Heart-Type Fatty Acid-Binding Protein (H-FABP) in Patients with Type 2 Diabetes Beneficiaries of Rehabilitation Program Post Coronary Artery Bypass Grafting

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Heart-type fatty acid-binding protein (H-FABP) is a non-invasive bio-marker, with high sensitivity and specificity, being capable to point out the myocardial injury and to predict major adverse cardiovascular events (MACE). Cardiac rehabilitation program, through a complex and sustained post-interventional management plays an important role in reducing the plasma levels of H-FABP. In the study, which included 120 post-coronary artery bypass (CABG) patients, we analyzed the link between low levels of general post-surgical health status and the presence of cardiovascular risk factors, common biochemical markers, and especially the role played by diabetic status in lowering the plasma H-FABP levels. From the group, 65 patients had been diagnosed with type 2 Diabetes Mellitus (T2DM). The H-FABP values decreased both in diabetics and in non-diabetics between the two phases of CR, 6 months away from CABG. More than half of the patients had important reduction of H-FABP, at 6 months after the onset of CR program. Half of the group registered a smaller reduction of H-FABP, but more noticeable in diabetics. Ischemic lesion during open heart surgery is linked to high levels of H-FABP and with an occurence risk of postoperative atrial fibrillation, that can be also triggered and sustained by multiple endocrine conditions related to aging. Thus, metabolic control should always remain a target of the complex management in cardiac rehabilitation.

Keywords: heart-type fatty acid binding protein, coronary-artery bypass graft, cardiac rehabilitation, type 2 diabetes mellitus

Heart-type fatty acid-binding protein (H-FABP) as well as other non-invasive bio-markers, like highly sensitive troponin T (hsTnT), was found to be an important indicator of myocardial injury and major adverse cardiovascular events (MACE) with high sensitivity and specificity [1].

Myocardial ischemia leads to mitochondrial edema and membranous disintegration, releasing intracellular constituents into the blood and increasing plasma levels of cardiac enzymes in acute myocardial infarction and after coronary artery bypass grafting (CABG). H-FABP binds long chain fatty acids in the cytosol and thus protects myocardial cells, whilst it is less protective for skeletal muscle, brain and kidney cells. H-FABP is released earlier than Troponin T (TnT) due to its smaller size (15 kDa), to the release of proteins from the ligand and low resistance to *p*H modulation. A high level of H-FABP has been shown to be a marker of cell necrosis correlated with the infarct size, and it can predict subsequent cardiovascular events (postoperative atrial fibrillation and acute renal injury) in patients with negative TnT and acute coronary syndrome [2]. There is a relationship between high H-FABP preoperative levels in patients undergoing coronary bypass surgery (CABG) and the higher probability of acute renal failure in postoperative time [3]. H-FABP concentration increases in the first 1.5 h, reaching a peak within 5-6 hand tends to decrease after 6 h; it returns to normal levels 24-30 h later.

In 1968, the Coronary Artery Bypass Grafting (CABG) was introduced by Rene Favaloro as the first technique for myocardial revascularization. Since then, some methodological changes have been made [4]. CABG is now reserved for patients with more complex coronary anatomy, defined by a Syntax score greater than 22, and in the presence of comorbidities, such as diabetes mellitus and renal failure [5, 6].

Cardiac rehabilitation (CR) program plays an important role in reducing the plasma levels of H-FABP protein, confirming 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 [7].

Prevention should be ensured by promoting a healthy lifestyle and by optimizing the management of risk factors from risk-free subjects to those at high risk of CVD. Eliminating health risk behaviors would make it possible

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to prevent at least 80% of CVD and even 40% of cancers [8, 9].

Experimental part

Material and Methods

The current research was part of a prospective study. With the help of the cardiovascular surgery and the rehabilitation physician's medical team of Iasi, subjects who met the inclusion criteria were randomized and included in the study.

All subjects who participated in the research signed in the informed consent, certifying that they agree with the investigations and analyzes that should be performed, as well as with the final publication of the data in scientific form and under permanent protection of anonymity. The Research Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy of Ia^{o}i endorsed the study.

