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The Role of Heart-Type Fatty Acid-Binding Protein (H-FABP) in Acute Myocardial Infarction (AMI) Compared to Conventional Cardiac Biochemical Markers

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Aim: To investigate the clinical implications of serum heart-type fatty acid-binding protein (H-FABP) compared to myoglobin, cardiac troponin I (cTnI), and creatine kinase MB isoenzyme (CK-MB) in patients with early phase acute myocardial infarction (AMI).

Material and Methods: Patients were grouped clinically according to the American College of Cardiology/European Society of Cardiology new definition of myocardial infarction (MI) and by clinician diagnosis of MI. Serum concentrations of H-FABP, myoglobin, cTnI, and CK-MB were determined in 21 patients with AMI and 44 non-AMI patients. From each patient 3 blood samples were obtained 1-2, 3, and 6 h after the onset chest pain. The samples were compared to those of 20 age-matched healthy subjects. All the patients and healthy subjects had normal renal function.

Results: At 1-2, 3, and 6 h after the onset of AMI, similar to myoglobin, the diagnostic sensitivity and specificity of H-FABP were higher than those of cTnI and CK-MB. Greater receiver operating characteristic (ROC) curve areas for the diagnosis of MI, by both sets of criteria, were obtained for H-FABP and myoglobin compared to both cTnI and CK-MB.

Conclusion: H-FABP and myoglobin are reliable biochemical markers for superacute phase AMI and the changes in their serum concentrations have clinical significance in the diagnosis of AMI.

Key Words: Heart-type fatty acid binding protein, acute myocardial infarction, myocardial injury

Akut Miyokard Enfarktüsünde Genel Kardiak Biyokimyasal Belirteçlerle Kıyaslandığında Heart-Type Fatty Acid-Binding Protein'in Rolü

Amaç: Akut miyokard enfarktüsünün (AMI) erken fazındaki hastalarda serum heart-type fatty acid-binding protein (H-FABP) ile birlikte miyoglobin, kardiak troponin I (cTn I), kreatin kinaz (CK-MB) izoenzim seviyelerinin klinik anlamını araştırmak.

Yöntem ve Gereç: Hastalar klinik olarak American College of Cardiology/European Society of Cardiology topluluklarının yeni tanımına göre ve klinisyenlerce miyokard enfarktüsü (MI) tanısı konularak gruplandırılmıştır. 21 AMI geçiren ve 44 AMI geçirmeyen hastalarda serum H-FABP, miyoglobin, cTn I, CK-MB konsantrasyonları ölçülmüştür. Göğüs ağrısının başlangıcından sonra, her hastadan 1-2.saat, 3. saat, 6.saatlerde 3 örnek alınmış ve aynı yaşlarda 20 sağlıklı kişilerle ölçümleri karşılaştırılmıştır. Hastaların ve sağlıklı grubun böbrek fonksiyonları normaldir.

Bulgular: AMI'ın 1-2, 3, 6.saatlerinde miyoglobin ile benzer olarak H-FABP'in tanısının duyarlılığı ve özgüllüğü, cTn I ve CK-MB'den daha yüksektir. MI tanısında, H-FABP ve miyoglobinin ROC (receiver operating characteristic) eğrilerinin alanları, cTn I ve CK-MB'den daha büyüktür.

Sonuç: H-FABP ve miyoglobin, AMI'ın superakut fazı için güvenilir biyokimyasal belirteçlerdir ve serum konsantrasyonlarındaki değişimler AMI'ın tanısında klinik olarak önemlidir.

Anahtar Sözcükler: Heart-type fatty acid-binding protein, Akut miyokard enfarktüsü, miyokardiyal hasar

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Introduction

Acute myocardial infarction (AMI) is a common cause of sudden death. Serial measurement of biochemical markers is now universally accepted as an important determinant in AMI diagnosis; however, the early diagnosis of AMI is still problematic. Therefore, a rapid method for early diagnosis of AMI is crucial (1).

The biochemical markers myoglobin, creatine kinase-MB isoenzyme (CK-MB), and cardiac troponin I (cTnI) or troponin T (cTnT) are currently used in the diagnosis of AMI

(2). These cardiac marker proteins, however, are not satisfactory for detecting AMI in the early phase, especially within 3-6 h of the onset of AMI (3). Myoglobin is a small protein (18 kDa), which appears in the plasma after myocardial infarction (MI) and is considered a useful marker for the early detection of AMI (4). Myoglobin lacks specificity because myoglobin that is released from skeletal muscles cannot be distinguished from that released from the heart; therefore, it has been reported to be less specific for myocardial damage (5).

cTnI and CK-MB are more specific for myocardial injury, but lack early sensitivity because their blood concentrations do not increase until 6-8 h after the onset of AMI (6,7).

