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STUDY OF HEART TYPE FATTY ACID BINDING PROTEIN AS A MARKER OF MYOCARDIAL INJURY IN INFANTS AND YOUNG CHILDREN WITH CONGENITAL ACYANOTIC HEART DISEASES

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ABSTRACT

Background: The progression of heart failure is associated with a progressive loss of cardiomyocytes that can be detected clinically as continuously increased serum levels of H-FABP. However the clinical value of serum H-FABP levels in children and adolescents with congenital heart disease (CHD), has not yet been elucidated. **Aim**: To assess H-FABP serum level in infants and young children with congenital acyanotic heart disease as a marker of cardiac myocyte injury and correlate it with the severity of heart failure. **Subjects and Methods**: This case control study was conducted on 72 infants and young children with congenital acyanotic heart disease (left to right\ shunt). They were selected from outpatients' pediatric clinics, pediatric department and pediatric ICU of National Heart Institute during the period from May 2013 to July 2015. The study also included 30 healthy infants and children, age and sex matched with patients, as controls. Assessment of H-FABP was performed in the same line with routine investigations for both groups. Radiological investigations included plain chest x-ray and conventional transthoracic echocardiogram. **Results**: Significant increase in H-FABP serum levels in patients (1.61 $\pm$ 1.27 ng / mL) compared to the controls (0.43 $\pm$ 0.18 ng / mL) with p (0.000) and significant relation to the severity of heart failure. Positive correlation between H-FABP and pulmonary pressure was detected. However, H-FABP showed a negative correlation with ejection fraction (EF) % and fraction shortening (FS) %. **Conclusion**: Levels of H-FABP can serve as a new monitoring tool to provide information about clinical heart failure severity and optimize therapy in management of patients with congenital heart defects.

KEYWORDS: Congenital acyanotic heart disease, H-FABP, Heart failure.

1. INTRODUCTION

Congenital heart disease (CHD) occurs in 1% of live born infants, making it the most common birth defect worldwide. Many of these children develop heart failure. Heart failure occurs when the myocardium is unable to meet the body's metabolic demands. Unlike some organs, the heart has limited, if any, capacity for repair after injury (Bernstein and Srivastava, 2012).[1]

CHD can be classified into cyanotic and acyanotic ((left-to-right shunts or obstructive lesions). The condition of acyanotic heart defect occurs when shunting (flowing) of blood occurs from the left side of the heart to the right side of the heart due to a structural defect (hole). Patients retain normal levels of oxyhaemoglobin saturation in systemic circulation ***(Nclex, 2006).***[2]

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood ***(Yancy et al., 2013).***[3] HF can be classified according to the pathophysiology into systolic and diastolic HF, or according to the severity by The Ross Heart Failure Classification modified to apply to all pediatric ages. The modified Ross Classification incorporates feeding difficulties, growth problems, and symptoms of exercise intolerance ***(Norozi et al., 2007).***[4]

Cardiac biomarkers are protein macromolecules that are found in myocardial cells, and their increase in serum is indicative of cell damage or loss of cell membranes integrity ***(Singh et al., 2010; Shaddy and Tani, 2013).***[5-6]. As additive to traditional markers of myocardial damage, among proposed new biomarkers of myocardial injury is heart fatty acid binding protein (H-FABP) ***(Ozdemir et al., 2011).***[7]**.** It is a protein with low molecular weight, found at high concentrations in the cytoplasm of cardiac myocytes (4-8%). As a result of its relatively small size and its primary location in the cytosol rather than in myofibrils, H-FABP is released earlier and in larger amounts into the circulation than cardiac troponin I (cTnI) and creatine kinase MB (CK-MB) when membrane integrity is compromised because of myocardial injury ***(Arıtürk et al., 2013).***[8]. H-FABP can be detected within 20 minutes (min) of cardiac damage. It reaches peak levels at 3-4 hours and returns to normal range in 24 hours ***(Erenler et al., 2013).***[9]

H-FABP can be used as a reliable marker for hypertrophic and dilated cardiomyopathy, HF, early estimation of infarct size, a reperfusion marker and for the early detection of postoperative myocardial tissue loss in patients undergoing coronary bypass surgery, stroke, and obstructive sleep apnea syndrome ***(Claudia et al., 2010).***[10] H-FABP significantly predicts mortality in patients with pulmonary embolism at intermediate risk ***(Boscheri et al., 2010).***[11]

