Clinical Characteristics of Heart Disease Patients With a Good Prognosis in Spite of Markedly Increased Plasma Levels of Type-B Natriuretic Peptide (BNP)

— Anomalous Behavior of Plasma BNP in Hypertrophic Cardiomyopathy —

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Background Although it is not rare to encounter patients with plasma B-type natriuretic peptide (BNP) levels unequivalent to the severity of heart failure (HF), there has been little investigation to clarify the causative background of this phenomenon.

Methods and Results Among the 1,838 outpatients whose plasma BNP was measured, persistently increased levels of BNP above 500 pg/ml was observed for more than 6 months in 14 subjects with few HF symptoms. Among these, all of 4 patients without any following cardiac events (E-/high) for 12 months showed hypertrophic nonobstructive cardiomyopathy (HNCM). When we compared the clinical parameters of these patients with those of 22 HNCM patients without any following cardiac events whose plasma BNP levels were less than 200 pg/ml, there were only 2 clinical characteristics to be distinguished: (i) plasma renin activity (PRA) and nor-epinephrine (NE) levels were low in spite of markedly increased levels of plasma BNP in E-/high HNCM; and (ii) echocardiographic investigation revealed that only global left atrial fractional shortening was significantly lower in E-/high HNCM.

Conclusions Plasma BNP levels do not always reflect the severity of HF in HNCM. It might be considered to utilize other clinical parameters such as NE and PRA to recognize HF severity in such patients. (*Circ J* 2005; 69: 277–282)

Key Words: Heart failure; Hypertrophic cardiomyopathies; Natriuretic peptides; Prognosis

Type-B natriuretic peptide (BNP) is a predominantly ventricle-derived, cardiac neurohormone that promotes natriuresis and reduces vascular tone in an endocrine fashion to relieve heart failure (HF) status! As plasma levels of BNP are associated well with the severity² and prognosis^{3,4} of HF, BNP is now widely used as a useful clinical marker for differential diagnosis^{5–7} and adequate management^{8,9} for HF. It is not rare, however, to encounter patients with plasma BNP levels unequivalent to the severity of HF. This finding might suggest that BNP levels should be individually evaluated according to the patients' background including basal cardiac diseases.

In the present study, we focused on the profiles of clinically-stable outpatients with markedly increased plasma

BNP levels in spite of few HF symptoms, especially those with hypertrophic cardiomyopathy (HCM). The causative mechanism of the discrepancy between HF severity and plasma BNP levels is discussed.

Methods

Study Patients

The study population consisted of a consecutive series of 1,838 outpatients whose plasma concentration of BNP was measured at Kitasato University Hospital from January 2001 to July 2002. Among these, 42 patients who were admitted because of HF exacerbation soon after the BNP measurement and 7 patients with end-stage renal failure with hemodialysis were excluded from the analyses.

Clinical Measurement of HF

At the outpatient visit on the first measurement of plasma BNP, functional capacity according to the New York Heart Association (NYHA) was classified and clinical status including physical exams, blood tests, chest X-rays and ultrasound echocardiograms (UCG) were undertaken. Survival and cardiac events of HF exacerbation recognized by medical intensification or hospital admission were assessed at 12-month follow-up from the first measurement of plasma BNP.

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Table 1 Comparison of Basal Characteristics Between Stable Outpatients Whose Plasma Type-B Natriuretic Peptide (BNP) was Markedly Increased With and Without Following Cardiac Events

	E+/high	E-/high	
n	10	4	
Age	67±10	68±18	NS
Men:women	8:7	1:3	NS
NYHA			
I	8	4	NS
II	2	0	
III	0	0	
IV	0	0	
Basal heart disease			
HCM	0	4	
DCM	3	0	
IHD	7	0	
LVDd (mm)	5.4±0.4	5.0±0.3	NS
LVEF (%)	35.8±9.8	64.7±3.6	<0.01
(IVSt + PWt)/2 (mm)	9.4±1.9	15±2.0	<0.01
BNP (pg/ml)	596±117	565±51	NS
Hb (g/dl)	11.3±3.9	13.9±0.6	NS
Cre (mg/dl)	1.1±0.2	1.0±0.1	NS

