

Serum concentrations of myoglobin vs human heart-type cytoplasmic fatty acid-binding protein in early detection of acute myocardial infarction

JUNNACHI ISHII,^{1*} JIAN-HUA WANG,¹ HIROYUKI NARUSE,¹ SHINN TAGA,¹
MASATOMO KINOSHITA,¹ HIROSHI KUROKAWA,¹ MASATSUGU IWASE,¹ TAKESHI KONDO,¹
MASANORI NOMURA,¹ YOUICHI NAGAMURA,² YOSHIHIKO WATANABE,¹ HITOSHI HISHIDA,¹
TAKAO TANAKA,³ and KEISHIRO KAWAMURA³

We compared the diagnostic utility of serum concentrations of human heart-type cytoplasmic fatty acid-binding protein (H-FABPc), myoglobin, and their ratio for the early diagnosis of acute myocardial infarction (AMI) in 104 healthy volunteers and 165 patients at admission within 6 h of the onset of chest pain. The ROC curves of the H-FABPc [0.946, 95% confidence interval (CI) = 0.913–0.979] and myoglobin (0.895, 95% CI = 0.846–0.944) between patients with AMI and healthy volunteers were significantly greater than the area under the ratio of myoglobin to H-FABPc (0.823, 95% CI = 0.765–0.881). In 165 patients, the sensitivity (81.8%, 95% CI = 74.2–89.4%), specificity (86.4%, 95% CI = 78.1–94.6%), and predictive accuracy (83.6%, 95% CI = 78.0–89.3%) of H-FABPc >12 µg/L in diagnosing AMI were significantly higher than those of myoglobin, and were similar to those of the combination of H-FABPc >12 µg/L and the ratio ≤14. We conclude that H-FABPc is a more sensitive and specific marker than myoglobin for the early diagnosis of AMI, and that their ratio cannot give a clear advantage over the measurement of H-FABPc alone.

INDEXING TERMS: biochemical markers • myocardial injury

Human heart-type cytoplasmic fatty acid-binding protein (H-FABPc), like myoglobin, is a low-molecular-mass pro-

tein that is abundant in the cytoplasm of myocardial cells.⁴ It has been proposed as an early biochemical marker for the diagnosis of acute myocardial infarction (AMI) [1–3]. We have previously shown that the serum H-FABPc concentration rises sharply after reperfusion, and that measurements of serum H-FABPc concentration accurately predict the success of coronary reperfusion as early as 15 min after the onset of reperfusion [4]. Both H-FABPc and myoglobin are present in the heart and skeletal muscle. However, the H-FABPc content of skeletal muscle is only 10–30% of that found in cardiac muscle, whereas the skeletal muscle content of myoglobin is approximately twice that of cardiac muscle [5–8]. Hence, H-FABPc would be expected to be a more sensitive and specific marker than myoglobin for use in early detection of myocardial injury. The ratio of the plasma concentrations of myoglobin and H-FABPc is reportedly useful in differentiating myocardial injury from skeletal muscle injury [7, 8]. Our objective was to compare the diagnostic efficacy of H-FABPc concentration with that of myoglobin concentration in the early diagnosis of AMI in patients admitted within 6 h of onset of chest pain. In addition, the utility of the concentration ratio of myoglobin over H-FABPc in serum at admission was also evaluated for the early diagnosis of AMI.

Materials and Methods

PATIENT POPULATION

The study population consisted of 104 age-and-gender-matched healthy Japanese adult volunteers (normal elec-

¹ Department of Internal Medicine, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-11, Japan.

² Department of Clinical Chemistry, Fujita Health University School of Health Sciences, Toyoake, Aichi, Japan

³ Third Division, Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan.

*Author for correspondence. Fax 81 562 93 2315; e-mail tkondo@fujita-hu.ac.jp.

Received December 3, 1996; revised April 2, 1997; accepted April 3, 1997.

⁴ Nonstandard abbreviations: H-FABPc, human heart-type cytoplasmic fatty acid-binding protein; AMI, acute myocardial infarction; CKMB, creatine kinase MB isoenzyme; and CI, confidence interval.

trocardiographic finding and no history of cardiovascular disease; 76 men, 28 women, mean age \pm SD 61.5 ± 7.5 years; range 40–75 years) and 165 adult Japanese patients (123 men, 42 women, 63.3 ± 9.7 years; range 41–81 years) admitted to the coronary care unit of Fujita Health University for evaluation of suspected AMI within 6 h of onset of chest pain. All patients underwent serial clinical evaluations by cardiologists. Standard 12-lead electrocardiograms were obtained in the coronary care unit at least once each day. Serum creatine kinase MB isoenzyme (CKMB) activity was routinely measured at admission, at least twice within the first 24 h, and once daily until discharge. The time of onset of symptoms was recorded for each patient at the time of admission. Patients received sublingual administration of nitroglycerin or oxygen inhalation if necessary before hospital admission. Two patients with AMI received intravenous thrombolytic therapy in the emergency ambulance. No patients had trauma or muscle disorders. The purpose of the study was explained to the patients and the members of the family and informed consent was obtained before beginning the study.

