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ORIGINAL ARTICLE

Comparative study of high sensitivity troponin T and heart-type fatty acid-binding protein in STEMI patients

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Abstract *Aim and background:* Heart-type fatty acid-binding proteins (H-FABP) which are detected within 2–3 h of acute myocardial infarction are involved in uptake of free fatty acids in the myocardium. Our aim in the present study is to compare window periods of H-FABP to high sensitivity troponin T (hs-Trop T) in acute ST elevation myocardial infarction (STEMI).

Methods: 160 STEMI diagnosed patient's serum samples are analyzed for hs-Trop T and H-FABP. Different window periods of chest pain onset (<3 h, 3–6 h and >6 h) are compared with complications, in-hospital mortality and statistically analyzed.

Results: From 160 patients, 53 (33%) cases are presented in <3 h, 75 (47%) in 3–6, and 32 (20%) after >6 h respectively. Accordingly sensitivity of hs-Trop T was 92%, 94% and 97% while H-FABP was 75%, 88% and 84%, respectively. Overall sensitivity was 94% and 82% respectively. Statistically significant difference between mean hs-Trop T values with respect to window period <3, 3–6 and >6 h was 0.21, 0.35 and 0.80 ng/ml respectively, p value < 0.0001. No significant difference in H-FABP values was observed.

Hs-Trop T positively correlated with age ($r = 0.153$, $P = 0.05$), window period ($r = 0.363$, $P < 0.0001$), TIMI score ($r = 0.208$, $P = 0.008$), ejection fraction ($r = 0.191$, $P = 0.008$), serum H-FABP ($r = 0.229$, $P = 0.004$), and serum hs-CRP ($r = 0.326$, $p < 0.001$). There was a statistically significant difference of mean hs-Trop T values with or without in hospital mortality (0.35 vs. 0.85 ng/ml, respectively, $p = 0.008$).

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No significant correlation to age, TIMI score, ejection fraction and hs-CRP values for H-FABP was observed.

Conclusion: It appears that hs-Trop T is a more sensitive marker than H-FABP in early hours of AMI and higher hs-Trop T predicts increase in-hospital mortality.

1. Introduction

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight protein involved in the intracellular uptake and buffering of free fatty acids in the myocardium (Glatz et al., 1997). It was first noted to be a marker of myocardial infarction (MI) in 1988 Glatz et al., 1988. Heart-type fatty acid-binding protein is smaller in size (14–15 kDa) than troponin I or T (21–37 kDa) and is concentrated in the cytoplasm of cardiomyocytes. Owing to its small size, H-FABP is released quickly into the circulation when membrane integrity is compromised in response to myocardial injury. Levels of H-FABP are detectable as early as 2–3 h and typically return to baseline levels within 12–24 h of the initial insult (Tanaka et al., 1991; Kleine et al., 1992). Moreover, because of its rapid release kinetics, H-FABP might be useful for the detection of reperfusion after ST-segment elevation MI (de Lemos et al., 2000). These properties make H-FABP theoretically, an attractive marker both for the detection of myocardial ischemia in the absence of necrosis and possibly for the early detection of recurrent myocardial injury.

Based on this background we wanted to assess the role of H-AFBP in early hours of acute myocardial infarction, and compare its window period response with that of high sensitive troponin T (hs-TnT).

2. Methods

We selected 160 consecutive patients with diagnosis of acute ST elevation myocardial infarction (STEMI) admitted to the coronary care unit (CCU) at Sri Jayadeva Institute of Cardiology and Research, Bangalore. Following Helsinki declaration and Institute regulatory board guidelines, patient consent was obtained and a cross sectional study, conducted from December 2012 to April 2013.

Inclusion criterion was, patients diagnosed as STEMI based on European Society of Cardiology ESC/American College of Cardiology Foundation ACCF/American Heart Association AHA/World Heart Foundation WHF Third Universal Definition of MI Thygesen et al. (2012) while exclusion criteria were that, patients with diagnosis of unstable angina, No ST elevation myocardial infarction (NSTEMI), and STEMI patients who underwent primary Percutaneous Coronary Intervention (PCI).

