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Serum Heart-Type Fatty Acid Binding Protein Predicts Cardiac Events in Elderly Patients With Chronic Heart Failure

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Abstract

Background and Objectives. Heart-type fatty acid binding protein (H-FABP) is released into the circulation from the damaged myocardium of patients with severe chronic heart failure. Chronic heart failure is the most frequent cause of death and disability in the elderly. However, there are no data for the prognostic value of H-FABP in the elderly population. This study investigated whether H-FABP can effectively predict the prognosis in elderly patients ($\geq$ 70 years) with chronic heart failure.

Methods. Serum H-FABP levels were measured in 90 chronic heart failure patients $\geq$ 70 years old (mean age 77 $\pm$ 4 years, range 70–92 years), and patients were followed-up for 421 $\pm$ 326 days.

Results. There were 35 cardiac events (38.9%) including cardiac deaths and readmissions for worsening chronic heart failure. Multivariate analysis with the Cox proportional hazard model showed that H-FABP was the only independent predictor of cardiac events ($\chi^2 = 6.640$, $p = 0.0100$). Kaplan-Meier analysis revealed that H-FABP effectively risk stratified elderly patients with chronic heart failure for cardiac events.

Conclusions. These findings suggest that H-FABP is a reliable marker for prognosis in elderly patients with chronic heart failure.

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Key Words

■**Heart failure** ■**Prognosis (heart-type fatty acid binding protein)** ■**Elderly**

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INTRODUCTION

The incidence and prevalence of chronic heart failure increase dramatically with advancing age[1−3]. The first diagnosis of chronic heart failure is established at age > 65 and > 80 years in 88% and 49% of patients, respectively[4]. Chronic heart failure is associated with a variety of pathophysiological changes, which trigger deterioration of ventricular function and disease progression[5]. Increasing age is associated with higher mortality among heart failure patients[6−8]. However, the prognostic assessment of elderly patients with chronic heart failure still remains unclear.

Cardiac biomarkers continue to be important in the evaluation and risk stratification of patients presenting with possible heart failure. However, prognostic parameters in elderly patients have not been definitively identified, because the most common presentations of chronic heart failure in this population (dyspnea, edema, reduced exercise tolerance, *etc.*) may be caused by other common diseases in the elderly such as pulmonary disease, obesity, orthopedic limitations, or simply deconditioning. Therefore, objective parameters are needed to identify and assess the severity of the disease.

Several studies have shown that heart-type fatty acid binding protein (H-FABP), a low molecular weight protein (about 15 kDa) that is abundant in the cytosol of cardiomyocytes, is rapidly released into the circulation from the damaged myocardium[9−11], and serum levels of H-FABP are increased in patients with advanced heart failure[12]. We previously demonstrated that H-FABP is a promising novel marker for myocardial cell injury and prognosis in patients with heart failure[13]. Ongoing myocardial cell injury documented by elevated serum levels of H-FABP is also critical in the pathophysiology of chronic heart failure[12−15].

The present study investigated whether H-FABP can effectively predict the prognosis in the elderly patients (≥ 70 years) with chronic heart failure. Serum H-FABP levels were measured at admission and the association with subsequent cardiac events examined in 90 consecutive patients hospitalized for chronic heart failure during a mean follow-up period of 421 ± 326 days.

SUBJECTS AND METHODS

Study design

This prospective study included 90 consecutive patients (45 men and 45 women, mean age 77 ± 4 years, range 70−92 years) admitted for the treatment of worsening chronic heart failure, for the diagnosis and pathophysiological investigation, or for therapeutic evaluation of heart failure from April 1996 to April 2004. Baseline characteristics of the patients are presented in **Table 1**. Exclusion criteria were clinical or electrocardiographic evidence suggestive of acute coronary syndrome within 3 months preceding admission, renal failure characterized by serum creatinine concentration ≥ 1.5 mg/m*l*, and active hepatic or pulmonary disease. Informed consent was obtained from all patients