The highest levels of H-FABP were related with hypertension (HT), obesity and ECG changes. Arterial stiffness increases in hypertensive individuals. Arterial stiffness is also associated with impairment of systolic and diastolic myocardial function in HT. It was suggested that arterial stiffness is associated with increased serum H-FABP levels, a sensitive marker of myocardial damage, in patients with newly diagnosed HT ***(Gedikli et al., 2008).***[12]

2. PATIENTS AND METHODS

This case control study was conducted on 72 infants and young children (group I) with congenital acyanotic heart disease (left to right shunt). Their age ranged from 1-36 months. They were selected from outpatients' pediatric clinics, pediatric department and pediatric ICU of National Heart Institute during the period from May 2013 to July 2015. They were subdivided into three subclasses according to heart failure severity (modified Ross criteria) ***(Ross, 2012).***[13]: Class I: 27 asymptomatic patients. Class II: 30 patients suffering from mild tachypnea or diaphoresis with feeding in infants and dyspnea on exertion in older children. Class III: 15 patients suffering from marked tachypnea or diaphoresis with feeding in infants, marked dyspnea on exertion and prolonged feeding times with growth failure. A group of 30 healthy infants and children (group II), age and sex matched with patients served as controls. Infants and children with acute and chronic illness (chest, hepatic, renal, GIT and muscle disease etc…) as well as those suffering from congenital valvular or cyanotic heart disease were excluded from the study.

All the studied population was subjected to full medical history taking including cardiac symptoms and medications (e.g. diuretics, digoxin), thorough clinical examination including full cardiac examination, assessment of oxygen saturation (O_2 sat %) by pulse oximeter as well as laboratory and radiological investigations. An informed written consent was obtained from all patients' parents and control groups before including them in the study.

2.1. Laboratory investigations

1. Two ml blood were withdrawn on an EDTA vacutainer tube for complete blood picture on Sysmex Kx 21N automated cell counter.
2. Five ml blood were withdrawn into a gel vacutainer tube, centrifuged within 30 minutes. Serum was then separated into two parts:

• One part was used on the same day for the measurement of blood urea nitrogen (BUN), creatinine and creatine kinase (CK) on automated Pentra 200 chemistry analyzer.

• The second part was stored at - 20º C until the H-FABP assay by enzyme-linked immunoassay (ELISA) using the kits supplied by Wuhan EIAab Science Co., Ltd. The microtiter plate provided in the kit had been pre-coated with an antibody specific to Fatty-acid binding protein – heart. Standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated monoclonal antibody preparation specific for Fatty acid-binding protein – heart and Avidin conjugated to Horseradish peroxidase (HRP) was added to each microplate well and incubated. Then a TMB standard solution was added to each well. Only those wells that contain Fatty-acid binding protein – heart, biotin-conjugated antibody and enzyme-conjugated Avidin exhibited a change in color. The enzyme-substrate reaction was terminated by the addition of sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm $\pm$ 2 nm. The concentration of Fatty-acid binding protein – heart in the sample was then determined by comparing the optical density (O.D.) of the samples to the standard curve.

2.2. Radiological investigations

- Plain chest x- rays: for the diagnosis of cardiomegaly, quantification of pulmonary blood flow, presence of associated chest infection, pleural effusion etc…..
- Echocardiography assessment:

a) Conventional transthoracic echocardiogram (TTE): Echocardiographic examination was performed at echocardiography lab National Heart Institute using GE system Vivid-7 Matrix probe M3S,M5S,M7S multi frequency 2.5 MHz, TTE t M-Mode, 2D, Doppler (pulsed and continuous wave), color flow mapping in the standard views from all accessible windows were obtained with ECG physio-signal displayed with all detected echo-Doppler study. TTE was done to assess the anatomy, prove the diagnosis and assess cardiac lesion severity.

b) Two dimensional echocardiography: Routine examination was done from the parasternal, apical and sub costal views focusing on the type of congenital heart disease and guidance for M-Mode and color Doppler.