DIAGNOSIS OF AMI

The diagnosis of AMI was finally established at hospital discharge by a cardiologist without knowing serum concentrations of H-FABPc and myoglobin if a patient had at least two of the following three findings: (a) clinical history of ischemic chest discomfort of >30 min duration; (b) evolution of typical changes in at least two leads of the electrocardiogram, appearance of Q-waves of >0.04 -s duration or an R wave increment leading to an R/S ratio >1 in leads V_1 and V_2 (defined as Q-wave infarctions), or ST segment depression of >0.1 mV 0.08 s after J point or ST segment elevation >0.1 mV persisting for at least 24 h (defined as non-Q-wave infarctions); (c) time-dependent changes in serum CKMB activity with an initial rise [to a peak value exceeding twice the upper reference limit (24 U/L)] and subsequent fall.

MEASUREMENT OF MARKERS

Samples were obtained by venipuncture into a standard serum tube, centrifuged at 1800g for 15 min, and stored at -80°C . The serum concentration of H-FABPc was determined by a recently developed sandwich ELISA, the accuracy and reproducibility of which have been described previously [9]. This assay method can also measure H-FABPc concentration in plasma. The lower detection limit for H-FABPc was $1.25 \mu\text{g/L}$. The value below the lower detection limit of H-FABPc was defined as $1.0 \mu\text{g/L}$. The concentration of myoglobin was measured by turbidimetric latex agglutination method (Mb-latex Seiken; Denka Seiken, Tokyo, Japan) with an automated chemical analyzer (30R; Toshiba Medical, Tokyo, Japan) [10–13]. The detection limit for myoglobin was $10 \mu\text{g/L}$. The measurement of myoglobin concentration required 10 min and that of H-FABPc concentration required 90 min.

Serum CKMB activity was determined by an immunoinhibition assay (CKMB-NAC; Boehringer Mannheim, Tokyo, Japan) with an automated chemical analyzer (30R). The ratio of myoglobin over H-FABPc was obtained by dividing the serum concentration of myoglobin with that of H-FABPc.

STATISTICAL ANALYSIS

Results are expressed either as mean \pm SD or as median and interquartile range. Differences in clinical characteristics between groups were analyzed by Student's *t*-test, χ^2 test, or Fisher's exact test, as appropriate. Differences in serum H-FABPc concentration, serum myoglobin concentration, and the concentration ratio of myoglobin over H-FABPc between groups were compared by the non-parametric Mann-Whitney *U*-test, Kruskal-Wallis *H*-test, or Scheffé type multiple comparison, as appropriate. The 95% confidence intervals (CI) and ROC curves [14] were used to assess the discriminatory ability of indicators. A univariate *Z*-test was used to compare the areas under the ROC curves of indicators, as described by Hanley and McNeil [15]. Differences in sensitivity, specificity, and predictive accuracy between indicators were evaluated by the sign test. $P < 0.05$ was considered statistically significant.

Results

CLINICAL CHARACTERISTICS

On the basis of the diagnostic material described previously, 99 patients diagnosed with AMI were assigned to the AMI group and the other 66 patients were placed in the non-AMI group (Table 1). Patients in the AMI group were admitted earlier after the onset of chest pain than those in the non-AMI group ($P < 0.01$). Forty-seven patients in the AMI group were admitted within 3 h (1.9 ± 0.6 h) and 52 from 3 to 6 h (4.4 ± 0.9 h) after onset of chest pain. Coronary angiography was performed in 90 patients of the AMI group at 22–32 days after onset of chest pain (25 ± 4.1 days).

In the non-AMI group, 24 patients complained of unstable angina with the clinical classes being III B in 18 and I B in 6 [16]. Coronary angiography was performed within the interval from 4 h to 1 week after admission (4.2 ± 2.6 days) in all patients with unstable angina. Significant obstruction ($\geq 75\%$ stenosis in vessel diameter) of a major coronary artery was found in 22 patients (91.7%) and not in two. In these two patients, the clinical diagnosis was variant angina.