E+/high, patients with persistently increased levels of plasma BNP above 500 pg/ml for more than 6 months who had cardiac events during the 12 months follow up period; E-/high, patients with persistently increased levels of plasma BNP above 500 pg/ml for more than 6 months who had no cardiac events during the same follow up period; NYHA, New York Heart Association; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; IVSt, wall thickness of interventricular septum; PWt, left ventricular posterior wall thickness; Hb, hemoglobin; Cre, serum creatinine; NS, not significant.

Venous blood samples for neurohumoral factors were taken from an antecubital vein after 15 min of rest. Plasma BNP and type-A natriuretic peptide (ANP) were determined by immunoradiometric assay (Shionoria BNP/ANP®). Plasma renin activity (PRA) was measured using the radioimmunoassay (RIA) double-antibody method, and the plasma aldosterone concentration (PAC) was measured using the RIA solid-phase method. Plasma norepinephrine (NE) was determined by high-performance liquid chromatography.

Pulmonary capillary wedge pressure (PCWP) was estimated by 2 blind observers using radiographic pulmonary vasculature and alveolar/interstitial edema as Turner has reported!¹⁰ Briefly, presumed PCWP was calculated using 5-grade estimation according to the pulmonary capillary redistribution compared with the upper and lower lung, and interstitial edema of chest X-rays at the upright position. The inter- and intra-observer variance was less than 5%.

M-mode images of UCG were obtained in left parasternal long-axis views using a SONOS 500 (Hewlett Packard, USA) to measure chamber dimensions and wall thicknesses. Global left atrium fractional shortening (gLAFS: $100 [(LAd_{max} - LAd_{min}) / LAd_{max}]$ (LAd_{max} , maximum left atrial (LA) diameter at the ventricular end-systole; LAd_{min} , minimum LA diameter at the end of atrial contraction)¹¹ and left ventricular (LV) mass (LVM: $1.04 [(IVSt + LVDd + PWt)^3 - LVDd^3] - 13.6$) (IVSt, wall thickness of intraventricular septum; LVDd, LV end-diastolic dimension; PWt, LV posterior wall thickness)¹² were calculated as previously reported. The LV ejection fraction (LVEF) was derived from 2-dimensional apical 4-chamber views with a modified Simpson's rule algorithm.¹³ The transmitral pulsed Doppler velocity recordings were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction, respectively, and deceleration time was the interval from the E-wave peak to the decline of the velocity to baseline. The peak instantaneous LV outflow tract (LVOT) gradient

was estimated under basal conditions with continuous-wave Doppler and the patients with hypertrophic cardiomyopathy (HCM) with a LVOT gradient >30 mmHg were classified as having hypertrophic obstructive cardiomyopathy (HOCM). The diagnosis of HCM was made according to the definition and classification proposed by the World Health Organization/International Society and Federation of Cardiology Task Force!⁴

Soon after UCG analysis, thallium-201 (²⁰¹Tl) myocardial scintigraphy was performed by peak exercise using a multi-stage bicycle ergometer or intravenous infusion of dipyridamole (0.57 mg/kg) in HCM patients. Stress-induced myocardial ischemia was defined as the presence of a reversible regional perfusion abnormality at the late phase redistribution in the images of single-photon emission computed tomography (SPECT). In patients without specific electrocardiographic findings for LV hypertrophy including ST-T strain pattern who rejected the scintigraphy, more than 0.2 mV of ST-segment depression at peak exercise during the treadmill exercise stress test was considered to be positive for myocardial ischemia.

All the study subjects signed informed consent forms before the study, and the study protocol was approved by the research council of our institution.

