Australasian Medical Journal AMJ 2010, 3, 11, 691-694

Importance of Cardiac FABP as diagnostic marker of ischaemic heart injury in conjunction with chronic liver disease: A cohort study

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RESEARCH

Please cite this paper as: Hussain.T, Shu L.Y and Sosorburam. T. Importance of Cardiac FABP as diagnostic marker of ischaemic heart injury in conjunction with chronic liver disease: A cohort study. AMJ 2010, 3, 11, 691-694.
Doi 10.4066/AMJ.2010.424

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Abstract

Background
Cardiac-fatty acid binding-protein(C-FABP) is a potential marker for the early diagnosis of acute myocardial infarction (AMI), and is one of the abundant proteins in heart.It is not totally Heart bound and is also found in liver, skeletal muscle, kidney and brain.Over or under calculation of the levels of C-FABP is because of its simultaneous co-expression with hepatic-FABP and solely cardiac-FABP in brain. Due to the rising incidence of chronic liver diseases CLD among cardiac patients,serum markers may crossover and create confusions while making the diagnosis, so the aim of this study was to demarcate the behaviour of fundamental serum markers of both diseases , specially when the two diseases coexists simultaneously.

Method
This study was carried at Union Hospital, Tongji Medical College,Wuhan,China over a period of about 1year from January2009 to January2010.A total of 100 patients were recruited. Study group included 50 patients with end stage chronic liver disease CLD, mean age 56.16±7.24 years.60%(n=30) were females.The control group included 50 participants who were healthy blood donors, mean age 61.34 ±9.76 years.Patients with cardiovascular complications like uncontrolled blood pressure, chronic ischaemic cardiomyopathies, cardiac cirrhosis, endocrine disorders, renal failure, ischaemic hepatitis and thyroid problems were excluded from the study. Serum levels of ALT,AST, Bilirubin and H-FABP were measured.Results were analyses statistically by using SPSS-12 and were compared by using ANOVA-Analysis.Significant results were indicated by probability values less than or equal to 0.05.

Results
Only hepatic markers, Alanine aminotransferase ALT (196.37 ±127.8 Study group Vs 27.6 ±16.5 Control group, $p < 0.0005$) and serum Bilirubin(104.79 ±84.3 Study group Vs 10.4 ±3.6 Control group,$p < 0.0001$) were statistically significantly raised among study group in comparison to control group. There was no significant difference between the concentration of C-FABP in the study group and controls (6.54 ±2.8Study group Vs 6.88 ±2.4 Control group, p=NS).

Conclusion
The concentration of C-FABP in those with liver disease was not statistically different from normal controls indicating that Liver-FABP (L-FABP) is a separate factor with negligible or no cross-reactivity with C-FABP assays. Measurement of C-FABP in the first 24 hours after onset of symptoms may be potentially useful for the diagnosis of Acute Myocardial Infarction in patients with chronic liver diseases.

Key Words
Cardiac Fatty Acid Binding Proteins(C-FABP)
Acute Myocardial Infarction (AMI)
Chronic Liver Disease (CLD)

Background

Acute coronary syndrome especially myocardial infarction is diagnosed clinically either by electrocardiographic changes or raised relevant serum markers commonly including Trop-T and CPK-Mb or by the combination of both. While discussing chemical markers of acute MI, another factor called Cardiac-FABP has got recent fame. Cardiac-fatty acid binding-protein (C-FABP) has been reported to be a potential novel biochemical marker for the early diagnosis of acute myocardial infarction (AMI) [1].Actually the fatty-

acid-binding proteins (FABPs) include a group of carrier proteins specially for fatty acids and other compounds like eicosanoids and retinoids.[2] These proteins facilitate the transfer of fatty acids between extracellular and intracellular membranes.[3] Some are also believed to transport lipophilic molecules from outer cell membrane to certain intracellular receptors.[4] The distribution of FABPs in the body is shown in Table 1.