2.1. Method

At study entry, a relevant history was taken and focused physical examination was done, the data acquired included age, gender, body mass index (BMI), blood pressure, and assessment of risk factors including a history of MI/old coronary vascular atherosclerosis CVA. During baseline evaluation, symptoms were assessed, vitals recorded, Killip class was assessed, and TIMI score was calculated for all patients. Patient's blood samples were drawn at admission to the Critical Care Unit (CCU) for analysis of random blood glucose, renal function test, serum electrolytes, lipid parameters, complete blood count, hs-TnT and HAFBP. An echocardiographic evaluation of the left ventricular ejection fraction (LVEF) was performed in all participants within 24 h of hospital admission.

2.2. Laboratory analyses

Hs-Trop T was measured with the Elecsys Troponin T immunoassay (Roche Diagnostics, Germany), the cut off value used was $0.014 \leqslant$ ng/ml which represented the lowest concentration at which the coefficient of variance (CV) was 10%. An increased hs-Trop T concentration is defined as a value exceeding the 99th percentile of a normal reference population [upper reference limit (URL)] Thygesen et al., 2012.

The H-FABP was measured with the Biochip array technology (Randox Laboratories, Ltd., Co.,Antrim, United Kingdom). As per the manufacturer's claim this biochip uses a high precision assay for measuring H-FABP with 2 mouse monoclonal antibodies with a sensitivity of <2.5 ng/ml and linearity up to 120.0 ng/ml. The 99th percentile cut-off value is $\leqslant$6.32 ng/ml with the inter-assay CV to be $<5\%$ at a concentration of 6.32 ng/ml (99th percentile values). An increased H-FABP concentration is defined as a value exceeding the 99th percentile of a normal reference population [upper reference limit (URL)].

2.3. Statistical analysis

The statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 16.0. (SPSS Inc., Chicago, Illinois). Baseline characteristics were assessed with Student's *t*-test (parametric) and Mann–Whitney *U* test (non-parametric) for continuous variables, and the Chi-square test (χ^2 test) for categorical variables, with two-tailed *P*-values, <0.05 taken as significant. The Mann–Whitney *U* test was used to compare biomarker levels between two independent groups.

3. Results

3.1. Baseline characteristics

Out of total 160 patients analyzed, 142 (88%) were males, 18 (11%) were females, mean age was 54 .31 ± 11. Window period (WP) varied from 0.5 h to 24 h, with a mean WP of 5.15 ± hours. Coronary risk factor frequencies were: high blood pressure in 37% and diabetes in 39%, past history of Ischemic heart disease IHD or CVA present in 11%, current smoking habit present in 54%; family history of IHD present in 2.5% of patients, and dyslipidemia present in 83% of

Table 1 Patient distribution of window period.

Window period	*n*	%
< 3 h	53	33
3–6 h	75	47
> 6 h	32	20
Total	160	10

patients. Elective PCI revealed anterior wall myocardial infarction (AWMI) as most common type of MI occurring in 81 patients (51%). Lateral wall MI (LWMI) was least common type occurring in only 1.2% of patients.

Table 1 shows number of patients based on window period. 53 (33%) patients presented within 3 h, 75 (47%) patients presented between 3 and 6 h, and 32 (20%) patients presented after 6 h. Out of 160 patients, 9 (5.4%) patients had hs-Trop T value ⩽0.01 ng/ml, 26 (16.2%) patients had H-FABP value ⩽6.32 ng/ml (p value < 0.001), in 134 (83.8%) patients both biomarkers were elevated (positive) while in 6 (3.8%) patients both were less than 99th percentile values (negative).