M-Mode echocardiography: Parameters were obtained by the guidance of two dimensional (2-D) echocardiography from the parasternal long axis view, at the level of the papillary muscle and at the level of the aorta and left atrium using the leading edge to measure the following: Left ventricular internal dimensions at the end systole and diastole (LVESD, LVEDD) respectively, fractional shortening (FS%), ejection fraction (EF%) and left atrium diastolic dimension. FS % varies with age (ranges from 35-45%) and EF% normal value is approximately 55-65% in children ***(Lohr and Sivanandam, 2009).***[14]

Estimated systolic pulmonary artery pressure (ESPAP) was calculated through Doppler tracing of the peak velocity of the tricuspid regurgitation jet by using the Bernoulli equation: ESPAS= $4(v)^2$ + RAP where V=Peak velocity of the tricuspid regurgitation jet. An arbitrary 10 mmHg is added to the gradient as the RAP ***(Lopez et al., 2010).***[15]

2.3. STATISTICAL ANALYSIS

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 21. Spearman correlation coefficients were used to assess the relation between two studied parameters in the same group. Receiver operating characteristic curve was used to assess the best cut off point with sensitivity and specificity.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered not significant (NS) if p was > 0.05; significant (S) if p was < 0.05 and highly significant (HS) if p was < 0.01.

3. RESULTS

Table 1 shows demographic data and anthropometric measurements in the study groups. It revealed: no significant difference regarding age and sex while there is significant decrease in Wt and Ht in patients' group compared to their controls.

Table 2 shows significant decrease in weight and height (length) percentiles in patients compared to the controls, 51.4% and 18.1% of patients with congenital heart disease were below 3rd percentile regarding weight and height respectively.

Table 3 shows significant increase in heart rate, respiratory rate and decrease in O_2 saturation by pulse oximetry in patients compared to their controls. Also the same table shows significant increase in CK and H-FABP serum levels in patients compared to their controls.

Table 4 shows comparison between patients' group and the controls regarding conventional echo parameters; it revealed significant decrease in EF% and FS% in patients' group compared to the controls, while it shows significant increase in pulmonary pressure in patients' group compared to the controls.

Fig1 clinical classification of heart failure severity in the study patients'group, it revealed that class II was the commonest, 30 patients (41.7%) followed by class I, 27 patients (37.5%) and finally class III, 15 patients (20.8%).

Table 5 shows comparison between class I, II, III of heart failure severity and H-FABP serum level, it revealed: significant increase in H-FABP in class III and II versus class I; class III showed the highest levels.

Fig 2,3,4 demonstrate correlation between H-FABP with EF%, FS%, and pulmonary pressure, it revealed significant negative correlation between H-FABP with EF% and ES% while it shows positive correlation with pulmonary pressure.

Table 6, fig 5 show the best cutoff point between patients' group and the controls regarding pulmonary pressure was > 18 with sensitivity 86.11% and specificity 100%, while the best cutoff point between patients' group and the controls regarding EF% was < 69 with sensitivity 38.89% and specificity 100% and the best cutoff point between patients' group and the controls regarding FS% was < 37 with sensitivity 41.67% and specificity 100%. Also it shows the best cutoff point between patients' group and the controls regarding H-FABP was > 0.72 with sensitivity 55.56% and specificity 100%.

Table (1): Comparison between the patients' group and the controls regarding demographic data and anthropometric measurements.

Variable	Control group No=30	Patients' group No=72	Independent t-test		Sig
	Mean ± SD	Mean ± SD	t	p-value	
Age (months)	16.47 ± 6.20	12.78 ± 10.89	1.734	0.086	NS
Wt/kg	12.89 ± 1.21	6.99 ± 3.16	-9.904	0.000	HS
Height/cm	84.13 ± 5.48	70.75 ± 13.81	-5.132	0.000	HS
Sex n%					
Female	n.14 46.70%	n.38 52.80%	0.316	0.574	NS
Male	n.16 53.30%	n.34 47.20%			

Table (2): Comparison between patients' group and their controls regarding weight and height percentiles.

