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Serum Concentration of Heart-Type Fatty Acid-Binding Protein in Children and Adolescents With Congenital Heart Disease

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Background: Serum heart-type fatty acid-binding protein (H-FABP) is widely applied as a marker of cardiac myocyte injury. Recently, it has been reported that levels of H-FABP are elevated in adult patients with chronic heart failure and thus provide useful prognostic information. The aim of the present study was to examine the relationships between serum H-FABP levels and pathophysiological characteristics in children and adolescents with congenital heart disease (CHD).

Methods and Results: Serum H-FABP levels were preoperatively and postoperatively measured in 238 consecutive patients with CHD aged 1–31 years. The relationships between H-FABP levels and severity of heart failure, circulatory status and laboratory data were cross-sectionally analyzed. Multivariate regression analysis indicated that serum H-FABP levels are independently affected by age, New York Heart Association functional class, creatine kinase MB, creatinine and arterial oxygen saturation (standard regression coefficients, –0.378, 0.237, 0.422, 0.615, and –0.210, respectively). Neither left ventricular ejection fraction nor B-type natriuretic peptide correlated with H-FABP levels.

Conclusions: H-FABP could serve as a new monitoring tool to provide information that will guide the optimal therapy and management of CHD patients. (*Circ J* 2011; **75:** 1992–1997)

Key Words: Chronic heart failure; Congenital heart disease; Hypoxia; Pediatrics

Progressive heart failure is a common problem in patients with preoperative and postoperative congenital heart disease (CHD).[1,2] Patients with chronic heart failure (CHF) have high hospitalization rates and a poor prognosis despite the significant reduction in mortality rates achieved in clinical trials.[1–3] Assessment of prognosis and determination of risk stratification are thus important to prevent readmission. Although many biomarkers have been extensively studied in adults with structurally normal hearts,[4–8] the question of whether they correlate with heart failure in children and adolescents with CHD has not been completely elucidated.

The 14–15-kDa cytoplasmic and non-enzymatic protein heart-type fatty acid-binding protein (H-FABP) transports long-chain fatty acids in cardiomyocytes, and the damaged myocardium rapidly releases them into the circulation.[9–11] Therefore, H-FABP is regarded as an early and sensitive diagnostic marker of acute myocardial infarction. In contrast, serum H-FABP levels are increased in adult patients with advanced heart failure.[12,13] Furthermore, measurement of H-FABP levels is useful to identify patients at high risk and to predict the long-term prognosis of those with CHF.[14]

The clinical value of serum H-FABP levels in children and adolescents with CHD, however, has not yet been elucidated and the determinants that influence serum H-FABP levels are unknown. Therefore, the aim of the present study was to assess the relationship between serum H-FABP and cardiac pathophysiological characteristics in younger patients with preoperative and postoperative CHD.

Methods

Subjects

We prospectively enrolled 238 consecutive patients (130 male, 108 female; mean age 8.5±8.2 years; range, 1–31 years) with CHD who underwent regular check-ups at Tokushima University Hospital to assess worsening CHF between January 2005 and December 2009. Furthermore, we measured serum H-FABP in 20 age-matched normal individuals (control group: mean age, 9.1±4.1 years; range, 1–20 years). The exclusion criteria consisted of clinical or electrocardio-

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graphic evidence suggesting acute cardiac ischemia, renal failure characterized by a serum creatinine concentration of >1.5 mg/dl, and active hepatic or pulmonary diseases. Written, informed consent was obtained from either the enrolled patients or their parents before participation in this study, which was performed with the approval of the Ethics Review Board, Department of Pediatrics, University of Tokushima.

The diagnoses of CHD were confirmed on echocardiography, multidetector-row computed tomography and cardiac catheterization or surgery.

