Heart-Type Fatty Acid-Binding Protein (H-FABP) in Patients with Coronary Artery Bypass Graft Surgery Undergoing Cardiac Rehabilitation Program

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Heart-type Fatty Acid-Binding Protein (H-FABP), compared with classical biomarkers, proved to have high sensitivity for myocardial damage size in patients undergoing cardiac surgery. High H-FABP levels are strongly associated in case of death, post-operatively acute kidney injury and atrial fibrillation. Cardiac rehabilitation is an instrument of medical management in cardiovascular diseases; beyond prevention, it can improve heart and muscle functioning in patients that were undergoing CABG, and cardiac and vascular adaptation. Over a 2-year period, 110 subjects were randomized and comprehensively evaluated. The mean age of the patients under study was 65.70 ± 9.91 years old. For the H-FABP, the mean value in the Phase I was 67.40 ± 9.81 ng/mL, while the mean value in Phase III was 4.80 ± 2.30 ng/mL. The difference registered between the plasma H-FABP value in the first 24 h after cardiac surgery and the value in 6 months after the onset of cardiac rehabilitation program was important and statistically significant, as $p < 0.05$. Fibrinogen showed significant phase-to-phase reductions of plasmatic values. Lipid profile values showed a statistically significant decrease. The renal filtration function evaluated by plasma creatinine showed statistically significant improvement and, in terms of absolute values, creatinine level was reduced in a range between 0.2-0.4 mg/dL. Also, it was recorded a significantly lower level of blood urea. The reduction of plasma H-FABP values were registered between the first phase (the first 24 h) after cardiac surgery and the third phase of the cardiac rehabilitation program. H-FABP protein had a higher sensitivity and specificity when compared to other enzymes of myocardial cytolysis.

Keywords: heart-type fatty acid binding protein, coronary-artery bypass graft, cardiac rehabilitation

Heart-type Fatty Acid-Binding Protein (H-FABP; FABP3) is a small cytoplasmic unbound protein of 15 kDa (smaller than Myoglobin =18 kDa, Troponin I =22 kDa, Troponin T=37 kDa and CK-MB =86 kDa) released from the cytoplasm of the cardiac myocytes following an ischemic cardiac episode. H-FABP takes part in the intracellular uptake of long chain fatty acids in the myocardium [1].

The specific feature of this protein is the association with myocardial damage size in patients undergoing cardiac surgery. Elevated H-FABP serum concentrations could also be found in other conditions, like heart failure, chronic kidney disease, diabetes mellitus, and metabolic syndrome. The characteristic of the Fatty Acid-Binding Proteins family is the transport of free fatty acid molecules in the cytosol. Up to now, 10 variants were found in this family, expressed in different tissues. Heart fatty acid-binding protein (H-FABP) is largely expressed in the cytosol of the myocardium with limited expression in other tissues, like the distal tubular cells of the kidneys. H-FABP is released less than 30 min after myocardial injury in both humans and animals, and its renal excretion is within 24 hours [2].

The state of the art in research offers new directions in detecting cardiac lesions (myocardial infarction, post-operative myocardial injury and ongoing ischemic damage in heart failure) by discovering the H-FABP [3,4]. In the conditions mentioned above, high H-FABP levels are strongly associated in case of death [5-7].

Otaki and colleagues published in 2014 a study upon the relation between the elevated pre-operative H-FABP levels in patients undergoing elective coronary artery bypass graft (CABG) surgery and the higher likelihood to experience post-operatively acute kidney injury (AKI) [4]. H-FABP concentration increases in the first 1.5 h, reaches the peak point within 5-6 h and tends to decrease after 6 h. It returns to normal levels 24-30 h later. It is thought to have an important place in the diagnosis of myocardial injury. In perioperative and postoperative period of cardiac surgery, a severe and frequent complication that can occur is myocardial infarction [8].

Apart from myocardium, H-FABP is found in skeletal (striated) muscle, brain, mammary gland and placenta. There are recent studies which state that it can be used especially in the early diagnosis of acute coronary syndrome, cardiac failure, kidney and liver injury, pulmonary embolism and some poisonings [9,10].

Cardiovascular conditions put a burden on every family and health care system, leading the list of mortality and morbidity etiology [11]. Among the instruments of medical management in cardiovascular (CV) diseases, the guidelines have foreseen the role of CV prevention and its usefulness in primary, secondary, and tertiary prevention. The components of cardiac rehabilitation (CR) program are: medical evaluation and treatment, supervised exercises, education and counseling of patients. CR has proved to be an essential and safe part of the care in postoperative program after CABG [12].