Variable		Control group No=30		patients' group No=72		Chi-square test	
		No.	%	No.	%	X^2	P-value
Weight (kg)	below 3rd	0	0.0%	37	51.4%	50.445	0.001
	5-10	0	0.0%	7	9.7%		
	10-25	0	0.0%	7	9.7%		
	25-50	4	13.3%	6	8.3%		
	50-75	12	40.0%	7	9.7%		
	75-90	11	36.7%	6	8.3%		
	90-95	3	10.0%	0	0.0%		
	above 97	0	0.0%	2	2.8%		
Height (cm)	below 3rd	0	0.0%	13	18.1%	53.589	0.001
	3rd	0	0.0%	1	1.4%		
	5-10	5	16.7%	4	5.6%		
	10-25	13	43.3%	2	2.8%		
	25-50	4	13.3%	8	11.1%		
	50-75	4	13.3%	24	33.3%		
	75-90	0	0.0%	15	20.8%		
	90-95	4	13.3%	0	0.0%		
	above 97	0	0.0%	5	6.9%		

Table (3): Comparison between Patients' group and the controls regarding heart rate, respiratory rate, O_2 saturation by pulse oximetry, serum level of CK and H-FABP.

Variable	Control group No=30 Mean ±SD	Patients' group No=72 Mean ±SD	Independent t-test t	p-value	Sig
HR b/m Median (IQR)	109 (104 – 110)	146 (125 – 160)	9.741	0.000	HS
RR c/m	16.00 ± 1.14	41.49 ±16.55	8.400	0.000	HS
O_2sat %	98.27 ± 0.58	97.79 ± 0.41	-4.688	0.000	HS
CKmg/dl	70.70±34.76	131.54±134.98	2.429	0.017	S
H-FABP ng/ml	0.43±0.18	1.61±1.27	5.067	0.000	HS

Table (4): Comparison between patients' group and the controls regarding conventional echo parameters.

Variable	Control group No=30 Mean ± SD	patients' group No=72 Mean ± SD	Independent t-test t/z	p-value	Sig.
LVEDD	2.65 ± 0.66	2.68 ± 0.71	0.198	0.844	NS
LVESD	1.54 ± 0.58	1.64 ± 0.48	0.894	0.373	NS
EF%	76.33 ± 7.27	69.76 ± 7.04	-4.251	0.000	HS
FS%	43.67 ± 6.54	37.60 ± 5.95	-4.556	0.000	HS
Septum/cm	0.48 ± 0.04	0.51 ± 0.11	1.672	0.098	NS
PW/cm	0.53 ± 0.11	0.49 ± 0.12	-1.701	0.092	NS
RV/cm	1.06 ± 0.12	1.15 ± 0.29	1.739	0.085	NS
LA/cm	1.65 ± 0.13	1.77 ± 0.44	1.381	0.170	NS
AO/cm	1.54 ± 0.16	1.44 ± 0.32	-1.634	0.105	NS
Pul pre/ mmhg	14.57 ± 2.05	36.02 ± 18.18	7.241	0.000	HS

LVEDD: left ventricle end diastolic dimensions; LVESD: left ventricle end systolic dimensions; EF: ejection fraction; FS: Fraction shortening; PW: Posterior wall: Pul pre: Pulmonary pressure

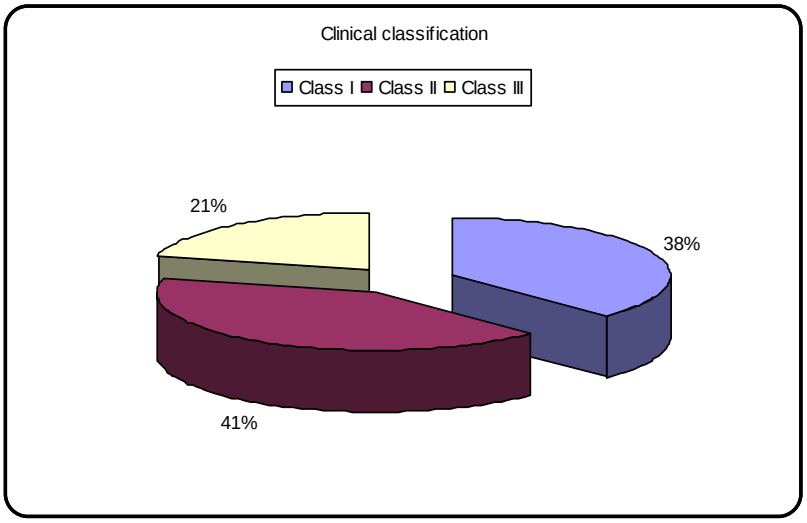

Fig (1): Clinical classification of heart failure severity in children with congenital acyanotic heart disease.