The patients were assigned to groups depending upon cardiac diseases and circulatory conditions as follows. Group 1 (n=80) consisted of patients with preoperative CHD associated with increased pulmonary blood flow (atrial septal defect [ASD], n=21; ventricular septal defect [VSD], n=40; patent ductus arteriosus [PDA], n=12; atrioventricular septal defect [AVSD], n=5; and Ebstein's anomaly with ASD, n=2). Group 2 (n=33) consisted of patients with preoperative CHD associated with decreased pulmonary blood flow (tetralogy of Fallot (TOF), n=15; pulmonary atresia with VSD [PA/VSD], n=8; double outlet right ventricle [DORV], n=2; single ventricle, n=5; and tricuspid atresia, n=3). Twenty-five patients in this group had received systemic pulmonary shunts. Group 3 (n=34) consisted of patients with totally repaired CHD associated with increased pulmonary blood flow (ASD, n=7; VSD, n=16; PDA, n=3; AVSD, n=7; VSD with coarctation, n=1). Group 4 (n=62) consisted of patients with totally repaired CHD associated with decreased pulmonary blood flow (TOF, n=32; PA/VSD, n=17; transposition of great arteries with pulmonary stenosis, n=5; DORV, n=5; and pulmonary atresia with intact ventricular septum, n=3). Group 5 (n=29) consisted of patients who had undergone the Fontan operation (after the Bjork procedure, n=1; after atriopulmonary connection, n=8; after the lateral tunnel procedure, n=4; and total cavopulmonary connection, n=16). The interval between the operation and measurement of H-FABP was 3.5±4.1 years (range, 0.5–18 years) in groups 3, 4, and 5.

Arterial oxygen saturation (SO_2) was measured transcutaneously using fingertip pulse oximetry. An experienced cardiologist without knowledge of the biochemical data examined the patients on 2-dimensional echocardiography within 1 week after blood sampling. Clinical data, including age, gender and New York Heart Association (NYHA) functional class, and laboratory data were obtained from interviews of the patients or their parents and from hospital medical records. The NYHA classification was originally defined as limitations to physical activity caused by symptoms of undue fatigue, palpitations, dyspnea or angina due to cardiac disease.[15] Class I indicated no limitations to activity; patients in class II had these symptoms during ordinary physical activity; patients in class III had symptoms with less than ordinary activity and those in class IV had symptoms at rest. Some investigators have developed a categorical system to grade congestive heart failure in children as follows.[16,17] Patients in class I have no limitations or symptoms; those in class II exhibit mild tachypnea or diaphoresis during feeding when infants, or dyspnea on exertion when older, and retarded growth; patients in class III show marked tachypnea or diaphoresis upon feeding or exertion and prolonged feeding times with growth retardation; patients in class IV have symptoms at rest with tachypnea, retractions, grunting or diaphoresis. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method according to the recommendations of the American Society of Echocardiography.[18]

Table 1. Patient Characteristics

Age (years)	8.5±8.2 (1–31)
Gender (M/F)	130/108
NYHA functional class (I/II/III)	191/39/8
Diseases	
Group 1 (n=80)	ASD 21; VSD 40; PDA 12; AVSD 5; Ebstein/ASD 2
Group 2 (n=33)	TOF 15; VSD/PA 8; DORV 2; SV 5; TA 3
Group 3 (n=34)	ASD 7; VSD 16; PDA 3; AVSD 7; VSD/CoA 1
Group 4 (n=62)	TOF 32; VSD/PA 17; TGA/PS 5; DORV 5; PPA 3
Group 5 (n=29)	Bjork 1; APC 8; lateral tunnel 4; TCPC 16
Blood examination	
H-FABP (ng/ml)	2.6±1.5 (1.1–10.0)
BNP (pg/ml)	58.1±106.3 (2.3–804.0)
RBC ($\times 10^4$/ml)	468.2±73.5 (341–884)
Hb (g/dl)	13.4±2.2 (8.3–21.8)
EPO (mU/ml)	33.1±42.0 (8.4–276.0)
CK (IU/L)	110.0±61.8 (20–420)
CK-MB (IU/L)	20.4±10.4 (3–68)
BUN (mg/dl)	12.9±4.6 (4–41)
Creatinine (mg/dl)	0.41±0.21 (0.17–1.31)
SO_2 (%)	96.4±7.1 (65–100), $SO_2 \geq 90\%$ 199; $SO_2 < 90\%$ 39
Echocardiography	
LVEF (%)	67.4±11.1 (30–84), LVEF ≥50% 109; LVEF <50% 29
Drug treatment	
Loop diuretics	32
Spironolactone	29
Digoxin	7
ACE inhibitor or ARB	9
HOT	5
PMI	8

