Effect of Angiotensin-Converting Enzyme Inhibitor on Left Ventricular Parameters and Circulating Brain Natriuretic Peptide in Elderly Hypertensives With Left Ventricular Hypertrophy

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In the elderly, left ventricular hypertrophy (LVH) is a powerful risk factor for cardiovascular events and cardiovascular death. The purpose of the present study is to investigate the effect of long-term effective blood pressure control with the angiotensin-converting enzyme (ACE) inhibitor temocapril on left ventricular (LV) mass and function indices and the circulating concentration of the cardiac hormone brain natriuretic peptide (BNP) in elderly hypertensives with LVH. Temocapril treatment was administered for 1 year to 11 elderly hypertensives (mean age, 72 years) with LVH. Cardiac dimensions and circulating concentrations of BNP were monitored before initiation of treatment and after 1 year of treatment. At entry, BNP levels were positively correlated with the LV mass index, but were not correlated with the mean blood pressure, LV ejection fraction, or E/A ratio (the ratio of peak transmitral flow velocity in early diastole, peak E, to that in late diastole, peak A). After 1 year, temocapril treatment resulted in effective control of blood pressure. The treatment did not affect the LV ejection fraction, but modestly increased the E/A ratio. Temocapril significantly reduced septal and posterior wall thickness and the LV mass index. BNP significantly declined after 1 year. Changes in BNP were significantly related to changes in the LV mass index, but were not related to changes in the mean blood pressure, LV ejection fraction, or E/A ratio. The results suggest that long-term ACE inhibitor treatment with temocapril can induce the regression of LV mass and reduce elevated plasma BNP in elderly hypertensive patients with LVH. In this study, changes in BNP reflected the magnitude of regression of LVH.

LEFT VENTRICULAR HYPERTROPHY (LVH) increases the risk of cardiovascular events, cardiovascular death, and all-cause mortality in patients with hypertension.[1-3] Especially in the elderly, LVH carries a powerful risk not only for stroke, coronary artery disease, and arrhythmias, but also for left ventricular (LV) failure.[4-8] Therefore, the reversal of LVH and regression of LV mass are believed to be an important therapeutic goal, besides controlling high blood pressure, in hypertensive patients to minimize the risk of cardiovascular events and cardiovascular death.[9-11] Although high blood pressure is the leading cause of LVH, the cardiac renin-angiotensin system may also be involved.[12-14] Angiotensin II, a major effector peptide of the renin-angiotensin system, stimulates cardiac protein synthesis and cardiac growth.[15-17] Angiotensin-converting enzyme (ACE) is involved in the production of angiotensin II and thus may modulate cardiac growth. A meta-analysis has shown that ACE inhibitors are more effective than other first-line antihypertensive agents in reducing LV mass in hypertensive patients.[14]

The role of the heart as an endocrine organ was conclusively demonstrated by de Bold et al[18] in 1981, and atrial natriuretic peptide (ANP), the first member of the natriuretic peptide family, was identified by Kangawa and Matsuo in 1984.[19] The second member of this family, brain natriuretic peptide (BNP), was first identified in the porcine brain and later isolated from the porcine heart.[20,21] Porcine BNP consists of 26–amino acid residues that share considerable homology with the sequence of ANP. BNP elicits a spectrum of diuretic, natriuretic, and hypotensive effects similar to those induced by ANP. Subsequently, a low–molecular weight form of human BNP precursor deduced from the cDNA sequence was found in human atrium and plasma.[22,23]

In man, ANP and BNP are cosecreted through the coronary sinus from the heart, but ANP is secreted mainly from the atria and BNP from the cardiac ventricles.[24,25] Plasma levels of ANP and BNP are elevated in patients with essential hypertension.[23,24,26] Plasma BNP levels increase progressively with increasing severity of hypertension, particularly when LVH is present.[25,27]

Accordingly, the purpose of this study was to investigate the effect of long-term effective blood pressure control with the ACE inhibitor temocapril on LV mass and function indices and circulating BNP concentrations in elderly hypertensives with LVH. The associations between LV mass or function indices and circulating BNP were examined in these elderly hypertensives.