Statistical Analysis

Statistical analyses were performed by the Mann-Whitney U-test. Data are expressed as mean ± SD. Statistical significance was defined as $p < 0.05$.

Results

Persistently increased levels of plasma BNP above 500 pg/ml were observed for more than 6 months in 14 (0.78%, out of 1,789) outpatients. There were no lethal events in these patients during a 12-month follow-up. However, 10 patients (7 with ischemic heart disease and 3 with dilated cardiomyopathy) had cardiac events with HF

Fig 1. Comparison of plasma type-B natriuretic peptide (BNP) levels among patients with hypertrophic cardiomyopathy (HCM). The plasma BNP was higher in E-/high nonobstructive hypertrophic cardiomyopathy (HNCM) than not only that in E-/low HNCM but also most of hypertrophic obstructive cardiomyopathy (HOCM).

E-/high, event-free HNCM patients with persistently increased levels of plasma BNP above 500pg/ml for more than 6 months; E-/low, event-free HNCM patients with plasma BNP less than 200pg/ml.

Table 2 Comparison of Patients' Characteristics Including Ultrasound Echocardiograms (UCG) Findings and Neurohumoral Factors Between Event-Free Hypertrophic Nonobstructive Cardiomyopathy (HNCM) With High and Low Levels of Plasma BNP

	E-/high HNCM	E-/low HNCM	
<i>n</i>	4	22	
Age	68±18	58±12	NS
Men: women	1:3	15:7	NS
NYHA			
I	4	21	NS
II	0	1	
III	0	0	
Af	1	1	NS
HR (/min)	62±7	65±5	NS
sBP (mmHg)	116±12	129±10	NS
Hb (g/dl)	13.9±0.6	14.5±2.9	NS
Cre (mg/dl)	1.0±0.1	1.0±0.1	NS
p-PCWP (mmHg)	11±3	10±1	NS
Positive for MI	0	2	NS
UCG findings			
LVEF (%)	64.7±3.6	61.6±3.6	NS
IVSt (mm)	18.5±3.1	17.3±1.9	NS
PWt (mm)	11.2±2.0	11.4±1.5	NS
IVSt/PWt (mm)	1.5±0.3	1.5±0.2	NS
LAd (mm)	44.5±4.6	45.5±8.4	NS
DCT (ms)	218±59	239±43	NS
E/A	0.97±0.7	0.95±0.45	NS
gLFAS (%)	10.3±3.0	17.9±5.4	<0.05
LVOT-PG (mmHg)	6.6±5.2	8.2±8.1	NS
LVMI (g/m ²)	270±53	223±34	NS
Neurohumoral factors			
BNP (pg/ml)	565±51	108±63	<0.01
ANP (pg/ml)	173±70	57±40	<0.01
PRA (ng/ml/h)	0.6±0.5	1.8±1.2	<0.05
PAC (pg/ml)	52±26	79±47	NS
NE (pg/ml)	498±232	704±321	NS
BNP/NE	1.3±0.5	0.3±0.2	<0.01

E-/high, event-free HNCM patients with persistently increased levels of plasma BNP above 500pg/ml for more than 6 months; E-/low, event-free HNCM patients with plasma BNP less than 200pg/ml; Af, atrial fibrillation; HR, heart rate; sBP, systolic blood pressure; p-PCWP, pulmonary capillary wedge pressure presumed by radiographic pulmonary vasculature; MI, myocardial ischemia; LAd, left atrium dimension; DCT, deceleration time; E/A, the ratio of E wave to A wave; gLFAS, global left atrium fraction shortening; LVOT-PG, left ventricular outflow pressure gradient; LVMI, left ventricular mass index; ANP, type-A natriuretic peptide; PRA, plasma renin activity; PAC, plasma concentration of aldosterone; NE, plasma norepinephrine.

exacerbation (E+/high) during an observational period, while all 4 patients without any following cardiac events (E-/high) had hypertrophic nonobstructive cardiomyopathy (HNCM) as basal heart diseases (Table 1).