Heart-type fatty acid-binding protein (H-FABP) is a low molecular mass, soluble protein (15 kDa), which is abundant in the cytoplasm of myocardial cells. It constitutes a biological marker that is quickly released into the circulation after myocardial injury (8).

Recent data suggest that H-FABP concentration increases well before markers of cardiac necrosis and that it is a sensitive indicator of ischemia in AMI. Plasma H-FABP increases within 3 h of AMI and returns to reference values within 12-24 h (9). Furthermore, H-FABP has been proven to be an independent factor for prognosis in patients with a serious condition on arrival at emergency departments (10).

In the present study, we compared the diagnostic efficiency of the H-FABP test with cTnI, CK-MB, and myoglobin in the early phase (1-2, 3, and 6 h) of AMI. We sought to determine if H- FABP levels during early stage AMI (1-2 h) have high sensitivity and specificity for AMI diagnosis, which if they did would contribute greatly to clinical practice and reduce useless emergency examinations to a minimum.

Material and Methods

Blood samples were collected with the approval of the local ethics committee of Gazi University Faculty of Medicine. Blood samples are obtained from 65 patients, who were admitted within 1-2 h of the onset of chest pain (21 AMI and 44 non-AMI) to the coronary emergency department. Mean age of the patients was 58.2 ± 12 years. After the start of chest pain, most patients delay calling for emergency medical help. Thus, it takes nearly 4-5 h to get to coronary emergency departments, and we excluded such patients from our study. The study included 20 age-matched healthy controls (mean age: 57.1 ± 10 years). Patients and controls had normal renal function and no muscle trauma. Chest pain patients who did not have AMI (non-AMI) were diagnosed with unstable angina, stable angina, or other cardiovascular diseases. Blood samples were collected from each patient at 1-2, 3, and 6 h after the onset of chest pain. Samples from 20 healthy controls were assayed for all cardiac markers. Blood samples were centrifuged, serum was separated, and all were stored at –80 ºC until assayed.

H-FABP was assayed using a solid-phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle (Life Diagnostics, Inc, ELISA Test Kit, 2310). Myoglobin, cTnI, and CK-MB tests were assayed using ELISA test kits (DRG Instruments GmbH, Germany, EIA-3955, myoglobin, EIA-2952 cTnI, EIA-4112, CK-MB). The recommended reference range for H-FABP is 1.6-19 ng/ml (cut-off for AMI: > 19). For myoglobin, cTnI, and CK-MB, the reference ranges were 8.1-54.5 ng/ml, 0-1.5 ng/ml, and 2-5.2 ng/ml, respectively.

Diagnostic Definition of AMI

Diagnoses were classified into 2 groups: AMI and non-AMI chest pain. AMI was defined according to the European Society of Cardiology/American College of Cardiology Committee criteria (11).

Either one of the following criteria satisfies the diagnosis for an acute, evolving, or recent MI: 1) Typical rise and gradual fall (troponin), or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis, with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty); 2) Pathologic findings of an acute MI. Criteria for established MI. Any one of the following criteria satisfies the diagnosis for established MI:

1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.

2) Pathologic findings of a healed or healing MI.

Statistical Analysis

Samples were grouped according to designated time-frames for onset of symptoms within 1-2, 3, and 6 h. The diagnostic value of tests was evaluated by the sensitivity, specificity, and receiver operating characteristic (ROC) curves. The 95% confidence intervals were calculated. Differences in sensitivity and specificity were evaluated by ROC curve. Results are given as mean ± SD, P values, and cut-off values according to sample times (asymptotic 95% confidence interval). P values < 0.05 were considered statistically significant.

Results

There were 21 patients in the AMI group, 44 patients in the non-AMI group, and 20 healthy participants in the control group. Serum concentrations of H-FABP, myoglobin, cTnI, and CK-MB are given as mean ± SD in Tables 1-3. In blood samples collected at 1-2 and 3 h, H-FABP and myoglobin in the AMI group were significantly higher (P = 0.00) than in the non-AMI and control groups. cTnI and CK-MB in the AMI group were not yet significantly higher than in non-AMI and control groups at 1-2 h. cTnI in the AMI group was higher than in the non-AMI and control groups at 3 h. CK-MB in the AMI group was higher than in the control group, but not in the non-AMI group at 3 h. All parameters in the AMI group were significantly higher than in the non-AMI and control groups at 6 h (Tables 1-3).