The relation of H-FABP and hs-Trop T with regard to different window periods showed that 53 (33%) patients presented within 3 h of chest pain, among these 4 (7.5%) patients had normal hs-Trop T values whereas 13 (24.5%) patients had normal H-FABP values (p value = 0.015). In this group only 3 (5.7%) patients had normal values for both the biomarkers. Among patients who presented between 3 and 6 h, 4 (5.3%) patients had normal hs-Trop T, whereas 9 (12%) patients had normal H-FABP ($P < 0.0001$). In patients with history of more than 6 h of chest pain there was no significant difference between hs-Trop T and H-FABP values ($p > 0.05$). In this study it has been seen that combined H-FABP and hs-Trop T values were elevated in 49 (30%) patients in ⩽3 h group while only 3 patients had both biomarkers normal. Similarly it is observed that 71 out of 75 patients who presented between 3 and 6 h had both biomarkers elevated only 3 patients had normal values. Among those presenting more than 6 h 27 (16%) had both bio markers elevated.

Statistically significant difference between mean hs-Trop T values with respect to window period < 3 h, 3–6 h, and > 6 h was 0.21, 0.35 and 0.80 ng/ml, respectively, p value < 0.0001. Similarly when we analyzed H-FABP (Table 2) with respect to window periods < 3 h, 3–6 h, and > 6 h, though the mean values increased in these groups respectively, however there was no statistical significant difference among these groups (71.97, 76.36 and 119.95 ng/ml, respectively, $p = 0.206$).

Sensitivity of hs-Trop T and H-FABP with respect to window period is that hs-Trop T was 92% sensitive and whereas H-FABP was 75% sensitive in patients presenting with < 3 h of onset of symptoms, this appears different, than that claimed by the manufacturer. The sensitivity of hs-Trop T and H-FABP in patients presenting between 3 and 6 h was 94% and 88%, respectively. Similarly the sensitivity of hs-Trop T and H-FABP in patients presenting after 6 h was 97% and 84%, respectively. Overall sensitivity for hs-Trop T and H-FABP in this study was 94% and 82%, respectively (Table 3).

Relation of hs-Trop T and H-FABP to various biochemical and clinical co-relations is that, hs-Trop T positively correlates with age ($r = 0.153$, $P = 0.05$), window period ($r = 0.363$, $P < 0.0001$), TIMI score ($r = 0.208$, $P = 0.008$), ejection fraction ($r = 0.191$, $P = 0.008$), serum HAFBP ($r = 0.229$, $P = 0.004$), and serum hs-CRP ($r = 0.326$, $p < 0.001$) .

Similar analysis with H-FABP showed a positive correlation with window period, hs-Trop T ($r = 0.229$, $P = 0.004$), and hs-CRP ($r = 0.986$, $p < 0.001$). There was no correlation between H-FABP and important parameters like age, TIMI score, and ejection fraction.

When we analyzed hs-Trop T and H-FABP with respect to the presence or absence of hospital complications, there was no statistically significant difference between these two biomarkers.

Out of 160 STEMI patients, 9% (15) patients died during their in hospital stay. In hospital mortality and mean values of hs-Trop T, HFABP, and hs-CRP showed no statistically significant difference for H-FABP and hs-CRP values between patients with or without mortality ($p = 0.18$, and $p = 0.81$ respectively Table 4). There was a statistically significant difference of mean hs-Trop T values with or without in-hospital mortality (0.35 vs. 0.85 ng/ml, respectively, $p = 0.008$).

4. Discussion

Cardiac troponin remains the cornerstone in the diagnosis and risk stratification of patients with suspected ACS. One of the important criteria for a biomarker is to help early clinical

Table 2 H-FABP mean values with respect to window period.

Window period	*n*	Mean	Std. deviation	SE of mean	95% CI for mean		Min	Max.	*P*-Value
					Lower bound	Upper bound			
< 3 h	53	**71.97**	173.60	23.85	24.12	119.82	0.22	1178.45	**0.206**
3–6 h	75	**76.36**	78.03	9.01	58.41	94.32	0.77	457.65	
> 6 h	32	**119.95**	140.17	24.78	69.41	170.49	2.77	647.00	

Table 3 showing sensitivity of hs-Trop T and H-FABP.

