Original Article

Brain Natriuretic Peptide as a Risk Marker for Incident Hypertensive Cardiovascular Events

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We examined the effects of aging and hypertensive left ventricular hypertrophy on the plasma level of brain natriuretic peptide (BNP), and assessed BNP as a risk marker for incident hypertensive cardiovascular events. One hundred and eighty-five hypertensive patients were echocardiographically divided into a hypertensive group with normal left ventricular mass ($n = 96$; age range, 37–86 years; left ventricular mass, 97 ± 14 g/m²) and a hypertensive group with left ventricular hypertrophy ($n = 89$; 37–90 years; 140 ± 20 g/m²). Forty-four normotensive subjects served as the normotensive group (32–84 years; 91 ± 15 g/m²). We examined the association of age with BNP in the three groups and also evaluated BNP as a risk marker for incident cardiovascular events by following up all patients for 40 months. All three groups demonstrated a significant positive relationship between age and BNP. The slope of the relation between age and BNP was steepest in the hypertensive group with left ventricular hypertrophy ($p < 0.0001$ vs. the other two groups). Multiple regression analysis revealed that age, pulse pressure and left ventricular mass index were significantly associated with the increase in BNP. Multivariate Cox proportional hazards regression analysis, which was used to assess the potential association of age, pulse pressure, left ventricular mass index and BNP with the cardiovascular events during follow-up, revealed the highest correlation between BNP and incident cardiovascular events (risk ratio = 1.011; $p = 0.0011$). BNP, which is synergistically increased with aging and left ventricular hypertrophy, may be an important risk marker for hypertensive cardiovascular events. (*Hypertens Res* 2002; 25: 669–676)

Key Words: hypertension, aging, cardiac hypertrophy, cardiovascular events, natriuretic peptides

Introduction

Left ventricular hypertrophy and aging are well recognized as independent risk factors for cardiovascular events in hypertension (1–3). With regard to variables for the prediction of poor outcome in hypertension, only age and left ventricular mass have been demonstrated to be independent predictors of cardiovascular death, cardiovascular events, or all-cause mortality (4). Despite the importance of identifying high risk hypertensive patients whose cases are complicated

by aging and left ventricular hypertrophy, no significant risk marker for incident hypertensive cardiovascular events has yet been identified.

The plasma level of brain natriuretic peptide (BNP) has been well established as a powerful marker for cardiac dysfunction and prognosis in patients with critical cardiovascular diseases (5, 6). We recently reported that BNP can identify patients with hypertension who are undergoing progressive left ventricular hypertrophy (7). In the present study, we examined the association of aging and left ventricular hypertrophy on BNP in patients with hypertension, and assessed

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the efficacy of BNP as a risk marker to identify hypertensive patients with high risk for incident cardiovascular events.

Methods

Study Population

One hundred and eighty-five outpatients with essential hypertension (93 men and 92 women; mean age, 66 ± 11 years) were studied. All subjects provided their informed consent, and the study protocol was approved by the Human Study Committee of Yawatahama City General Hospital. Among the 185 participating patients, 103 (56%) were untreated and 82 (44%) were receiving antihypertensive drugs. All antihypertensive drugs were discontinued at least 2 weeks before the study. Blood pressure was measured at our outpatient clinic, and hypertension was defined as systolic pressure greater than or equal to 140 mmHg, diastolic pressure greater than or equal to 90 mmHg, or both (7, 8). Cases showing clinical or laboratory evidences of renal failure, secondary causes of hypertension, valvular diseases, or coronary artery disease were excluded.

Echocardiography

Echocardiographic examinations were performed using an SSD-2200 (Aloka Co, Ltd., Tokyo, Japan). Left atrial dimension, left ventricular septal and posterior wall thicknesses and left ventricular chamber dimensions were measured according to the guidelines of both the American Society of Echocardiography (9) and the Penn Convention (10). Left ventricular mass (LVM) and left ventricular relative wall thickness (RWT) were calculated using the following equations (7, 11): $LVM = 1.04 \times \{(D_d + PWT_d + IVST_d)^3 - D_d^3\} - 14$ (g), $RWT = 2 \times PWT_d / D_d$, where D is the left ventricular chamber diameter, PWT is the posterior wall thickness, $IVST$ is the septal thickness, and the subscript "d" indicates diastole. LVM was divided by body surface area to derive the left ventricular mass index.