The purpose of this study was to compare the plasmatic level of H-FABP in patients post CABG surgery, undergoing a cardiovascular recovery program, comparing results between patients with Type 2 Diabetes Mellitus and patients free of diabetes. The levels of H-FABP were determined in the first phase of CR program, representing the time of the first postoperative week, and in the third phase, carried out later, after 6 months. We followed-up, in a prospective study, a lot of 120 patients admitted first 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 inclusion criteria, used to enroll the patients in the study, were as follows: the main diagnosis of aortic-coronary by-pass surgery (less than one week), second diagnosis of mixed dyslipidemic syndrome (hypercholesterolemia and hypertriglyceridemia), age between 40 and 80 years old, BMI > 25 kg/m², and intellectually capable to follow the rehabilitation cardiovascular program. The age range considered was optimal because the cardiovascular risk in this age group should be determined steadily, and any additional investigations are needed in order to evaluate the true vascular age.

The paraclinical evaluation, performed in every cardiovascular rehabilitation phase, comprised lab exam for hematological, biochemical, lipid, coagulation, and inflammatory profile, the ECG, and the echocardiography, measuring LVDd, LVSd, IVSd, PWd, LVM, LVMI, EF, and SF. Other monitored parameters were the blood pressure, the heart rate, and the effort capacity (METs).

Statistical Analysis

To collect the information for the database we used Microsoft Office Excel 2010 version. In order to perform the data analysis, we applied statistics in the IBM SPSS Statistics v.20. For the numerical parameters we calculated the averages, frequencies, standard deviations, and the differences between the maximum and minimum values. The significance of the difference between two frequencies was performed through the Chi-square test of independence. The test t Student was applied in order to reveal the significance of the difference between two average values. The statistical significance level of the test was considered when $p < 0.05$. Furthermore, we also turned into account the regression equations and correlation coefficients.

Results and discussions

This statistic analysis included 120 post – coronary artery bypass subjects who agreed to be evaluated in the research. Approximately 25% of them were female subjects (29 patients), and 91 were male.

The age of the patients studied was between 40-80 years, women being younger (43-77 years) than men. The average age was 65.47 ± 10.18 for male patients, and 67.34 ± 8.67%, respectively, for female patients. The median of age was 65 years old, representing a good homogeneity of the studied group.

Most people were from urban area (88.3% = 106 patients), and only 11.7% came from rural environment. Smoking status was present in 60.8% (73 patients), and absent in 39.2% of cases. The marital status for all patients in the group was married. The educational level was high (81.7% of patients), meaning at least university studies.

Most individuals in the group were overweight or obese with the median of BMI (body mass index) values > 29 kg/m², with a predominance for Ist and IIIrd degree of obesity, thus confirming the upward trend in obesity at national and global levels. The mean height was lower for women than for men.

The body weight (BWT) in phase I (BWT-1) was compared with phase III weight (BWT-3), and with BMI at both times, resulting in high statistical significance, meaning that the patients decreased by weight over time following both diet and a balanced lifestyle, together with cardiovascular gymnastics, featured in the rehabilitation program (table 1).

Regarding the echocardiographic parameters, we obtained statistical significance for 7 of the variables. LVDd, LVSd, IVSd, PWd, MVS, and IMVS showed a phase III reduction (confirmed by the average values) compared to the first phase of CR. EF and SF variables showed an increase in phase III, with statistical significance for the ejection fraction. The statistical significance was a confirmation that these changes were not random, but were based on a factor that actually influenced the values in Phase III compared to Phase I. For RWT, indicating altered LV remodeling, we hadn't noticed any significant change in phase III compared to Phase I, possibly explained by the early CABG intervention that the patient benefited from.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as heart rate (HR) were controlled under rehabilitation treatment, the diurnal values attaining the normality range. For the heart rate, the McNemar test

Table 1

COMPARISON OF DATA AND THEIR STATISTICAL SIGNIFICANCE BETWEEN PHASE I AND III

Group	Comparisons	Body Weight and Body Mass Index Statistics							p significance
		Mean	95% Confidence Interval for Mean		Median	Std. Deviation	Min	Max	
			Lower Bound	Upper Bound					
1	BWT-1	81.43	79.21	83.65	85.00	12.279	60	104	0.000
	BWT-3	77.89	75.58	80.20	82.00	12.778	56	101	
2	BMI-1	29.42	28.87	29.96	29.00	3.028	24	38	0.000
	BMI-3	28.17	27.55	28.78	29.00	3.414	24	37	