To investigate the clinical characteristics and causative mechanisms of paradoxical phenomenon as E-/high, we compared the clinical parameters of these 4 E-/high HNCM patients with those of another 22 consecutive clinically-stable HNCM patients without following cardiac events whose plasma BNP levels were less than 200 pg/ml (E-/low), as well as 9 HOCM patients. The plasma BNP was higher in E-/high HNCM (565 ± 51 pg/ml), not only in E-/low HNCM (108 ± 63 pg/ml), but also in most of HOCM (387 ± 238 pg/ml) (Fig 1). Among estimated clinical parameters for neurohumoral factors, PRA, PAC and NE was low in spite of markedly increased levels of plasma BNP in E-/high HNCM. The significant difference of the ratio of BNP to NE between the 2 groups of HNCM demonstrated the discrepancy between plasma BNP and NE, a representative biomarker for HF severity¹⁵ other than BNP, in E-/high HNCM (Table 2). However, the UCG study demonstrated that there was no significant difference of LV diastolic properties implied from transmitral Doppler flow, LVM and LVOT pressure gradients between E-/high and E-/low HNCM. gLFAS was the only echocardiographic parameter to significantly differentiate these 2 groups. There was no significant difference of positive myocardial ischemia between E-/high HNCM (n=0) and E-/low HNCM (n=2) (Table 2).

Discussion

The plasma level of BNP is determined under the balance sheet between myocardial production and peripheral clearance of BNP. In addition to the secretion from the kidney, enzymatic and receptor clearance pathways contribute to natriuretic peptide clearance through neutral endopeptidase and the guanylyl cyclase (GC)-A and GC-C receptors, respectively.¹⁶ It has been reported that renal dysfunction, age, anemia, or gender could influence these clearance pathways to cause elevation of plasma BNP levels.¹⁷⁻²⁰ We could not, however, find any significant difference of such clinical parameters as to affect BNP clearance between E-/high and E-/low HNCM (Table 2).

However, BNP release appeared to be directly proportional to ventricular volume expansion and pressure overload.²¹ Nevertheless, there were no significant differences of hemodynamic status which could influence ventricular wall stress such as systemic blood pressure or the degree of LVOT obstruction between the 2 HNCM groups (Table 2). As clinically stable outpatients with few HF signs were focused on in the current study, we had to utilize noninvasive clinical parameters to imply LV overload. Doppler-derived transmitral velocity profiles are routinely used to evaluate LV diastolic properties together with LV filling pressure.²² However, this is not the case with HCM; gLAFS from the M-mode echocardiographic profiles of the left atrium, not mitral Doppler indexes, has a reverse correlation with left ventricular end-diastolic pressure (LVEDP).¹¹ Although the significantly lower gLAFS could suggest that elevated LVEDP might be one of the causes of increased BNP in the E-/high HNCM. However, pulmonary venous pressure presumed from pulmonary vasculature in chest X-rays according to Turner's calculation¹⁰ was not elevated in this group. Why did the E-/high HNCM patients have

few signs of pulmonary congestion in spite of elevated LVEDP? Braunwald and Frahm reported the relationship between mean LA pressure (MLAP) and LVEDP using direct intracardiac pressure measurement.²³ Unlike the subjects with normal cardiovascular systems, the LVEDP exceeded MLAP by 9 mmHg on average in patients with left ventricular hypertrophy, especially with concomitant elevated LVEDP. Although the specific mechanism was not clarified, the volume of blood contributed by atrial systole might be greater than normal in the patients with LVH as the thickened LV wall presumably results in diminished compliance. Hence the dissociation between LVEDP and LA internal pressure in determining the symptoms of left heart failure could be the causative mechanism of the clinically stable status without pulmonary congestion in spite of elevated LVEDP in E-/high HNCM.