In assessing left ventricular systolic function, mid-wall left ventricular fractional shortening (mFS) was determined as follows (7, 12): $mFS = \{(D_d + H_d) - (D_s + H_s)\} / (D_d + H_d) \times 100$ (%), where D is the left ventricular chamber diameter, H is the inner half of the posterior wall plus the inner half of the septum, and the subscripts "d" and "s" denote diastole and systole. The value of H_s was calculated. As an index of left ventricular diastolic function, the E/A ratio was measured using transmitral Doppler flow (7). Left ventricular end-systolic meridional wall stress (ESWS) was calculated as an index of left ventricular afterload using echocardiographic dimensions and cuff blood pressure according to the following formula (11): $ESWS = 0.86 \times [(0.334 \times D_d \times \text{systolic blood pressure}) / \{PWT_d \times (1 + PWT_d / D_d)\}] - 27 \times 10^3$ (dyne/cm²).

Assay for Natriuretic Peptides and Other Hormones

Plasma levels of atrial natriuretic peptide (ANP) and BNP were measured by specific immunoradiometric assay (Shiono RIA ANP assay kit and Shiono RIA BNP assay kit; Shionogi Co., Ltd., Osaka, Japan) as previously reported (7). In addition, we measured plasma catecholamines by high performance liquid chromatography and plasma renin activity and aldosterone by radioimmunoassay.

Study Protocol

Echocardiography and blood sampling were performed in all subjects after 30 min of supine rest. Using echocardiographically calculated left ventricular mass index, hypertensive patients were divided into a hypertensive group with normal left ventricular mass ($n = 96$; age range, 37–86 years; left ventricular mass, 97 ± 14 g/m²), and a hypertensive group with left ventricular hypertrophy ($n = 89$; 37–90 years; 140 ± 20 g/m²). Forty-four normotensive subjects (32–84 years; 91 ± 15 g/m²) who had no history of hypertension and no evidence of cardiac disease served as the normotensive group. Based on our previous study (13), the cut-off value for left ventricular hypertrophy was defined as 108 and 104 g/m² in males and females, respectively (2SD above the mean).

Long-Term Follow-Up

To assess the predictive value of BNP for hypertensive cardiovascular events, all patients were followed up to a maximum of 40 months. Cardiovascular events (angina pectoris, myocardial infarction, arrhythmia, stroke, cardiovascular death, sudden death, etc.) were evaluated in our outpatient clinic.

Statistical Analysis

All data were presented as the means $\pm$ SD. Comparisons among groups were performed by one-way analysis of variance using Bonferroni's correction for multiple comparisons. Correlation coefficients were calculated by linear regression analysis. Analysis of covariance was used for comparison of the slopes of regression lines and post-hoc analysis was performed using Bonferroni's correction. Proportional variables were assessed by the chi-square test. When univariate regression analysis showed a significant difference in BNP ($p < 0.05$), multiple regression analysis was applied for analysis of the dependency between variables. The potential association of clinical parameters with cardiovascular events was assessed with univariate Cox proportional hazard regression analysis, and if the univariate p value was less than 0.05, multivariate Cox proportional hazards regression analysis was performed. The cardiovascular event-free survival was analyzed by Kaplan-Meier curves. Differences between