The data from ROC analysis are summarized in Figure 1; areas under the ROC curves and P values are summarized in Table 4. In the areas under the ROC curves H-FABP and myoglobin in the AMI group were significantly higher (P = 0.00) than in the non-AMI group at 1-2, 3, and 6 h. cTnI in the AMI group was significantly higher (P = 0.00) than in the non-AMI group at 3 and 6 h, and CK-MB in the AMI group was significantly higher (P = 0.00) than in the non-AMI group at 6 h (Table 4)

The sensitivity and specificity of the cut-off values for H-FABP, myoglobin, cTnI, and CK-MB are shown in Table 5.

Discussion

The principal characteristics that would make a marker of myocardial damage ideal for the early clinical diagnosis of AMI by analyzing its plasma concentration include: (1) small size; a small-size molecular marker is more rapidly released into the circulation, allowing early identification of myocardial damage; (2) absence or presence only in trace amounts in the circulation under physiological conditions, because this implies a very narrow reference range; thus, detection as abnormal with even minimal increases of the marker in plasma is possible; (3) absolute specificity for the myocardium, since most proteins in the heart also are abundant in skeletal muscle, especially under pathological conditions (12). Wu et al. (13) recommended that 2 biochemical

Table 1. Results are given as mean ± SD for 1-2 h after symptom onset.

	H-FABP (1-2 h)		Myoglobin (1-2 h)		cTnI (1-2 h)		CK-MB (1-2 h)	
Population	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Control n = 20	9.33 ± 3.9	0.00 [a]	10.42 ± 4.63	0.00 [a]	0.42 ± 0.50	0.232 [a] (NS)	1.52 ± 0.56	0.771 [a] (NS)
AMI n = 21	70.38 ± 41.35	0.00 [b]	61.50 ± 46.48	0.00 [b]	0.55 ± 0.47	0.882 [b] (NS)	1.58 ± 0.92	0.499 [b] (NS)
Non-AMI n = 44	11.51 ± 3.8	0.040 [c]	13.40 ± 5.15	0.016 [c]	0.52 ± 0.40	0.082 [c] (NS)	1.82 ± 1.24	0.695 [c] (NS)

NS: not significant
P value < 0.05 was considered statistically significant.

[a] control vs. AMI
[b] AMI vs. non-AMI
[c] Non-AMI vs. control

Table 2. Results are given as mean ± SD for 3 h after symptom onset.

Population	H-FABP (3h)		Myoglobin (3h)		cTnI (3h)		CK-MB (3h)	
	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Control n = 20	9.33 ± 3.9	0.00 [a]	10.42 ± 4.63	0.00 [a]	0.42 ± 0.50	0.007 [a]	1.52 ± 0.56	0.009 [a]
AMI n = 21	83.42 ± 40.90	0.00 [b]	83.69 ± 49.83	0.00 [b]	0.95 ± 0.69	0.009 [b]	2.79 ± 1.70	0.072 [b] (NS)
Non-AMI n = 44	11.20 ± 3.35	0.047 [c]	12.91 ± 5.03	0.045 [c]	0.45 ± 0.36	0.100 [c] (NS)	2.03 ± 1.28	0.217 [c] (NS)

NS: not significant
P value < 0.05 was considered statistically significant.

[a] control vs. AMI
[b] AMI vs. non-AMI
[c] Non-AMI vs. control

Table 3. Results are given as mean ± SD for 6 h after symptom onset.

Population	H-FABP (6h)		Myoglobin (6h)		cTnI (6h)		CK-MB (6h)	
	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Control n = 20	9.33 ± 3.9	0.00 [a]	10.42 ± 4.63	0.00 [a]	0.42 ± 0.50	0.00 [a]	1.52 ± 0.56	0.00 [a]
AMI n = 21	99.33 ± 41.8	0.00 [b]	109.50 ± 47.08	0.00 [b]	2.17 ± 1.89	0.00 [b]	4.40 ± 2.16	0.00 [b]
Non-AMI n = 44	11.31 ±3.32	0.039 [c]	14.13 ± 5.88	0.013 [c]	0.50 ± 0.40	0.043 [c]	2.16 ± 1.37	0.110 [c] (NS)

NS: not significant.
P value < 0.05 was considered statistically significant.

