 times higher than those of non-AMI patients. The release kinetics of FABP based on the 94 AMI patients indicates that an early FABP elevation can be detected within 1 hour after the onset of symptoms and quickly reaches its peak level at 3 hours, which is much faster than those of CPK and cTnI. The re-

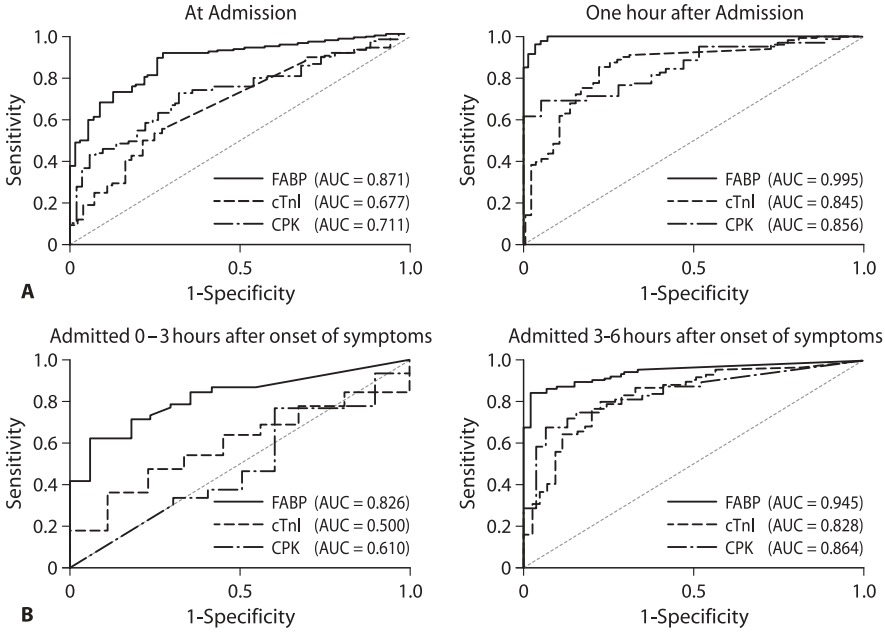

Fig. 5 Plots show the ROC curves for detection of AMI in 218 patients presenting with chest pain and suspected MI. The area under the ROC curve (AUC) represents the diagnostic test performance (**A**) at admission and one hour after admission, and (**B**) for those patients admitted 0–3 hours and 3–6 hours after the onset of symptoms

Table 2 The sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) of FABP, cTnI and CPK tests

Hours after admission	FABP				
	Cutoff values	Sensitivity %	Specificity %	PPV %	NPV %
0	7.3	72	87	90	67
1	10.0	100	88	92	100
3	11.9	100	89	98	100
8	13.6	100	94	99	100
12	15.2	79	100	100	51
Hours after admission	cTnI				
	Cutoff values	Sensitivity %	Specificity %	PPV %	NPV %
0	0.26	51	78	78	51
1	1.08	71	84	87	67
3	1.69	94	86	98	71
8	2.13	99	100	100	92
12	6.09	99	100	100	93
Hours after admission	CPK				
	Cutoff values	Sensitivity %	Specificity %	PPV %	NPV %
0	163	54	80	79	55
1	209	69	82	91	50
3	224	96	86	98	80
8	229	99	94	99	94
12	247	100	94	99	100

sults are in agreement with previous studies, where 3.5 hours and 5 hours peak times have been reported [22, 26]. The difference in time in the different studies might be due to the subjective reports of the patients about the onset of chest pain. The small molecular weight of FABP (15 kDa) favors its early release, due to the higher permeability of the endothelial barrier for small proteins [13]. FABP is also quickly eliminated from the blood stream by renal clearance, as indicated by the rapid return to normal

levels within 30 hours after the onset of the first symptoms. Indeed, this protein has been found in urine from patients with AMI [22, 23]. In patients with chronic renal failure the preinfarct plasma concentration of FABP is very likely to be high and elevates over a longer period of time [11, 14, 18]. In addition, FABP presents not only in the heart but also in skeletal muscle. This feature makes it difficult to discriminate between heart and skeletal muscle injury when plasma level of this protein is used as marker for loss of muscle cell viability [10, 24]. Thus, caution must be taken when using FABP for early diagnosis of myocardial infarction in cases of renal insufficiency and skeletal muscle injury.

