

Bedside heart type fatty acid binding protein (H-FABP): Is an early predictive marker of cardiac syncope

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Abstract

Objective: To determine the value of bedside heart-type fatty acid binding protein in diagnosis of cardiac syncope in patients presenting with syncope or presyncope.

Methods: The prospective study was conducted at Ankara Numune Training and Research Hospital, Ankara, Turkey, between September 1, 2010, and January 1, 2011, and comprised patients aged over 18 years who presented with syncope or presyncope. Patients presenting to emergency department within 4 hours of syncope or presyncope underwent a bedside heart-type fatty acid binding protein test measurement. SPSS 16 was used for statistical analysis,

Results: Of the 100 patients evaluated, 22(22%) were diagnosed with cardiac syncope. Of them, 13(59.1%) patients had a positive and 9(40.9%) had a negative heart-type fatty acid binding protein result. Consequently, the test result was 12.64 times more positive in patients with cardiac syncope compared to those without.

Conclusions: Bedside heart-type fatty acid binding protein, particularly at early phase of myocardial injury, reduces diagnostic and therapeutic uncertainty of cardiac origin in syncope patients.

Keywords: Syncope, H-FABP, Emergency department. (JPMA 65: 1156; 2015)

Introduction

Syncope is a short-term loss of consciousness due to transient cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery. Presyncope, on the other hand, is used to describe an event similar to syncope prodrome that is not accompanied by loss of consciousness.¹ Syncope has a wide clinical spectrum ranging from benign conditions to life-threatening disorders.²

Syncope is responsible for 1-3% of all emergency department (ED) presentations and 2-6% of all hospital admissions.³ According to the Framingham study, the annual incidence of syncope is 6.2/1000 persons and the 10-year cumulative incidence is about 6%. It is the 6th leading cause of hospitalisation among patients over 65 years of age.⁴

Syncope is classified into 4 major groups, including vasovagal, orthostatic, cardiac and idiopathic. Cardiac syncope has the highest mortality and morbidity rates among all types of syncope and aetiology consists of

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acute coronary syndromes (ACS), arrhythmias and structural heart diseases.¹ Traditionally troponins are routinely used in diagnosis of cardiac syncope but given the relatively delayed positivity and peak times of them, use of markers such as heart-type fatty acid binding protein (H-FABP) that appear earlier in serum has recently begun to increase.⁵

Recently qualitative rapid immunochemical point-of-care-tests (POCT) are reliably used to detect H-FABP in capillary blood samples in rapid determination of myocardial damage.⁶ In PubMed and Medline databases we found no studies that investigated the correlation between cardiac syncope and H-FABP.

The present study was planned to determine the value of bedside H-FABP in diagnosis of cardiac syncope in patients presenting to ED with syncope or near-syncope.

Patients and Method

The prospective observational single-centre study was conducted between September 1, 2010, and January 1, 2011, at the ED of Ankara Numune Training and Research Hospital (ANTRH), Ankara, Turkey, which is an urban teaching hospital. Consecutive patients presenting with syncope or near-syncope were enrolled after approval from the institutional ethics committee and written consent from the patients.

Patients were 18 years or older and presenting to ED with

syncope or near-syncope within 4 hours. Syncope was defined as transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery with no requirement of resuscitative efforts. Near-syncope or pre-syncope was defined as the prodrome of syncope but which is not followed by LOC as mentioned in the guidelines for the diagnosis and management of syncope (version 2009) of European Society of Cardiology (ESC).¹

Those who refused to participate or presented to ED 4 hours after syncope or near-syncope, matching the criteria of clinical conditions without global cerebral hypoperfusion but incorrectly diagnosed as syncope (epilepsy, metabolic disorders, including hypoglycaemia-hypoxia- hyperventilation with hypocapni, intoxication, vertigo, vertebrobasilar transient ischaemic attack) or without impairment of consciousness (cataplexy, psychogenic pseudosyncope, trauma, carotid transient ischaemic attack), as mentioned in the guidelines for the diagnosis and management of syncope (version 2009) of ESC, were excluded.

At initial evaluation, patients were risk stratified in terms of cardiac syncope with Evaluation of Guidelines in Syncope Study-Multivariate (EGSYS-M) score which consists of six items: palpitations preceding syncope (4 points), history of heart disease or abnormal electrocardiogram in the ED (3 points), syncope during effort (3 points) or while supine (2 points), precipitating or predisposing factors (-1 point), and autonomic prodrome (-1 point). Patients with a score of ≥ 3 were accepted likely to have a cardiac cause.

