

Usefulness of heart-type fatty acid binding protein in the emergency department

Ali Kemal Erenler,¹ Turker Yardan,² Latif Duran,³ Ahmet Baydin⁴

Abstract

The early diagnosis of many diseases is critical, especially in the Emergency Department. Biochemical markers can be helpful for emergency physicians in these critical situations. Heart-type fatty acid binding protein (H-FABP) is one of the promising plasma markers for the detection of tissue injury. H-FABP is known to be released from injured myocardium. It is also expressed in skeletal muscle, the kidney, brain, lactating mammary gland, and placenta. It can be useful in the management of acute coronary syndromes, heart failure, pulmonary embolism, renal and hepatic injury, and some cases of poisonings. In this review, an updated overview of the role of H-FABP in the management of diseases seen frequently in the Emergency Department is presented.

Keywords: Biochemical markers, H-FABP, Emergency department.

Introduction

The early detection and diagnosis of fatal diseases has been a highly controversial subject in the Emergency Department (ED). Investigations on more sensitive and specific markers still continue. One of the promising plasma markers for the detection of tissue injury is a low molecular weight cytoplasmic protein, the heart-type fatty acid binding protein (H-FABP).¹ In this review, in light of the literature, we aimed to evaluate whether H-FABP might be a useful marker in the management of diseases seen frequently in the ED.

The FABP Family

The FABP family is a superfamily of intracellular lipid-binding proteins that have roles in the transport and storage of lipids.² Its functions are facilitation of intracellular long-chain fatty acid transport, regulation of gene transport and protection of cardiac myocytes against detergent-like effects of long-chain fatty acids, especially during ischaemia. As a member of this family,

H-FABP is a low molecular weight protein (15-20 kDa) that is abundant in the cytoplasm of myocardial cells with its special tissue distribution.³ H-FABP is known to be released from injured myocardium. It is abundantly expressed in cardiomyocytes, but also in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary gland, and placenta. Liver-type fatty acid binding protein (L-FABP) is mainly present in hepatocytes, but can also be found in ileal and jejunal enterocytes, colonocytes and proximal tubular cells of the kidney. In the brain and intestine, brain-type fatty acid protein (B-FABP) and intestine-type fatty acid protein (I-FABP) are tissue-specific, but H-FABP and L-FABP are co-expressed.¹

H-FABP

Like other members of the FABP family, H-FABP is a protein with low molecular weight. It is found at high concentrations in the cytoplasm of cardiac myocytes (4-8%). It is rapidly released into the circulation following myocardial damage. It can be detected within 20 minutes (min) of cardiac damage. It reaches peak levels at 3-4 hours and returns to normal range in 24 h.⁴ H-FABP can be detected by enzyme linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), microparticle enhanced immunoassay, fully automated latex-agglutination assay, and qualitative lateral-flow assay.¹ There are authors that independently propose an upper reference limit of 6 µg/L for H-FABP.⁵⁻⁷ Its early elevation and rapid clearance by the kidneys make it a candidate for becoming a useful tool in the early detection of cardiac damage.

H-FABP and Cardiovascular Diseases

With a wide variation from acute myocardial ischaemia to peripheral venous occlusion, cardiovascular diseases represent a large group of diseases with high mortality and morbidity. In the literature, there are many studies that have investigated possible biochemical markers for earlier detection of heart tissue damage.

Unstable Angina Pectoris (UAP) and H-FABP

The phrase "unstable angina pectoris" (UAP) refers to chest pain with no ST elevation on electrocardiogram (ECG) and negative serum biomarkers after the onset of chest pain

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¹Department of Emergency Medicine, Hitit University, Corum Education and Research Hospital, Çorum, ²⁻⁴Department of Emergency Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