SUBJECTS AND METHODS

Entry Criteria and Screening

Between January 1997 and June 1998, we recruited 11 elderly hypertensive patients with LVH from a population of about 300 hypertensive patients in our department. All patients underwent routine laboratory studies including assays for serum electrolytes, serum creatinine, blood urea nitrogen (BUN), fasting blood glucose, urinalysis, chest roentgenogram, and electrocardiogram. We selected subjects with essential hypertension based on the results of the laboratory tests and guidelines of the World Health Organization.[28] Hypertension was defined as systolic pressure 140 mm Hg or higher or diastolic pressure 90 mm Hg or higher. Secondary hypertension was excluded based on a clinical history, physical examination, routine laboratory tests including measurements of plasma renin activity, aldosterone, catecholamines, and cortisol, and an excretory urogram or renal arteriogram. None of the patients had signs or symptoms of cardiac or renal failure, diabetes,

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Submitted December 8, 1999; accepted March 9, 2000.

Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

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0026-0495/00/4910-0004$10.00/0

doi:10.1053/meta.2000.9508

pulmonary disease, angina pectoris, or myocardial infarction. Only hypertensive patients without prior treatment with antihypertensive agents (n = 5) or with antihypertensive therapy discontinued for at least the preceding month (n = 6) were included in the study. Patients who had been treated with ACE inhibitors or angiotensin II receptor antagonists were excluded. LVH was estimated by echocardiography as described previously.[25] Patients with disproportionate septal LVH were excluded from this study. Informed consent was obtained from all participants.

Study Design

After the initial evaluation, patients were treated with the oral ACE inhibitor temocapril. All patients continued this therapy for 1 year. However, seven patients required the addition of a calcium-channel blocker, amlodipine, to adequate reduce their blood pressure. Plasma BNP concentrations were determined before the initiation of therapy and after 1 year of antihypertensive therapy with temocapril. LV anatomy and LV function were monitored at the same time point.

Measurements

Blood samples for BNP assays were drawn directly into ice-chilled siliconized disposable tubes containing Trasylol (500 KIU/mL; Bayer, Leverkusen, Germany) 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 BNP was extracted from the plasma by a Sep-Pak C18 cartridge (Waters Associates, Milford, MA) according to a method previously described.[25,29] The recovery rate of BNP was calculated by the 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 (Peninsula Laboratories, Belmont, CA) and [^{125}I]-labeled human BNP as previously described.[25,29] This antibody reacts 100% with human BNP-32 and cross-reacts 0.04% with rat BNP-32. It did not have any cross-reactivity with human prepro BNP(27-102), porcine BNP-26, rat BNP-45, α-human ANP (1-28), angiotensin II, vasopressin, or endothelin-1. To calculate the coefficient of variation, we analyzed 10 human plasma samples 4 times each for the interassay variation and 20 human plasma samples for the intraassay variation. The interassay variation was 11.7% and intraassay variation 7.0%.

LVH was established by M-mode echocardiography (Sonolayer α SSA-270A; Toshiba, Tokyo, Japan) as previously described.[29,30] Measurements were made using the ''leading-edge to leading-edge'' convention according to the recommendations of the American Society of Echocardiography.[31] The LV internal dimension, ventricular septum, and LV posterior wall thickness were measured at end-diastole, as defined by the onset of the QRS complex. The LV ejection fraction was calculated by standard techniques.[30] The E/A ratio, an indicator of LV diastolic function, was calculated as the ratio of peak E (peak transmitral flow velocity in early diastole) and peak A (peak transmitral flow velocity in late diastole) as previously described by Bello et al.[32] Two measurements were made by a single investigator who was unaware of the subject's blood pressure. LVH was diagnosed if the mean thickness of the LV septal or posterior wall was at least 11.0 mm. Measurements were made in accordance with American Society of Echocardiography criteria using the formula of Troy et al[33]: LV mass (g) = 1.05× (LV internal diameter^3). LV mass was normalized for body surface area (values are reported as LV mass indices).