	WP ⩽ 3 h (%)	WP > 3–6 h (%)	WP > 6 h (%)	Overall sensitivity (%)
Hs-Trop T	92	94	97	94
H-FABP	75	88	84	82
Combined	84	91	92	89

Table 4 Hs-Trop T, H-FABP, hs-CRP and in hospital mortality.

	In hospital mortality	*N*	Mean	Std. deviation	Std. error mean	*P*-Value
H-FABP	Absent	145	73.5712	95.17411	7.90378	0.184
	Present	15	109.5502	108.49279	28.99592	
Hs-CRP	Absent	145	0.7028	0.86859	0.07213	0.816
	Present	15	0.6479	0.39184	0.10472	
Hs-trop T	Absent	145	0.3557	0.62770	0.05231	0.008*
	Present	15	0.8502	0.89294	0.23865	

* indicates value of Hs Troponin T is most significant that other biomarkers.

decision-making and thus influence patient management (Morrow and de Lemos, 2007). Growing number of studies have shown that H-FABP is a sensitive marker for the diagnosis of myocardial infarction (MI) Tanaka et al., 1991; Glatz et al., 1998; Okamoto et al., 2000; Seino et al., 2003. The characteristic release of H-FABP after acute MI is that a rise is detectable as early as 1.5 h after symptom onset, reaches a peak level after 4–6 h and the level returns to baseline within 20 h due to rapid renal clearance (Alhadi and Fox, 2004) H-FABP is present at high concentrations within cardiac myocytes, and at lower concentrations in other tissues such as skeletal muscle, kidney, specific parts of the brain, lactating mammary glands, and placenta (Pelsers et al., 2005). Early assays used antibodies which had high degrees of cross-reactivity with other FABP types. This may have hampered their clinical utility. More modern assays rely on monoclonal antibodies that have shown no or minimal cross-reactivity (Roos et al., 1995).

Whereas troponin's relative large size and location bound within the contractile apparatus of the cardiomyocyte, make its release typically delayed for several hours after the onset of ischemic injury. Thus, blood must be sampled at least 6 h after the onset of ischemic discomfort in order to achieve adequate sensitivity. As such, for a large number of patients without classic symptomatology or electrocardiographic changes, significant irreversible myocardial injury might occur before a definitive therapeutic plan is implemented. In addition, troponin levels might remain elevated for 7–14 days after the initial ischemic insult, thereby limiting sensitivity for detecting recurrent myocardial injury (de Lemos, 2007).

Our study was a cross sectional study, we compared hs-Trop T and H-FABP in patients presenting with STEMI with regard to window period. Also we analyzed these two biomarkers with respect to various in hospital complications and in hospital mortality. This study demonstrated that hs-Trop T is more sensitive than H-FABP in patients who presented to hospital within 6 h. This present study showed that measurement of H-FABP in patients with AMI at the time of admission is useful and complements the measurement of hs-Trop T although Hs-Trop T is a better marker than HFABP. Our study demonstrated no significant difference in levels of both of these markers in the presence or absence of in hospital complications.

In our study we evaluated sensitivity of hs-Trop T and H-FABP with respect to window period. It is seen that hs-Trop T was 92% sensitive and whereas H-FABP was 75% sensitive in patients presenting with <3 h of onset of symptoms. This observation further explains that HFABP did not perform superior to hs-Trop T at <3 h of history of chest pain although it complements the performance. The sensitivity of hs-Trop T and H-FABP in patients presenting between 3 and 6 h was 94% and 88%, respectively, the detection range being somewhat similar in this period. Similarly the sensitivity of hs-Trop T and H-FABP in patients presenting after 6 h was 97% and 84%, respectively. Overall sensitivity for hs-Trop T and H-FABP in this study was 94% and 82%, respectively. Studies evaluating the diagnostic accuracy of H-FABP have reported variable sensitivities and specificities (Ishii et al., 1997; Okamoto et al., 2000; Tanaka et al., 2006; Seino et al., 2003; Glatz et al., 1998; Mad et al., 2007; Valle et al., 2008).