Table 1 Clinical characteristics of 90 patients with chronic heart failure

	All patients (n=90)
Age (yr)	77±4
Sex (male/female)	45/45
NYHA functional class (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	16/32/34/8
Hypertension	53 (59)
Diabetes mellitus	22 (24)
Hyperlipidemia	17 (19)
Current smoking	16 (18)
Etiology of chronic heart failure	
Dilated cardiomyopathy	34 (38)
Ischemic heart disease	22 (24)
Valvular heart disease	16 (18)
Hypertensive heart disease	12 (13)
Tachycardia-induced cardiomyopathy	6 (7)
Blood examination on admission	
H-FABP (ng/m*l*)	7.17±5.18
BNP (pg/m*l*)	626±742
Echocardiography on admission	
LVEDd (mm)	52±10
LVEF (%)	51±19
Medical treatment	
ACE inhibitors and/or ARBs	64 (71)
Beta-blockers	34 (38)
Calcium channel blockers	27 (30)
Spironolactone	24 (27)
Loop diuretics	61 (68)
Digoxin	34 (38)
Statins	14 (16)

Continuous values are mean±SD. ( ): %.
NYHA=New York Heart Association; H-FABP=heart-type fatty acid binding protein; BNP=brain natriuretic peptide; LVEDd=left ventricular end-diastolic dimension; LVEF=left ventricular ejection fraction; ACE=angiotensin converting enzyme; ARB=angiotensin Ⅱ receptor blocker.

before participation in this study, and the protocol was approved by the Human Investigations Committee of our institution.

Blood samples were obtained on admission for measurement of serum H-FABP and plasma brain natriuretic peptide (BNP) levels. Two-dimensional echocardiography was performed by experienced personnel within 1 week of measurements of biochemical markers.

End-points and follow-up

No patients were lost to follow-up (mean follow-up 421 ± 326 days, range 5−1,080 days) after admission to Yamagata University Hospital. Events were adjudicated using medical records, electrocardiograms, chest radiographs, autopsy reports, death certificates, and witness statements[13]. The end points were 1) cardiac death, defined as death from worsening heart failure or sudden cardiac death, and 2) worsening heart failure requiring readmission. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

Assay of H-FABP levels

Blood samples were obtained on admission for measurements of serum concentrations of H-FABP. H-FABP concentrations were measured using a two-step sandwich enzyme-linked immunosorbent assay kit (MARKIT-M H-FABP, Dainippon Pharmaceutical Co Ltd.) as reported previously[13].

Statistical analysis

Results are presented as mean ± SD values for continuous variables and as the percentage of total patients for categorical variables. The independent sample *t*-test and chi-square test or linear regression analysis were used for comparison of continuous and categorical variables, respectively. Values below the lower detection limit of the assay were defined as zero. A value of $p < 0.05$ was considered statistically significant. Cox proportional hazard analysis was performed to determine the independent predictor of cardiac events for the entire population. Independent predictors selected by univariate analysis were investigated by multivariate analysis. The cardiac event-free curve was calculated according to the Kaplan-Meier method and compared by the log-rank test. Statistical analysis was performed with a standard statistical program package (StatView, version 5.0, SAS Institute Inc.).

RESULTS

Relationship between H-FABP levels and severity of chronic heart failure in the elderly

Based on the criteria from a previous study[14], H-FABP levels were high (≥ 4.3 ng/m*l*) in 5 of 16 patients (31.3%) in New York Heart Association (NYHA) functional class Ⅰ, in 19 of 32 patients (59.4%) in functional class Ⅱ, in 26 of 34 patients (76.5%) in functional class Ⅲ, and in 8 of 8 patients (100%) in functional class Ⅳ ($p < 0.001$). Patients with high H-FABP levels had significantly lower left ventricular ejection fraction than those with normal H-FABP levels (47 ± 20% vs 59 ± 13%, $p = 0.0058$). Left ventricular end-diastolic dimension was not significantly different between patients with high and normal H-FABP levels (53 ± 9.6 vs 48 ± 9.6 mm, $p = 0.0871$). H-FABP levels were not different between patients with ischemic and non-ischemic heart disease (5.7 ± 2.9 vs 7.7 ± 5.6 ng/m*l*, $p = 0.1175$). In addition, H-FABP levels were not different between patients with and without dilated cardiomyopathy (7.4 ± 5.7 vs 6.4 ± 4.7 ng/m*l*, $p = 0.971$).

Clinical outcome in elderly chronic heart failure

All patients were followed-up completely. There were 4 noncardiac deaths (2 suicides, 1 cerebral hemorrhage, and 1 gastric cancer) and 35 cardiac events (38.9%), including 15 cardiac deaths (2 in-hospital deaths) and 20 readmissions for worsening heart failure during a mean follow-up period of 421 ± 326 days. Twenty-two of all cardiac events (62.9%) occurred within 12 months after admission (2 in-hospital cardiac deaths, 10 cardiac deaths, and 12 readmissions for worsening heart failure). The cause of the cardiac death was worsening chronic heart failure in 11 patients, fatal acute myocardial infarction in 2 patients and sudden death in 2 patients. The causes of the 2 in-hospital cardiac deaths were worsening chronic heart failure.