Statistical Analysis

Statistical analysis was performed using Scheffe's test for multiple comparisons (preceded by ANOVA when appropriate).[34] Pretherapeutic and posttherapeutic values were compared using paired ANOVA and reexamined by the method of Greenhouse and Geisser.[35] Values are expressed as the mean ± SD. Statistical significance was set at a *P* level less than .05 (2-sided).

Table 1. Clinical Characteristics of the Patients at Study Entry

Characteristic	Mean ± SD	Range
Age (yr)	72 ± 6	67-87
Sex, n (male/female)	9/2	
Body mass index (kg/m^2)	29.5 ± 3.6	22.8-34.2
Systolic BP (mm Hg)	171 ± 15	152-200
Diastolic BP (mm Hg)	96 ± 7	88-110
Heart rate (bpm)	68 ± 11	54-83
Ejection fraction (%)	71.2 ± 8.9	59-87
E/A ratio	0.9 ± 0.3	0.71-1.38
LVDd (mm)	52.3 ± 5.8	41.8-60.6
Posterior wall thickness (mm)	12.5 ± 2.0	9.0-17.4
Septal wall thickness (mm)	11.3 ± 1.9	8.7-15.5
LV mass (g)	323 ± 112	177-576
LV mass index (g/m^2)	198 ± 65	127-348
Plasma BNP (pg/mL)	19.6 ± 5.1	13-29
BUN (mg/mL)	17.2 ± 5.1	7-26
Serum creatinine (mg/dL)	0.8 ± 0.2	0.5-1.3

Abbreviations: BP, blood pressure; LVDd, LV internal diameter at end-diastole.

RESULTS

Patient Characteristics

Table 1 lists the characteristics of the study group at entry. Elderly patients with mild to moderate hypertension comprised the study group. The LV ejection fraction and E/A ratio in most patients were normal, but these parameters in some patients were modestly decreased. For all patients at study entry, BNP levels were significantly elevated above the normal range (19.6 ± 5.1 *v* 2.1 ± 0.4 pg/mL). At study entry, BNP levels were positively correlated with the LV mass index (Fig 1). In contrast, BNP levels were not correlated with the mean blood pressure (n = 11, *r* = .31, nonsignificant [NS]), LV ejection fraction (n = 11, *r* = .33, NS), or E/A ratio (n = 11, *r* = .27, NS).

BUN and serum creatinine levels were within the normal

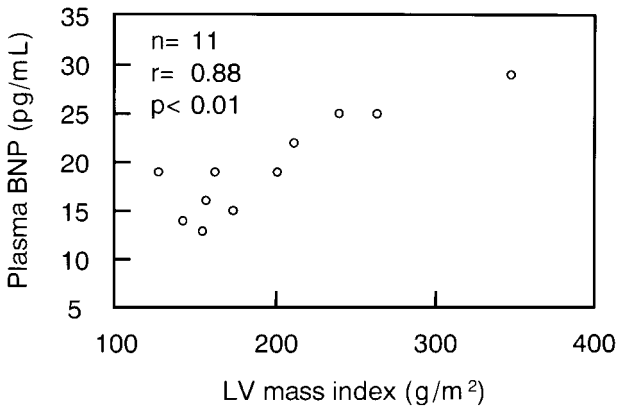

Fig 1. Relation between plasma BNP concentration and LV mass index at study entry.