Table 1: FABP Categorical distribution sites in the Body

No	Protein name	Tissue distribution
1	FABP 1	Liver/Hepatic
2	FABP 2	Intestine/Gut
3	FABP 3/C-FABP*	Heart and Muscle*
4	FABP 4	Adipocyte/Fat
5	FABP 5	Adipocyte/Fat
6	FABP 6	Ileum
7	FABP 7	Brain/CNS
8	FABP 8	Peripheral nervous system

Cardiac- fatty acid binding protein (C-FABP) is composed of 132 amino acids [5] and is one of the most abundant proteins in the heart comprising 5-15% of the total cytosolic protein pool [6-7]. It is not totally cardiac specific and also found in skeletal muscle in concentrations varying between 0.05-0.2 mg per gram, depending on muscle fibre type. [8]. It has also been reported in very low concentrations in tissues like the kidney, aorta, testes, mammary glands, placenta, brain, adrenal glands, adipose tissue, and stomach. [9-10]

Under normal circumstances, the plasma concentration of cardiac-FABP is usually below 5 µg/L, but soon after the injury especially with ischemia, its concentration begins to rise till significant levels for diagnosis of cell damage can be measured [11] and this becomes the basis for making the detection and estimation of severity of cellular injury primarily in the myocardiocytes.Clinically, the measurement of cardiac-FABP in earliest 12 to 24 hours of the onset of cardiac symptoms may be potentially useful for the diagnosis and prognosis of patients with acute myocardial infarction; along with the identification of patients who need reperfusion treatment early; identification of patients who reperfuse their infarct related artery; detection of re-infarction if it occurs early, and estimation of infarct size. . [12]

One problem that gives rise to either over or under calculations of the levels of cardiac FABP is the simultaneous co-expression of cardiac-FABP and hepatic-FABP in kidney and solely cardiac-FABP in brain. This study was the continuation of the previous study carried out under the title, cardiac parameters among end stage liver diseased patients. [13] Due to the rising number of chronic liver disease CLD patients conjugated with myocardial diseases in Asia ,serum markers may crossover and create complicated confusions while making exact diagnosis, so focus was given to demarcate the behaviour of fundamental serum markers of both diseases , specially when the two diseases coexists simultaneously. The presence of C-FABP in the liver has not been reported. However, an isoform specific to the liver called liver-type FABP exists. [14]. The interferences of this protein and chronic liver diseases on the concentration of C-FABP along with the release of C-FABP from other tissues have not yet been fully evaluated. [15]. Therefore; the basic aim of this study was to evaluate the effect of chronic liver disease on the normal concentration of C-FABP so as to make a formulation for the standardization of using C-FABP as a marker of cardiac injury especially in coexistence with hepatic diseases.

Method

This study was carried out at Medical department of Union Hospital, Tongji Medical College, and Wuhan, China over a period of about 1 year from January 2009 to January 2010.Cardiology and gastroenterology departments collaborated simultaneously in addition to the clinical laboratory medicine department of the hospital.

This study recruited a total number of 100 patients, 50 each in study and the control groups. Study group (50n) comprised of patients having chronic liver diseases (CLD) .Mean age 56.16 ±7.24 years.60 %(n=30) were females. All the subjects were end stage liver disease patients presenting with a variety of conditions including infective hepatitis and cirrhosis. But none of them were a case of ischaemic hepatitis or cardiac cirrhosis. They were further subdivided based on aetiology of CLD. 20 patients were with chronic hepatitis B and hepatitis C.Almost 15 patients were in complications of Alcoholic hepatitis end stage and the same number with cirrhosis due to miscellaneous causation. The control group included 50 participants who were healthy blood donors. Mean age 61.34 ±9.76 years. Patients with cardiovascular complications like uncontrolled blood pressure, valvular heart diseases, chronic ischaemic cardiomyopathies, endocrine disorders, renal failure, stroke and thyroid problems were excluded from the study.

Informed consent was obtained from each participant of the study. Serum levels of ALT, AST, Bilirubin and H-FABP were measured in the study group and were compared with the controls. H-FABP was analyzed by an enzyme linked immunosorbent assay method (ELISA). ALT, AST and Bilirubin were measured on an automated analyzer. Results were analyses statistically by using SPSS-12.The study and control groups were compared by using ANOVA-Analysis. Significant results were indicated by probability values less than or equal to 0.05.