Table (5): Comparison between heart failure subclasses regarding H-FABP serum level.

Clinical classification	H-FABP ng/ml	One Way ANOVA	
	Mean ± SD	F	P-value
Class I	0.52 ± 0.59	50.899	0.000
Class II	1.84 ± 1.12		
Class III	3.12 ± 0.21		
Post hoc test: Tukey's test			
Class I vs. class II	Class I vs. class III	Class II vs. Class III	
< 0.001	< 0.001	< 0.001	

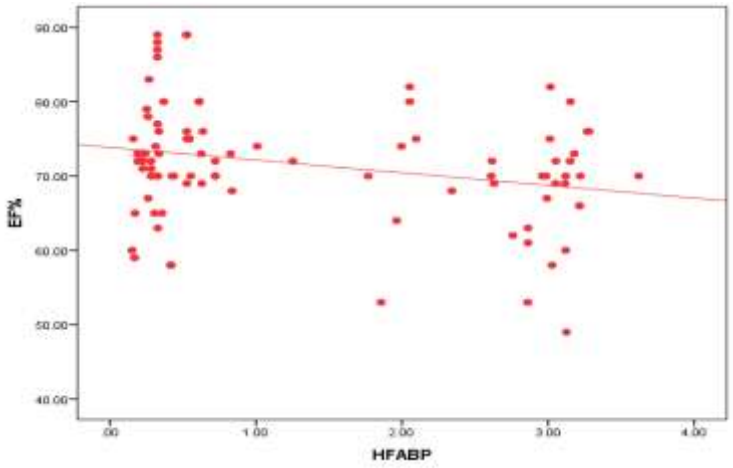

Fig (2): Correlation between H-FABP and EF% in patients' group.

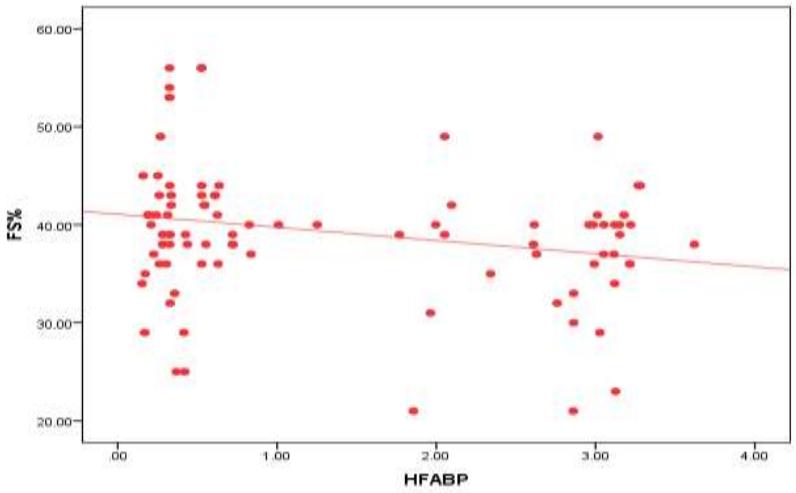

Fig (3): Correlation between H-FABP and FS% in patients' group.