Participants who matched the study design criteria and presented to ED within 4 hours of syncope or near-syncope underwent H-FABP measurement with one-step test cassette H-FABP kit of World of Health Biotech Co. Ltd company, in which bedside fingertip blood immunochromatography technique is used for qualitative determination of H-FABP in whole blood samples with a threshold of 6.5ng/ml mentioned by the manufacturer. Three drops of capillary whole blood from the patient's finger were applied onto the test-strip. Within 15 minutes H-FABP test result were read as positive (two red lines for elevated plasma H-FABP) and negative (one red line for non-elevated plasma H-FABP). As mentioned by the manufacturer, the red line by the letter C in the result window was the internal control which confirmed sufficient specimen volume, correct procedural performance, and good product quality. As a reference standard, cardiac Troponin I (cTnI) measurements were

performed on admission and 12th hour according to the instructions of manufacturer using the Access AccuTnI Troponin I assay (Beckman Coulter) which is a two-site immunoenzymatic ("sandwich") assay. The reference value for normalisation established by the laboratory was lower than 0.15 ng/mL.

Patients' data were collected on a pre-established proforma where name, age, gender, co-morbidities, medications, family history of cardiac arrest, history characteristics of syncopal episode, including presence of predisposing factors and loss of consciousness, position of the body before syncope, associated symptoms, previous syncope characteristics, physical examination findings, including orthostatic provocation test to diagnose orthostatic syncope, initial and serial 12-lead electrocardiogram (ECG) results, EGSYS-M score, laboratory findings, including serum electrolytes, complete blood count (CBC), cardiac enzyme (Troponin I, creatine kinase [CK], and creatine kinase myocardial b fraction CK-MB) measurements, imaging studies (emergency echocardiography, coronary angiography, holter) results, diagnosis and the course of patient (admission defined as remaining in the ED for >12 h - observation in ED and discharge) were recorded. Patients were classified into 4 groups as vasovagal, orthostatic, cardiac, and idiopathic.

Statistical analyses were performed using SPSS 16. Mean \pm Standard Deviation (SD), median and frequencies and percentages were calculated for demographic and clinical features. Categorical data was evaluated using either Pearson's chi-square test or Fisher's exact test, whichever applicable. The Mann-Whitney U test was used for the analysis of time differences between positive and negative H-FABP results and cTnI levels. Comparison of diagnostic performances of H-FABP and cTnI from patients were analysed using Receiver Operating Characteristic (ROC) curve methodology. Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy rates were calculated. The results were evaluated with a confidence interval (CI) of 95% and $p < 0.05$ or less was considered statistically significant.

As there was no similar study in literature, sample size determination could not be done before study. Thus, post-hoc power analyses were performed with the existing number of samples ($n=100$) to determine the relationship between cardiac syncope and H-FABP (Table-1). With the rate of positive H-FABP in patients diagnosed as cardiac syncope 22 (59%) and non-cardiac syncope 78 (10.1%) and the Type I margin of error determined as 0.05 the power of the study was calculated as 99.6%. Power

analysed were performed with G-Power 3.1.7.

Results

Of the 213 patients meeting the criteria, 100(47%) were enrolled (Figure-1). Of them, 44(44%) were female and 56(56%) were male, with an overall mean age of 59.54±18.77 years (Range: 18- 111 years). Of the 100, 64(64%) patients had associated comorbidities, including hypertension, diabetes, congestive cardiac failure, coronary artery disease or other comorbid disorders. Besides, 52(52%) were on 1 or more medications for their co-morbidities and 9(9%) had a family history of death under the age of 45 due to cardiac causes.

Fifty-three (53%) participants had a history of syncopal attack at least once. Among them, cause of syncope had not been determined in 15(27.8%), while 12(22.2%) were diagnosed as cardiac syncope. Overall, 22(22%) patients were diagnosed as cardiac syncope and of these, 5(22.72%) presented as near-syncope, and 17(77.28%) as syncope. Besides, of the patients who were diagnosed as cardiac syncope, 10(45%) had a history of syncopal attack before and 6(60%) of these were cardiac in origin.