Serum concentrations of H-FABPc and myoglobin in the AMI group were significantly ($P < 0.01$) higher than the respective concentrations in the non-AMI group and in the healthy volunteers (Table 2). The serum concentration of myoglobin in the non-AMI group was significantly ($P < 0.01$) higher than that in the healthy volunteers, whereas no significant difference of H-FABPc concentration was found between the non-AMI group and healthy volunteers. The normal serum H-FABPc concentration

Table 1. Patient characteristics.

	AMI group	Non-AMI group
Number	99	66
Age, years	63.0 ± 9.2	63.9 ± 9.8
Gender (M/F)	74/25	49/17
Time to admission (h after pain onset)	3.5 ± 1.6	4.3 ± 1.2 ^a
Diagnosis		
Q-wave infarct	73 (74.7) ^b	
Non-Q-wave infarct	26 (26.3)	
Unstable angina		24 (36.4) ^b
Arrhythmia		9 (13.6)
Heart failure		4 (6.1)
Cardiomyopathy		4 (6.1)
Pericarditis		2 (3.0)
Extracardiac disease		23 (34.8)
Nonspecific thoracic pain		14
Gastric ulcer		2
Aortic dissection		2
Pulmonary infarction		2
Pleuritis		1
Gall stone		1
Rupture of aortic aneurysm		1
History		
First infarct	86 (86.9)	
History of infarct	13 (13.1)	
Infarct-related coronary artery		
Left anterior descending	40 (44.4)	
Left circumflex	11 (12.2)	
Right coronary	38 (42.2)	
Left main trunk	1 (1.1)	

^a Indicates $P < 0.01$ vs the AMI group.
^b Percent of total.

was low with a narrow range similar to that reported by Kleine et al. ($9 \pm 5 \mu\text{g/L}$) [2]. Serum H-FABPc concentration ranged between 1.0 and $11.4 \mu\text{g/L}$, and myoglobin concentration between 24 and $94 \mu\text{g/L}$. The upper normal values, defined as the 97.5% percentile in healthy volunteers, were $10.5 \mu\text{g/L}$ for H-FABPc and $92 \mu\text{g/L}$ for myoglobin.

The concentration ratio of myoglobin over H-FABPc in the AMI group was significantly ($P < 0.01$) lower than the ratio in the non-AMI group and in the healthy volunteers (Table 2, Fig. 1). There was no significant difference of the

ratio between the non-AMI group and healthy volunteers. In the AMI group, 72 patients with H-FABPc concentration $>12 \mu\text{g/L}$ had a significantly ($P < 0.01$) lower ratio (median 6, interquartile range 5.1–7.0) than 17 patients with H-FABPc concentration $\leq 12 \mu\text{g/L}$ (median 8.6, interquartile range 6.1–12.7). The upward and leftward shift in the ROC curve of the ratio between AMI group and healthy volunteers was markedly less than the shift in H-FABPc and myoglobin concentration (Fig. 2), indicating that it is difficult to discriminate healthy subjects from patients with AMI by the ratio alone. The area under the ROC curve of the ratio (0.823, 95% CI = 0.765–0.881) between AMI group and healthy volunteers was significantly ($P < 0.01$ and $P < 0.05$, respectively) smaller than the area under the H-FABPc (0.946, 95% CI = 0.913–0.979) and the myoglobin curves (0.895, 95% CI = 0.846–0.944).

For the detection of AMI within 6 h of onset of chest pain, the upward and leftward shift in the ROC curve between the AMI group and the non-AMI group was greater for H-FABPc concentration than for myoglobin concentration and the ratio of myoglobin over H-FABPc (Fig. 3). The area under the ROC curve of H-FABPc (0.898, 95% CI = 0.849–0.946) was significantly ($P < 0.01$) greater than the area under the myoglobin curve (0.782, 95% CI = 0.713–0.852), whereas no significant difference was found between the area under the ROC curve of H-FABPc and that of the ratio of myoglobin over H-FABPc (0.831, 95% CI = 0.764–0.898).

