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Original Article

Could heart-type fatty acid binding protein predict clinical outcome in coronary artery bypass graft surgery?

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Abstract

Background: Detection of myocardial damage and its degree during open heart surgery were studied previously using different biomarkers. Heart fatty acid binding protein (h-FABP) was used in the diagnosis of myocardial infarction with variable results. In this study, we aimed to find the possibility of the use of this biomarker as a predictor of myocardial damage after coronary artery bypass graft (CABG) surgery.

Methods: We conducted a prospective study on 47 patients who had CABG surgery. Blood samples (4 ml) were drawn from patients at 5 points: before induction of anesthesia, after aortic declamping, 1 hour after declamping, 6 hours after declamping and one day after surgery. Levels of h-FABP and creatine kinase muscle/brain (CK-MB) were estimated, and the relationship between h-FABP and operative and postoperative outcomes were recorded.

Results: There were statistically significant correlations between higher levels of h-FABP measured immediately after aortic declamping and need for intra-aortic balloon (116.55 + 9.26 vs, 84.34 + 19.55 ng/ml; p= 0.022), inotropes (107.04+ 14.79 vs, 79.95 + 17.59ng/ml; p< 0.001), defibrillators (97.73 + 15.18 vs 81.59 + 20.31 ng/ml; p=0.016), and postoperative atrial fibrillation (99.94 + 17.83 vs 80.84 + 18.89ng/ml; p= 0.004). No mortality was detected in our study. h-FABP levels showed an early peak just after aortic declamping and reached baseline by postoperative day one. CK-MB peaked 1 hour after aortic declamping and remained elevated for more than 24 hours.

Conclusion: h-FABP is a cardiac biomarker that could be used as a rapid indicator of ventricular dysfunction and atrial fibrillation post-CABG surgery.

KEYWORDS
Heart fatty acid binding protein (h-FABP); Coronary artery bypass graft (CABG) surgery; Myocardial injury; CK-MB

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Introduction

Detecting myocardial dysfunction during the reperfusion phase after coronary artery bypass grafting (CABG) significantly affects patient management as it can predict the need for inotropic support or assisted devices during weaning from cardiopulmonary bypass (CPB) [1, 2]. Detection of myocardial damage and its degree during open heart surgery were studied previously using different biomarkers such as creatine kinase

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muscle/brain (CK-MB) and troponin I. However, these biomarkers peak several hours after surgery and return to normal values several days after the operation which limits their role after cardiac surgery [3].

Heart fatty acid binding protein (h-FABP) is a small hydrophilic protein found in cardiomyocytes that leaks rapidly after myocardial damage with early clearance from circulation [4]. Heart fatty acid binding protein was used in the diagnosis of myocardial infarction and myocardial injury with variable results [5]. Currently, the role of h-FABP in cardiac surgery is limited; however; it emerged as a potential outcome predictor for cardiac disease and after surgery [6].

In this study, we aimed to find the relation between h-FABP levels and the degree of myocardial damage after CABG surgery by studying its correlation with different outcomes. Additionally, we evaluated the possibility of using this biomarker as a predictor of ventricular dysfunction after CABG.

Patients and Methods:

Design and Patients:

This study was a prospective cohort study conducted on 47 patients who had CABG during six months period from January 2018 till June 2018. Patients who had an emergency, redo surgery, and those with combined valve and CABG surgery were excluded. Informed consent was taken from all patients, and the local Ethical Committee approved it.

Data and technique:

All patients enrolled in the study were subjected to complete examination, including full history taking, routine laboratory investigations, preoperative electrocardiography (ECG), echocardiography, and coronary angiography. All vessels showing more than 70% stenosis were bypassed.

All patients were subjected to standard median sternotomy, cardiopulmonary bypass via direct aortic cannulation and right atrial cannulation. Antegrade crystalloid cardioplegia was given, and surgery was done under hypothermic cardiac arrest. Left internal mammary artery (LIMA) was harvested to bypass left anterior descending (LAD) artery, and saphenous vein grafts were used to bypass other vessels. All distal anastomoses were done under complete cardiac arrest, and proximal anastomoses were done using partial aortic cross-clamp. After removal of the aortic clamp, an electrical defibrillator was used if there was ventricular fibrillation [7].

