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Abstract

Objectives: To investigate the relationship between the plasma B-type natriuretic peptide (BNP) level and the occurrence of atrial fibrillation (AF) in nonobstructive hypertrophic cardiomyopathy (HCM) patients.

Methods: Patients (n=97) were classified into chronic AF (CAF; n=14), paroxysmal AF (PAF; n=18) and normal sinus rhythm (NSR; n=65) groups. The plasma BNP values were analyzed with logarithmic transformation.

Results: The PAF group showed significantly higher plasma BNP levels than the NSR group [mean (range; -lSD and +1SD); 248.3 (143.5, 429.5) vs 78.2 (27.9, 218.8 ng/L), $p<0.0001$]. The CAF group also showed significantly higher plasma BNP levels than the NSR group [291.1 (161.4, 524.8 ng/L), $p<0.0001$]. Multivariate analysis with other clinical factors selected association of PAF as one of the factors that increased the plasma BNP level.

Conclusions: The present study indicated that plasma BNP level is clinically useful for identification of nonobstructive HCM patients who have a risk of PAF.

Keywords: clinical study, cardiomyopathy, tachyarrhythmia, enzyme immunoassay, peptide, sensitivity and specificity

Introduction

B-type natriuretic peptide (BNP) is a peptide hormone derived from atrial and ventricular cardiomyocytes [1-3]. Circulating plasma BNP levels have been well documented to be elevated in conditions characterized by various cardiac overloads [3-7]. BNP activation reflects hemodynamic alterations and left ventricular dysfunction. The plasma BNP level thus provides prognostic information and is an important clinical tool [1, 8-10]. Atrial fibrillation (AF) causes ventricular hemodynamic alterations as well as atrial overload, and the plasma BNP level has also been reported to be increased in patients with AF [11], even after controlling for demographic and clinical variables [12]. Conversely, cardioversion from AF to sinus rhythm decreased the plasma BNP level [13-15].

AF is a common complication of hypertrophic cardiomyopathy (HCM), with an incidence ranging between 10 and 40% [16-19]. AF causes deterioration in hemodynamic conditions, progression of heart failure and increased risk of thromboembolism in HCM [20, 21]. Treatment of association of paroxysmal AF (PAF) usually requires anticoagulant and/or antithrombotic therapy. The opportunity for detection of PAF is thought to be low in nonobstructive HCM patients compared

with obstructive HCM patients or HCM patients with heart failure, since the latter two types of patients require extensive treatment and frequent examination. From these considerations, even in nonobstructive HCM patients in the early phase of HCM, detection of PAF at an early time is quite important with respect to choosing a treatment strategy.

Based on these reported findings, we hypothesized that the plasma BNP level would be elevated in HCM patients, including nonobstructive HCM patients, with PAF compared to those with normal sinus rhythm (NSR). There are, however, no studies that measured plasma BNP levels in nonobstructive HCM patients in connection with AF. Accordingly, we determined plasma BNP levels in nonobstructive HCM patients and compared the values among nonobstructive HCM patients with NSR, those with PAF and those with chronic AF (CAF).

Patients and methods

Enrollment of outpatients with nonobstructive HCM in the present study was carried out from July, 2001 to December, 2005 at Sakakibara Hospital (Okayama, Japan) and Takamatsu Red Cross Hospital (Takamatsu, Japan). Patients with pathological conditions other than arrhythmia status associated with HCM that cause an increase in

plasma BNP level were excluded from the study. The underlying pathological conditions for the exclusion were disturbed renal function (serum creatinine greater than our institutional normal range: 100 μmol/L), lung disease, hypertension and other organic heart disease such as valvular heart disease. From a clinical standpoint, classification of HCM based on hemodynamic overload is important. Patients with subaortic, outflow tract and midventricular obstruction at rest or on provocation were excluded from the present study. Patients with decreased left ventricular systolic function [left ventricular ejection fraction (LVEF) < 50%] or with heart failure [New York Heart Association (NYHA) functional class ≥ III] were also excluded from the present analysis. During enrollment of patients in the present study, among a total of 122 HCM outpatients, 21, 2 and 2 patients had outflow tract obstruction, heart failure with NYHA functional class ≥ III and LVEF < 50%, respectively. The present study finally included 97 outpatients with nonobstructive HCM without significantly reduced ventricular performance. The patients' clinical characteristics are listed in Table 1. The study was in compliance with the rules of the Helsinki Declaration, informed consent was obtained from all these patients, and the study was approved by institutional ethics committee for human research [22].