The value that offered the maximal predictive accuracy in patients was taken as the cutoff value for the diagnosis of AMI. The cutoff values were $12 \mu\text{g/L}$ for H-FABPc and $105 \mu\text{g/L}$ for myoglobin and exhibited a 100% specificity in healthy volunteers. The sensitivity, specificity, and predictive accuracy of H-FABPc concentration beyond the cutoff value were 81.8%, 86.4%, and 83.6%, respectively, for detection of AMI within 6 h of onset of chest pain, and were significantly ($P < 0.05$, $P < 0.05$ and $P < 0.01$, respectively) higher than those of myoglobin (Table 3). The sensitivities of H-FABPc concentration for the detection of AMI were 72.3% within 3 h, and 90.4% from 3 to 6 h after the onset of chest pain. The sensitivity of H-FABPc concentration within 3 h of onset was significantly ($P < 0.05$) higher than that of myoglobin, but was similar to myoglobin from 3 to 6 h of onset.

For the maximal predictive accuracy in patients and a 100% specificity in healthy volunteers, H-FABPc concentration $>12 \mu\text{g/L}$ combined with the ratio ≤ 14 was

Table 2. Values of serum markers for AMI in the AMI group, the non-AMI group, and healthy volunteers.

	AMI group (n = 99)	Non-AMI group (n = 66)	Healthy volunteers (n = 104)
H-FABPc, $\mu\text{g/L}$	29.1 ^{a,b} (13.4–87)	5.6 (3.8–8.7)	4.1 (3.2–6.0)
Myoglobin, $\mu\text{g/L}$	196 ^{a,b} (95–472)	72 ^a (51–104)	54 (41–70)
Ratio of myoglobin over H-FABPc	6.3 ^{a,b} (5.2–8.7)	13.3 (8.9–18.8)	12.3 (8.9–15.9)

Data given are medians (interquartile ranges).
^a Indicates $P < 0.01$ vs healthy volunteers; ^b indicates $P < 0.01$ vs the non-AMI group.

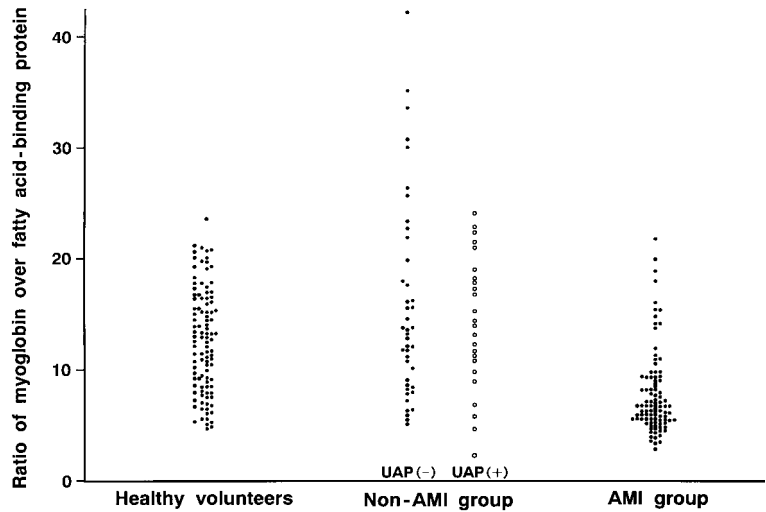


Fig. 1. Concentration ratio of myoglobin over H-FABPc in healthy volunteers, the non-AMI group, and the AMI group. In the non-AMI group, patients without unstable angina [UAP(-)]; patients with unstable angina [UAP(+)].

defined as the diagnostic criterion for AMI. The sensitivity, specificity, and predictive accuracy of this criterion for the detection of AMI within 6 h of chest pain were 79.8%, 90.9%, and 84.2%, respectively (Table 3). These values were similar to the single criterion of H-FABPc concentration >12 $\mu\text{g/L}$.

In the non-AMI group, H-FABPc was increased at admission in nine patients (Table 4), and myoglobin in 16. In patients with unstable angina, H-FABPc concentration exceeded the cutoff concentration in two patients (8.3%), and myoglobin in three (12.5%). There was no significant difference in the frequency of increased concentration of H-FABPc and myoglobin in patients with unstable angina. The frequency of increased concentration of H-FABPc was significantly ($P < 0.05$) lower than that of myoglobin in patients without unstable angina in the

non-AMI group. Three patients of non-AMI group with increased H-FABPc concentration had a ratio >14, and the ratio was helpful in differentiating AMI from skeletal muscle injury. In two patients with AMI, serum concentrations of both H-FABPc and myoglobin were increased, with a ratio >14. The increased ratio may reflect an injury to both myocardial and skeletal muscle because the chest pain appeared while the patients were playing golf or jogging.