After adequate hemostasis, the chest was closed in a routine manner, and patients were transferred into the intensive care unit (ICU). Postoperative complications including prolonged mechanical ventilation, renal dysfunction defined as doubling of preoperative creatinine level [8], need for inotropes, neurological insults, and atrial fibrillation (AF) were recorded.

Cardiac biomarkers assay:

Blood samples (4 ml) were drawn from patients at 5 points: before induction of anesthesia, after removal of the aortic clamp, one hour after declamping, 6 hours after declamping, one day after surgery. Blood samples were collected in a Becton Dickinson BD® vacutainer serum separator tube. The separated serum samples after centrifugation were divided into two portions. The first portion was collected for assessment of creatine kinase muscle/brain (CK-MB) activity. The second portion was collected and stored at -70 °C until h-FABP levels were assessed. The serum levels of h-FABP were measured by enzyme-linked immunosorbent assay kits, according to the manufacturer's instructions (Shanghai Sun red Biological Technology®, China), using Awareness Technology® (USA) ELISA Reader. h-FABP concentration was expressed in ng/ml.

CK-MB activity was determined by immune-inhibition UV method, according to the manufacturer's instructions (BioSystems®, Spain), using Shimadzu® (Japan) Spectrophotometer. CK-MB activity was expressed in U/L. Relations between levels of h-FABP and postoperative outcomes were assessed. Additionally, the relationship between CK-MB and h-FABP levels was studied.

Statistical analysis:

Statistical analysis was performed using SPSS (statistical package for social sciences) version 23 (SPSS, Chicago, IL, USA). Data were expressed as numbers and frequencies for categorical variables and mean+ standard deviation (SD) or median and range for continuous variables.

Table 1: Patients characters, operative and postoperative data. (Continuous variables are presented as mean± SD and categorical variables as number and percent)

	N= 47
Age (years, mean ± SD)	57.45 + 8.28
Sex (Male)	32 (68.1%)
Diabetes mellitus	19 (40.4%)
Hypertension	26 (55.3%)
History of myocardial infarction	6 (12.8%)
Preoperative ejection fraction (%, mean ±SD)	53.49 + 6.14
Pre-renal dysfunction	2 (4.3%)
Number of anastomosis [median (range)]	3 (1-4)
Cardiopulmonary bypass time [min, median (range)]	90 (50-160)
Aortic cross clamp time (min, mean ± SD)	62.34 + 16.08
Need for intra-aortic balloon	2 (4.3%)
Need for defibrillator	12 (25.5%)
Need for >2 inotropes in ICU	10 (21.3%)
Duration of mechanical ventilation [hours, median (range)]	6 (3-72)
Postoperative atrial fibrillation	12 (25.5%)
Postoperative renal dysfunction	4 (8.5%)

ICU: Intensive care unit

Continuous variables were compared using student's t-test. For non-parametric data, Mann-Whitney U test was used instead. Correlations between serum levels of h-FABP and preoperative, operative, and postoperative data were performed using Pearson's correlation coefficient for normally distributed data and Spearman' s rank correlation coefficient for non-normally distributed. P values < 0.05 were considered statistically significant.

Results

Thirty-two patients were male (68%), and the mean age was 57.45+8.28 years. Forty percent of patients were diabetic (n=19), and 55% were hypertensive (n=26). The number of anastomoses used ranged from 1-4 with a median of 3, whereas cardiopulmonary bypass (CPB) time ranged from 50-160 minutes with median of 90 minutes. Cross-clamp time was 62.34+16.08 minutes. Two patients needed an intra-aortic balloon, and ten patients needed more than two inotropes as indicators of left ventricular dysfunction. Patients' characters, operative data, and postoperative complications were demonstrated in Table 1.

Correlations between serum levels of h-FABP and preoperative, operative and postoperative data are shown in Table 2 - 4. The level of h-FABP was not correlated with any of the preoperative patients' characteristics, CPB or ischemic times. There were statistically significant correlations between higher levels of h-FABP measured immediately after aortic declamping and need for intra-aortic balloon (116.55 + 9.26 vs, 84.34 + 19.55 ng/ml; p= 0.022) inotropes (107.04+ 14.79 vs, 79.95 + 17.59ng/ml; p< 0.001)

Table 2: Correlation between serum levels of hFABP (ng/ml) and preoperative data.