Overall, 21(21%) patients had a positive H-FABP test, while 79(79%) had a negative test result. Among the 22 diagnosed with cardiac syncope, 13(59.1%) had a positive and 9(40.9%) had a negative H-FABP result (Table 1). Consequently, H-FABP test result was 12.64 times more positive in patients with cardiac syncope compared to those without ($p<0.001$) (Table-2). There was no

Table-1: H-FABP test results in patients diagnosed with cardiac syncope.

	HFABP (+)	HFABP (-)	p
Cardiac syncope	13 (59.1%)	9 (40.9%)	<0.001
Non-cardiac syncope	8 (10.3%)	70 (89.7%)	
OR = 12.64 (95% CI [4.12-38.79])			

H-FABP: Heart-type fatty acid binding protein
OR: Odds ratio.

Table-2: Comparison of diagnostic performances of H-FABP and troponin.

	Sensitivity %	Specificity %	PPV %	NPV %	AUC	95% CI
H-FABP	59.1	89.7	61.9	88.6	0.744	0.647-0.826
Admission Troponin level	59.1	92.3	68.4	88.9	0.757	0.689-0.859
12th hour Troponin level	59.1	97.4	86.7	89.4	0.783	0.661-0.837
12th hour Troponin level and H-FABP positivity	81.8	88.5	66.7	94.5	0.851	0.766-0.915

H-FABP: Heart-type fatty acid binding protein
PPV: Positive predictive value
NPV: Negative predictive value
AUC: Area under curve
CI: Confidence interval

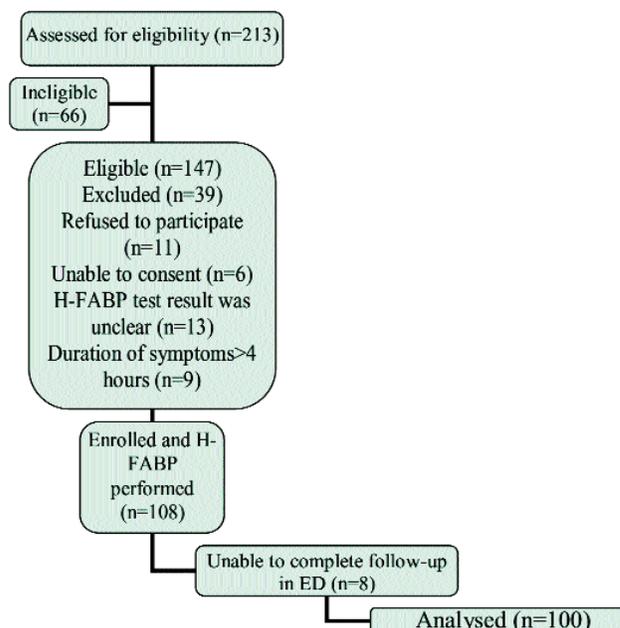


Figure-1: Flow chart.

statistically significant difference in terms of gender, age and comorbidities between H-FABP positive and negative patients diagnosed as cardiac syncope ($p=0.666$; $p=0.535$; and $p=0.655$).

In terms of sensitivity and specificity of diagnostic tests H-FABP alone had a sensitivity of 89.7% while admission and 12th hour troponin levels had a sensitivity over 90% and H-FABP, admission and 12th hour troponin had a sensitivity of 59.1% on their own. Yet, use of H-FABP and troponin I together yielded a sensitivity of 81.8% and a specificity of 88.5%. Combined measurement of H-FABP and troponin was found to be statistically significant at diagnosing cardiac syncope compared to measurement of either marker alone ($p=0.021$). Comparison of diagnostic performances and ROC curves of the diagnostic tests were noted separately (Figure-2).

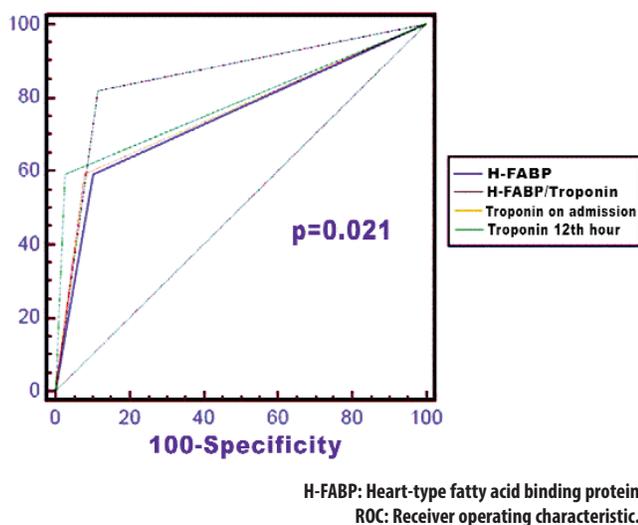


Figure-2: Evaluation of H-FABP and Troponin I in ROC curves.