Correspondence: Turker Yardan. Email: tyardan@yahoo.com

(cardiac troponin T (cTnT) level $<0.03 \mu\text{g/L}$ 12h after admission).^{8,9} According to the characteristics of the pain, angina is divided into three groups: Rest, new-onset and increasing.¹⁰ In patients with UAP, elevated plasma levels of cTnT and cardiac Troponin I (cTnI) are the indicators of minor myocardial injury due to ischaemia.¹ Kathrukha et al.⁶ proved in their study that H-FABP levels elevate earlier than cTnI levels in patients with UAP. Another study, reported that H-FABP levels elevate in the pericardial fluid in UAP patients.¹¹ Nagahara et al.⁸ revealed that, among the biomarkers (creatine kinase MB isoenzyme (CK-MB), myoglobin (Mb), cTnT, and H-FABP), H-FABP had better overall diagnostic value for the detection of myocardial injury in patients who presented with chest pain. They also found that H-FABP had high positive predictive values (PPVs) (84-91%), high sensitivities (75-77%) and better negative predictive values (NPVs) (nearly 40%). A prospective study, reported that H-FABP assessed within 4h of symptoms was superior to cTnT for the detection of acute myocardial infarction (MI). It was, thus, concluded that measuring H-FABP in addition to cTnT at the time of admission with chest pain would assist in the early diagnosis of acute MI.⁹ Current data suggest that H-FABP may be an early biochemical marker to indicate minor myocardial damage in patients with UAP.

Acute Myocardial Infarction and H-FABP

Ischaemic heart disease is the leading cause of death among adults and represents a spectrum from chronic stable angina to acute MI. It is responsible for more than 500,000 deaths annually.¹⁰ Acute MI is a common cause of sudden and unexpected death.¹¹ Early diagnosis of acute MI is crucial, as this allows earlier initiation of appropriate treatment and improves patient outcome. Although ECG remains the best test to detect acute MI in the ED, it has relatively low sensitivity. Generally, ST segment elevations in a standard 12-lead ECG suggest transmural injury, while ST segment depressions suggest subendocardial ischaemia. However, in the initial ECG, 50% of patients will not have diagnostic ST segment elevations.¹² Cardiac markers are also useful tools in the diagnosis of acute MI. Cardiac troponins are the preferred markers. However, their delayed appearance in serum (rise to a peak level in 12h following an acute MI with a prolonged elevation for 7-10 days before returning to baseline), gives rise to the need for an earlier biochemical marker.^{13,14} Nakata et al.¹⁴ reported that, among the other biochemical markers, H-FABP had the highest sensitivity in the evaluation of hospitalisation, angiography and interventional therapy requirement. In 2004, Chan et al.¹⁵ claimed that two samples of H-FABP (one at admission, the other 1h after admission) could reliably diagnose acute MI, and 100% of

non-acute MI patients could be excluded with no false negative results. O'Donoghue et al.¹⁶ reported that among 2287 patients with acute coronary syndromes (ACS), those who had high levels of H-FABP had increased risk of recurrent MI, heart failure (HF), death or the composite of these endpoints. They demonstrated that H-FABP is an independent and strong predictor of adverse cardiac events in ACS. Ishii et al.¹⁷ reported that H-FABP is an independent predictor of cardiac events within six months of patient admission (with a median value of $9.8 \mu\text{g/L}$ as the cut-off for predicting cardiac events). It was also reported that H-FABP might provide prognostic information superior to cTnI in the early hours of ACS. Liyan et al.¹³ reported that in patients presenting to the ED with chest pain without elevation in cTnT levels and ST segment elevation on ECG, the combination of ischaemia-modified albumin and H-FABP levels is an independent sensitive method for the identification of ACS. In another study, H-FABP was found to be inadequate to diagnose acute MI by itself (the sensitivity and specificity at presentation were 83.3% and 30.0%, respectively). It was also found that when positive, it was faster than cTnI. It was suggested to evaluate H-FABP in combination with other markers.¹⁸ H-FABP is a promising biomarker for the early exclusion of acute MI in the ED, but cannot be used alone to rule out the diagnosis.¹⁹ In a review and meta-analysis,²⁰ it was concluded that H-FABP did not fulfil the diagnostic requirements needed for a safe and early diagnosis of MI when applied as a stand-alone diagnostic test. It was also concluded that sound diagnostic studies examining the additional role of H-FABP combined with clinical findings and other diagnostic tests are needed to further clarify a potential future role for this cardiac biomarker.