NYHA, New York Heart Association; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; VSD/PA, VSD with pulmonary atresia; DORV, double outlet right ventricle; SV, single ventricle; TA, tricuspid atresia; VSD/CoA, VSD with coarctation; TGA/PS, transposition of great arteries with pulmonary stenosis; PPA, pure pulmonary atresia; APC, atriopulmonary connection; TCPC, total cavopulmonary connection; H-FABP, heart-type fatty acid-binding protein; BNP, B-type natriuretic peptide; RBC, red blood cell; Hb, hemoglobin; EPO, erythropoietin; CK, creatinine kinase; CK-MB, creatine kinase MB; BUN, blood urea nitrogen; SO_2, arterial oxygen saturation; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; HOT, home oxygen therapy; PMI, pacemaker implantation.

Assay of Serum H-FABP, B-Type Natriuretic Peptide (BNP), and Erythropoietin Levels

Blood samples were centrifuged at 2,500×g for 15 min at 4°C within 30 min of collection, and serum samples were stored at –70°C until analysis. Levels of H-FABP were measured using a 2-step sandwich enzyme-linked immunosorbent assay kit (MARKIT-M H-FABP; Dainippon Pharmaceutical, Tokyo, Japan). The calibrators for the assay covered the range 1–250 ng/ml. Plasma BNP concentrations were measured on chemiluminescent enzyme immunoassay using a