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Regular physical activity is fundamental in CR program, improving heart and muscle functioning in patients that were undergoing CABG. The benefits of exercise training are seen in cardiac and vascular adaptation with an enhanced blood flow towards the muscles, a reduction in the oxidative stress, and an amelioration of the endothelial dysfunction and arterial stiffness [13]. The positive effects of CR and exercise training programs are highlighted by many studies that measured the modifying effects on the coronary risk factors, as well as hypertension, arrhythmia, depression, and obesity [14,15]. Researchers have pointed out the very important risk reduction of 40% of cardiac morbidity and mortality by following the CR programs [16]. The diagnosis of elevated H-FABP levels in the case of post-cardiac surgery regional acute myocardial infarction is occasionally challenging [17].

Experimental part

Material and Methods

The purpose of this study was to compare the plasmatic level of H-FABP in patients post CABG surgery, undergoing a cardiovascular recovery program. The levels were compared between the first phase developed during the first postoperative week, and the third phase carried out after 6 months.

We followed-up, in a prospective study, a lot of 110 patients that were admitted in the Clinic of Cardiovascular Surgery of the Institute of Cardiovascular Disease, and later in the Cardiovascular Rehabilitation Clinic of the Rehabilitation Hospital of Iasi. The following inclusion criteria have been used: CABG patients (less than 1 week), aged 40-80 years old, BMI > 25 kg/m², and mixed dyslipidemia. The study was approved by the University Ethics Committee and all participants signed an informed consent.

Every patient benefited of a hematological, biochemical, lipid, coagulation, and inflammatory profile evaluation. ECG and echocardiography (echocardiographic parameters: LVDd, LVSd, IVSd, PWd, LVM, LVMI, EF, and SF) were performed in both phases. During the rehabilitation program, other necessary parameters were monitored: the cardiac parameters (blood pressure, heart rate) and the effort capacity (METs).

H-FABP (fig. 1) has increased sensitivity of 20.6% over troponin at 3–6 hfollowing chest pain onset. This sensitivity may be justified by the high H-FABP concentrations in myocardium cells compared to other tissues, the stability and solubility of H-FABP, the low molecular weight, and its rapid release into plasma after myocardial injury – 60 min after an ischemic episode.

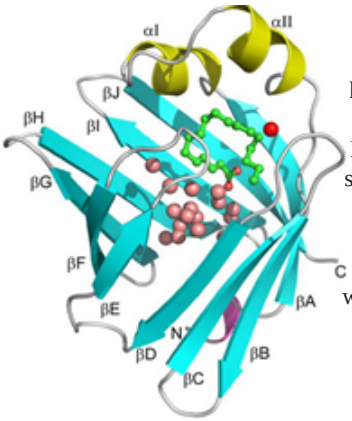

Fig. 1. Structure of human heart-type fatty acid-binding protein. FABP3 has a clum-like shell structure which consists of a pair of five-stranded antiparallel β-sheets that surround a large water – filled cavity (13 water molecules and a fatty acid covered on the top by two short parallel α-helices)

Myoglobin is a sensitive marker for muscle injury, but it has a low specificity for acute myocardial infarction (AMI). Creatine kinase – a marker of damaged CK-rich tissue – is a blood tests in myocardial infarction, rhabdomyolysis, muscular dystrophy, autoimmune myositis, and acute kidney injury. Cardiac I and T subtypes of troponin are very sensitive and specific indicators of myocardial necrosis, assayed to differentiate the chest pain and to sustain the diagnosis of acute coronary syndrome. Troponins levels may remain high for up to 2 weeks.

Statistical analysis

The database was compiled in Microsoft Office Excel 2010 version, and statistical analysis in the IBM SPSS Statistics v.20. The averages, frequencies, standard deviations, differences between the maximum and minimum values of the numerical parameters were calculated. By the Chi-square test of independence was determined the significance of the difference between two frequencies, and *t* Student test revealed the significance of the difference between two average values. The regression equations and correlation coefficients were calculated where necessary. The threshold values for p were considered < 0.05, providing a statistical significance level of the test.

Results and discussions

The mean age of the patients under study was 65.70 ± 9.91 years old, of which male age was 65.26 ± 10.26, respectively 66.96 ± 8.89 for female patients. Approximately one third of these, 29 patients, were female and 81 were male. The median age was 65 years.

Most people were from urban areas (89%) and only 11% from rural areas. The educational level was high in 57% of patients, meaning minimal university studies. The smoking status was present in 58% of the cases and absent in 42% of the cases.