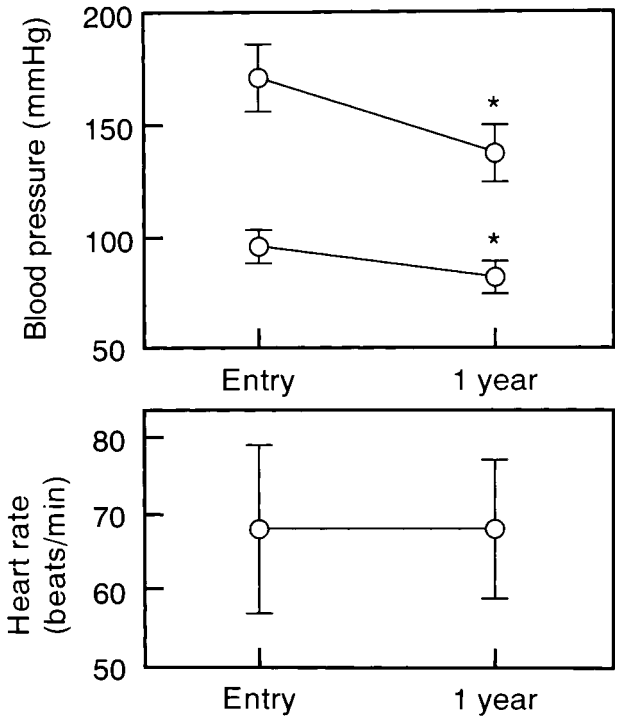

Fig 2. Changes in blood pressure and heart rate by temocapril-based treatment in elderly hypertensives with LVH. *$P < .05$ *v* entry.

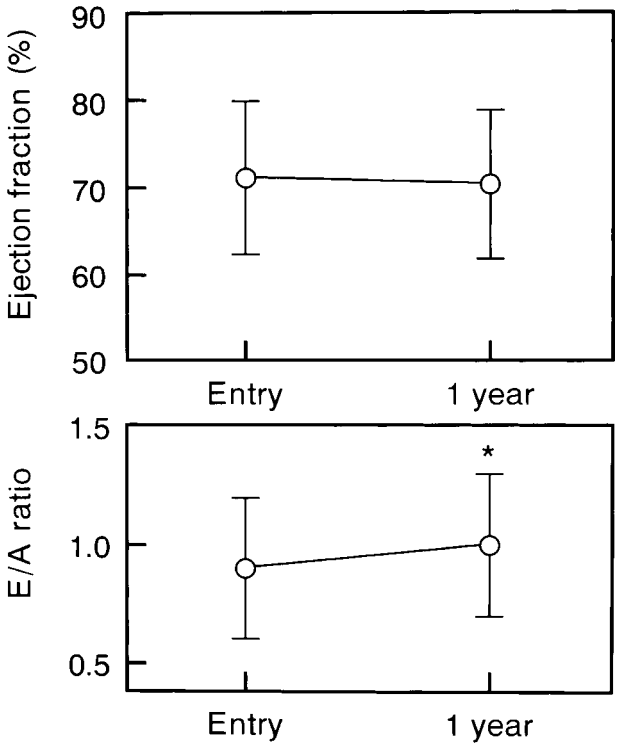

Fig 3. Changes in LV ejection fraction and E/A ratio by temocapril-based treatment in elderly hypertensives with LVH. *$P < .05$ *v* entry.

range. BNP was not correlated with BUN or serum creatinine (n = 11, $r = .32$, NS and n = 11, $r = .39$, NS, respectively).

Treatment Effect on Hemodynamic and Endocrine Parameters

Figure 2 demonstrates changes in blood pressure and heart rate by temocapril-based treatment in elderly hypertensives with LVH. After 1 year, monotherapy with temocapril resulted in effective control of blood pressure in 4 patients. Seven patients had effective control on combination therapy with temocapril and amlodipine. The median daily dose of temocapril was 2.4 mg (range, 2 to 4) and amlodipine 5.7 mg (range, 5 to 10). The heart rate did not change significantly over the course of the study.

Figure 3 shows changes in the LV ejection fraction and E/A ratio by temocapril-based treatment in elderly hypertensives with LVH. Temocapril treatment did not affect the LV ejection fraction significantly. In contrast, this treatment modestly increased the E/A ratio.