Discussion

The present study showed that the sensitivity, specificity, and predictive accuracy of H-FABPc concentration >12 $\mu\text{g/L}$ were significantly higher than those of myoglobin for detection of AMI within 6 h of onset of chest pain. Furthermore, the sensitivity of H-FABPc concentration

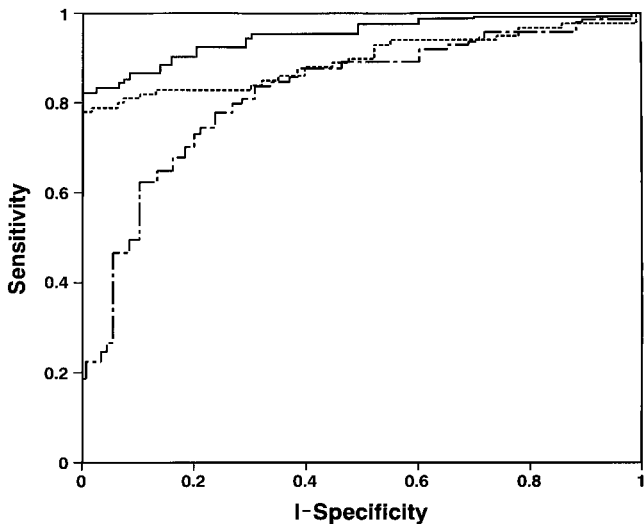


Fig. 2. ROC curves of H-FABPc concentration, myoglobin concentration, and the concentration ratio of myoglobin over H-FABPc between the AMI group and the healthy volunteers.

Solid line, H-FABPc concentration; dashed line, myoglobin concentration; solid/dashed line, concentration ratio of myoglobin over H-FABPc.

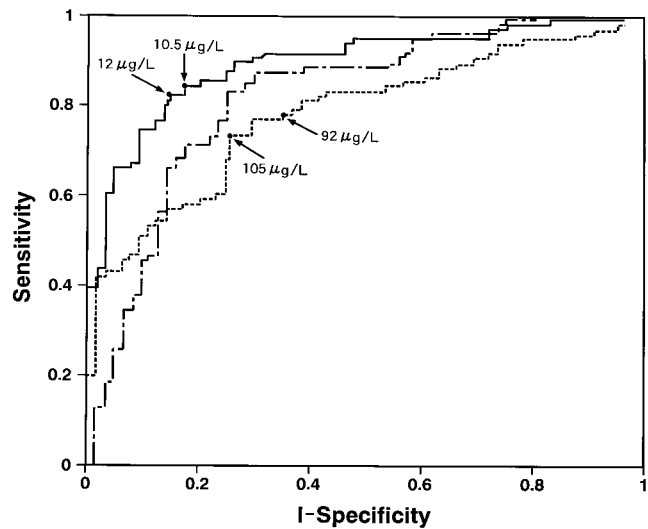


Fig. 3. ROC curves of H-FABPc concentration, myoglobin concentration, and the concentration ratio of myoglobin over H-FABPc between the AMI group and the non-AMI group.

Solid line, H-FABPc concentration; dashed line, myoglobin concentration; solid/dashed line, ratio of myoglobin over H-FABPc.

Table 3. Diagnostic performances (and 95% confidence intervals) of serum markers in AMI.

H-FABPc (>12 µg/L)	
Within 6 h of onset of chest pain	
Sensitivity (overall), %	81.8 (74.2–89.4) ^a
Non-Q-wave only	69.2 (51.5–87.0)
Q-wave only	86.3 (78.4–94.2)
First infarct	82.6 (74.5–90.6)
History of infarct	76.7 (67.8–85.7)
Specificity, %	86.4 (78.1–94.6) ^a
Predictive accuracy, %	83.6 (78.0–89.3) ^b
Within 3 h of onset of chest pain	
Sensitivity, %	72.3 (59.5–85.1) ^a
Between 3 and 6 h of onset of chest pain	
Sensitivity, %	90.4 (82.4–98.4)
Myoglobin (>105 µg/L)	
Within 6 h of onset of chest pain	
Sensitivity (overall), %	72.7 (64.0–81.6)
Non-Q-wave only	57.7 (38.7–76.7)
Q-wave only	78.1 (68.6–87.6)
First infarct	75.6 (66.5–84.7)
History of infarct	53.8 (26.7–80.9)
Specificity, %	75.8 (65.4–86.1)
Predictive accuracy, %	73.9 (67.2–80.6)
Within 3 h of onset of chest pain	
Sensitivity, %	57.4 (43.3–71.6)
Between 3 and 6 h of onset of chest pain	
Sensitivity, %	86.5 (77.2–95.8)
H-FABPc >12 µg/L and the ratio of myoglobin over H-FABPc ≤ 14	
Within 6 h of onset of chest pain	
Sensitivity, %	79.8 (71.9–87.7)
Specificity, %	90.9 (84.0–97.8) ^b
Predictive accuracy, %	84.2 (78.7–89.8) ^b