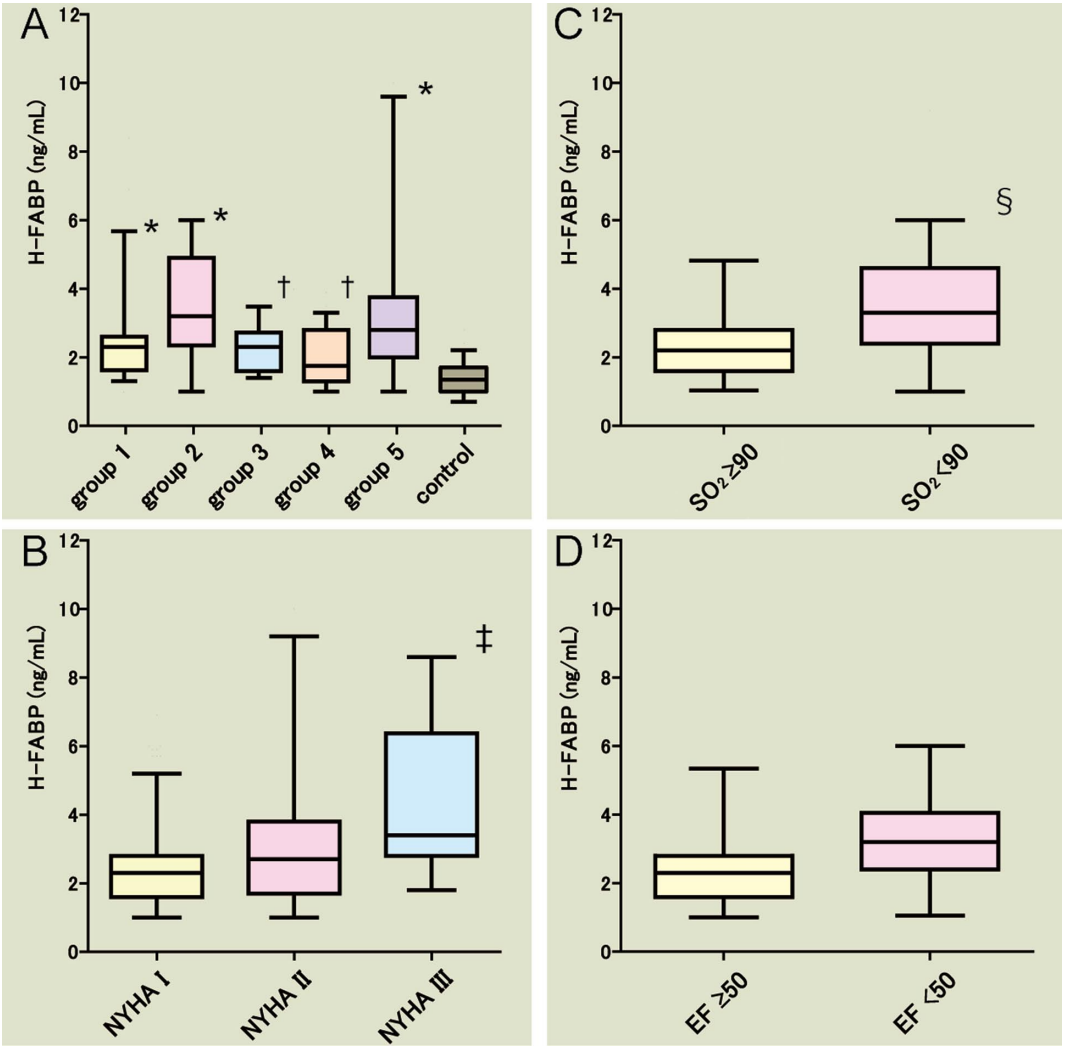

Figure. Heart-type fatty acid-binding protein (H-FABP) level vs. patient group. Patients were assigned to groups depending on (**A**) type of cardiac disease, (**B**) arterial oxygen saturation (SO_2), (**C**) New York Heart Association (NYHA) functional class, and (**D**) left ventricular ejection fraction (LVEF). Boxes, distribution of serum H-FABP level (25th and 75th percentiles; central line, median). Vertical lines, range between 5th and 95th percentiles. *P<0.01 vs. control group and <0.05 vs. groups 3 and 4; †P<0.05 vs. control group; ‡P<0.0001 vs. NYHA classes I and II; §P<0.001 vs. SO_2≥90%.

commercially available kit (PATHFAST, Mitsubishi Chemical Medience, Tokyo, Japan). Serum erythropoietin concentrations were determined by radioimmunoassay according to manufacturer instructions (Mitsubishi Chemical Medience, Tokyo, Japan).

Statistical Analysis

Data are presented as mean±SD or medians with 5th–95th percentiles. Statistical significance was determined using the Kruskal–Wallis and Mann–Whitney tests. Independent predictors selected on univariate analysis were entered into multivariate analysis. All statistical calculations were performed using Windows Excel 2007 (Microsoft, Redmond, WA, USA) and Prism version 5.0 (GraphPad Software, San Diego, CA, USA) installed on a desktop computer. P<0.05 was considered statistically significant.

Results

Patient Characteristics and H-FABP

The mean age of the enrolled patients was 8.5±8.2 years; 55% of them were male and 45% were female. Most of them (80%) were assessed as being in NYHA functional class I, and 16% and 4% were assessed as being in classes II and III, respectively. LVEF was reduced to <50% in 29 patients (21%), and arterial oxygen saturation was <90% in 29 (16%). The baseline characteristics of the patients are shown in **Table 1**. No patients died during the follow-up period.