	Before induction	after aortic declamping	1 hour after declamping	6 hours after declamping	POD 1
Age (years)					
r	0.244	0.34	0.001	0.099	0.017
P value	0.098[a]	0.820[a]	0.995[a]	0.202[a]	0.198[a]
Sex					
Male	3.32 ± 1.02	86.95 ± 19.89	77.89± 19.25	43.77 ± 8.22	14.92 ± 4.96
Female	3.43 ± 0.86	83.07 ± 21.48	71.98 ± 18.06	40.97 ± 9.47	13.92 ± 4.88
P value	**0.678[c]**	**0.546[c]**	**0.322[c]**	**0.307[c]**	**0.520[c]**
Diabetes mellitus					
Yes	3.38 ± 1.22	82.42 ± 17.19	73.29 ± 14.88	42.07 ± 8.09	13.71 ± 4.21
No	3.33 ± 0.77	87.95 ± 22.13	77.85 ± 21.24	43.42 ± 9.10	15.21 ± 5.32
P value	**0.853[c]**	**0.364[c]**	**0.422[c]**	**0.606[c]**	**0.310[c]**
Hypertension					
Yes	3.26 ± 0.92	88.72 ± 21.13	78.94 ± 20.48	44.07 ± 8.73	15.46 ± 5.12
No	3.45 ± 1.03	81.99 ± 18.97	72.37 ± 16.47	41.39 ± 8.49	13.54 ± 4.52
P value	**0.506[c]**	**0.262[c]**	**0.240[c]**	**0.295[c]**	**0.184[c]**
History of myocardial infarction					
Yes	2.95 ± 1.08	91.72 ± 22.94	79.17 ± 18.82	45.13 ± 7.63	15.82 ± 5.39
No	3.41 ± 0.95	84.84 ± 20.00	75.55 ± 19.08	42.54 ± 8.81	14.42 ± 4.88
P value	**0.202[d]**	**0.426[d]**	**0.630[d]**	**0.426[d]**	**0.408[d]**
Pre-renal dysfunction					
Yes	3.05 ± 0.78	92.50 ± 23.33	81.00 ± 15.56	45.85 ± 7.57	16.50 ± 5.52
No	3.36 ± 0.98	85.41 ± 20.36	75.79 ± 19.14	42.74 ± 8.74	14.52 ± 4.93
P value	**0.703[d]**	**0.566[d]**	**0.599[d]**	**0.599[d]**	**0.566[d]**
Pre-operative ejection fraction (%)					
r	0.123	-0.050	-0.032	-0.001	-0.045
P value	0.409[a]	0.737[a]	0.083[a]	0.413[a]	0.141[a]

* Statistically significant (p < 0.05)
a Pearson correlation coefficient
c Student's t-test
d Mann-Whitney U test
POD: Postoperative day

defibrillators (97.73 + 15.18 vs 81.59 + 20.31 ng/ml; p=0.016) and postoperative atrial fibrillation (AF) (99.94 + 17.83 vs 80.84 + 18.89ng/ml; p= 0.004). No mortality was detected in our study.

The change in levels of h-FABP and CK-MB was different as illustrated in Figure 1. h-FABP showed early peak just after aortic declamping and reached the baseline by postoperative day one; whereas, CK-MB peaked 1 hour after aortic declamping but did not reach baseline after 24 hours.

Discussion

Early recognition of perioperative myocardial damage is essential to prevent complications post-CABG surgery [9, 10]. Different biomarkers were used for the detection of myocardial damage like CK-MB, myoglobin, lactate dehydrogenase (LDH), brain natriuretic peptide, and troponin [11].