^a Indicates $P < 0.05$ vs myoglobin; ^b indicates $P < 0.01$ vs myoglobin.

was higher than that of myoglobin for detection of AMI within 3 h of onset, but was similar to myoglobin concentration from 3 to 6 h of onset. H-FABPc concentration was increased as frequently as myoglobin concentration in

patients with unstable angina. However, H-FABPc concentration was increased less frequently than myoglobin concentration in noninfarcted patients without unstable angina. These findings indicate that H-FABPc is a more sensitive and specific marker than myoglobin for the detection of AMI within 6 h, especially within 3 h, after the onset of chest pain, and the measurement of serum H-FABPc concentration can provide valuable information for the early diagnosis of AMI.

Recently, Van Nieuwenhoven et al. reported that the ratio of the increase in the plasma concentrations of myoglobin and H-FABPc above basal concentrations could be an index to discriminate myocardial injury from skeletal muscle injury [8]. For the calculation of the ratio of the increased plasma concentrations, it is necessary to obtain the basal plasma concentrations. This is too complicated and time consuming to use in an emergency situation. We therefore calculated the ratio of the serum concentrations on admission.

In healthy volunteers, one expects that the concentration ratio of myoglobin to H-FABPc in serum corresponds to the content ratio found in skeletal muscle, the major source of these proteins in normal circulation. However, for skeletal muscle the content ratio of myoglobin to H-FABPc was reported to be 20–70 [7, 8], which was considerably higher than the concentration ratio in healthy volunteers. The relatively low ratio of serum concentrations of myoglobin to H-FABPc in healthy subjects may be due to the difference in renal clearance of these proteins. The isoelectric points of H-FABPc (pI 5.1) and myoglobin (pI 7.0) were different, and this makes H-FABPc more negatively charged, causing H-FABPc to be cleared less rapidly by the kidneys and hence to stay longer in circulation than myoglobin [17]. In animal studies, the disappearance half-time for H-FABPc (27.5 min) is approximately four times as long as that of myoglobin (5.5–8.9 min) [18–20]. Under normal conditions, because only a small amount of these proteins is continuously released into the bloodstream, the effect of

Table 4. Eleven special cases.

Age, years	Gender	Diagnosis	H-FABPc, µg/L	Myoglobin, µg/L	Ratio of myoglobin over H-FABPc
Non-AMI group					
67	M	Nonspecific thoracic pain, exercise	12.3	210	17.1
79	F	Nonspecific thoracic pain, practicing judo	13.6	181	13.3
81	F	Unstable angina, minor myocardial injury	13.5	156	11.6
61	F	Arrhythmia, frequent intramuscular injections	16.5	273	15.4
53	M	Aortic dissection	16.8	562	33.5
70	F	Aortic dissection, chronic renal failure	17.1	132	7.7
77	F	Pulmonary infarction	21.9	115	5.3
81	M	Unstable angina, minor myocardial injury	33.2	223	6.7
76	M	Rupture of aortic aneurysm	45.5	254	5.6
AMI group					
71	M	AMI, history of playing golf	23.4	367	15.7
72	M	AMI, history of jogging	24.2	472	19.5

the difference in renal clearance of proteins is much more than in conditions under which a great deal of these proteins is released into bloodstream abruptly because of myocardial or skeletal muscle damage. Therefore, the concentration ratio in healthy subjects shows a lower concentration than the content ratio for skeletal muscle.

There was a considerable overlap in the ratio distribution in healthy volunteers and patients with AMI within 6 h after onset (Fig. 1), indicating that it is difficult to use the ratio alone for early detection of AMI. There are several possible explanations for the overlap of the ratio between the healthy subjects and the patients with AMI within 6 h after onset. Healthy subjects have relatively low concentration ratios of myoglobin over H-FABPc, as mentioned above. Also, a significant change in the ratio requires the release of significant amounts of proteins from injured muscle, which makes the ratio difficult to use in patients without sufficiently increased concentrations of these proteins. Finally, a wide variation in the ratio in healthy individuals may exist, resulting from a wide variation in the distribution of both proteins in the type of skeletal muscle [7, 8]. In the AMI group, patients with H-FABPc concentration $>12 \mu\text{g/L}$ had a significantly lower ratio than patients with concentration $\leq 12 \mu\text{g/L}$, suggesting that the more proteins are released, the more useful the ratio may become in differentiating myocardial injury from skeletal muscle injury. In the present study, the sensitivity, specificity, and predictive accuracy for the combination of H-FABPc concentration above the cutoff value and the ratio ≤ 14 were similar to H-FABPc alone for early diagnosis of AMI. Thus, the ratio was not more useful than the measurement of H-FABPc alone for the detection of AMI within 6 h after the onset of chest pain.