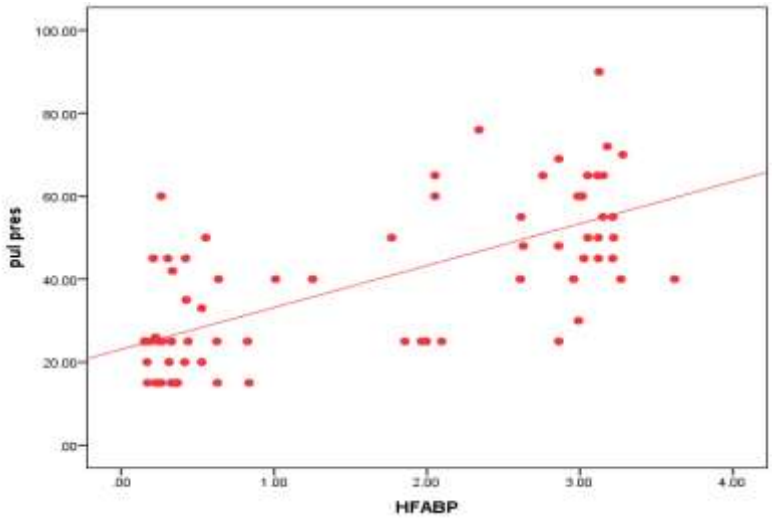

Fig (4): Correlation between H-FABP and pulmonary pressure in patients' group.

Table (6): Cutoff point, sensitivity and specificity regarding pulmonary pressure, EF%, FS% and H-FABP serum level in predicting myocardial cell injury in patients with congenital acyanotic heart disease.

Variable	Cutoff point	AUC	Sensitivity%	Specificity%	+PV	-PV
Mean Pulmonary pressure mmHg	> 18	0.944	86.11%	100.00%	100.0	75.0
EF%	< 69	0.708	38.89%	100.00%	100.0	40.5
FS%	< 37	0.727	41.67%	100.00%	100.0	41.7
H-FABP ng/ml	> 0.72	71.8%	55.56%	100.00%	100.0	48.4

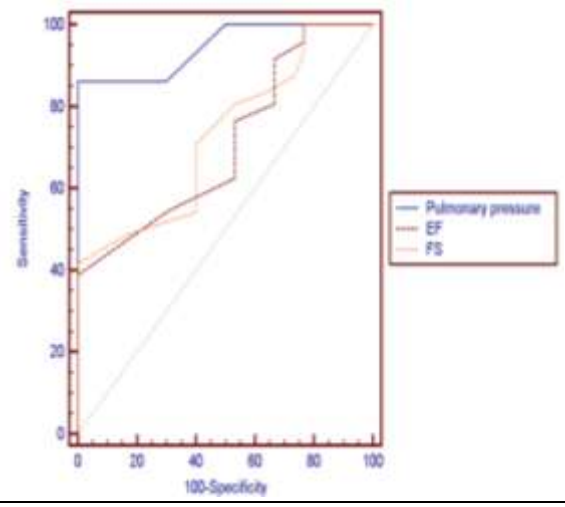

Fig (5): (ROC) of pulmonary pressure, FE% and FS% in predicting myocardial cell injury in patients with congenital acyanotic heart disease.

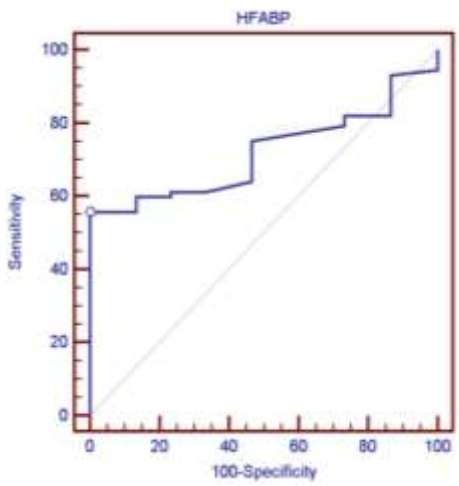

Fig (6): (ROC) of H-FABP in predicting myocardial cell injury in patients with congenital acyanotic heart disease.

4. DISCUSSION

H-FABP is a protein with low molecular weight. It is found at high concentrations in the cytoplasm of cardiac myocytes (4-8%). It is rapidly released into the circulation following myocardial damage ***(Erenler et al., 2013).***[9]

We observed significant increase in the serum H-FABP level in patients with congenital acyanotic disease' group compared to the controls. Our result was in agreement with ***Hayabuchi et al. (2011) and Zhou et al. (2014).***[16,17] who found significant increase in H-FABP serum level in children with congenital acyanotic heart disease. This explained that patients with most congenital heart diseases (CHDs) have specific hemodynamics, including volume and pressure overload, as well as cyanosis and pulmonary hypertension (PH), associated with anatomical abnormalities. These overloads can result in necrosis, apoptosis, and mechanical stressors, such as direct pressure and stretching of myocardial cells, which are believed to cause myocardial damage ***(Sugimoto et al., 2015).***[18]

The present study showed significant decrease in EF% and FS% in patients' group compared to the controls, indicating increased volume and pressure loads in left to right shunt leading to ventricular dysfunction and myocardial remodeling. In agreement with our results, ***Hayabuchi et al. (2011)***[16] reported significant decrease in EF% and FS% in patients with congenital acyanotic heart disease compared to the controls.