The initial evaluation of H-FABP levels among the 5 groups classified according to disease indicated significant differences (**Figure A**; P<0.001). Serum H-FABP level in the control group was 1.57±0.73 ng/ml (median, 1.67 ng/ml). These 5 patient groups had significantly higher serum H-FABP levels than the control group (P<0.05 or P<0.01). Serum H-FABP

Table 2. Patients Grouped According to Cardiac Disease

	Group 1 (n=80)	Group 2 (n=33)	Group 3 (n=34)	Group 4 (n=62)	Group 5 (n=29)
Age (years)	6.4±6.2 (1–18)	4.3±6.6 (1–16)	11.3±8.8 (2–29)	8.5±7.7 (2–28)	15.8±9.7 (3–31)
Gender (M/F)	46/34	15/18	20/14	38/24	11/18
NYHA functional class					
I	71	21	34	51	14
II	9	10	0	10	10
III	0	2	0	1	5
SO_2					
≥90%	80	5	34	62	18
<90%	0	28	0	0	11
LVEF					
≥50%	77	31	32	51	18
<50%	3	2	2	11	11

Abbreviations see in Table 1.

Table 3. Regression Analysis With H-FABP as Dependent Variable

	Uunivariate		Mmultivariate			
	R^2	P value	β	SE	t	P value
Age	0.027	0.011	–0.378	0.020	–3.445	0.001
Gender	0.002	0.810	–	–	–	–
NYHA functional class	0.079	<0.0001	0.237	0.176	3.980	<0.001
BNP	0.012	0.086	–	–	–	–
RBC	0.154	0.056	–	–	–	–
Hb	0.001	0.820	–	–	–	–
EPO	0.015	0.056	–	–	–	–
CK	0.069	0.001	–	–	–	–
CK-MB	0.164	<0.0001	0.422	0.011	5.403	<0.0001
BUN	0.001	0.885	–	–	–	–
Creatinine	0.143	0.003	0.615	0.769	5.628	<0.0001
SpO_2	0.061	<0.0001	–0.210	0.169	–3.350	0.001
LVEF	0.155	0.071	–	–	–	–

Abbreviations see in Table 1.

levels were significantly higher in groups 1, 2 and 5 than in groups 3 and 4 (P<0.05 for each). Groups 1, 2 and 5 did not significantly differ. The patient characteristics of each group are listed in Table 2.

Figure B shows the relationship between serum H-FABP level and NYHA functional class. The H-FABP level in patients in NYHA class III was significantly higher than that in patients in NYHA classes I and II (4.31±2.32 ng/ml, median 3.40 ng/ml vs. 2.43±1.16 ng/ml, median 2.30 ng/ml, and 3.17±2.14 ng/ml, median 2.70 ng/ml, respectively; P<0.0001). We assigned the patients to groups based on SO_2 ≥90% and <90% (Figure C). H-FABP levels were higher among patients with SO_2 <90% than ≥90% (3.58±1.78 ng/ml, median 3.30 ng/ml; 2.43±1.32 ng/ml, median 2.20 ng/ml; P<0.001). We then compared serum H-FABP levels between patients with preserved and reduced LVEF and found no significant difference between them (Figure D).

Correlation of H-FABP Levels With Physiological Variables

Univariate and multivariate regression analyses of clinical variables are given in Table 3. Age, NYHA functional class, creatine kinase (CK), CK-MB, and SO_2 were identified as determinants of serum H-FABP level. After multivariable adjustment, age, NYHA class, CK-MB, creatinine and SO_2 were significantly associated with H-FABP level (standard regression coefficients, –0.378, 0.237, 0.422, 0.615, and –0.210, respectively). Thus, aging, clinical heart failure, myocardial cell injury (CK-MB), renal function (creatinine) and oxygen saturation appeared to significantly correlate with H-FABP level. In contrast, gender, anemia, liver dysfunction, BNP level and left ventricular contractility did not significantly correlate with serum H-FABP level.