When evaluating the diagnostic value of the concentration ratio of myoglobin to H-FABPc, one must use a sensitive method for both determinations. In the present study, the concentration of H-FABPc was determined by a recently developed and considerably sensitive sandwich ELISA [9]. For the measurement of myoglobin, the turbidimetric latex agglutination method was used because it is the most practical method in an emergency situation for its rapid and easy assay and has been proved to be sensitive, accurate, and precise [10, 11]. The detection limit for myoglobin is $10 \mu\text{g/L}$ [10]. In none of the 104 healthy volunteers and 165 patients was serum concentration of myoglobin lower than the detection limit. Thus, we believe if we measure myoglobin concentration with a more sensitive assay such as RIA, we can get the same results for the diagnostic utility of the ratio of myoglobin to H-FABPc.

Application of H-FABPc as an early marker of AMI requires a rapid assay procedure with high diagnostic accuracy. The sandwich ELISA applied in the present study requires an analysis time of ~ 90 min, too long to be practical in emergency situations. However, a rapid assay

system is being developed to facilitate H-FABPc analysis in clinical practice [8, 21].

There are limitations to clinical application of the H-FABPc concentration for early detection of AMI. Serum H-FABPc concentration increased beyond the cutoff concentration in two patients with unstable angina. Both patients had severe chest pain, electrocardiographic changes, and abnormal angiographic findings, suggesting that the increase of biochemical markers may be attributed to minor myocardial injury. One of the patients developed AMI on the second day after admission and died. Thus, H-FABPc concentration may increase in patients with minor myocardial injury. However, this limitation is not necessarily serious. Patients with H-FABPc concentration $>12 \mu\text{g/L}$ who had unstable angina may be at increased risk of cardiac events and may require further therapy.

Serum H-FABPc concentration exceeded the cutoff concentration in four patients with skeletal muscle injury due to exercise, dissection of aneurysm, or frequent intramuscular injections. Three of these four patients had a ratio >14 . Skeletal muscle injuries have less effect on the serum concentration of H-FABPc than the myoglobin concentration. However, the false-positive findings for H-FABPc resulting from these skeletal muscle injuries should be considered. The ratio of myoglobin over H-FABPc may be helpful in discriminating myocardial injury from skeletal muscle injury in patients with sufficiently increased concentrations of H-FABPc and myoglobin, as suggested by Yoshimoto et al. and Van Nieuwenhoven et al. [7, 8].

Serum H-FABPc concentration exceeded the cutoff concentration in three patients with shock, severe hypoxemia, or renal failure. These three patients had a ratio ≤ 14 . Thus, the H-FABPc concentration may exceed the cutoff value and lead to a false-positive result in such complicated cases. It may be also difficult to interpret the meaning of the ratio of myoglobin over H-FABPc in complicated cases. In such cases, markers such as troponin I and T that become increased later than H-FABPc or myoglobin may be useful in the diagnosis of myocardial injury [22, 23].

In conclusion, H-FABPc is a more sensitive and specific marker than myoglobin for the detection of AMI within 6 h, particularly within 3 h, after the onset of chest pain; the ratio of myoglobin over H-FABPc cannot give a clear advantage over the measurement of H-FABPc alone. Serum H-FABPc concentration at admission can provide a tool for early triage of patients.

We thank Dainippon Pharmaceutical Co., Ltd. for gifts of H-FABPc reagents and technical assistance.