We also detected significant increase in pulmonary pressure in patients' group compared to the controls. Pulmonary hypertension results from abnormal constriction development or

obstruction of pulmonary vessels. Severe cases may progress to right heart failure and even death ***(Berger et al., 2012).***[19] Our results were in agreement with ***Ivy et al. (2013).***[20] who reported increased pulmonary pressure in patients with congenital heart disease.

We were not surprised to find that patients with severe form of HF (class III) have higher H-FABP levels than class II and class II more than class I. Because H-FABP is a low molecular weight protein, cytosolic H-FABP is easily released into the circulation through the porous membranes of damaged myocardial cells ***(Viswanathan et al., 2010).***[21]

A significant increase in the serum level of H-FABP that was proportional to the severity of HF and adverse outcome was reported by ***Zoair et al. (2015).***[22]. Similarly, ***Sun et al. (2013).***[23]**,** showed that serum H-FABP levels increase in children with CHF and are closely related to the severity of the condition**.** ***Zhou et al. (2014).***[17] also showed that H-FABP was significantly higher in children with HF than in children without HF. The positive rate of H-FABP was up to 81.8%, and no significant difference was observed in patients with different classes of heart function. This indicates that H-FABP level is up-regulated during the early stage of HF and can be used as a biomarker for early-stage HF. ***Niizeki et al. (2007).***[24] also reported that patients with advanced heart failure had high concentration of H-FABP. They suggested that sustained release of H-FABP reflects the ongoing myocardial injury, and high levels indicate worse prognosis. ***Cabiati et al. (2010).***[25] also reported significant positive correlation between H-FABP and severity of HF.

In our study; we found a significant positive correlation between H-FABP level and pulmonary pressure, and a significant negative correlation between H-FABP level and EF%, FS%. In the same line ***Bursi et al. (2012).***[26]***, Lam et al. (2009).***[27] ***and Guglin and Khan (2010).***[28] reported significant increase in pulmonary pressure with severity of heart failure. Also, ***Zoair et al. (2015).***[22] reported significant negative correlation between serum levels of H-FABP and echocardiographic parameters of LV systolic function (EF% and FS %). Our results were in disagreement with ***Hayabuchi et al. (2011).***[16] who showed that left ventricular contractility did not significantly correlate with serum H-FABP level. Also, ***Fuseya et al. (2014).***[29] showed no significant correlation between H-FABP level and LV end-diastolic dimension, LV ejection fraction or LV mass index. ***Sun et al. (2013).***[23]**,** reported that serum H-FABP concentrations were negatively correlated with LVEF, and LVSF in the CHF group.

Regarding the anthropometric characteristics of the study population, we observed significant decrease in anthropometric measurements including wt and Ht, although this study did not include the aim of evaluating nutritional status, but it reflects the prognosis of chronic diseases.

In the present study; we found that H-FABP serum level has higher sensitivity for the detection of HF among children with congenital acyanotic heart disease as compared to EF% & FS%. This finding demonstrated that early expression of H-FABP appears to occur before evident HF and thus it may be more useful for predicting cardiomyocyte injury in patients with congenital acyanotic heart disease even before marked impairment of ventricular functions.

***Zoair et al. (2015)*[22] *and Chan et al. (2004)*[30]** showed that, using a cutoff point of ≥ 2 ng/ml, H-FABP was valid as a diagnostic predictor of myocardial injury in CHF with high sensitivity and specificity

In conclusion, H-FABP can be used as a diagnostic and prognostic marker of cardiomyocyte injury. Pulmonary pressure is superior than other echocardiographic parameters in predicting severity of heart failure in infants with congenital acyanotic heart disease.

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