More recently, Mad et al. evaluated H-FABP levels in 280 patients presenting within 24 h of chest pain. H-FABP had a sensitivity of 69% and specificity of 74% (Mad et al., 2007). Valle et al. evaluated 419 patients presenting within 3 h of chest pain, H-FABP had a sensitivity of 60% and specificity of 88% (Valle et al., 2008). Seino et al. evaluated 371 patients with chest pain and suspected MI. H-FABP had a sensitivity of over 90% and a specificity of 50%. Thus all these studies show a widely variable sensitivity and specificity of H-FABP (Seino et al., 2003).

In a study McCann et al. demonstrated that, sensitivity of cTnT for acute MI was 75% (95% CI 69–81). The sensitivity of initial cTnT was at its lowest for patients who presented within 4 h of symptom onset [55% (95% CI 44–66)]. It increased with increasing time from symptom onset to admission, with a sensitivity of 97% (95% CI 83–99) for patients who presented >12 h, the sensitivity of HFABP 73% in, 4 h, 78% >4 h (McCann et al., 2008). In a study done by Koenig et al. (ROMICAT Study) in 377 ACS patients sensitivity, specificity, positive predictive value and negative predictive value of hs-Trop T were 62.2%, 88.9%, 37.7% and 95.6%, respectively. Therefore the variation in performance of HFABP may be due to several other factors and needs larger studies to confirm its utility as an early marker.

In our study hs-Trop T positively correlates with age ($r = 0.153$, $P = 0.05$), window period ($r = 0.363$, $P < 0.0001$), TIMI score ($r = 0.208$, $P = 0.008$), ejection fraction ($r = 0.191$, $P = 0.008$), serum HAFBP ($r = 0.229$, $P = 0.004$), and serum hs-CRP ($r = 0.326$, $p < 0.001$).

Similar analysis with H-FABP shows a positive correlation with window period, hs-Trop T ($r = 0.229$, $P = 0.004$), and hs-CRP ($r = 0.986$, $p < 0.001$). There was no correlation between H-FABP and important parameters like age, TIMI score, and ejection fraction.

There was no statistically significant difference of H-FABP and hs-CRP values between patients with or without mortality ($p = 0.18$, and $p = 0.81$ respectively). There was a statistically significant difference of mean hs-Trop T values with or without in-hospital mortality (0.35 vs. 0.85 ng/ml, respectively, $p = 0.008$), suggesting that higher hs-Trop T level is associated with increased in hospital mortality.

The findings of this study are similar to study done by Matsui et al. the diagnostic and prognostic value of serum level of hs-Trop T relative to H-FABP in the early hours of acute coronary syndrome (ACS) in 460 consecutive patients hospitalized to the cardiac emergency department for suspected ACS within 6 h after the onset of chest symptom. It showed that increased hs-TnT (relative risk 14.5, $P = 0.009$), but not H-FABP, was independently associated with cardiac events. Patients with increased hs-TnT had a higher risk of cardiac events within 12 months compared with those without (14.1% vs. 0.5%, $P < 0.0001$). In that study the sensitivity and specificity of hs-Trop T and H-FABP were 88% and 76% <3 h of presentation respectively and 91% and 76% in patients presenting within 3 to 6 h. Overall sensitivity for hs-Trop T and H-FABP was 90% and 76% respectively (Matsui and Ishii, 2011). Antman et al. studied 597 patients with acute coronary syndrome (ACS), and showed that the composite end point of the sum of death, nonfatal myocardial infarction or recurrent ischemia through day 14 occurred in 33.6% of patients with a positive assay for hs-Trop T compared with only 22.5% of patients with a negative assay ($p < 0.01$) Antman et al., 1998. This finding supports our study that in hospital mortality was higher in patients with higher hs-Trop T values.

The findings of our study are also supported by a study done by Schoos et al. who studied 601 consecutive unselected chest pain patients with 59 (9.8%) acute myocardial infarctions (MI) and showed that in a single sample strategy, admission hs c TnTs are equipotent and superior to copeptin and H-FABP. Hs-TnT has slightly better 'ruling out' and hs-TnI better 'ruling in' capacities in diagnosing MI. In this study numerically best diagnostic strategy was regardless of symptom onset, the combination of hscTnI and H-FABP (Mikkel, 2013).