Figure 4 depicts changes in the posterior wall thickness, septal wall thickness, and LV mass index by temocapril-based treatment in elderly hypertensives with LVH. Temocapril treat-

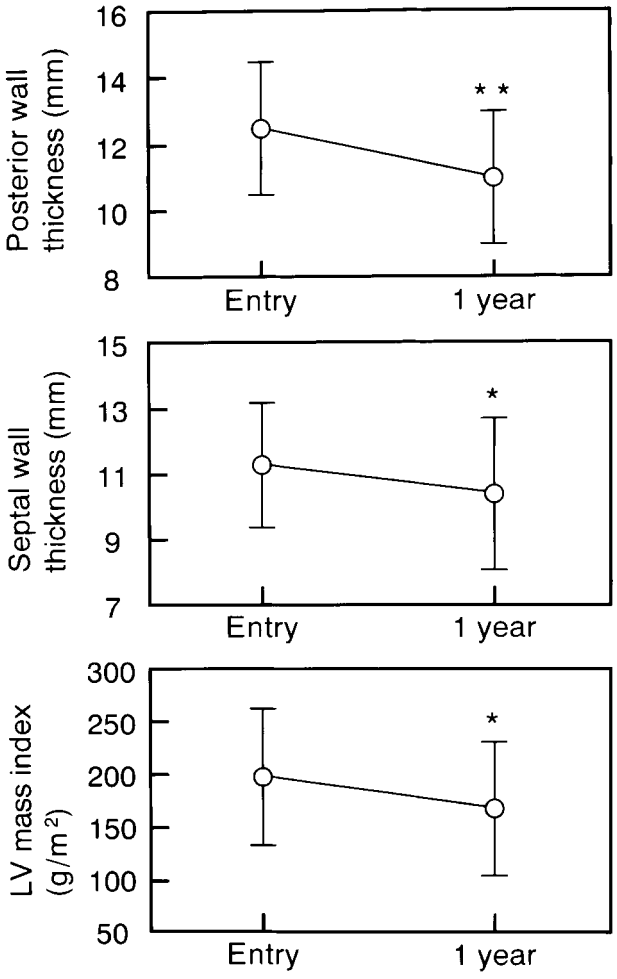

Fig 4. Changes in posterior wall thickness, septal wall thickness, and LV mass index by temocapril-based treatment in elderly hypertensives with LVH. *$P < .05$ *v* entry, **$P < .01$ *v* entry.

ment significantly reduced the posterior and septal wall thickness and LV mass index at 1 year.

Figure 5 shows the effects of temocapril-based treatment on circulating BNP concentrations. BNP levels significantly declined at 1 year. There was a significant relation between the reductions in BNP and in the LV mass index (Fig 6). In contrast, changes in BNP were not related to changes in the mean blood pressure (n = 11, r = .36, NS), LV ejection fraction (n = 11, r = .14, NS), or E/A ratio (n = 11, r = .16, NS).

DISCUSSION

The present study shows that circulating concentrations of BNP are significantly elevated in elderly hypertensive patients with LVH compared with our previously determined normal ranges.[25] Previously, we have shown in middle-aged subjects that plasma BNP levels are elevated in hypertension: this is more pronounced when LVH is present.[25] In our elderly patients, BNP levels at entry were positively correlated with the LV mass index and were not correlated with the mean blood pressure, LV ejection fraction, or E/A ratio. Therefore, it seems likely that the observed elevation of BNP in plasma is associated with LVH in our elderly hypertensive patients.