Heart Failure and H-FABP

With approximately 550,000 new patients every year in the United States and its poor prognosis, HF is an important public health problem. Loss of the heart's pump function is the main mechanism causing HF. The most common cause of HF seen in the ED is MI. Among the signs and symptoms, breathlessness, orthopnea, jugular venous distension, rales, and possibly S3 can be counted. After development of pulmonary oedema (PE), only 50% survive one year, and after cardiogenic shock, 85% die within one week. Diagnosis is based upon history, physical examination, chest radiographs (dilated upper lobe vessels, cardiomegaly, interstitial oedema, enlarged pulmonary artery, pleural effusion, alveolar oedema, prominent superior vena cava, and Kerley lines), echocardiography, and laboratory studies (natriuretic peptide measurement $>100 \text{ pg/mL}$).²¹ Sugiura et al.²² investigated the utility of myosin light chain-I, cTnT, H-

FABP, and CK-MB in the prediction of prognosis of patients with congestive heart failure (CHF). They demonstrated that these proteins are related to increased risk of future acute deterioration of CHF. Ishino et al.²³ reported that when combined measurement of B-type natriuretic peptide (BNP), H-FABP, and pentraxin 3 (PTX3) is elevated in CHF, patients are at greater risk of adverse cardiac events than patients with a lower number of elevated biomarkers. In a study by Niizeki et al.,²⁴ it was reported that combined measurement of BNP and H-FABP at admission might be useful in risk stratification for future cardiac events in patients with CHF. Their results suggested that the H-FABP and BNP concentrations at admission are associated with both cardiac death and nonfatal cardiac events in patients hospitalised for CHF. Niizeki et al.²⁵ reported in another study that serial measurement of H-FABP levels (at both admission and discharge) provides additional prognostic information in CHF. They found that the group with high levels of H-FABP both at admission and discharge had the highest risk of cardiac events (death from worsening CHF, sudden cardiac death and worsening CHF requiring re-admission). These data suggests that H-FABP may be a useful tool for detection of myocardial injury and risk assessment of patients with CHF.

Cardiomyopathies, Myocarditis and Pericardial Diseases and H-FABP

Cardiomyopathy results from altered cardiac structure and impaired myocardial function. Four types are currently recognised: dilated cardiomyopathy (DCM); hypertrophic cardiomyopathy (HCM); restrictive cardiomyopathy; and arrhythmogenic right ventricular cardiomyopathy. Heart muscle diseases due to specific cardiac or systemic disorders (toxins, infections, systemic rheumatic disorders, hypersensitivity cardiomyopathy, peripartum cardiomyopathy, metabolic disorders) are classified as specific cardiomyopathies. Myocarditis is a non-specific inflammation of the heart muscle presenting with fever, sinus tachycardia and symptoms of progressive heart failure in severe cases. Myocarditis is frequently associated with pericarditis. Pericarditis may present with low-grade intermittent fever, dyspnoea and dysphagia. Chest pain is usually described as sharp or stabbing, radiating to the back and aggravated by inspiration or movement. In a study, Komamura et al.²⁶ showed that a serum concentration of H-FABP before discharge independently predicted the long-term risk of critical cardiac events with a power comparable to that of BNP in non-cardiac cardiomyopathy. Likewise, it was shown that increased serum H-FABP levels indicate ongoing myocardial damage in patients with HCM. When the

extent of thallium 201 perfusion defects and serum H-FABP levels were compared in patients with HCM and HF, a relationship was demonstrated.²⁷ Tambara et al.¹¹ reported that pericardial fluid level of H-FABP is an indicator of myocardial ischaemia occurring within 24h of their measurement. H-FABP may be secreted into the interstitial space by increased permeability of the myocardial cell membrane associated with severe myocardial ischaemia. The authors concluded that pericardial fluid reflects pathophysiological conditions of cardiomyocytes more sensitively than circulating blood. Further investigations are needed to demonstrate the utility of H-FABP in cardiomyopathies, myocarditis and pericardial diseases.