Dekker et al. in a study of 486 ACS suspected patients presenting to the emergency department within 24 h of symptom onset, showed that H-FABP testing improves diagnostic accuracy in addition to clinical findings and ECG. H-FABP however, has limited clinical diagnostic value in addition to cTnI measurements in daily practice (Dekker et al., 2011).

There are various studies which support the role of H-FABP in both diagnosis and prognosis of patients with acute coronary syndrome. In a study done by McCann et al. in patients with ACS showed that sensitivity of H-FABP for acute MI was superior to cTnT for patients admitted within 4 h of symptom onset. For patients who were admitted 4 h or more following symptom onset there was no significant difference between the sensitivity of H-FABP and cTnT. The results of this trial supported the use of H-FABP, measured in combination with cTnT at the time of admission, to improve upon early detection of acute MI. This combined approach (either marker elevated) significantly improved sensitivity for acute MI of patients admitted within 12 h of symptom onset (McCann et al., 2008).

In another study Kilcullen et al. evaluated the prognostic utility of H-FABP in a registry of 1448 patients with ACS from West Yorkshire, United Kingdom. Heart type fatty acid-binding protein was powerfully and independently associated with the risk of death when measured within 12–24 h of symptom onset after ACS. Moreover, H-FABP identified subjects at increased risk of death even when troponin levels were normal (Kilcullen et al., 2007).

In a study Kilcullen et al. showed that the occurrence of a negative test result for both TnI and H-FABP was associated with zero mortality (no deaths) before 6 months. This appears to represent a particularly worthwhile clinical outcome, especially because it was observed in patients admitted into hospital for suspected ACS. Such an observation would give confidence to physicians assessing unselected suspected ACS patients in the emergency room, particularly if reproduced using much earlier blood samples (Kilcullen et al., 2007).

In a study done by Viswanathan et al. in 1080 patients consecutively admitted to the hospital with suspected ACS the H-FABP concentration was an independent predictor of death or myocardial infarction, after multivariate adjustment. Patients with H-FABP concentrations >6.48 μg/l had significantly increased risk of adverse events (adjusted hazard ratio: 2.62, 95% confidence interval: 1.30–5.28, $p < 0.007$). Among troponin-negative patients (which constituted 79.2% of the cohort), the aforementioned cutoff of 6.48 μg/l identified patients at very high risk of adverse outcomes (Viswanathan et al., 2010).

4.1. Study limitations

Limitations of the present study include the fact that we studied a high-risk cohort of patients with confirmed ACS (STEMI) and the results presented may not necessarily be applicable to lower risk populations, such as all patients with chest pain presenting to the emergency department. Second limitation was the single blood sample taken for the study. Sequential measurements were not investigated. Third limitation of the study was small sample size. This is still an early evaluation of H-FABP in terms of diagnostic utility more studies, clinical, and scientific questions remain to be answered, and further large scale studies are required to assess the diagnostic ability of H-FABP.

5. Conclusion

Our study was intended to confirm the theoretical report that HFABP is a better marker to be used in the emergency setting for patients with history of chest pain, but our research suggests that hs-Trop T appears to have better sensitivity as a biomarker than H-FABP in early hours of STEMI acute myocardial infarction. Compared to HFABP an abnormal increase or levels of hs-Trop T is a better predictor of increased in-hospital mortality. Therefore measurement of H-FABP in patients with acute myocardial infarction at the time of admission is useful and complements the measurement of hs-Trop T. Since a better confirmation of the diagnosis can be made with HFABP and hs-Trop T, using these markers together maybe beneficial.

Disclosure

The study has been independently carried out at Jayadeva Institute of cardiology. There was no funding from any source, HFABP has been give free of cost by Randox U.K. and Roche India has supplied the Hs-Troponin T assay Kit. We are grateful to Mr. Shivkumar of the department of Biochemistry and Mr. Thejesvi for carrying out the statistical analysis of the work.

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