The quick clearance rate and rise and fall pattern of FABP makes it an ideal myocardial marker for the detection of reinfarction [26]. These characteristics, along with a low physiological concentration for the identification of myocardial damage, enable FABP to have an improved diagnostic capability when compared with other early biochemical markers, e.g. myoglobin. The myocardial tissue content of FABP (0.57 mg/g wet weight) is four- to five-fold lower than that of myoglobin (2.7 mg/g wet weight), yet the plasma reference concentration of FABP (1.8 μg/L) is 19-fold lower than that of myoglobin (34 μg/L). This means that after injury the tissue to plasma gradient is almost five-fold steeper for FABP than for myoglobin, making plasma FABP rise above its upper reference concentration at an earlier point after AMI onset, thus permitting an earlier diagnosis of AMI [7, 9, 20, 24, 26]. In the *EUROCARDI* multi-center study [6], patients admitted 0–3 hours after onset of symptoms showed an area under the ROC curve of 0.845 for FABP and of 0.717 for myoglobin, while patients admitted 3–6 hours after onset of symptoms showed areas of 0.945 for FABP and 0.892 for myoglobin, indicating that FABP was an earlier marker than myoglobin. As a result, FABP has a markedly higher sensitivity than that of myoglobin at an earlier stage for detection of myocardial infarction, thus FABP appears as an excellent marker for early confirmation or exclusion of AMI.

Early confirmation and exclusion of AMI

The appropriate handling of patients with suspected AMI depends on the availability of results from simple, sensitive and specific diagnostic tests. In patients with typical early ECG changes of ST-segment elevation, the diagnosis of AMI is easily and rapidly established. However, at least 40% of patients with AMI show no diagnostic ECG changes on admission [2]. Also, in approximately 60 to 70% of patients admitted to the hospital because of chest pain, the suspicion of AMI will ultimately be dismissed because of lack of diagnostic ECG changes and negative biochemical tests [17].

For early confirmation and exclusion of AMI, the sensitivity and NPV of the assay are critical. For patients admitted to the hospital within 24 hours after the onset, the sensitivity and NPV of the first sample monitored were both low for CPK (54% and 55%) and cTnI (51% and 51%). In contrast, FABP had a better sensitivity and NPV (72% and 67%). Furthermore, both the sensitivity and NPV for FABP increased quickly to 100% for samples monitored one hour after admission, whereas this was not the case for either CPK or cTnI. Therefore sequential FABP monitoring, using two samples, can identify almost all patients with ongoing AMI within 1 hour, and 100% of non-AMI patients were excluded with no false negative results.

The performance of FABP demonstrates that the test has a role as an early marker but is less meaningful as a late marker, due to its rapid clearance. Therefore, samples should be obtained as soon as possible after the onset of symptoms to maximize their clinical utility. As the therapeutic window for AMI is within the first 12 hours, and an earlier intervention has a better success rate, the availability of an early rapid test is important. This early test offers two subtest possibilities: one immediately and one 1 hour later. In order to decrease the risk of falsely excluded patients with ongoing AMI, a combined measurement of two biochemical markers, an early one such as FABP and a later marker such as troponins may provide the optimum diagnostic performance [1, 12].

The present study has only investigated patients admitted to the CCU and Chest Pain Unit. Substantial enrichment of the population with patients with high clinical probability of acute coronary syndrome may limit the relevance of the results of this study to a general population of patients undergoing evaluation in the Emergency Department for non-traumatic chest pain. Utility of FABP in the Emergency Department would also shorten the time delay between onset of chest pain and blood sampling.

Conclusion

Early identification of patients suspected of AMI is important for proper patient care. Current methods used in the diagnosis, pathologic examination, ECG recordings, measurement of myocardial proteins in the blood and imaging modalities, are unreliable in the first few hours of infarction [3]. The present study indicates that FABP displays a superior perfor-

mance for detection of myocardial infarction similar to the current "gold standard" cTnI but almost 7 hours earlier. Two consecutive FABP tests, at admission and 1 hour after admission, give 100% sensitivity and NPV for exclusion of patients, and thus will reduce unnecessary admission in intensive care units.

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