Table 1. Clinical Characteristics

Parameter	Normotensive group	Hypertensive group (n = 185)		P
		Normal left ventricular mass	Left ventricular hypertrophy	
Male/female	23/21	45/51	48/41	0.6134
Age (years)	61 ± 14	63 ± 9	66 ± 13	0.0604
(range)	(32–84)	(37–86)	(37–90)	
Body surface area (m ²)	1.59 ± 0.11	1.58 ± 0.18	1.54 ± 0.14	0.1714
Body mass index (kg/m ²)	24.3 ± 3.6	24.2 ± 3.2	23.3 ± 2.9	0.0847
Systolic blood pressure (mmHg)	128 ± 10	155 ± 13 [†]	150 ± 20 [†]	< 0.0001
Diastolic blood pressure (mmHg)	77 ± 8	89 ± 9 [†]	85 ± 10 [†]	< 0.0001
Pulse pressure (mmHg)	51 ± 8	66 ± 13 [†]	65 ± 16 [†]	< 0.0001
Heart rate (bpm)	67 ± 12	68 ± 14	66 ± 12	0.1253
Left atrial dimension (mm)	30.3 ± 3.4	30.6 ± 3.0	32.2 ± 4.3	0.0575
Left ventricular end-diastolic diameter (mm)	47.9 ± 3.4	46.7 ± 3.9	49.5 ± 3.6	0.0548
Left ventricular end-systolic diameter (mm)	29.1 ± 4.3	28.1 ± 3.5	30.5 ± 4.1	0.0648
Septal thickness (mm)	8.1 ± 1.1	8.5 ± 1.4	10.1 ± 1.6 ^{†,§}	< 0.0001
Posterior wall thickness (mm)	8.3 ± 1.0	8.6 ± 1.2	10.0 ± 1.3 ^{†,§}	< 0.0001
Mid-wall left ventricular fractional shortening (%)	19.6 ± 2.8	19.1 ± 2.6	17.5 ± 2.5 ^{†,§}	0.0002
E/A ratio	1.04 ± 0.50	0.83 ± 0.24 [*]	0.81 ± 0.33 [*]	0.0078
Left ventricular mass index (g/m ²)	91.1 ± 15.3	96.8 ± 14.4	140.1 ± 19.8 ^{†,§}	< 0.001
Left ventricular relative wall thickness	0.35 ± 0.05	0.37 ± 0.07	0.41 ± 0.07 ^{†,§}	< 0.001
Left ventricular end-systolic wall stress (× 10 ³ dyne/cm ²)	72.3 ± 13.7	83.3 ± 15.5 [*]	83.2 ± 17.8 [*]	0.0015
Duration of hypertension (years)	-	3.6 ± 4.0	7.5 ± 6.5 [§]	0.0005
Medications (n(%))				
Angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker		13 (13.5)	14 (15.7)	0.6737
Ca-channel blocker		31 (32.3)	27 (30.3)	0.7746
β-Blocker		8 (8.3)	9 (10.1)	0.6757
Diuretics		1 (1.0)	2 (2.3)	0.5136

Data are the means ± SD. * $p < 0.05$, † $p < 0.01$ vs. the normotensive group; ‡ $p < 0.05$, § $p < 0.01$ vs. the hypertensive group with normal left ventricular mass.

event-free survival curves were tested with the log-rank chi-square statistic. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Clinical Characteristics

Each of the two hypertensive groups showed higher pulse pressure than the normotensive group (Table 1). Echocardiographic data revealed no differences in left atrial or left ventricular dimensions among the three groups, but demonstrated increased left ventricular wall thickness and left ventricular relative wall thickness in the hypertensive group with left ventricular hypertrophy. Midwall left ventricular fractional shortening was decreased in the hypertensive group with left ventricular hypertrophy. In comparison with the normotensive group, the two hypertensive groups showed lower E/A ratio and higher left ventricular end-systolic wall stress. Known periods of hypertension were longer in the hyperten-

sive group with left ventricular hypertrophy than in the hypertensive group with normal left ventricular mass.

Neurohumoral Characteristics

No significant differences were observed in plasma catecholamines, plasma renin activity or aldosterone among the three groups (Table 2). In the hypertensive group with left ventricular hypertrophy, both ANP and BNP were significantly increased. The BNP/ANP ratio was also high in the hypertensive group with left ventricular hypertrophy. Figure 1 demonstrates the significant positive relation between age and logarithmic BNP in all three groups. The slope of this relation was steepest in the hypertensive group with left ventricular hypertrophy ($p < 0.0001$).