We determined plasma BNP levels during NSR within 3 months (mean±SD, 1.7±0.8, range 1 to 3 months) after an AF episode in 18 patients with PAF. AF was demonstrated by 12-lead ECG when patients visited our hospital with symptoms of palpitation, dyspnea and/or chest discomfort. PAF was diagnosed based on guidelines for the management of AF [23]. Plasma BNP was measured at the time of enrollment in 14 patients with CAF, which was defined as ECG documentation of AF at the time of plasma BNP measurements and electrocardiographic AF documentation in every visit to our outpatient clinic [23]. In addition, plasma BNP levels were determined at the time of enrollment in 65 nonobstructive HCM patients with NSR, which was defined as NSR in 12-lead ECG recorded at every visit for outpatients or in Holter ECG examination, and the absence of any symptoms that suggested transient AF attacks. We followed-up these patients until February 2007 and the follow-up periods were > 1 year (4.39±2.00 years; 1.1 - 6.8 years) after the initial measurement of plasma BNP level. We followed these patients basically once every 4 - 8 weeks at our out-patient clinic. During the follow-up period, we examined the 12-lead ECG and carefully checked symptoms that suggested transient AF attacks. Holter ECG was not recorded at scheduled intervals and was performed only when needed. No patients with PAF or NSR progressed to recurrent persistent AF or permanent AF, at

least within 1 year after the plasma BNP measurements. Patients with NSR and CAF showed stable conditions for at least 1 year after the plasma BNP measurements.

Blood sampling

As stated above, blood sampling was performed during NSR within 3 months after an AF episode in PAF patients and the time of enrollment in CAF and NSR patients. Blood was drawn from a peripheral vein into ethylenediaminetetraacetic acid-containing tubes and plasma was immediately separated. Plasma BNP levels in all samples were subsequently determined immediately using a sandwich fluoroenzyme immunoassay method with automatic immunoassay equipment (AIA 600II, TOSOH, Tokyo, Japan) with a reagent kit [E test, TOSOH II (BNP)] at the central laboratory of each hospital (Sakakibara Hospital and Takamatsu Red Cross Hospital) by medical technologists who were experienced experts in bioassays and not aware of the any clinical information about the patients. The measurements were thus completed within less than 30 minutes. This assay system uses two monoclonal antibodies against human BNP: one recognizing the carboxy-terminal sequence (amino acids 27-32) and the other the ring structure of human BNP (amino acids 14-21), and does not cross react with atrial or C type natriuretic peptide [24, 25]. Both antibodies

were supplied by Shionogi & Co., Ltd. (Osaka, Japan) and have been widely used to demonstrate the clinical usefulness of BNP measurements. BNP measurements were performed according to manufacturer's instruction manual and calibration was performed by a 6-point calibration using BNP samples with known concentrations with appropriate timing, as indicated by the instruction manual. The upper reference value is 18.4 ng/L, with a detection limit of 1.9 ng/L. The intra-assay coefficient of variation in the automated assay system was 2.1%, 1.9% and 1.1% at 32.5, 185.3 and 715.0 ng/L, respectively. The coefficient of variation for between-run reproducibility was 1.3%, 1.2% and 1.7% at 30.0, 180.0 and 696.4 ng/L, respectively.

Echocardiographic Measurements

Transthoracic M-mode, two-dimensional and Doppler echocardiography were performed using Toshiba SSA390A equipment (Toshiba Medical Systems, Tokyo, Japan) on the day of plasma BNP measurements or within 2 weeks after plasma BNP measurements. All examinations were performed by 2 medical technologists who were experienced experts in echocardiographic measurements and not aware of the clinical background of the patients. Echocardiographic recordings were performed in the long-axis parasternal plane and in the apical four- and two-chamber plane.

Measurements were made according to the guidelines laid down by the American Society of Echocardiography [26]. The left atrial dimension (LAD) and left ventricular end-diastolic (LVEdD) and end-systolic dimension (LVEsD) were assessed by M-mode echocardiography in a standard fashion. LV hypertrophy was determined with two-dimensional echocardiographic recordings according to established criteria [27]. The greatest thickness measured at any site in the LV wall was considered to represent maximal LV wall thickness [16]. Peak instantaneous LV outflow gradient was estimated under basal conditions with continuous-wave Doppler [28]. Diagnosis of HCM was based on echocardiographic features of a hypertrophied, non-dilated LV in the absence of other cardiac or systemic diseases that cause cardiac hypertrophy [19, 29].