Most people in the group of individuals were overweight or obese, having a BMI > 25 kg/m², confirming the upward trend of obesity at national and global levels. The weight (W) in phase I (W1) was compared with the weight in phase III (W3), respectively the BMI at the two moments, resulting in a difference of high statistical significance, resulting by following both diet and a balanced lifestyle, and cardiovascular gymnastics recommended in the rehabilitation program (table 1).

For the H-FABP, the mean value in the Phase I was 67.40 ± 9.81, while the mean value in Phase III was 4.80 ± 2.30. The difference registered between the H-FABP plasmatic value in the first 24 h after cardiac surgery and the value in 6 months after the onset of cardiac rehabilitation program was important and statistically significant as $p < 0.05$.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as heart rate, were controlled under rehabilitation treatment, reaching diurnal values within the

Weight and BMI	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
W1 (kg)	81.80	12.595	1.260	.000
W3	78.41	13.020	1.302	
BMI 1 (kg/m2)	29.55	3.147	.315	.000
BMI 3	28.36	3.492	.349	

Table 1
ANTHROPOMETRIC PARAMETERS IN PHASE I AND III POST CARDIAC SURGERY

Table 2

COMPARATIVE ANALYSIS OF ANTHROPOMETRIC AND ECHOCARDIOGRAPHIC PARAMETERS BETWEEN THE STAGES OF CARDIOVASCULAR RECOVERY: PHASE I – PHASE III

Echocardiographic parameters	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
LVDd 1 (mm)	52.14	8.914	.891	.000
LVDd 3	48.89	9.195	.919	
LVSd 1 (mm)	36.65	8.776	.878	.000
LVSd 3	33.02	9.497	.950	
IVSd 1 (mm)	13.10	2.389	.239	.000
IVSd 3	12.26	2.623	.262	
PWd 1 (mm)	12.25	1.445	.145	.000
PWd 3	11.49	1.648	.165	
EF 1 (%)	43.55	7.615	.761	.000
EF 3	52.35	10.593	1.059	
SF 1 (%)	25.55	6.420	.642	.000
SF 3	27.78	6.907	.691	
LVM 1 (g)	276.43	94.761	9.476	.000
LVM 3	228.86	89.106	8.911	
LVMI 1 (g/m2)	143.11	47.403	4.740	.000
LVMI 3	120.45	46.232	4.623	
RWT 1 (mm)	.4805	.08739	.00874	.680
RWT 3	.4834	.10875	.01088	

normal range. For the echocardiographic parameters, we obtained statistical significance for the first 8 variables. These variables LVDd, LVSd, IVSd, PWd, LVM, and LVMI showed a reduced value in phase III (confirmed by the mean values) compared to first phase. EF and SF variables registered an increased value in Phase III. The statistical significance was a confirmation that these changes were not random, but based on a factor that actually influenced the values in Phase III compared to Phase I (table 2).

Plasma glucose values have been decreasing in both absolute and percentage terms, proving to improve the profile of carbohydrate metabolism, with an important role in the cardiovascular risk. For biochemical samples, we obtained high statistical significance for all pairs of data that were compared, except for the serum *gamma-glutamyl transpeptidase* (GGT). According to the calculated means, a decrease of the values in Phase III was observed for all the studied variables. GGT did not undergo Phase III changes compared to Phase I.

Inflammatory samples, represented by C-reactive protein (CRP), and fibrinogen showed significant phase-to-phase reductions. In the first stage, white blood cells (WBC) were elevated, most likely indicating an inflammatory syndrome, also confirmed by low hemoglobin (Hb) and hematocrit (Ht). These latter two values may also have been low in the context of postoperative hemorrhage. At six months later, in the third phase, the anemic syndrome was absent and it was confirmed by the improvement of hematological profile. In the same context, an increase in the blood platelet counts also occurred (table 3).

Lipid profile values showed a statistically significant decrease, although in those in whom the initial values exceeded the upper limits of normality, the reduction did not bring the patient to a lower cardiovascular risk range. The plasma ionogram showed an improvement of electrolytes values between the two phases, but with no importance for the post-infarction clinical evolution (table 3).

The renal filtration function evaluated by plasma creatinine showed statistically significant improvement and, in terms of absolute values, creatinine level was reduced in a range between 0.2-0.4 mg/dL. Also, it was recorded a significantly lower level of blood urea.

The aspect of electrocardiogram (ECG) changes revealed the presence of atrial fibrillation in Phase I in 76 patients, whilst in Phase III only 9% of patients experienced this rhythm disorder. In the cardiovascular rehabilitation program, the cycloergometer testing has an important place, both immediately after myocardial infarction and in the first stage of rehabilitation, followed by physical endurance training, which is recognized for increasing physical exercise capacity, walking distance and improving the quality of life.