Table 2

BIOCHEMICAL PARAMETERS - COMPARATIVE DATA

Group	Comparisons	Bleeding Time Tests Statistics							p significance (t – test)
		Mean	95% Confidence Interval for Mean		Median	Std. Deviation	Min	Max	
			Lower Bound	Upper Bound					
1	APTT-1	34.05	32.78	35.32	36.00	6.98	25.00	57.00	0.000
	APTT-3	31.94	30.87	33.01	36.00	5.89	23.00	39.00	
2	INR-1	1.26	1.15	1.38	1.06	0.62	0.94	3.83	0.000
	INR-3	2.06	1.94	2.18	2.40	0.64	0.96	2.90	
3	PT-1	17.00	15.84	18.15	15.00	6.34	13.00	46.00	0.000
	PT-3	13.72	13.04	14.40	13.00	3.72	11.00	31.90	

had statistical significance, p <0.001, so in Phase III we had more cases in sinusal rhythm on ECG compared to Phase I.

Regarding bleeding times, there was statistical significance in all three variables: p <0.001. Activated partial thromboplastin time (APTT) decreased in Phase III, international normalized ratio (INR) increased in Phase III, and prothrombin time (PT) test decreased in Phase III (table 2).

Plasma glucose values have been reduced in both absolute and percentage values, showing improvement in the glucose metabolism, with an important role for the cardiovascular risk (table 3).

Table 3

BIOCHEMICAL PARAMETERS - COMPARATIVE DATA

Group	Comparisons	Biochemical Values Statistics							p significance (t – test)
		Mean	95% Confidence Interval for Mean		Median	Std. Deviation	Min	Max	
			Lower Bound	Upper Bound					
1	ALT-1	39.74	33.02	46.46	30.00	37.16	15.00	285.00	0.000
	ALT-3	26.11	23.48	28.73	22.50	14.52	9.00	93.00	
2	AST-1	34.63	29.89	39.38	27.50	26.25	17.00	164.00	0.000
	AST-3	24.53	21.41	27.66	20.00	17.30	10.00	159.00	
3	GGT-1	40.93	36.53	45.32	33.50	24.32	15.00	180.00	0.676
	GGT-3	39.23	31.21	47.25	30.00	44.37	12.00	456.00	
4	Glycemia-1	138.53	128.15	148.92	120.00	57.44	80.00	320.00	0.000
	Glycemia-3	120.63	112.30	128.96	104.00	46.09	75.00	284.00	
5	Proteins-1	7.71	7.62	7.80	7.90	0.49	6.80	8.90	0.000
	Proteins-3	7.11	7.01	7.21	7.10	0.56	6.21	8.02	
6	Albumine-1	4.61	4.49	4.73	4.66	0.67	3.50	7.90	0.000
	Albumine-3	4.23	4.17	4.30	4.14	0.36	3.38	4.96	
7	TB-1	0.74	0.70	0.78	0.79	0.21	0.35	1.07	0.000
	TB-3	0.59	0.55	0.62	0.55	0.18	0.31	1.04	
8	DB-1	0.37	0.33	0.41	0.30	0.23	0.12	1.00	0.000
	DB-3	0.22	0.20	0.23	0.18	0.07	0.12	0.42	
9	CRP-1	3.74	3.20	4.27	3.00	2.96	1.00	20.00	0.000
	CRP-3	1.62	1.17	2.06	0.99	2.46	0.21	13.40	
10	Fibrinogen-1	636.96	605.43	668.48	600.00	174.41	290.00	1000.00	0.000
	Fibrinogen-3	441.62	421.08	462.15	439.00	113.61	109.00	793.00	
11	Chol-1	181.54	173.16	189.92	178.50	46.37	104.00	390.00	0.000
	Chol-3	168.10	159.27	176.93	155.00	48.86	102.00	318.00	
12	HDL-1	40.19	36.35	44.04	40.00	21.27	10.00	180.00	0.000
	HDL-3	50.33	45.72	54.94	45.00	25.50	4.04	200.00	
13	LDL-1	144.26	138.71	149.81	150.00	30.71	100.00	250.00	0.000
	LDL-3	122.03	116.81	127.24	110.00	28.85	90.00	234.00	
14	TG-1	147.95	137.66	158.24	136.00	56.95	69.00	300.00	0.000
	TG-3	132.64	122.33	142.94	116.00	56.99	43.00	294.00	
15	Na-1	141.27	140.29	142.24	142.00	5.41	131.00	152.00	0.000
	Na-3	138.71	137.66	139.76	141.00	5.79	123.00	148.00	
16	K-1	4.66	4.59	4.72	4.70	0.37	4.00	5.51	0.000
	K-3	4.39	4.32	4.46	4.37	0.39	3.73	5.08	
17	Urea-1	45.42	42.78	48.05	43.00	14.56	20.00	86.00	0.000
	Urea-3	41.45	39.27	43.63	40.00	12.07	18.00	65.00	
18	Creatinine-1	1.28	1.20	1.36	1.20	0.44	0.80	3.80	0.000
	Creatinine-3	1.09	1.05	1.12	1.08	0.21	0.60	1.57	