Clinical characteristics were compared between patients with and without cardiac events (**Table 2**). Patients with cardiac events had more severe NYHA functional class ($p < 0.001$), higher rates of hypertension ($p = 0.0429$), and higher levels of H-FABP ($p = 0.0349$) compared with those without cardiac events. Other parameters including age, sex, the number of patients with ischemic heart dis-

Table 2 Clinical characteristics of 90 patients with and without cardiac events

	Event free (n=55)	Cardiac event (n=35)	p value
Age (yr)	77±4	77±6	0.8534
Sex (male/female)	25/30	20/15	0.2796
NYHA functional class	2.2±0.8	2.7±0.8	<0.001
Hypertension	37(67)	16(63)	0.0429
Diabetes mellitus	15(27)	7(20)	0.4296
Hyperlipidemia	9(16)	8(23)	0.4464
Current smoking	7(13)	5(14)	0.3427
Etiology of chronic heart failure			
Dilated cardiomyopathy	18(33)	16(46)	
Ischemic heart disease	15(27)	7(20)	
Valvular heart disease	12(22)	4(11)	
Hypertensive heart disease	5(9)	7(20)	
Tachycardia-induced cardiomyopathy	5(9)	1(3)	0.2089
Blood examination on admission			
H-FABP (ng/m*l*)	6.25±4.88	8.61±5.37	0.0349
BNP (pg/m*l*)	574±779	706±684	0.4141
Echocardiography on admission			
LVEDd (mm)	50±8	53±11	0.1148
LVEF (%)	53±17	48±21	0.2542

Continuous values are mean±SD. ( ): %.
Abbreviations as in Table 1.

Table 3 Cox proportional hazard analysis for cardiac events

Variable	Univariate analysis		Multivariate analysis	
	χ^2	p value	χ^2	p value
H-FABP	10.97	0.0009	6.640	0.0100
NYHA functional class	9.984	0.0187	3.784	0.2858
Hypertension	9.157	0.0025	3.592	0.5812
Calcium channel blockers	4.802	0.0284	0.789	0.3745
BNP	5.557	0.0184	0.071	0.7892

Variables with significance by univariate analysis at a p level of <0.05 were entered into the multivariate analysis.
Abbreviations as in Table 1.

ease, levels of BNP, and left ventricular ejection fraction were not significantly different between patients with and without cardiac events. Medical treatment with digitalis, angiotensin converting enzyme (ACE) inhibitors, angiotensin type II receptor blockers, statins, calcium antagonists, and β-blockers was also similar in both groups.

Independent predictors of cardiac events in the elderly population

Univariate and multivariate Cox proportional hazard analyses to identify predictors of cardiac events are summarized in **Table 3**. H-FABP, NYHA functional class, hypertension, calcium channel blockers, and BNP were significantly associated with subsequent cardiac events by univariate analysis. These five parameters were entered into multivariate analysis. Multivariate analysis showed H-FABP was the only independent predictor of cardiac events in elderly patients with chronic heart failure ($\chi^2 = 6.640, p = 0.0100$).

Kaplan-Meier curves were constructed for patients with normal and high serum H-FABP lev-

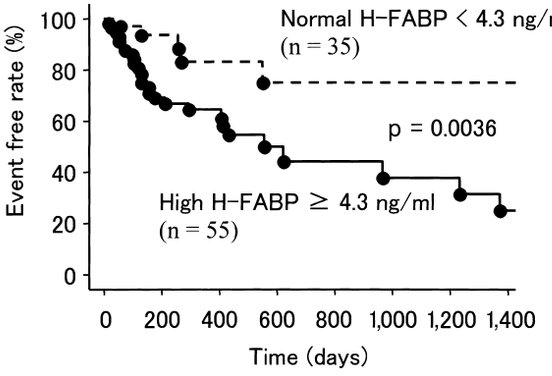

Fig. 1 Kaplan-Meier analysis of cardiac event-free rate in patients with chronic heart failure stratified into two groups based on the H-FABP values
Abbreviation as in Table 1.

els(**Fig. 1**). Patients with high H-FABP levels(≥ 4.3 ng/m*l*) had significantly higher cardiac event rates than those with normal H-FABP levels(＜4.3 ng/m*l*). H-FABP could reliably risk stratify elderly patients for cardiac events.

