Plasma Brain Natriuretic Peptide During Ergometric Exercise in Hypertensive Patients With Left Ventricular Hypertrophy

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Cardiac ventricle is shown to be an important source of circulating brain natriuretic peptide (BNP) in hypertensive rats with left ventricular hypertrophy (LVH). This study examined the effect of short-term exercise with a bicycle ergometer on plasma BNP concentrations in 21 essential hypertension patients with LVH established by echocardiography. The results were compared with those from 24 age-matched hypertensives without LVH. Blood pressure, heart rate, plasma renin activity (PRA), and plasma norepinephrine level increased during exercise, but the mean increases of these parameters were not different in the two groups. Resting BNP levels were slightly but significantly higher in the LVH group than in the non-LVH group. This peptide increased during exercise in the two groups, but the exercise-induced increase (percent increase) in plasma BNP was significantly greater in the LVH group than in the non-LVH group (207% ± 50% *v* 141% ± 36%, $P < .05$). The exercise-induced increase in BNP was significantly correlated with the left ventricular (LV) mass index ($N = 45$, $r = .60$, $P < .01$). By contrast, the exercise-induced increase in BNP was not correlated with the exercise-induced increase in heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, PRA, or noradrenaline level. These results suggest that short-term exercise induces an accelerated increase of plasma BNP in hypertensive subjects with LVH. The LV mass appeared to be related to the observed increase of plasma BNP concentration, at least in our hypertensive patients with LVH.

BRAIN NATRIURETIC PEPTIDE (BNP) was first identified in the porcine brain[1] and later isolated from porcine heart.[2] Porcine BNP consists of 26 amino acid residues that share considerable homology with the sequence of atrial natriuretic peptide (ANP).[1] BNP elicits a spectrum of diuretic, natriuretic, and hypotensive effects similar to those of ANP.[1] BNP interacts with the same receptors as ANP in vascular smooth muscle cells.[3,4] Recently, a low–molecular-weight form of human BNP, BNP-32, which corresponds to the C-terminal sequence (77-108) of the human BNP precursor deduced from the cDNA sequence, was found in the human atrium.[5] Subsequently, Mukoyama et al[6] and our group[7] have shown that this peptide is secreted together with ANP through the coronary sinus from the heart. We[7] and Villa et al[8] have also shown that the plasma BNP concentration is high in patients with essential hypertension. In addition, in hypertensive rats with left ventricular hypertrophy (LVH), plasma BNP concentration is markedly high and the major source of circulating BNP is the hypertrophied ventricles.[9,10] Therefore, we examined the effects of ergometric exercise on the plasma concentration of BNP in essential hypertension patients with LVH established by echocardiography. The results were compared with results from matched hypertensive patients without LVH. Furthermore, we focused on the relationship between the exercise-induced increase in BNP and left ventricular (LV) mass.

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SUBJECTS AND METHODS

Study Population

Forty-five essential hypertension patients aged 37 to 72 years took part in the study. They had a mean systolic blood pressure of 160 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher. Secondary hypertension was excluded by clinical history, physical examination, routine laboratory urogram, and renal arteriogram. None of the patients had signs or symptoms of cardiac, renal, or hepatic failure or diabetes, and none had clinical evidence of pulmonary disease, angina pectoris, or myocardial infarction. Only hypertensive patients who had not been treated with antihypertensive drugs or whose antihypertensive drug therapy had been discontinued for at least the preceding 2 weeks were included in the study. The patients were divided into two groups, LVH and non-LVH.

LVH was established by M-mode echocardiography (Sonolayer αSSA-270A; Toshiba, Tokyo, Japan). Measurements were made according to the recommendations of the American Society of Echocardiography with the leading-edge to leading-edge convention.[11] The LV internal dimension, ventriculus septum, and LV posterior wall were measured at end diastole as defined by the onset of the QRS complex. The LV ejection fraction was calculated by standard techniques.[7] Two measurements were made and averaged. All measurements were performed by a single investigator who was unaware of the subjects' blood pressure and BNP levels. LVH was diagnosed if the mean thickness of the LV posterior wall was 12 mm or greater.[7]

Measurements made in accordance with American Society of Echocardiography criteria were used in the formula reported by Troy et al[12]: LV mass (g) = 1.05[LV internal diameter + LV septal thickness + posterior wall thickness)^3 − (LV internal diameter)^3]. LV mass was normalized for body surface area (values are reported here as LV mass indices).