For biochemical samples, we obtained high statistical significance for all the compared data pairs, except the third pair, respectively GGT. According to the calculated averages, a decrease of the values was observed for all studied variables in Phase III of CR. GGT did not undergone changes in Phase III compared to Phase I.

The glomerular filtration rate estimated from plasma creatinine showed statistically significant improvement and, in terms of absolute values, it showed a reduction interval of 0.2-2.23 mg/dL. Also, there was recorded a significant decrease in blood urea. The ionogram showed improvement between the two phases, but with no clinical importance in the post-infarction progression.

Lipid profile values showed a statistically significant decrease, although, in those whose initial value exceeded the normality limit, the reduction did not bring the patient back to low cardiovascular risk range, as we have shown in a previous study (10).

In the first stage of CR, the white blood cells (WBC) were elevated, most likely indicating an inflammatory syndrome, also confirmed by low hemoglobin (Hb) and hematocrit (Ht) values. The Hb and Ht values could also have been low in the context of post operative bleeding. At six month interval, in the third phase of CR, the anemic syndrome was absent, as evidenced by the improvement of haematological profile. The same reactive context of post operative hemorrhage could explain the blood platelet count changes. Inflammatory samples, represented by C-reactive protein (CRP) and fibrinogen, showed significant phase-to-phase reductions.

In the first phase of recovery (one week after the myocardial infarction occurred), in almost 50% of cases, patients were able to perform only a minimal effort of one or two METs of almost 50%. In the third phase of cardiovascular recovery, all patients who initially achieved a minimum effort of 1-2 METs have improved and even exceeded their poor physical condition, by this time performing average efforts classified in the 4-5 METs group, and more than 50% of patients performed efforts in the 5 METs group (table 4).

In our study, 55 patients were free of diabetes, and 65 had been diagnosed with T2DM. The H-FABP values decreased in both groups between the two phases of CR, 6 months away from CABG. The decrease in H-FABP in diabetics was also statistically significant ($p = 0.03$) (fig. 1). As shown in the box-plot, more than half of the patients had important reduction of H-FABP, at 6 months after the onset of CR program. Half of the group registered a smaller reduction of H-FABP, but more noticeable in diabetics. The median value is a little bit lower and better for non-diabetics (fig. 1).

Compared to single bypass patients, in those who benefited from bi- or tri-coronary revascularization, serum H-FABP values reduced more significantly ($p = 0.000$) (fig. 2). In patients with multiple coronary artery by-pass, the ~20 ng/mL reduction in H-FABP levels showed the benefit of multiple interventions on atherosclerotic lesions which caused coronary flow obstruction.

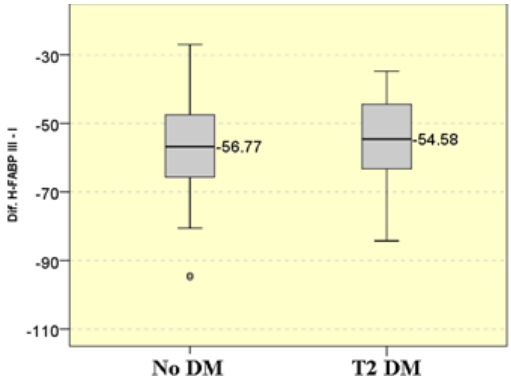

Fig. 1. H-FABP difference between phases in diabetics vs. nondiabetics

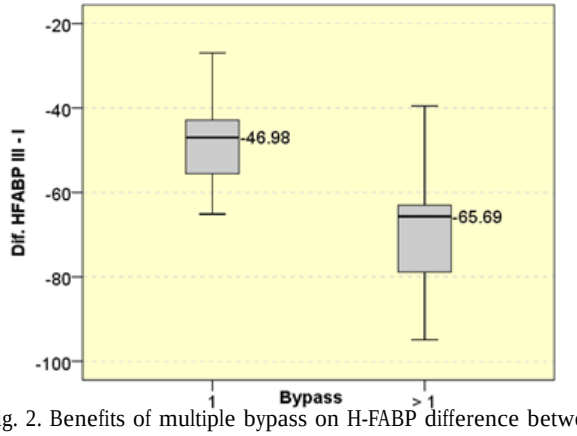

Fig. 2. Benefits of multiple bypass on H-FABP difference between CR phases

In the study, which included 120 post-coronary artery bypass patients, we analyzed the link between low levels of general post-surgical health status and the presence of cardiovascular risk factors, common biochemical markers, and especially the role played by diabetic status in lowering the plasma H-FABP levels.