Pulmonary Embolism (PE) and H-FABP

Acute PE is a relatively frequent cardiovascular emergency and a major cause of mortality and morbidity in the population. Diagnosis begins with the recognition of risk factors that predispose to thrombosis (hypercoagulability, stasis and venous injury). Thrombosis leads to PE. Patients with PE may present to the ED with intermittent shortness of breath, chest pain, haemoptysis, fever, hypotension, tachycardia, and also cardiac arrest. Shortness of breath is the most common symptom of PE and results from the cardiopulmonary stress caused by the clot in the lung. Diagnosis is made by computed tomography (CT) and pulmonary angiography. Ventilation-perfusion lung scanning and measurement of D-dimer can be used for excluding PE. Some of the biochemical markers have diagnostic and prognostic features in the evaluation of PE. Kaczynska et al.²⁸ determined the serum concentrations of Mb, cTnT and N-terminal fragment of proBNP (NT-proBNP) as well as H-FABP in 77 patients with acute PE. They reported that measured H-FABP level on admission is a useful tool for short-term risk stratification. Increased level of H-FABP was found to be superior to Mb, cTnT and proBNP. Boscheri et al.²⁹ reported that H-FABP significantly predicted mortality in patients with pulmonary embolism at intermediate risk. They also reported that it was significantly associated with impaired right ventricular function and showed better correlation with mortality than troponin I. They concluded that it might be a novel prognostic parameter enabling the optimization of management strategy in the very difficult population of pulmonary embolism at intermediate risk. Lankeit et al.³⁰ also reported that in the population with chronic thromboembolic pulmonary hypertension (CTEPH), baseline H-FABP levels were significantly higher in patients with an adverse outcome during the follow-up period compared with those with a favourable course. The results of their study indicated that H-FABP could be a reliable

novel predictor of outcome in patients with CTEPH.

Hypertension and H-FABP

A systolic blood pressure greater than 140 mmHg and a diastolic blood pressure greater than 90mmHg constitute hypertension (HT), which increases the risk of cardiovascular, renal and cerebrovascular diseases. Niizeki et al.³¹ measured H-FABP levels in 2099 subjects who were followed up. Among these subjects, 1303 were hypertensive. The highest levels of H-FABP were related with HT, obesity and ECG changes. Arterial stiffness increases in hypertensive individuals. Arterial stiffness is also associated with impairment of systolic and diastolic myocardial function in HT. It was suggested that arterial stiffness is associated with serum H-FABP levels, a sensitive marker of myocardial damage, in patients with newly diagnosed HT.³² Further studies are needed to evaluate the possible relation between H-FABP and hypertensive emergencies in patients in ED.

Aortic Dissections ADs, Aneurysms and H-FABP

Aortic dissections (ADs) occur from a violation of the intima that allows blood to enter the media and dissect between the intimal and adventitial layers. Common sites for tear are the ascending aorta and the region of the ligamentum arteriosum. Hazui et al.³³ reported increased H-FABP levels as well as a correlation between absolute value for H-FABP and dissection length score in patients with AD. According to the results of that study, an increased serum H-FABP concentration in patients with AD is caused by the protein being released not only from myocardial muscle, but also from skeletal muscle or possibly the aortic wall. Moreover, while using H-FABP for myocardial injury detection, it must be kept in mind that patients with long or ascending AD will also show an elevated serum H-FABP level.

FABP and Other Diseases

Skeletal Muscle Injury

Since H-FABP can be found in various tissues, high values can be measured in different diseases causing tissue damage. H-FABP is mainly expressed in the heart but to a lesser extent also in skeletal muscle.¹ Sorichter et al.³⁴ reported for the first time that plasma FABP increases after physical exercise in healthy subjects. They concluded that FABP, like Mb, allows earlier assessment of exercise-induced skeletal muscle injury than does CK. Simultaneous measurement of H-FABP and Mb in plasma could be helpful for the early diagnosis of skeletal muscle damage.¹ However, the relation between H-FABP and muscle injury is less clear in the literature.

Hepatocellular Injury

The presence of H-FABP in the liver has not been reported.

However, an isoform specific to the liver called L-FABP exists. Pelters et al.³⁵ showed that L-FABP is a sensitive marker of rejection-related hepatocellular injury in patients with liver transplantation. Al-Hadi et al.³⁷ illustrated that there is no significant interference with the normal concentration of H-FABP in the presence of chronic liver diseases, despite the significant elevation of liver enzymes and proteins. They reported that this is consistent with the reduced cross-reactivity between H-FABP and other FABPs, including L-FABP. They also suggested that these findings may support a useful role of H-FABP in the diagnosis of myocardial injury in patients with chronic liver diseases.