[a] Control vs. AMI
[b] AMI vs. non-AMI
[c] Non-AMI vs. control

markers should be used for routine AMI diagnosis; an early marker (reliably increased in blood within 6 h of the onset of symptoms) and a definitive marker (increased in blood after 6-9 h, with high sensitivity and specificity for myocardial injury, and remaining abnormal for several days after onset). A recent substantial increase in the use of cTnI or cTnT, CK-MB mass, and myoglobin assays for the detection of MI has been observed (14). Collinson et al. (15) showed that measurement of cTnT was diagnostically equivalent to CK-MB and that both were better than myoglobin 12 h after symptom onset. CK-MB is unsuitable as a diagnostic gold standard, even at the proposed lower threshold. Diagnosis of AMI cannot be made solely on the basis of a cardiac troponin T result. Yamamoto et al. (16) demonstrated that a rapid, quantitative test for cTnT and myoglobin is useful for early diagnosis of AMI and as an indicator of its severity at 6, 12, 24, 48 h after onset of MI. To date, myoglobin has been used as a biochemical cardiac marker for the diagnosis of AMI in the hyperacute phase, that is, within 3 h after the onset of symptoms. However, myoglobin is not very specific for myocardial damage because of its abundance in skeletal muscle as well as the myocardium (12). H-FABP is released rapidly from the myocardium

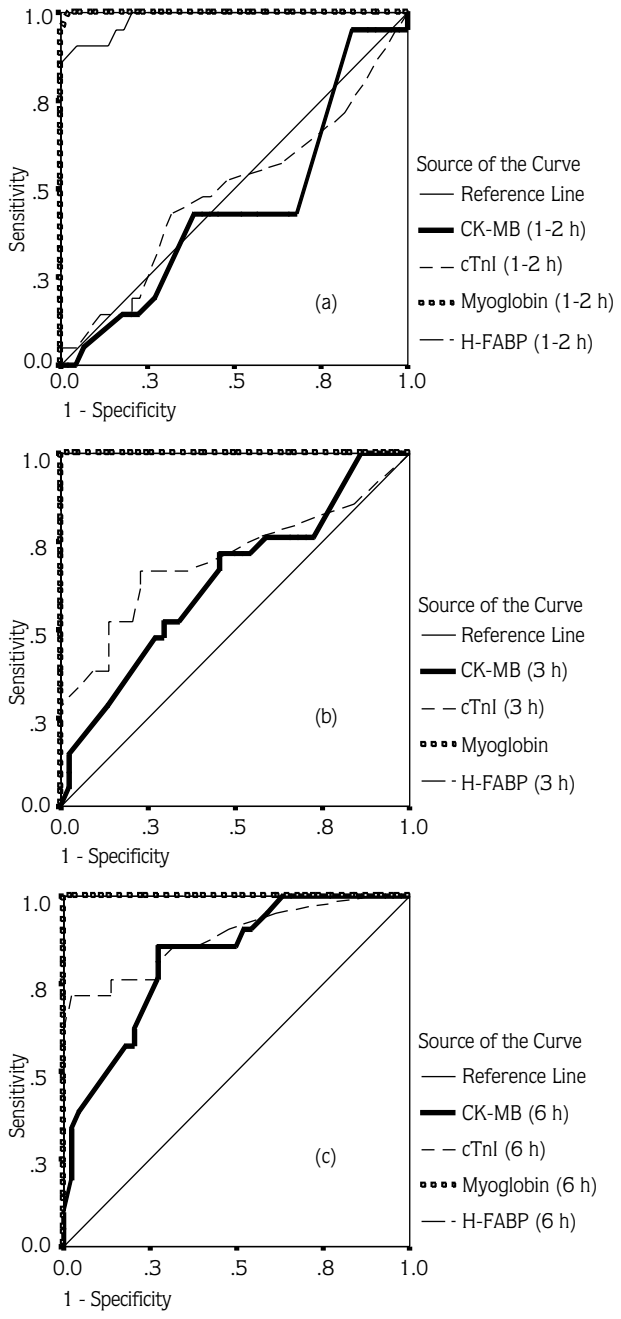

Figure 1 A-C. ROC plots of the AMI group versus the non-AMI group, according to sample times (1-2, 3 and 6 h after symptom onset).
A. ROC plot of the AMI group versus the non-AMI group 1-2 h after symptom onset.

B. ROC plot of the AMI group versus the non-AMI group 3 h after symptom onset.

C. ROC plot of the AMI group versus the non-AMI group 6 h after symptom onset.

into the bloodstream after ischemic injury (17). Since H-FABP is a smaller molecule than myoglobin, cTnI, and CK-MB, it peaks earlier than these other molecules when there is cardiomyocyte damage.

We have demonstrated the sensitivity and specificity of H-FABP for the detection of early phase AMI, and compared it to the routinely used markers, myoglobin, cTnI, and CK-MB. The present data indicates that for AMI detection, serum H-FABP shows a significantly higher diagnostic sensitivity and specificity than cTnI and CK-MB, similar to myoglobin, especially soon after (within 1-2 and at 3 h) the onset of symptoms.