References

1. Tanaka T, Hirota Y, Sohmiya K, Nishimura S, Kawamura K. Serum and urinary human heart fatty acid-binding protein in acute myocardial infarction. *Clin Biochem* 1991;24:195–201.
2. Kleine AH, Glatz JFC, Van Nieuwenhoven FA, Van der Vusse GJ. Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man. *Mol Cell Biochem* 1992;116:155–62.
3. Tsuji R, Tanaka T, Sohmiya K, Hirota Y, Yoshimoto K, Kinoshita K, et al. Human heart-type cytoplasmic fatty acid-binding protein in serum and urine during hyperacute myocardial infarction. *Int J Cardiol* 1993;41:209–17.
4. Ishii J, Nomura M, Ando T, Hasegawa H, Kimura M, Kurokawa H, et al. Heart fatty acid-binding protein and myoglobin can accurately detect successful reperfusion as early as 15 min after reperfusion [Abstract]. *J Am Coll Cardiol* 1995;25:147A.
5. Sylvén C, Jansson E, Böök K. Myoglobin content in human skeletal muscle and myocardium: relation to fiber size and oxidative capacity. *Cardiovasc Res* 1984;18:443–6.
6. Lin L, Sylvén C, Sotonyi P, Somogyi E, Kaijser L, Jansson E. Myoglobin content and citrate synthase activity in different parts of normal human heart. *J Appl Physiol* 1990;69:899–901.
7. Yoshimoto K, Tanaka T, Sohmiya K, Tsuji R, Okamoto F, Kawamura K, et al. Human heart-type cytoplasmic fatty acid-binding protein as an indicator of acute myocardial infarction. *Heart Vessels* 1995;10:304–9.
8. Van Nieuwenhoven FA, Kleine AH, Wodzig KWH, Hermens WT, Kragten HA, Maessen JG, et al. Discrimination between myocardial and skeletal muscle injury by assessment of the plasma ratio of myoglobin over fatty acid-binding protein. *Circulation* 1995;92:2848–54.
9. Ohkaru Y, Asayama K, Ishii H, Nishimura S, Sunahara N, Tanaka T, Kawamura K. Development of a sandwich enzyme-linked immunosorbent assay for the determination of human heart fatty acid-binding protein in plasma and urine by using two different monoclonal antibodies specific for human heart fatty acid-binding protein. *J Immunol Methods* 1995;178:99–111.
10. Kawata Y, Fujita S, Katayama Y, Matsuyama T. Evaluation of the rapid method for the quantitation of serum myoglobin by the latex agglutination turbidimetry and studies on the changes in serum levels with acute myocardial infarction. (In Japanese) *Jpn J Clin Pathol* 1989;37:668–72.
11. Uji Y, Okabe H, Sugiuchi H, Sekine S. Measurement of serum myoglobin by a turbidimetric latex agglutination method. *J Clin Lab Anal* 1992;6:7–11.
12. Ishii J, Nomura M, Ando T, Hasegawa H, Kimura M, Kurokawa H, et al. Early detection of successful coronary reperfusion based on serum myoglobin concentration; comparison with serum creatine kinase isoenzyme MB activity. *Am Heart J* 1994;128:641–8.
13. Miyata M, Abe S, Arima S, Nomoto K, Kawataki M, Ueno M, et al. Rapid diagnosis of coronary reperfusion by measurement of myoglobin level every 15 min in acute myocardial infarction. *J Am Coll Cardiol* 1994;23:1009–15.
14. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36.
15. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–43.
16. Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410–4.
17. Glatz JFC, Kleine AH, Van Nieuwenhoven FA, Hermens WT, Van der Vusse GJ. Fatty-acid-binding protein as a plasma marker for the estimation of myocardial infarct size in humans. *Br Heart J* 1994;71:135–40.
18. Sohmiya K, Tanaka T, Tsuji R, Yoshimoto K, Nakayama Y, Hirota Y, et al. Plasma and urinary heart-type cytoplasmic fatty acid-binding protein in coronary occlusion and reperfusion induced myocardial injury model. *J Mol Cell Cardiol* 1993;25:1413–26.
19. Klocke FJ, Copley DP, Krawczyk JA, Reichlin M. Rapid renal clearance of immunoreactive canine plasma myoglobin. *Circulation* 1982;65:1522–8.
20. Ellis AK, Saran BR. Kinetics of myoglobin release and prediction of myocardial myoglobin depletion after coronary artery reperfusion. *Circulation* 1989;80:676–83.
21. Roos W, Eymann E, Symanek M, Duppenhaler J, Wodzig KWH, Pelsers MMAL, Glatz JFC. Monoclonal antibodies to human heart fatty acid-binding protein. *J Immunol Methods* 1995;183:149–53.
22. Katus HA, Remppis A, Neumann FJ, Scheffold T, Diederich KW, Vinar G, et al. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation* 1991;83:902–12.
23. Adams J, Bodor G, Davila-Roman V, Delmez JA, Apple FS, Ladsen JH. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation* 1993;88:101–6.