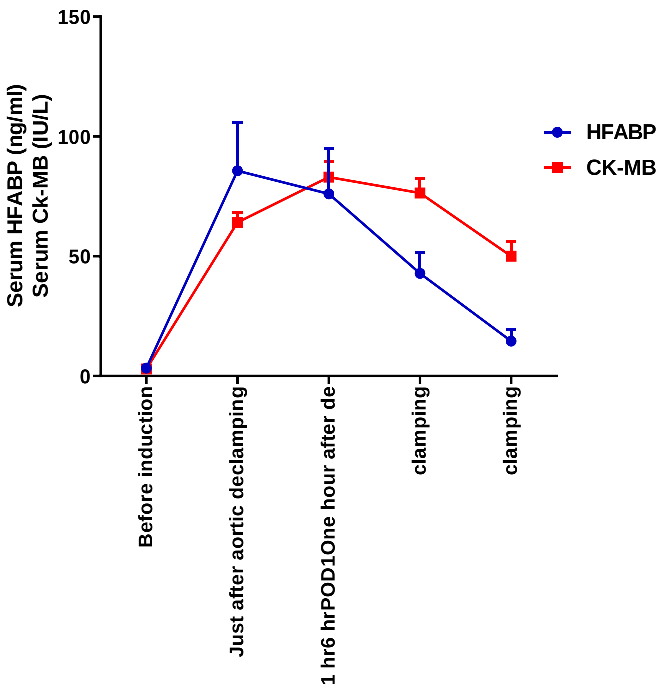

Figure 1: Difference between hFABP and CK-MB regarding rising and falling pattern during and after surgery.

Each biomarker has its drawbacks, and the predictability of each biomarker varies widely in clinical practice. h-FABP is a small cardiomyocyte protein consisting of 132 amino acid which is abundant in the cytoplasm. When myocardial damage occurs, it is released into the extracellular space, and as a result of its small size, water solubility, and physical properties, it enters the blood compartment in a rapid manner [12]. In the 1990s, h-FABP was used in early diagnosis of myocardial infarction with different modes of release comparable with other markers as it peaks early and declines early. However; owing to lack of availability and tissue specificity studies, its clinical application was limited. The value of h-FABP in cardiac surgery was restricted to small studies [13]. In our study, we measured h-FABP at 5 points when samples could be easily drawn without interruption to medical staff. We found that maximum peak occurred just after removal of the aortic clamp and declined earlier than CK-MB. Petzold and colleagues recommended drawing samples when ICU staff having time for sophisticated investigations [14].

Table 3:Correlation between serum levels of hFABP (ng/ml) and operative data

	Before induction	After aortic declamping	1 hour after declamping	6 hours after declamping	POD 1
Number of anastomoses					
r	0.170	0.033	0.056	0.043	0.309
P value	0.254[b]	0.826[b]	0.708[b]	0.772[b]	0.792[b]
Cardiopulmonary bypass time (min)					
R	0.141	0.124	0.138	0.135	0.131
P value	0.586[b]	0.358[b]	0.259[b]	0.394[b]	0.341[b]
Aortic cross-clamp time (min)					
R	0.069	0.190	0.191	0.161	0.179
P value	0.644[a]	0.200[a]	0.199[a]	0.206[a]	0.929[a]
Need for intra-aortic balloon					
Yes	3.90 ± 1.56	116.55 ± 9.26	102.55 ± 14.92	53.40 ± 1.98	22.50 ± 2.83
No	3.32 ± 0.95	84.34 ± 19.55	74.83 ± 18.29	42.41 ± 8.53	14.25 ± 4.69
P value	**0.535[d]**	**0.022*[d]**	**0.067*[d]**	**0.030*[d]**	**0.022*[d]**
Need for defibrillator					
Yes	3.53 ± 1.09	97.73 ± 15.18	86.90 ± 14.51	48.73 ± 4.51	17.62 ± 3.67
No	3.28 ± 0.93	81.59 ± 20.31	72.27 ± 18.93	40.87 ± 8.84	13.57 ± 4.89
P value	**0.444[c]**	**0.016*[c]**	**0.019*[c]**	**0.005*[c]**	**0.012*[c]**

* Statistically significant ($p < 0.05$)
[a] Pearson correlation coefficient
[b] Spearman rank correlation coefficient
[c] Student's t-test
[d] Mann-Whitney U test
POD: postoperative day

Table 4: Correlation between serum levels of hFABP (ng/ml) and postoperative data