Another point of view to explain the mechanism of increasing BNP production is the pathophysiology of myocardial hypertrophy in HCM. It is known that natriuretic peptides are overexpressed in hypertrophied myocardium as a result of retranscription of embryonic cardiac-specific genes.²⁴ Although it is certain that the plasma BNP levels are increased in hypertensive patients with left ventricular hypertrophy leading to LV diastolic dysfunction,²⁵ the mean value of plasma BNP in such patients appears to be approximately 40 pg/ml, as reported in Japanese subjects.²⁶ This means that the mechanism of the markedly increased levels of plasma BNP in some cases with HCM might differ from that in hypertensive heart disease. Hasegawa et al.²⁷ speculated that increased levels of plasma BNP disproportional to LVEDP or LVM^{28,29} in HOCM could be contributed to morphological changes such as interstitial fibrosis and myocardial disarray. In the present study histological assessment by cardiac biopsy was not performed because the study patients were clinically stable outpatients. Genetic analyses have shown causal mutation of genes encoding cardiac sarcomere proteins,³⁰ suggesting impaired force production³¹⁻³³ associated with the inefficient use of adenosine triphosphate (ATP) as the crucial disease mechanism.³² Therefore, hypertrophy could possibly be a means of compensation for low force generation although precise pathomechanisms have not yet been clarified.³⁴ Elucidating the causative mechanisms for myocardial hypertrophy could lead to understanding of the setting of plasma BNP levels through myocardial BNP production in HCM. Moreover, it has been reported that concomitant myocardial ischemia could induce the elevated plasma BNP in HCM;³⁵ myocardial ischemia was not evidently observed in E-/high HNCM.

Various circulating neurohumoral factors that increase in patients with HF are thought to play important roles in the pathogenesis of HF. Neurohumoral systems including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, vasopressin, endothelin, and natriuretic peptides cooperatively modulate both vascular tone and the retention of salt and water.² The natriuretic peptide family including BNP plays important roles to diminish neurohumoral activation for HF exacerbation.^{2,5} Inversely, neurohumoral activation, namely from RAAS and the sympathetic nervous system, induces the release and secretion of natriuretic peptides.³⁶ This means that the activity of accelerating factors such as NE and protective factors such as BNP should be simultaneously altered in HF.³⁷ We could notice in the current study, however, that plasma PRA and NE were disproportionately low to the markedly increased

levels of plasma BNP in E-/high HNCM. This could be derived from the different form of secretion into the systemic bloodstream. Circulatory NE in blood is secreted from sympathetic nerve terminals and the majority of which are located in peripheral vessels, some in the adrenal medulla, and only a few in the myocardium.³⁸ The major site of release of circulating renin is the juxtaglomerular apparatus of the kidney, where multiple stimuli may contribute to renal release of renin into the systemic circulation, including increased renal sympathetic efferent activity, decreased distal tubular sodium delivery, and reduced renal perfusion pressure.³⁹ That is to say, the majority of circulatory NE and renin is derived from the secretion from systemic organs other than the heart in situ. In patients with E-/high HNCM, the increased levels of plasma BNP might reflect myocardial hypertrophy peculiar to HCM, not the severity of HF implicated by ventricular overloading. Plasma NE levels or PRA, however, might rather reflect the general status or severity of HF adequately in such patients. That is, disproportion between BNP and PRA/NE may often be observed in compensated patients with HNCM.

Study Limitations

We attempted to compare the clinical values between E-/high and E-/low HNCM to draw the causative pathomechanism to increase BNP independently from the clinical HF status. It is certain that some limitations of the study must be acknowledged because there was insufficient statistical power in some analyses owing to only 4 E-/high HNCM to be compared. Despite these limitations, however, it was noteworthy that 4 patients whose level was over 500 pg/ml without following cardiac events abstracted from a large number of outpatients all showed HNCM as basal heart diseases. In other words, the increase in BNP concentration up to several hundred pg/ml does not often indicate the prognosis of HNCM patients. Further prospective studies addressing the pathogenesis of increasing BNP in HNCM in conjunction with the cardiac events seem warranted.

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