Patients were grouped accordingly by the degree of physical exercise that they were able to achieve during the first phase and, later, in the third phase of cardiovascular recovery.

The effects of the cardiac rehabilitation program in patients after cardiac surgery can be seen in decreasing complications, improving QoL, decreasing ten year mortality. In spite of the existing recommendations after CABG surgery, there is a low participation rate in centre-based cardiac rehabilitation programs. For that reason, the healthcare providers in Denmark have focused on home-based cardiac rehabilitation program [18]. By comparing

Biochemical tests	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
CRP 1	3.88	3.179	.318	.000
CRP 3	1.725	2.6791	.2679	
Fibrinogen 1	640.79	175.120	17.512	.000
Fibrinogen 3	442.75	115.201	11.520	
Chol 1	182.69	47.945	4.795	.003
Chol 3	170.31	50.619	5.062	
HDL 1	40.23	22.762	2.276	.000
HDL 3	50.04	26.586	2.659	
LDL 1	143.95	31.067	3.107	.000
LDL 3	122.06	29.619	2.962	
TG 1	146.63	55.629	5.563	.001
TG 3	131.62	56.238	5.624	
Na 1	141.13	5.200	.520	.000
Na 3	138.62	5.908	.591	
K 1	4.6370	.36700	.03670	.000
K 3	4.38	.392	.039	
Urea 1	46.17	14.424	1.442	.000
Urea 3	42.13	12.139	1.214	
Creatinine 1	1.2972	.46679	.04668	.000
Creatinine 3	1.0924	.21551	.02155	
Hematological tests	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
WBC 1	10497.40	10.6417	10.6417	.007
WBC 3	8500.40	82.3686	823.686	
RBC 1	3.7707	.55200	.05520	.000
RBC 3	4.2347	.56213	.05621	
Hb 1	10.95	1.158	.116	.000
Hb 3	12.57	1.819	.182	
Ht 1	34.07	4.279	.428	.000
Ht 3	37.96	5.386	.539	
MCV 1	91.1373	9.27110	.92711	.113
MCV 3	89.7194	5.52901	.55290	
MCH 1	29.3926	3.41060	.34106	.388
MCH 3	29.7209	2.30598	.23060	
MCHC 1	32.2865	2.24967	.22497	.005
MCHC 3	33.1510	2.04881	.20488	
PLT 1	362260.00	90041.586	9004.159	.000
PLT 3	316880.00	130334.866	13033.487	

Table 3
BIOCHEMICAL PARAMETERS – COMPARATIVE DATA

the settings and the medical care programs in elderly patients with coronary artery disease, it was concluded that home-based cardiac rehabilitation can improve exercise capacity in elders versus the standard care, result that was confirmed by many other researchers [19-21].

In our prospective study on hospitalized patients undergoing CABG, we observed as other researchers did, the correlation between the occurrence of postoperative atrial fibrillation (POAF) and the plasmatic level of H-FABP, as a sensitive marker of ischemic myocardial injury [22]. The return to sinus rhythm was spontaneous or under medication in most of the cases, within one hour to one week after CABG. Thus ischemic injury during open-heart surgery should represent a therapeutic goal in order to reduce POAF.

Ischemia leads to mitochondrial edema and disruption of membranes, releasing intracellular constituents into the blood and increasing the plasmatic level of cardiac enzymes in acute myocardial infarction and after CABG. H-FABP binds long chain fatty acids in the cytosol and thus it protects the myocardial cells, and less the skeletal muscle, brain and kidney cells. H-FABP is released earlier than Troponin, because of its smaller size (15 kDa), protein unbinding, and lower resistance to pH changes. A high level of H-FABP is proved to be a marker of cell necrosis, correlated to the infarct size, and predicting subsequent cardiovascular events (POAF, AKI) in TnT-negative patients with acute coronary syndrome [23-25].

Conclusions

The reduction of plasma H-FABP values were registered between the first phase (the first 24 h) after cardiac surgery and the third phase of the cardiac rehabilitation program.

H-FABP protein had a higher sensitivity and specificity when compared to other enzymes of myocardial cytolysis. The improvement in H-FABP values were linked to an increase in quality of life, blood pressure and heart rate, cardiac and renal function, inflammation and coagulation, as well as the improvement in all metabolisms.

In this prospective study conducted on 110 patients receiving coronary-artery bypass, we have demonstrated that an early and sustained post-interventional rehabilitation treatment plays an important role in reversing the atherosclerotic process and preventing postoperative complications such as: arrhythmias and cardiac insufficiency, myocardial ischemia, biological changes, and renal failure.

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