	Before induction	After aortic declamping	1 hour after declamping	6 hours after declamping	POD 1
Need for > two inotropes in the intensive care unit					
Yes	3.74 ± 1.10	107.04± 14.79	97.20 ± 14.31	51.44 ± 2.87	20.05 ± 3.79
No	3.24 ± 0.91	79.95 ± 17.59	70.33 ± 15.77	40.56 ± 8.21	13.13 ± 4.08
P value	**0.148[d]**	**<0.001*[d]**	**<0.001*[d]**	**<0.001*[d]**	**<0.001*[d]**
Duration of mechanical ventilation (hours)					
P value	**0.319[b]**	**<0.001*[b]**	**<0.001*[b]**	**<0.001*[b]**	**<0.001*[b]**
Postoperative atrial fibrillation					
Yes	3.45 ± 1.01	99.94 ± 17.83	87.05 ± 15.38	48.47 ± 5.50	17.83 ± 4.35
No	3.31 ± 0.96	80.84 ± 18.89	72.22 ± 18.66	40.96 ± 8.74	13.49 ± 4.63
P value	**0.672[c]**	**0.004*[c]**	**0.017*[c]**	**0.008*[c]**	**0.007*[c]**
Postoperative renal dysfunction					
Yes	3.2 ± 0.98	89.62 ± 29.40	77.40 ± 27.17	42.75 ± 11.67	7.24 ± 3.62
No	3.36 ± 0.97	85.35 ± 19.66	75.88 ± 18.38	42.89 ± 8.49	4.75 ± 0.72
P value	**0.783[d]**	**0.927[d]**	**0.840[d]**	**0.927[d]**	**0.927[d]**

* statistically significant ($p < 0.05$)
[b] Spearman rank correlation coefficient
[c] Student's t-test
[d] Mann-Whitney U test
POD= Postoperative day

Suzuki and associates were the first to investigate h-FABP in CABG surgery and reported a significant correlation between its value and postoperative myocardial damage [15]. Two studies later discussed the role of h-FABP as a predictor of clinical outcome in pediatric cardiac surgery. Evers and colleagues found a weak correlation between h-FABP and clinical outcomes [16]. However, Hasegawa and colleagues found it as a rapid prognostic indicator of myocardial damage post pediatric cardiac surgery [17].

In our study, we found statistically significant correlations between elevated levels of h-FABP after aortic declamping and the need for 2 or more inotropes post-surgery. This is similar to the study carried out by Muehlschlegel and associates. They used the requirement for inotropes as an indicator of ventricular dysfunction [18]. This could explain the increased requirement of patients with high levels of h-FABP for intra-aortic balloons and defibrillators. By comparing peaks of perioperative h-FABP and CK-MB, this study was in agreement with Suzuki, Petzold and Muehlschlegel and their colleagues. They demonstrated that CK-MB peaked 1 hour after aortic declamping, making its role limited to the prognosis [14, 15, 18]. Therefore, quantitative measurement of h-FABP can detect the severity of myocardial injury early during cardiac surgery [19]. We found no relations between serum levels of h-FABP and aortic cross-clamp time and cardiopulmonary bypass time. This was in contrast to the results reached by Evers and associates who found a weak correlation between CPB time and h-FABP levels [16]. In the present work, postoperative AF was significantly associated with increased levels of h-FABP. This was similar to Rader and associates who reported a strong relation between ischemic myocardial damage and postoperative AF [20]. There were no statistically significant correlations between higher levels of h-FABP and postoperative renal dysfunction. This was in contrast to Schaub and colleagues who found statistically significant associations between plasma levels of h-FABP and acute kidney injury following cardiac surgery.

Additionally, Kavsak and associates detected cutoff points for identification of acute kidney injury following cardiac surgery [21, 22].

The difference in the predictive value of h-FABPamong various studies could be attributed to the difference in patients' characteristics and the operation performed. However, these studies demonstrated the possibility of using h-FABP in predicting outcomes after cardiac surgery. This biomarker has an advantage over the commonly used CK-MB as it tends to peak and decline early. Therefore, the change in its level would be strongly related to the degree and extent of myocardial damage.

Limitations:

The limitations of this study are a small number of patients included, and the short postoperative follow-up period limited to the hospital stay. Additionally, this is a single center experience, and generalization of the results is an issue. However, the study explored the feasibility of using h-FABP as a biomarker predicting the hospital outcomes after CABG; more extensive studies with longer follow up periods are required.

Conclusion

h-FABP is a cardiac biomarker that could be used as a rapid indicator of ventricular dysfunction and atrial fibrillation post-CABG surgery. It could be used as a routine marker during cardiac surgery.

Conflict of interest: Authors declare no conflict of interest.

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