Statistics

Because the distribution pattern of plasma BNP values did not appear to be normal, and the values were considerably shifted to one side, the values were transformed into a common logarithm (LogBNP) [30]. Data are expressed as mean±SD range. The t-test or Mann-Whitney U test was used to compare data between the 2 groups when appropriate. We employed one-way analysis of variance (ANOVA) for comparison

of 3 groups' data. Bonferroni's post-hoc t-test was also used to assess the differences of data between any 2 of the CAF, PAF and NSR groups. Area under the curve (AUC) and optimum cutoff level of each factor were determined by analyses of receiver operating characteristic curves (ROC curves). In ROC curves, when various cutoff values were selected, the relationship between the values of (sensitivity) and (1-specificity) were plotted. The optimum cutoff was determined as the value that maximized the likelihood ratio (LR) obtained using the formula: LR = (sensitivity)/(1 -specificity) [31]. In other words, diagrammatically, the optimum cutoff can be chosen as the value that minimizes the distance from the upper left corner of the plot frame. The 95% confidence intervals for sensitivity and specificity were obtained using an appropriate program for a small number of cases that employs the relationship between inverse F-distribution, inverse beta function and binomial to get the "exact" binomial confidence interval [32, 33]. In patients with PAF and NSR, stepwise linear regression analysis was also performed with BNP as the dependent variable. Independent variables enrolled were association with PAF, age, gender, echocardiographic indices (LAD, LVEdD, LVEsD), drugs used, and association with diabetes mellitus. A p value of < 0.05 was considered significant.

Results

Plasma BNP levels

The PAF group showed significantly higher plasma BNP levels than the NSR group [plasma LogBNP level: 2.395±0.238 vs 1.893±0.447; plasma BNP level: mean (range –l SD and +1SD): 248.3 (143.5, 429.5) vs 78.2 (27.9, 218.8 ng/L) $p<0.0001$] (Fig. 1). There was not a large overlap of plasma LogBNP level between the PAF and NSR groups. The CAF group also showed significantly higher plasma BNP levels than the NSR group [plasma LogBNP levels: 2.464±0.256; plasma BNP levels: 291.1 (161.4, 524.8 ng/L) $p<0.0001$]. There were, however, no significant differences in plasma BNP levels between the PAF and CAF groups.

ROC curve analysis was performed to obtain cutoff values of the plasma BNP level for distinguishing the PAF group from the NSR group (Fig. 2). The area under the ROC curve (AUC) was 0.84 [standard error (SE) 0.05; 95% confidence interval (CI), 0.75 - 0.92; $p<0.001$), which indicted that plasma BNP level was useful for distinguishing HCM patients with PAF from those with NSR. The specificity-sensitivity curve indicated that 72.3% specificity (95% CI, 59.8 - 82.7%) and 83.3% sensitivity (95% CI, 58.6 - 96.4%) were obtained with a cut-off value of

151.4 ng/L (plasma LogBNP level; 2.18) for distinguishing the PAF group from the NSR group.

Relationship of plasma BNP level with echocardiographic indices

Plasma LogBNP level was significantly correlated with LAD ($r=0.47$, $p<0.0001$). There were, however, no significant differences in LAD between the PAF group (43.4±10.4 mm) and the NSR group (39.9±4.9 mm), and therefore no significant AUC was obtained in the ROC analysis. There was no significant correlation between plasma LogBNP level and LVEdD or LVEsD, and no significant differences in either of these dimensions between the PAF and NSR groups.

Drugs

There were no significant differences in plasma LogBNP levels between patients with compared to without drug treatment in the whole set of patients or in any sub-group of patients.

Multivariate Analysis

The results of stepwise multiple linear regression analysis are shown in Table 2. The

stepwise analysis selected association of PAF as one of the factors that increased plasma BNP ($p<0.0001$).

Discussion

The present study revealed that patients with PAF showed significantly higher plasma BNP levels than patients with NSR. ROC curve analysis revealed that plasma BNP level was clinically useful to identify HCM patients at risk for PAF.

The present results showed that plasma BNP levels were elevated even in nonobstructive HCM patients with NSR. Similar plasma BNP levels have been reported in nonobstructive HCM with NSR [34]. Another study observed similar plasma BNP levels in HCM patients of NYHA functional class I [35]. These reported results were in good agreement with the present results. Markedly elevated plasma BNP levels have been demonstrated in obstructive HCM and HCM with heart failure compared to uncomplicated nonobstructive HCM [34, 35]. These lines of evidence indicate that to examine the effects of AF on plasma BNP levels in HCM patients, it is essential to consider underlying pathological hemodynamic overload conditions. The present study therefore excluded HCM patients with LV obstructive condition, heart

failure or decreased LVEF and focused on identification of nonobstructive HCM patients with PAF. The fact that the basal data were identical with reported results indicated that the present analytical methods were valid.

The present results demonstrated that plasma BNP level was associated with AF. Increased plasma BNP level in patients with lone AF has recently been demonstrated [36]. Moreover, PAF patients without any structural heart disease have also been shown to exhibit increases in plasma BNP levels [37]. Our finding that plasma BNP levels were elevated, with mean values in decreasing order for CAF, PAF and NSR, were completely in agreement with these recently reported results.