Univariate and Multivariate Regression Analysis

The univariate correlation coefficients indicated that age, body mass index, duration of hypertension, pulse pressure,

Table 2. Neurohumoral Characteristics

Parameter	Normotensive group	Hypertensive group		<i>p</i>
		Normal left ventricular mass	Left ventricular hypertrophy	
Adrenaline (pg/ml)	36.8 ± 36.9	46.5 ± 29.7	61.6 ± 58.1	0.0624
Noradrenaline (pg/ml)	412.6 ± 227.2	415.6 ± 244.2	520.9 ± 296.2	0.0733
Plasma renin activity (ng/ml/h)	1.78 ± 2.80	1.02 ± 1.28	1.53 ± 2.47	0.1116
Aldosterone (ng/dl)	58.8 ± 59.8	58.6 ± 46.2	42.4 ± 44.3	0.0712
BNP (pg/ml)	19.5 ± 24.0	29.7 ± 28.3	57.3 ± 55.4 ^{†,§}	< 0.0001
ANP (pg/ml)	16.7 ± 11.2	23.0 ± 16.3	32.0 ± 26.6 ^{*,†}	< 0.0001
BNP/ANP ratio	1.16 ± 0.95	1.33 ± 0.97	1.98 ± 1.69 ^{†,§}	0.0002

Data are the means ± SD. * $p < 0.05$, [†] $p < 0.01$ vs. the normotensive group; [‡] $p < 0.05$, [§] $p < 0.01$ vs. the hypertensive group with normal left ventricular mass.

Fig. 1. A significant relation between age and logarithmic BNP was observed in all three groups. The hypertensive group with left ventricular hypertrophy showed the steepest slope among them ($p < 0.0001$).

Table 3. Regression Analysis with BNP as Dependent Variable

Variable	Univariate model			Multivariate model		
	Coefficient	SE	<i>p</i>	Coefficient	SE	<i>p</i>
Age	0.452	0.214	< 0.0001	0.256	0.362	0.0210
Body mass index	- 0.243	0.882	0.0002	- 0.118	0.819	0.0530
Duration of hypertension	0.317	0.646	0.0015	0.135	0.690	0.1975
Systolic blood pressure	0.104	0.156	0.1199	-	-	-
Diastolic blood pressure	- 0.128	0.282	0.0558	-	-	-
Pulse pressure	0.224	0.196	0.0007	0.231	0.235	0.0176
Left ventricular mass index	0.370	0.097	< 0.0001	0.266	0.158	0.0095
Left ventricular relative wall thickness	0.161	41.040	0.0159	- 0.067	64.148	0.4925
Mid-wall left ventricular fractional shortening	- 0.109	1.043	0.1014	-	-	-
E/A ratio	- 0.108	6.678	0.7956	-	-	-
Angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker	0.010	8.840	0.8806	-	-	-
Calcium channel blocker	0.100	6.535	0.1364	-	-	-
β -Blocker	0.056	11.161	0.4065	-	-	-
Diuretics	- 0.023	25.040	0.7273	-	-	-

Table 4. Univariate and Multivariate Cox Proportional Hazard Analysis of Cardiovascular Events in 185 Patients with Hypertension

Variable	Univariate analysis			Multivariate analysis		
	Risk ratio (95% CI)	Chi-square	<i>p</i>	Risk ratio (95% CI)	Chi-square	<i>p</i>
Age	1.081 (1.018–1.147)	6.496	0.0108	1.013 (0.943–1.088)	0.126	0.7224
Systolic blood pressure	1.025 (0.996–1.055)	2.798	0.0944	-	-	-
Diastolic blood pressure	0.963 (0.914–1.015)	1.952	0.1623	-	-	-
Pulse pressure	1.056 (1.018–1.095)	8.744	0.0031	1.050 (1.009–1.091)	5.870	0.0154
Left ventricular mass index	1.021 (1.007–1.036)	8.141	0.0043	1.020 (1.000–1.040)	3.851	0.0497
Left ventricular relative wall thickness	18.518 (0.028–12,150.974)	0.778	0.3778	-	-	-
Mid-wall left ventricular fractional shortening	0.951 (0.790–1.144)	0.287	0.5919	-	-	-
<i>E/A</i> ratio	0.626 (0.075–5.221)	0.187	0.6654	-	-	-
ANP	1.012 (0.995–1.030)	1.878	0.1706	-	-	-
BNP	1.015 (1.009–1.021)	26.108	<0.0001	1.011 (1.004–1.017)	10.586	0.0011