DISCUSSION

The present study showed that elevated serum level of H-FABP was an independent predictor of cardiac events in elderly patients with heart failure (aged＞70 years). These data suggest that the release of H-FABP, a cytosolic protein, from the damaged myocardium to the systemic circulation is critical for future cardiac events in elderly patients hospitalized for chronic heart failure. Measurements of H-FABP levels on admission is a novel method for the early risk stratification of elderly patients with chronic heart failure.

H-FABP in heart failure

H-FABP is rapidly released into the circulation when the myocardium is injured[10−12]. H-FABP leaks from cardiomyocytes in patients with severe heart failure[12−14]. This phenomenon may reflect ongoing myocardial damage in patients with severe heart failure, and several possible mechanisms such as cardiomyocyte necrosis, apoptosis, microcirculatory disorder, chronic inflammation, and oxidative stress have been suggested[12−15].

Study limitations

In this study, biochemical markers were measured only on admission, although serial measurements may be more informative. In addition, although high levels of plasma BNP are associated with cardiac events in patients with chronic heart failure[16], high plasma levels of BNP were not associated with cardiac events in elderly patients with chronic heart failure in this study. One possible reason is that BNP was not selected as a significant predictor in the elderly patients with heart failure (＞70 years), since the plasma levels of BNP increase with advancing age. Secondly, BNP is not as useful in patients with mild heart failure of NYHA class Ⅰ and Ⅱ as in patients with severe heart failure[17]. In the present study, more than 50% of patients had NYHA class Ⅰ and Ⅱ(16 and 32 patients, respectively). Finally, further studies with more patients are necessary to better delineate the utility of BNP in elderly patients with chronic heart failure.

Heart failure in the elderly population

The detailed mechanisms behind the increased mortality in older patients with heart failure are still unclear[6−9]. Ageing is associated with important structural and functional changes in the vascular system and the heart, but little is known about how ageing interacts with the pathophysiology underlying the process of developing heart failure. Our present data suggest that ongoing cardiomyocyte damage might be involved in this pathological process.

Older patients are less frequently treated with drugs that have a documented effect on mortality such as ACE inhibitors and β-blockers[5−8]. In the present study, rates of ACE inhibitor and β-blocker use were low. Higher frequency of contraindications or fear of side effects in the elderly are likely explanations. Also, a possible smaller effect on mortality of ACE-inhibition or β-blockade in older patients with heart failure has been reported. These findings could have discouraged some physicians from initiating therapy in this aged group. In addition, the present study started prior to the publication of the positive results of the major β-blocker trials in heart failure[18,19]. As the population achieves increased longevity, more research is needed to clarify the interaction between ageing and the heart failure syndrome.

CONCLUSIONS

H-FABP is a reliable marker for prognosis in elderly patients with chronic heart failure. This measurement should be included in routine clinical evaluations.

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要　　約

血清中の心臓型脂肪酸結合蛋白は高齢者心不全症例の予後予測因子である

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背景と目的：重症心不全症例では，血清中に心臓型脂肪酸結合蛋白（H-FABP）が検出される．心筋細胞が傷害されているために，血中に流出したと考えられている．一方，高齢者の心不全症例が近年増加している．また，高齢者の死亡原因として心不全の頻度は高い．しかし，高齢者心不全の予後を予測する因子はこれまでに十分に検討されていない．本研究の目的は，高齢者心不全症例（70歳以上）の予後を予測する因子として，H-FABPの有用性を検討することである．

方　法：90例の高齢者心不全症例（平均年齢77±4歳，範囲70−92歳）において血清中のH-FABP濃度を測定し，心血管事故の発生について平均421±326日間の追跡調査を行った．

結　果：追跡期間中，心血管死と心不全による入院を含む35件（38.9%）の心事故の発生を認めた．Cox比例ハザード解析では，H-FABPは高齢者心不全症例の予後を予測する唯一の独立した危険因子であった（$\chi^2=6.640$，$p=0.0100$）．Kaplan-Meier解析でもH-FABPは高齢者心不全のリスクの判別に有用であることが示された．

結　論：H-FABPは高齢者心不全の予後予測に有用であった．

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