The present study indicated that plasma BNP level may provide considerable information for distinguishing the PAF group from the NSR group. Although the present study did not find significant differences in LAD between nonobstructive HCM patients with PAF and those with NSR, there are reports of the detection of PAF patients with HCM using other markers such us echocardiographic measurements and 12-lead electrocardiographic findings [38-40]. LAD dimension, LA volume determined with area length methods and p wave duration obtained by signal-averaged electrocardiogram have also been used to attempt to detect association of PAF in HCM patients, and have been reported to possess similar distinguishing powers to those of

plasma BNP level. These measurements impose certain inconveniences on patients. Furthermore, these measurements require skillful and stable techniques, time-cost and/or special equipment for determination. In contrast, blood sampling itself for plasma BNP measurements does not have these disadvantages. Although plasma BNP measurements require precise standardization, plasma BNP level measured carefully using the automated equipment employed in the present study is clinically useful to identify HCM patients who have a risk for development of CAF.

There were no significant differences in LVEdD or LVEsD between patients with PAF and those without. In addition, plasma LogBNP level was not significantly correlated with these indices. Only HCM patients with preserved LV function and without outflow pressure gradient were enrolled in the present study. This strict patient selection may account for the lack of a significant difference in plasma LogBNP levels between the groups, and for the dissociation of plasma LogBNP levels and these LV indices. The present results comparing plasma BNP levels and echocardiographic indices among the 3 groups of HCM patients suggested that plasma BNP level was more sensitive than echocardiographic indices for detecting cardiac overloading caused by AF.

There were several limitations in the present study. First, it included a relatively

small number of patients due to the careful patient selection. Our careful patient selection based on theoretical criteria may have compensated for this limitation, and the fact that our results were consistent with those of reports that examined only HCM patients and patients with lone AF support this idea. Furthermore, significant and clinically useful differences between HCM patients with PAF and those with NSR were demonstrated by careful statistical analyses. This limitation was thus not a major weakness of the present study. Second, the relationship of the extent of PAF, that is, the frequency and duration of PAF, and plasma BNP level could not be clarified. Precise documentation of the frequency and duration of PAF was generally impossible. The present results, however, showed that plasma BNP level would at least be useful for identifying HCM patients with symptomatic PAF that occurred recently.

In conclusion, the present study indicated that plasma BNP level is clinically useful for the identification of HCM patients who have a risk of PAF.

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Figure Legends

Figure 1.

Box-plot representation of the common log transformed plasma BNP levels (LogBNP) distribution among HCM patients with normal sinus rhythm (NSR), those with paroxysmal atrial fibrillation (PAF) and those with chronic atrial fibrillation (CAF). Lines within boxes represent medians. The lower and upper boundaries of the boxes mark the 25^{th} and 75^{th} percentiles, and the bars below and above the boxes indicate the 10^{th} and 90^{th} percentiles. P, probability value.

Figure 2.

Receiver operating characteristic curves of logarithmic transformed plasma BNP level (LogBNP) for distinguishing paroxysmal AF (PAF) group from normal sinus rhythm (NSR) group. AUC, area under the curve.

Table 1. Patients' Characteristics

	NSR	PAF	CAF	p
Cases	65	18	14	
Age (years)	62.3 ± 12.1	62.4 ± 10.1	72.7 ± 7.4	<0.01
Gender (M:F)	42 : 23	14 : 4	10 : 4	ns
SBP (mmHg)	119.7 ± 10.1	120.1 ± 10.7	115.9 ± 12.6	ns
DBP (mmHg)	70.1 ± 9.0	71.4 ± 7.3	66.9 ± 8.4	ns
Diabetes mellitus (%)	5 (7.7)	3 (16.7)	3 (21.4)	ns
Drugs				
β blocker (%)	41 (63.1)	10 (55.6)	2 (14.3)	<0.005
ARB or ACEI (%)	26 (40.0)	6 (33.3)	8 (57.1)	ns
Verapamil (%)	6 (9.2)	3 (16.7)	5 (35.7)	<0.05
Diuretics (%)	0	0	0	/

M, male; F, female; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table 2. Results of stepwise multiple linear regression analysis

dependent variable	selected factors	regression coefficient	standard error of regression coefficient	standardized regression coefficient	partial correlation coefficient	p
BNP	association of PAF	159.22	32.90	0.4477	0.4829	0.00001
	LAD	6.31	2.23	0.2621	0.3067	0.00597
	β blocker	60.93	27.29	0.2023	0.2466	0.02847
	diabetes mellitus	-95.05	45.96	-0.1914	-0.2294	0.04199
	age	2.05	1.16	0.1612	0.1981	0.08012
			multiple regression coefficient r=0.623, p<0.0001			

BNP, B-type natriuretic peptide; PAF, paroxysmal atrial fibrillation; p, probability value. Use of values for each selected factor was as follows: association of PAF as 1, NSR as 0; LAD, actual values; β blocker, administered as 1, non-administered as 0; diabetes mellitus, association with diabetes mellitus as 1, without as 0; age, actual values.