The effects of cardiac recovery program in patients who have had a heart surgery can be seen in reducing complications, improving QoL, lowering mortality rate at 10 years. The high educational level of our patients may have influenced the great outcomes of the complex management and sustained it, ensuring a long-time compliance of the patients to the new lifestyle, regimen, treatment and follow-up control [10, 11].

Despite the recommendations made after CABG surgery, there is a low rate of patient participation in cardiovascular recovery programs. By comparing locations and health care programs in elderly patients with coronary artery disease, it was concluded that home cardiac recovery can improve the elders and diabetics effort versus standard care, as confirmed by many researchers [12, 13].

In our prospective study on hospitalized patients undergoing coronary artery bypass grafting, we noticed, like other researchers, the correlation between the occurrence of postoperative atrial fibrillation (POAF) and the plasmatic level of H-FABP, recognized as a sensitive marker for myocardial ischemic lesion. In most cases,

			METs-1			Total
			1	2	3	
METs-3	4	Count (% within METs-3)	21 (51.2%)	20 (48.8%)	0 (0%)	41 (100%)
	5	Count (% within METs-3)	45 (57%)	27 (34.2%)	7 (8.9%)	79 (100%)
Total		Count (% within METs-3)	66 (55%)	47 (39.2%)	7 (5.8%)	120 (100%)

Table 4
COMPARISON OF PHYSICAL EFFORT QUANTIFIED BY METS (CROSSTABULATION)

restoration of sinus rhythm was spontaneous or under medical treatment, within one hour to a week after CABG. Thus, ischemic lesion during open heart surgery should represent a therapeutic objective in order to reduce the occurrence of POAF [14]. Recent studies have shown that H-FABP can be used especially in early diagnosis of acute coronary syndrome, heart failure, liver and kidney lesions, pulmonary thromboembolism and some kind of intoxications. Atrial fibrillation can be triggered by endocrine conditions, relatively common in elderly and frequently associated to diabetes, by metabolic conditions, as diabetes and dyslipidemic syndrome, or can occur in liver conditions, as cirrhosis, that can generate abnormal cardiac features [15, 16].

We compared our results with those obtained from the Framingham Heart Study in April 2002, which identified major cardiovascular risk factors: hypertension (hypertension), diabetes, smoking, obesity, sedentarism, hypercholesterolemia and other lipid fractions (HDL-cholesterol, LDL-cholesterol, triglycerides), peculiarities related to gender and age group. Numerous prospective studies following the FRAMINGHAM trial confirmed the major impact of these risk factors on the development of cardiovascular disease and acute myocardial infarction [17].

Our study highlighted the role of lifestyle correction and cardiovascular rehabilitation program in improving blood pressure control, reducing obesity, smoking cessation, and normalizing paraclinical parameters, which subsequently led to a statistically significant decrease in cardiovascular risk scores. Various statistical models have been developed to predict mortality in the short and long term after a coronary bypass surgery. A simplified and friendly risk score has been created, in order to reduce the complexity of the prediction of death risk calculator, by using these statistical models in health care units. With the help of such risk scores, death prognostic scores can be obtained by summing the initial weight of the risk factors to obtain the total risk score, and to identify the prognosis of death score for that total. This information can be used by clinicians and patients in choosing the optimal treatment for severe coronary artery disease [18]. It is of great probability that the reduction of body weight during the 6 months period had influenced the lowering of plasma H-FABP level and the metabolic control in diabetics, revealed by the greater decreased of H-FABP in diabetics. Some other substances like chemerin, used to confirm myocardial acute lesions, showed reduction of plasma values when patients improved their anthropometric indices and metabolic profile [19].