The diagnostic sensitivity of H-FABP has been suggested to be high, greater than that of myoglobin in patients presenting within 6 h of the onset of chest pain (18). This superiority could be attributed to an earlier and more rapid rise in H-FABP than in myoglobin. After thrombolysis, serum concentrations of H-FABP peak approximately 4 h after the onset of chest pain and return to normal values within 24 h. Because of its rapid return to baseline, H-FABP can contribute as an early biological marker of post thrombolysis (19,20). In addition, when compared to myoglobin, H-FABP concentration in the heart muscle is greater than that in skeletal muscle, and its normal baseline concentration is several-fold lower than myoglobin. These advantages make H-FABP a potentially more suitable cardiac marker than myoglobin (21).

In contrast, Alansari and Croal (22) suggested that H-FABP and myoglobin provide little clinical value, compared to cTnI, when measured at presentation in patients presenting with chest pain (3-12 h). Xiano et al. (23) investigated the clinical implication of cTnI, myoglobin, and CK-MB in patients with AMI 2-4 h after chest pain onset and showed that cTnI and myoglobin are reliable biochemical markers for early diagnosis of MI. Consequently, Ishii et al. (24) suggested that H-FABP concentrations have a greater predictive capacity for cardiac events than cardiac troponin within 6 h of the onset of chest pain. Conflicting results about cardiac markers may be explained by the duration of MI at the time of sampling or other factors in MI studies. In our study, cTnI of the AMI group was higher than in the non-AMI and control groups at 3 h, but at not 1-2 h. This result showed that H-FABP and myoglobin are more sensitive than cTnI and CK-MB in the detection of

Table 4. Areas under ROC curves and P values according to sample times (asymptotic 95% confidence interval).

Population	Time (hours)	H-FABP			Myoglobin			cTnI			CK-MB		
		ROC	95% CI	P	ROC	95% CI	P	ROC	95% CI	P	ROC	%95 CI	p
AMI + Non-	1-2	0.983	0.957-1.008	0.00	0.999	0.997-1.002	0.00	0.489	0.330-0.647	0.883	0.449	0.298-0.600	0.505
AMI	3	1.00	1.00-1.00	0.00	1.00	1.00-1.00	0.00	0.701	0.548-0.854	0.009	0.638	0.492-0.784	0.074
	6	1.00	1.00-1.00	0.00	1.00	1.00-1.00	0.00	0.883	0.786-0.980	0.00	0.822	0.718-0.926	0.00

Table 5. The effect on sensitivity and specificity of the cut-off values for H-FABP, myoglobin, cTnI, and CK-MB in the AMI versus non-AMI groups.

Markers	1-2 h	sensitivity	specificity	3 h	sensitivity	specificity	6 h	sensitivity	specificity
HFABP (ng/ml)	19.5	0.90	0.95	18.50	1.0	0.97	19.50	1.0	0.97
Myoglobin (ng/ml)	21.75	1.00	0.89	24.50	1.0	1.0	44.25	1.0	1.0
cTnI (ng/ml)	0.25	0.57	0.36	0.55	0.66	0.70	1.35	0.71	0.97
CK-MB (ng/ml)	1.05	0.42	0.31	1.75	0.71	0.50	2.20	0.85	0.72

myocardial injury, especially within 1-2 h of symptom onset. Moreover, ROC curve areas for H-FABP and myoglobin were better than those of cTnI and CK-MB < 6 h after the onset of chest pain.

The combined measurement of serum H-FABP and myoglobin in the superacute phase (within 3 h) allows the discrimination between myocardial and skeletal muscle injury. The late markers cTnI and CPK showed similar diagnostic performance 6 h after symptom onset. Thus, late measurement of H-FABP allows the earliest immunochemical confirmation or exclusion of AMI (25). Furthermore, some studies showed that H-FABP is a useful biochemical plasma marker for the estimation of myocardial infarct size in humans and mice, which might be helpful in clinically anticipating infarction prognosis (26,27). Moreover, plasma H-FABP concentration can help in the postmortem diagnosis of AMI in rats (12).

In conclusion, H-FABP is a sensitive and specific marker for the early diagnosis of AMI. The H-FABP assay was suggested to effectively exclude non-AMI patients within 3 h of the onset of chest pain. For the use of H-FABP as an early marker in the detection of myocardial injury, the assay must have a fast turn-around time. Several biochemical assays of H-FABP have been described; however, the use of these assays in routine clinical practice is limited because of the fact that they are not automated. The clinical application of H-FABP requires the availability of rapid assay kits in routine automatic systems at emergency departments.

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