Discussion

The present study is the first to measure serum H-FABP level in various types of patients with CHD. We have shown that serum H-FABP level depends on the type of congenital cardiovascular disease and circulatory status. Preoperative patients with CHD with either increased or decreased pulmonary flow (groups 1 and 2) had higher H-FABP levels than postoperative patients (groups 3 and 4). The patients in group 5 had higher levels of serum H-FABP after Fontan procedure than after other kinds of repair (groups 3 and 4). This finding is presumed to have resulted from cardiac overload and the severity of heart failure in each group. Furthermore, we found that age, NYHA functional class, CK-MB, serum creatinine and oxygen saturation were associated with serum H-FABP level in children and

adolescents with CHD. Elevated circulating H-FABP level is considered a highly sensitive marker of ongoing myocardial damage in patients with CHF.[12,13] Details of the mechanism of deterioration in cardiac function associated with ongoing myocardial damage among patients with CHF remain obscure, but ventricular remodeling, cardiomyocyte necrosis, apoptosis, autophagic degeneration, microcirculatory disorders, chronic inflammation, oxidative stress, loss of myocytes with myocardial fibrosis and reductions in myofibril content have been suggested.[19–22]

Here, we showed that the serum level of H-FABP correlated with NYHA functional class. This result is compatible with other findings from adults with CHF.[12] The present data suggest that H-FABP is sensitive to ongoing myocardial damage in CHF and can identify patients with CHD who are at high risk for CHF. Arterial oxygen saturation also affected serum H-FABP levels. Hypoxia might stimulate the release of H-FABP,[23] induce ventricular remodeling and damage cardiomyocytes. Furthermore, renal function influenced serum H-FABP levels in a large group of adult volunteers.[24] Like BNP,[25] serum H-FABP levels correlated with renal function in the present study. Because renal function is an important determinant of future cardiac events in patients with heart failure, these data also support a cardio-renal association in patients with CHD.

We found that BNP and H-FABP levels were not correlated with each other. Levels of BNP and H-FABP predict adverse cardiac events in patients with CHF. The ventricle secretes BNP upon mechanical overload and thus it is the most established neurohormonal marker of pressure and/or volume overload.[26,27] In contrast, H-FABP is a marker of ongoing myocardial cell injury.[9–11] These pathophysiological aspects might be associated with the absence of a correlation.

Study Limitations

The present study had several limitations. The sample size was relatively small and thus follow-up studies of larger cohorts are needed to enable generalized correlations between serum H-FABP and pathophysiological parameters in children and adolescents with CHD. Moreover, the normal range of serum H-FABP level in infants, children, and adolescents is unknown. The influence of body weight, height, gender and age on H-FABP level should be elucidated in this population.

The NYHA classification is not appropriate for pediatric application because functional capacity and responses to states of heart failure differ between children and adults.[17,28] Children have an obviously different cardiac physiology, clinical presentation and compensatory mechanisms from adults. Moreover, the etiologies of heart failure in children are also very different from those in adults. Although several studies have developed scales that are useful for grading the severity of heart failure in infants and children,[17,28] a convenient and non-invasive heart failure index for use among pediatric patients of all ages does not exist. Therefore, we applied a proposed modified NYHA classification. When a novel appropriate classification is determined for infants and children, analyses of the relationships between biomarkers and symptoms of clinical heart failure will become more precise.

We did not identify an association between serum H-FABP levels and the prognosis of patients with CHD. There were no patients who had died during the follow-up period. Thus, future studies of a large cohort are necessary to define the prognostic value of H-FABP in patients with CHD.

Conclusions

The present data have demonstrated that serum H-FABP level is affected by age, clinical heart failure symptoms (NYHA functional class), arterial oxygen saturation, myocardial cell injury (CK-MB), and renal function (creatinine). These effects should be considered when determining appropriate reference values for H-FABP in patients with CHD. Levels of H-FABP can serve as a new monitoring tool to provide information that could guide the optimal therapy and management of patients with CHD.

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