left ventricular mass index, and left ventricular relative wall thickness but not mid-wall left ventricular fractional shortening, *E/A* ratio or any medications were significantly associated with BNP (Table 3). By multiple regression analysis, age, pulse pressure, and left ventricular mass index, but not duration of hypertension or left ventricular relative wall thickness, were significantly associated with BNP ($r^2 = 0.298$; $p < 0.0001$).

Long-Term Follow-Up Study

The mean duration of follow-up was 34 ± 6 months. Fourteen of the hypertensive patients (7.6%) had cardiovascular events, and 10 of these 14 (71%) were over 65 years of age. Of the 4 remaining patients who had cardiovascular events, 3 had normal left ventricular mass (sudden death at 55 years in one, acute coronary syndrome at 59 years in one, and atrial fibrillation at 60 years in one) and one patient had left ventricular hypertrophy (sudden death at 55 years). Univariate Cox proportional hazard analysis showed that age, pulse pressure, left ventricular mass index and BNP were significantly associated with cardiovascular events. By multivariate Cox proportional hazards regression analysis, BNP showed the highest correlation with incident cardiovascular events (risk ratio = 1.011; 95% confidence interval (CI) = 1.004–1.017; $p = 0.0011$) (Table 4). To assess the role of BNP as a risk marker in elderly hypertensive patients with left ventricular hypertrophy, we examined cardiovascular events in 63 patients who were over 65 years of age and showed left ventricular hypertrophy (Table 5). When compared cardiovascular events between 40 patients less than mean BNP of them (68 pg/ml) and 23 patients over mean BNP, significant higher events were observed in 23 patients (30.4%) over 68 pg/ml, which was also evidenced by Kaplan-Meier analysis (Fig. 2, $p = 0.016$ by log-rank test).

Discussion

The present study demonstrates that BNP is an important risk marker for incident cardiovascular events in patients with hypertension. Despite the established evidence that age and left ventricular hypertrophy are the best independent predictors of cardiovascular events or cardiovascular death in patients with hypertension (4), convenient clinical markers remain to be identified. Our findings, showing the synergistic effects of age and left ventricular hypertrophy on the increase in BNP, may back up the usefulness of this peptide as a risk marker for hypertensive cardiovascular events.

Association of Aging and Left Ventricular Hypertrophy with BNP

In the present study, we observed that age had a much greater influence on BNP in hypertensive patients with left ventricular hypertrophy than on BNP in hypertensive patients without left ventricular hypertrophy. Both experimental (14) and clinical studies (15) have shown an increase in BNP in proportion to left ventricular hypertrophy. Why, then, did aging enhance BNP much more in hypertensive patients with left ventricular hypertrophy? Using multiple regression analysis, we showed a significant association between each of three clinical variables—aging, high pulse pressure and left ventricular hypertrophy—and high BNP. As reported by both experimental and clinical studies (16, 17), the aged myocardium might be exposed to local ischemia. Aging has also been shown to produce a diffuse focal loss of ventricular myocytes, and to burden the remaining myocytes with stress, leading to reactive hypertrophy (16, 17). In a previous study employing thallium-201 cardiac imaging (18), myocardial relative ischemia was also observed in patients with hypertension. In view of previous studies (19, 20) showing that both myocardial hypertrophy

Table 5. Characteristics and Cardiovascular Events of Hypertensive Patients over 65 Years with Left Ventricular Hypertrophy