Study Protocol

After informed consent was obtained, an indwelling intravenous catheter for collection of blood samples was inserted into an antecubital vein. The exercise protocol consisted of three fixed workloads on a bicycle ergometer (Ergomed 840; Siemens) with the subject sitting.[13] The initial workload was 25 W for 4 minutes. Blood pressure and heart rate were measured at rest and at each

Table 1. Clinical Characteristics of the Hypertensive Patients With and Without LVH Established by Echocardiography

Variable	Without LVH (n = 24)	With LVH (n = 21)
Age (yr)	55.8 ± 7.9	56.7 ± 7.2
Sex (M/F)	9/15	8/13
Weight (kg)	60.6 ± 8.5	61.8 ± 9.3
Height (cm)	161.1 ± 7.3	162.6 ± 6.1
Blood pressure (mm Hg)		
Systolic	162 ± 13	162 ± 12
Diastolic	99 ± 9	98 ± 5
Mean	120 ± 8	120 ± 6
Heart rate (bpm)	77 ± 12	74 ± 11
BUN (mg/dL)	17.2 ± 5.0	18.7 ± 3.2
Serum creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2
LVEF (%)	75.9 ± 6.2	74.3 ± 7.5
Posterior wall thickness (mm)	9.5 ± 1.2	13.9 ± 1.1*
Septal wall thickness (mm)	9.4 ± 1.7	12.0 ± 2.3*
LV mass (g)	173 ± 30	264 ± 36*
LV mass index (g/m^2)	107 ± 17	161 ± 23*

Abbreviations: BUN, blood urea nitrogen; LVEF, LV ejection fraction.
*$P < .05$ *v* hypertensives without LVH.

exercise stage. Blood samples for assay of plasma renin activity (PRA), norepinephrine, and BNP were collected from the indwelling catheter at rest and at maximum exercise.

Blood pressure was measured by the standard cuff technique. All readings were made by the same investigator using the same calibrated sphygmomanometer. The heart rate was obtained from the electrocardiogram.

Hormonal Measurements

Blood samples for BNP assay were drawn directly into ice-chilled siliconized disposable tubes containing Trasylol (500 KIU/mL) and EDTA (1 mg/mL). The plasma was separated by centrifugation for 10 minutes at 4°C and then immediately frozen and stored at −80°C for several days. Immunoreactive (ir) BNP was extracted from the plasma by a Sep-Pak C18 cartridge (Waters Associates, Milford, MA) according to a method previously described.[7] The recovery rate of BNP was calculated by addition of 10 or 50 pg/mL cold human BNP-32 to hormone-free plasma prepared by passage through a Sep-Pak C18 cartridge. The recovery rate of human BNP-32 was 62%.

The concentration of plasma BNP was measured with an antibody against synthetic human BNP-32 and [^{125}I]-labeled human BNP-32 (Peninsula Laboratories, Belmont, CA) as previously described.[7] This antibody reacts 100% with human BNP-32 and cross-reacts 0.05% with human prepro-BNP (1-21), porcine BNP-26, rat BNP-45, α-human ANP (1-28), α-rat ANP (1-28), angiotensin II, vasopressin, or endothelin-1. The interassay variation was 11.7% and intraassay variation 7.0%.

Plasma norepinephrine level was measured by high-performance liquid chromatography. PRA was measured by radioimmunoassay. Serum creatinine and blood urea nitrogen were assayed by routine automatic methods.

Statistical Analysis

Parameters for hypertensive patients with and without LVH were analyzed by the unpaired *t* test. Comparisons between values obtained at rest and during exercise were analyzed by paired ANOVA and reexamined by the method of Greenhouse and Geissor.[14] Linear regression analysis was used to examine the relationship of the exercise-induced increase in BNP to various clinical parameters. Values are expressed as the mean ± SD.

RESULTS

Table 1 shows baseline characteristics of hypertensive patients with and without LVH. There were no significant differences in age and sex distribution, weight, height, blood pressure, heart rate, serum creatinine, and blood urea nitrogen. Patients with LVH tended to have a slightly lower LV ejection fraction than patients without LVH, but the difference was not significant. As expected, hypertensive patients with LVH had significantly greater posterior wall and septal wall thickness than hypertensives without LVH. The LV mass and LV mass index in the LVH group were greater than in the non-LVH group.