Results

Our study indicates that there is no significant difference between the concentration of C-FABP in the study group and controls; however, the concentrations of liver enzymes and protein (ALT and Bilirubin) were significantly elevated in the study group. The results are tabulated in Table 2.

Table 2: Age and concentrations of marker proteins in the control and study groups

No	Factors	Total	Study Group (Liver Disease)	Control group (Blood Donors)	P-Value
1	Patient .No	100	50	50	-
2	Age	-	56.16±7.24	61.34±9.76	NS
3	Bilirubin	-	104.79 ±84.3	10.4 ±3.6	< 0.0001
4	ALT	-	196.37 ±127.8	27.6 ±16.5	< 0.0005
5	C-FABP	-	6.54 ±2.8	6.88 ±2.4	NS

The rising level of hepatic markers among study group is obvious because of deranged hepatic functions due to chronic inflammatory and cirrhotic processes.

Discussion

The data clearly show that there is no significant relationship with the normal concentration of C-FABP among end stage liver disease patients, despite the significant elevation of liver enzymes and proteins. This is consistent with the reduced cross-reactivity between C-FABP and other FABP including L-FABP. These findings may support a useful role of C-FABP for the diagnosis of myocardial injury in patients with chronic liver diseases.

C-FABP was first introduced by in 1988 as a potential marker for the early diagnosis of acute myocardial infarction (AMI) [1]. Soon it was confirmed in many other studies [8-16, 17, 18, and 19]. It has also found to be in relationship as the biomarker for stroke [20-21]. Some recent studies have questioned the value of these early markers (C-FABP and myoglobin) when compared with specific markers like cardiac troponin I (cTnI) [22]. C-FABP is released into plasma within 2 hours after symptom onset and is reported to peak at about 4-6 hours and return to normal base line value in 20 hours [17]. Within the period of 30-210 minutes after symptom onset, C-FABP has > 80% sensitivity for the diagnosis of AMI [23] . Within the interval of 0-6 hours after symptom onset, the other cardiac markers such as creatine kinase (CK), CK-MB mass or activity, cTnI and T (cTnT) will only be starting to accumulate in the plasma, and their sensitivity has been reported to be around 64% [24] . Kidney may be the major route of excretion of C-FABP from circulation. A rise in serum and urine C-FABP concentration above normal values is seen in patients who present with AMI as early as 1.5 hours after symptom onset[25] .Studies in animals have also shown decreased myocardial tissue content and rising plasma and urine concentrations of C-FABP very early after coronary artery ligation [26-27] .C-FABP circulates for a longer time (> 25 hours) after AMI in the presence of renal failure[23].

The concentration of C-FABP in the study group was not statistically different from the control group. This finding leads to several assumptions. First, the Liver-FABP (L-FABP) is a separate factor with no or negligible cross-reactivity with C-FABP assays. Indeed, the cross-reactivity between these two proteins has been reported to be < 0.005 [15] . Second, the release of C-FABP from other tissues containing this protein is at best minimal in patients who have chronic liver diseases.

Previous studies have shown the major limitations for the use of C-FABP concentration for the diagnosis of myocardial injury in the presence of renal failure [28] . Applications of these proteins have been demonstrated for liver rejection, inflammatory and ischaemic bowel disease, traumatic brain injury and in the prevention of muscle injury in trained athletes.[29] Measurement of C-FABP in the first 24 hours after onset of symptoms may be potentially useful for the diagnosis of AMI; identification of patients who need reperfusion treatment early; identification of patients who reperfuse their infarct related artery; detection of re-infarction if it occurs early, and estimation of infarct size. [12]

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ACKNOWLEDGEMENTS

Mrs.Roshan Ara, Muhammad Ismail Anwar, Dr.Abbas Hayat, Engg, Tajammul Hussain and Dr.Aamra Sartaj

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

None