Parameter	Patients with BNP		<i>p</i>
	< 68 pg/ml (<i>n</i> = 40)	68 pg/ml (<i>n</i> = 23)	
Male/female	19/21	12/11	0.7209
Age (years)	74 ± 6	76 ± 6	0.3333
Body mass index (kg/m ²)	23.4 ± 2.7	22.6 ± 2.5	0.2731
Systolic blood pressure (mmHg)	149 ± 17	153 ± 23	0.4023
Diastolic blood pressure (mmHg)	83 ± 10	84 ± 9	0.6777
Pulse pressure (mmHg)	66 ± 14	69 ± 19	0.4377
Heart rate (bpm)	65 ± 13	63 ± 10	0.4858
Mid-wall left ventricular fractional shortening (%)	17.6 ± 2.5	17.6 ± 2.7	0.9599
E/A ratio	0.69 ± 0.20	0.78 ± 0.41	0.0548
Left ventricular mass index (g/m ²)	140.9 ± 20.3	143.0 ± 24.3	0.7045
Left ventricular relative wall thickness	0.41 ± 0.07	0.40 ± 0.07	0.9180
ANP (pg/ml)	26.5 ± 12.9	50.0 ± 30.8	< 0.0001
BNP (pg/ml)	35.7 ± 17.1	119.8 ± 49.4	< 0.0001
Follow-up periods (month)	35 ± 5	34 ± 5	0.5464
Event			
Stroke	1 (2.4%)	1 (4.3%)	0.6925
Coronary artery disease	0 (0%)	3 (13.0%)	0.0167
Congestive heart failure	0 (0%)	3 (13.0%)	0.0167
Sudden death	2 (4.9%)	0 (0%)	0.2758
Total events	3 (7.3%)	7 (30.4%)	0.0165

Data are the means ± SD.

Fig. 2. Event-free survival curves in hypertensive patients over 65 years of age with left ventricular hypertrophy with high BNP (≥ 68 pg/ml) and low BNP (< 68 pg/ml).

and ischemia enhance BNP production, the synergistic effects of aging and left ventricular hypertrophy on myocyte and vasculature changes (21, 22) may be related to the enhanced production of BNP. The association of pulse pressure with BNP in the present study may support previous evidences of a link between high pulse pressure and risk of cardiovascular diseases (23,24).

Comparison between ANP and BNP

As a biological marker for left ventricular abnormality, BNP has been reported to be more sensitive than ANP (25). As

shown in Table 2, the high BNP/ANP ratio observed in the hypertensive group with left ventricular hypertrophy may suggest that BNP production is much enhanced than ANP production in hypertensive patients with left ventricular hypertrophy. In the Cox proportional hazard regression analysis, ANP, in contrast to BNP, was not significantly associated with incident cardiovascular events in patients with hypertension.

This finding also indicated that BNP is a more sensitive marker than ANP for identifying hypertensive patients at high risk for incident cardiovascular events.

BNP as a Risk Marker for Incident Hypertensive Cardiovascular Events

The multivariate Cox proportional hazard regression analysis in the present study suggests that BNP may be useful as a risk marker for incident cardiovascular events in patients with hypertension. Elderly hypertensive patients with left ventricular hypertrophy who showed elevated BNP demonstrated a high incidence of cardiovascular events at follow-up. Thus, our findings suggest that BNP would play a significant role in cardiovascular risk identification in patients with hypertension.

Study Limitations

There are several issues that should be considered in inter-

preting our data. The first is the selection of our study population. Because the present study was not a randomized trial, the results may have been affected by selection bias. We excluded patients with coronary artery diseases by symptoms and physical examination, which consisted primarily of electrocardiography, exercise tests, and cardiac radionuclide imaging. Thus, it is possible that our cohort included hypertensive patients with undetected coronary artery disease at entry. A significant relation between E/A ratio and BNP was not observed in the present study. This finding is consistent with two previous studies (7, 15), but contrary to a third (26). One of the reasons for these disparate findings might be that several factors, such as age and loading conditions, affected the E/A ratio in the setting of the different cardiac diseases. To assess the role of BNP as a risk marker for hypertensive cardiovascular events, we included stroke and sudden death, as shown in Table 5. Because BNP is a potent cardiac rescue hormone, future studies will need to identify the role of BNP in risk stratification for incident heart attacks in large numbers of hypertensive patients as well as other cardiac diseases (27).

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