Table 2 shows changes in blood pressure and heart rate during exercise in hypertensive patients with and without LVH. Systolic and diastolic blood pressure and heart rate gradually increased during exercise, but the mean increases of these parameters were not different in the two groups.

Table 3 shows changes in PRA and plasma norepinephrine and BNP concentrations during exercise in hypertensive patients with and without LVH. PRA and plasma norepinephrine increased during exercise, but there were no significant differences in the mean increases in these parameters between the two groups. Plasma BNP concentration increased with exercise in the two groups. However, both the resting and exercise levels of BNP were significantly higher in the LVH group than in the non-LVH group.

Figure 1 shows the exercise-induced increase (percent increase) in plasma BNP in LVH and non-LVH groups. The exercise-induced increase in BNP was significantly greater in the LVH group than in the non-LVH group.

Figure 2 shows the correlation of the exercise-induced increase (percent increase) in plasma BNP concentration and LV mass index in the two groups. The exercise-induced increase in BNP was significantly correlated with the LV mass index. By contrast, the exercise-induced increase in BNP was not correlated with the exercise-induced increase in heart rate ($r = -.03$), systolic blood pressure ($r = -.04$), diastolic blood pressure ($r = -.13$), mean blood pressure ($r = -.19$), PRA ($r = .14$), or noradrenaline ($r = -.07$) (N = 45).

Table 2. Blood Pressure and Heart Rate During Exercise in Hypertensive Patients With and Without LVH

	SBP (mm Hg)				DBP (mm Hg)				Heart Rate (bpm)			
Group	Rest	25W	50W	75W	Rest	25W	50W	75W	Rest	25W	50W	75W
Non-LVH	162 ± 13	181 ± 15	196 ± 15	211 ± 17	99 ± 9	104 ± 6	106 ± 7	109 ± 6	79 ± 12	94 ± 13	112 ± 20	131 ± 22
LVH	162 ± 12	178 ± 15	196 ± 17	212 ± 14	98 ± 5	101 ± 5	105 ± 7	106 ± 6	74 ± 11	95 ± 15	111 ± 19	129 ± 24

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. PRA and Plasma Norepinephrine and BNP During Exercise in Hypertensive Patients With and Without LVH

Group	PRA (ng/mL/h)		Plasma Norepinephrine (pg/mL)		BNP (pg/mL)	
	Rest	75W	Rest	75W	Rest	75W
Non-LVH	1.2 ± 0.4	1.8 ± 1.0	239 ± 173	610 ± 368	4.6 ± 0.8	10.9 ± 2.2
LVH	1.0 ± 0.3	1.4 ± 0.4	214 ± 128	556 ± 310	7.3 ± 1.4*	22.3 ± 4.4*

*$P < .05$ *v* non-LVH.

DISCUSSION

We have confirmed our previous finding[7,15] that hypertensive patients with LVH have higher resting plasma BNP levels than age-matched hypertensives without LVH. We also showed that plasma BNP levels increased during ergometric exercise in both hypertensive groups with and without LVH. However, the exercise-induced increase in BNP was significantly greater in the LVH group than in the non-LVH group. Furthermore, the exercise-induced increase in plasma BNP was positively correlated with the LV mass index. By contrast, the exercise-induced increase in plasma BNP was not correlated with the exercise-induced increase in heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, PRA, or noradrenaline. These results suggest that LV mass is related to the exercise-induced increase in plasma BNP concentration, at least in our study population. However, Tanaka et al[16] have recently demonstrated that the major stimulus for the release of ANP and BNP is heart rate during exercise in hypertensive patients. The reasons for this difference are not clear at present. One possible explanation is that our study population contains many hypertensive patients with moderate to severe LVH.

A rat heart perfusion experiment by the Langendorff method before and after atrium removal showed that approximately 60% of all BNP is secreted from the ventricles.[7] Furthermore, using a rat model with severe LVH, we showed that BNP secretion from the hypertrophied ventricle is much greater than that from normal ventricle, and therefore the major origin of circulating BNP in this model is the hypertrophied ventricle.[10] It has also been shown that the BNP mRNA content and BNP secretory rate in the hypertrophied ventricle of stroke-prone spontaneously hypertensive rats were twice as large as in Wistar-Kyoto rats.[9] Taken together with these animal studies, our results suggest the hypothesis that in hypertensive patients with LVH, a considerable amount of BNP is secreted from the hypertrophied ventricle and the wall stress of the ventricle induced by acute exercise causes an exaggerated secretion of this peptide. However, we cannot completely exclude the possibility that the exercise-induced increase in plasma BNP is attributable to the decline in clearance of circulating BNP or the delay in degradation of BNP during exercise. Actually, the alteration in renal clearance of this peptide by exercise-induced renal hemodynamic changes