Discussion

Syncope is a common end-point of clinical conditions ranging from benign low-risk (i.e. vasovagal syncope) to potentially life-threatening diagnoses (i.e. cardiac syncope).⁷ Near-syncope, on the other hand, is an inadequately emphasised symptom, but can be an indicator of serious underlying conditions such as cardiac origin leading to mortality and morbidity.⁸

Cardiovascular diseases are the second most common cause of syncope with reported rates of 5-21% in different studies in ED, has the highest mortality and morbidity rates among all types of syncope and is more common at advanced age.^{1,4} Arrhythmias as the primary cause, structural cardiovascular and ischaemic heart diseases are the precipitating factors with inducing haemodynamic impairment as a result of maintaining cardiac output and systemic blood pressure leading to a decrease in cerebral blood flow.^{1,9}

Although syncope is not serious by itself, but it is a challenging symptom for the emergency physicians especially in the point of determining life-threatening conditions such as patients who are at risk of cardiac events.¹⁰ Lack of structured and algorithmic approach to these patients, however, complicates syncope management. Hence, a thorough history, risk stratification tool to identify high-risk patients who will need prompt hospitalisation upon initial evaluation such as Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL), San Francisco Syncope Rules, The Rose Rule, The Boston Study, EGSYS-M score which are based on multi criterion decision rules; specific diagnostic tests such as

echocardiography, telemetry, electrophysiological studies, tilt test and biomarkers such as troponin, N-Terminal pro-brain natriuretic peptide (NT-proBNP) and BNP, D-dimer, atrial natriuretic peptide (ANP), Copeptin although which are not recommended as routine screening tools by ESC syncope guidelines but have become popular in recent years are all decision-making and diagnostic steps in initial evaluation and management of ED syncope patients.^{7,11-15}

The challenging nature of syncope and difficulties in applying syncope guidelines in clinical practice especially in crowded ED, cardiovascular biomarkers are encouraging and of these H-FABP is a novel biochemical marker of myocardial tissue injury of growing attention, which is a protein responsible from intracellular translocation of long-chain fatty acids in cardiac myocytes, is not present in plasma under normal conditions and can release into the bloodstream within 20 minutes of myocardial damage in large quantities due to its solubility and smaller size than other cytosolic enzymes.^{6,16-19}

Diagnostic and prognostic effect of H-FABP in cardiovascular events such as acute coronary syndromes, cardiomyopathies, myocarditis, pericardial diseases, aortic dissections and aneurysms, hypertension and heart failure has been studied in several studies and significant correlations were found²⁰⁻²⁵ but H-FABP has never been tested for its possible role in diagnosing syncope or near-syncope in ED, which is cardiac in origin. Cardiac syncope can be a result of arrhythmic or non-arrhythmic mechanisms and the relationships between H-FABP were mentioned above. In our study, we found that H-FABP test results were 12.64 times more positive in patients with cardiac syncope. But use of H-FABP and troponin I together yielded a higher sensitivity and specificity (81.8% and 88.5%, respectively) and a NPV of 94.5% in patients with a negative H-FABP result and a 12th hour troponin level below the cut-off level.

Our study was a single-centre effort with a relatively small sample size. Yet, we were able to show some statistically significant results suggesting the value of H-FABP in timely diagnosis of cardiac syncope. Finally, although H-FABP was evaluated in cardiovascular diseases before, we could not design a clear Discussion section since H-FABP has not been studied in cardiac syncope.

Conclusion

Given the lack of algorithmic and structural approach to syncope patients in ED, our results suggest that H-FABP may be used as a promising early biomarker in determining the cardiac origin in patients presenting with syncope or near-syncope and furthermore H-FABP may be

used for prediction of short- and long-term clinical outcomes and it may even be incorporated into risk scoring systems. Nevertheless, future large-scale studies are needed to confirm these hypotheses.

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