Second, the present results demonstrate that 1 year of temocapril-based treatment causes LVH to regress by 14% and reduces the elevated BNP levels significantly in elderly hypertensives. Temocapril-based treatment also improved the E/A ratio, an indicator of LV diastolic function, in these patients, although this treatment did not affect LV systolic function. Furthermore, the decline in BNP levels significantly related to diminishing LV mass. In contrast, the decline in BNP was not related to changes in the mean blood pressure, LV ejection fraction, or E/A ratio. Thus, changes in plasma BNP appear to reflect the magnitude of regression of LVH rather than changes in blood pressure, LV systolic function, or LV diastolic function during antihypertensive treatment. Previously, we have shown that the reduction of ventricular mass by chronic ACE inhibition and angiotensin II receptor antagonism reduces the BNP secretory rate from the cardiac ventricles in hypertensive rats with LVH.[36] In addition, BNP is primarily synthesized in and secreted from the cardiac ventricles in humans and in rats.[24,37,38] Although we have no direct evidence, these observations

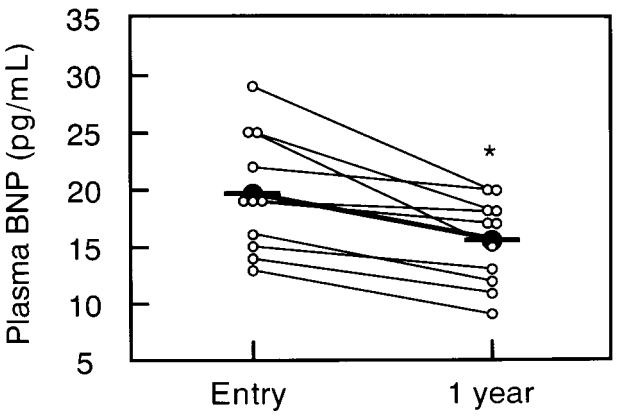

Fig 5. Changes in plasma BNP concentration by temocapril-based treatment in elderly hypertensives with LVH. *$P < .01$ *v* entry.

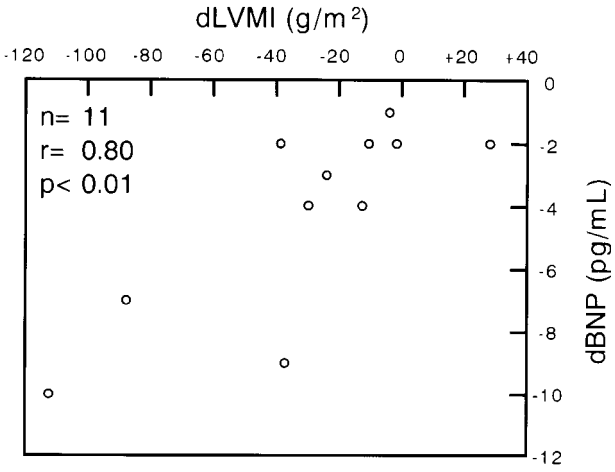

Fig 6. Relation between changes in plasma BNP (dBNP) and in LV mass index (dLVMI) during 1-year treatment with temocapril.

suggest that the regression of LVH by temocapril treatment may cause reduced secretion of BNP from the cardiac ventricles in elderly hypertensives with LVH.

In conclusion, the treatment of elderly hypertensives with temocapril for 1 year is accompanied by a regression of LV mass, a modest improvement in LV diastolic function, and a reduction in the circulating BNP level. In our elderly hypertensives, the reduction in BNP strongly reflected the regression of LV mass. LVH increases the hypertensive patient's risk of a cardiovascular event, cardiovascular death, and all-cause mortality.[1-3] Especially in the elderly, the risks are markedly increased.[4-8] These observations suggest that plasma BNP may be valuable as a prognostic predictor in elderly hypertension as well. Indeed, plasma BNP levels have an independent significant relationship to mortality in patients with congestive heart failure.[39] However, additional and longer clinical trials will be necessary to evaluate the usefulness of the measurement of plasma BNP in elderly hypertensive patients with LVH.

ACKNOWLEDGMENT

The authors gratefully acknowledge the technical assistance of Yuka Inoshita and Kazuko Shinagawa (Division of Hypertension and Atherosclerosis, First Department of Internal Medicine, Osaka City University Medical School).

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