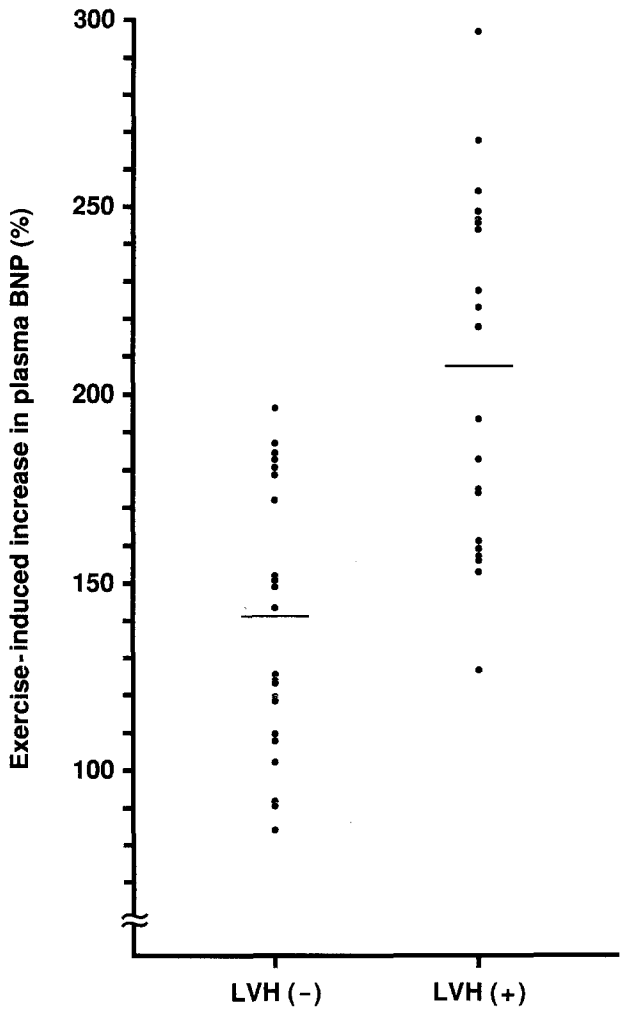

Fig 1. Comparison of the exercise-induced increase in plasma BNP in LVH and non-LVH groups. The increase in the LVH group was significantly ($P < .05$) greater than in the non-LVH group.

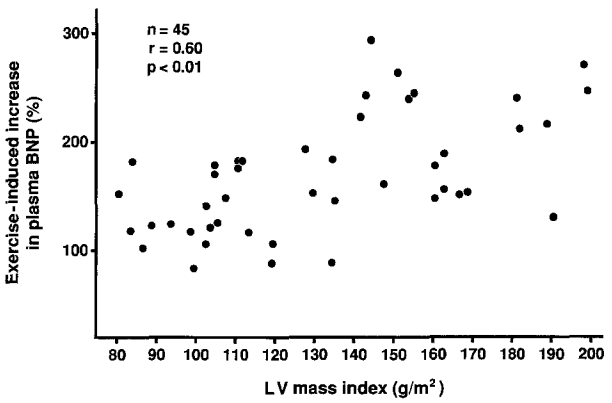

Fig 2. Correlation of the exercise-induced increase in plasma BNP concentration and LV mass index in LVH and non-LVH groups.

might contribute to the observed increase of plasma BNP concentration.

BNP elicits a spectrum of diuretic, natriuretic, and hypotensive effects similar to those of ANP.[1] Receptors in human vascular smooth muscle for natriuretic peptides, which have a guanylate cyclase domain, were identified by molecular cloning.[4] Furthermore, it is established that plasma ANP concentrations are increased by exercise in hypertensive patients.[13,16,17] Therefore, an increased plasma concentration of BNP and ANP during exercise may represent a mechanism to prevent a further increase in blood pressure via the vasodilatory and natriuretic effects of these peptides. However, more studies will be necessary to clarify the pathophysiological significance of the accelerated increase in plasma BNP during exercise in hypertensive patients with LVH.

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