Renal Injury

The exact route(s) of excretion of H-FABP from the circulation is not fully understood. As suggested by previous studies, the kidney may be the major route of excretion of H-FABP from circulation.³⁶ H-FABP may be a sensitive marker of injury affecting distal tubular cells in which it is present abundantly. El-Hadi et al.³⁷ reported that the diagnostic efficiency of H-FABP and cTnT for the diagnosis of AMI in the presence of renal failure might be limited and such patients may have high levels even in the absence of AMI. It was also suggested that plasma AST, H-FABP, and NGAL reflect the severity of initial kidney graft injury and predict graft dysfunction earlier and more accurately than creatinine (clearance) and histology. They may represent promising tools to improve patient care after kidney transplantation.³⁸ Teratani et al.² also reported that B-FABP is a sensitive marker for renal cell carcinoma (RCC). They reported that B-FABP was expressed in carcinoma tissue, but not in the noncancerous parts of the kidney samples resected from patients with RCC. H-FABP and L-FABP appear to be sensitive biomarkers for early detection of renal injury enabling better monitoring of patient treatment and status of kidney viability. As renal disease also appears to be an independent risk factor for cardiovascular disease (CVD), earlier detection with these biomarkers can stratify treatment and reduce death from CVD.³⁹

Brain Injury

The brain contains both H-FABP and B-FABP in specific regions.^{40,41} B-FABP and H-FABP are new potential markers for the detection of brain injury.¹ Pelters et al.⁴² have shown elevated serum levels of B-FABP and H-FABP in traumatic brain injury. The study of Wunderlich et al.⁴³ also demonstrated that elevated levels of B-FABP and H-FABP are associated with brain injury and clinical severity in patients with acute ischaemic stroke. Particularly high levels of H-FABP were significantly associated with the severity of neurological deficit and functional outcome. H-

FABP was also associated with the volume of the infarct. Cheon et al.⁴⁴ evaluated H-FABP levels in patients with neurodegenerative diseases such as Down's Syndrome (DS) and Alzheimer's Disease (AD). They reported that B-FABP was significantly increased in the occipital cortex and H-FABP was significantly decreased in the frontal, occipital and parietal cortices of adult patients with DS. H-FABP was also determined in low levels in the frontal, temporal, parietal and occipital cortices in patients with AD. In another study, the serum levels of brain-type fatty acid-binding protein (FABP) and H-FABP in patients with dementia-involving diseases were measured. In contrast to H-FABP, serum levels of brain-type FABP are elevated in a significant proportion of patients with various neurodegenerative diseases and can therefore have importance for defining subgroups of these patients.⁴⁵

Poisonings

In diseases resulting in generalised hypoxia and thus causing damage in several tissues (brain and heart particularly for their relatively high oxygen demand), elevated H-FABP levels may be related with clinical severity. Since carbon monoxide (CO) poisoning causes cardiac damage due to tissue hypoxia, biochemical markers are necessary to determine early myocardial damage. Yordan et al.⁴⁶ reported that H-FABP levels increase in CO poisoning in rats. The results of that study indicated that serum level of H-FABP increases in the early phase of CO poisoning prior to cTnI. It was suggested that H-FABP might have potential to serve as an early and quantitative parametre of clinical severity and prognosis in CO poisoning. An increased serum H-FABP level in acute CO poisoning was also reported by other clinical studies.^{47,48} Ischaemic damage of many organs such as the brain and heart in acute CO poisoning and their relation with elevated H-FABP levels suggest that H-FABP has the potential to serve as an early parametre of clinical severity and prognosis in acute CO poisoning. Moreover, further studies are needed to evaluate the possible relation between H-FABP and other poisonings, especially those resulting in damage to the brain and heart (organophosphate poisonings, cardiotoxic drug poisonings such as amitriptyline or some of the cancer drug overdoses, etc.).

Conclusions

H-FABP is a valuable early marker of cardiac injury in acute coronary syndromes and minor myocardial injury in heart failure. Its utility increases when evaluated in combination with other biochemical markers. Nevertheless, investigations to expose an excellent marker that has cardiospecificity and a prolonged detectability in plasma are required. Recent researches seem to suggest a role of

H-FABP in the management of other diseases seen frequently in the ED.

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