The Framingham Risk Score (FRS) is a common and simplified clinical tool used to assess the risk level of coronary artery disease (CAD), and to individualize for each patient the maximum benefit of changing certain risk factors. This instrument is made up of components of coronary risk including gender, age, smoking status, systolic blood pressure and lipid profile. FRS is the most appropriate method of measuring a person's likelihood of developing long-term cardiovascular disease. Due to the fact that this risk score provides a view over the possible benefits of prevention, its utility can be extended, patients and clinicians being able to choose between lifestyle modification and/or preventive medical treatment [20]. Comparing the Phase I and Phase III results of the Framingham score, it was noted that the median value of the cardiovascular risk at 10 years could have a reduction of nearly 6% ($p < 0.05$).

However, the cardiovascular risk is also related to family history, inflammation markers – such as high sensitivity C-reactive protein (hs-CRP), and hemoglobin A1c (HbA1c) for diabetics.

In our study group, addressability to the cardiovascular rehabilitation service appears to be greater for male patients (as has been shown in other studies), with cardiovascular pathology being at higher risk for them compared to women. In addition, patients at extreme age enrolled in the study demonstrate the benefit of interventional cardiology and cardiovascular surgery in very old male patients.

Between phase I and phase III of the cardiovascular recovery program, for six months duration, patients with atrial fibrillation converted to sinus rhythm.

The echocardiographic parameters, as left ventricular (LV) telediastolic and telesistolic diameter, left ventricular wall thickness (interventricular septum, posterior wall), and the LV mass showed improvement in the third phase of the cardiovascular rehabilitation program with statistically significant reduction of volumes, diameters and LV mass.

Significant echocardiographic changes were not recorded for the right ventricle (RV), as patients only presented an impairment of the left anterior descending artery (LAD) during acute myocardial infarction.

With regard to glucose metabolism, glycemic values improvement may be the result of patient participation in the kinetotherapy program, their compliance with the hygiene-dietary regimen, and the significant reduction of anthropometric indices.

Lipid profile values showed a statistically significant decrease, although in those in whom the baseline exceeded the normality limit, the reduction experienced did not return the patient to the limit of no cardiovascular risk. Even when the lipidic values are corrected, a residual cardiovascular risk remains. Thus, we have to test further the ratio between TG and HDL-cholesterol, the Reaven index; where the ratio exceeds the normal limit of 3.5, it will notify the presence of insulin resistance – an important underlying mechanism for hypertension, as well as for diabetes and metabolic syndrome [21]. In this regard, statistical analysis can bring to front the implication of every parameter in the positive or negative clinical evolution and in lowering the H-FABP after CABG.

The complex cardiovascular rehabilitation program included cyclogergometer testing, both immediately after myocardial infarction and in the first phase of rehabilitation to assess patients' exercise capacity. The testing was followed by physical endurance training with beneficial effects on increasing physical exercise capacity, walking perimeter, and improving the quality of life.

In Phase I (one week after myocardial infarction), the physical capacity of the patients was limited, being able to do only a minimum of 1-3 METs. None has been able to perform more than 3 METs in this phase.

In the third phase of cardiovascular recovery, all patients initially achieving a minimum effort of 1-3 METs have improved and even exceeded their poor physical condition by performing at this time average efforts in the 4-5 MET group with nearly 2/3 of patients in class 5 METs.

Conclusions

The reduction in plasma levels of H-FABP was recorded between the first phase (the first 24 h) after the cardiac surgery and the third phase of the cardiac recovery program. The H-FABP protein had a higher sensitivity and specificity compared to other myocardial cytolysis enzymes. Improvement of H-FABP values was related to improvement in quality of life, blood pressure and heart

rate, cardiac and renal function, inflammation and coagulation, and improvement of all metabolic parameters.

The degree of physical exercise that patients were able to achieve on the cycloergometer, measured by METs, showed an evolution from 1-3 METs to 4-5 METs within 6 months. Those who have initially performed only easy and very easy physical effort managed in the third phase of CR program to reach an effort of 4-5 METs. Basically, from the point of view of the clinical effect of the cardiac rehabilitation program, there were major differences between the two phases: in Phase III there were no patients performing only minimal efforts of 1, 2, or 3 METs.

Type 2 Diabetes Mellitus complicated with hyperglycemia, dyslipidemic syndrome, and obesity, can accelerate the atherosclerosis process with very high cardiovascular risk for major adverse cardiovascular events and for mortality. Through the pathogenic mechanism, including inflammation and insulin resistance, T2DM can trigger and sustain heart arrythmias even in patients without CABG. Thus, metabolic control should always remain a target of the complex management in cardiac rehabilitation.

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