Relation of Plasma Brain and Atrial Natriuretic Peptides to Left Ventricular Geometric Patterns in Essential Hypertension

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We investigated whether plasma brain and atrial natriuretic peptide (BNP and ANP, respectively) levels could reflect left ventricular (LV) geometry and function in patients with mild to moderate essential hypertension. A positive correlation was found between LV mass index (LVMI) and plasma ANP levels in 84 untreated, hypertensive patients, but not between LVMI and plasma BNP levels. As compared with other geometric patterns, plasma BNP levels were increased in concentric hypertrophy, in which LVMI was increased and LV diastolic function was decreased. These data suggest that production of BNP was increased in hypertensive patients with concentric hypertrophy via LV overload or depression of diastolic function. Am J Hypertens 1999;12:921–924 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Natriuretic peptides, essential hypertension, left ventricular hypertrophy, left ventricular geometry.

It is known that abnormal left ventricular (LV) geometry, especially concentric hypertrophy, is associated with a higher level of cardiovascular morbidity and mortality than normal geometry. Therefore, it seems important to elucidate determinants of LV geometric pattern in the management of patients with hypertension.

Previous studies have shown that the human heart secretes both brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) in response to pressure or volume overload. BNP is produced mainly in the left ventricle, and ANP, mainly in the atrium, indicating that different types of cardiac overload may lead to increased production of different natriuretic peptides. Recent studies demonstrated that plasma levels of BNP and ANP were elevated in some types of cardiovascular diseases including heart failure, renal failure, and hypertension, suggesting that plasma BNP level could be a useful hormonal marker for detection of LV hypertrophy (LVH) and LV dysfunction. However, it is still unclear whether plasma BNP is better than plasma ANP as a hormonal marker for different LV geometric patterns in mild to moderate hypertension. Therefore, the present study was designed to investigate the relation of plasma BNP and ANP levels to LV geometrical and functional changes in mild to moderate essential hypertension.

MATERIALS AND METHODS

Patients Eighty-four consecutive outpatients with essential hypertension were studied after giving informed consent. They had systolic blood pressure (SBP) of ≥ 160 mm Hg or diastolic blood pressure (DBP) of 90 ≈ 114 mm Hg on three separate occasions.
All patients had a serum creatinine level of < 1.2 mg/dL and a normal urinalysis. The severity of hypertension was stage I to II by the WHO classification. There were 44 men and 40 women, with ages ranging from 22 to 71 years (mean ± SEM: 50 ± 1 years). These patients had not received any antihypertensive agents or had been withdrawn from all antihypertensive treatment for at least 4 weeks before the study. Patients with heart failure, valvular disease, hepatic disease, renal disease, or diabetes mellitus were excluded from the study.

Protocol On the day of study, patients ate a light breakfast 3 h before the investigation and abstained from using caffeine, drinking alcohol, or smoking for 12 h before the investigation. After resting for 10 min in the supine position, conventional transthoracic echocardiography was performed. After 30 min of rest, blood samples for measurement of plasma levels of BNP, ANP, norepinephrine (PNE), and epinephrine (PE), plasma renin activity (PRA), and plasma aldosterone concentration (PAC) were taken from an indwelling antecubital venous cannula. Both plasma BNP and ANP levels were determined by immunoradiometric assay.9 PRA and PAC were determined by radioimmunoassay. PNE and PE were determined according to the trihydroxyindole method, using high-performance liquid chromatography.

Echocardiography After 10 min of rest, conventional M-mode echocardiography was performed with two-dimensional monitoring. Echocardiograms were read blindly by two independent observers. The left ventricular mass (LVM) was calculated according to the formula of Devereux and Reichek10: LVM(g) = 1.04[(LVIDd + PWTd + IVStd)³ − LVIDd³] − 13.6, where LVIDd is LV internal dimension in diastole, PWTd is LV posterior wall thickness in diastole, and IVStd is interventricular septal thickness in diastole. Left ventricular mass index (LVMI) was derived by dividing the calculated LVM by the patient’s body surface area (BSA). Relative wall thickness (RWT) was calculated as the ratio of (IVStd + PWTd)/LVIDd. Percent fractional shortening (%FS), cardiac output (CO), and total peripheral resistance (TPR) were calculated by standard formulas. Cardiac index (CI) was derived by dividing the calculated CO by the patient’s BSA.

LV diastolic function was assessed by the ratio of peak velocity of early filling (E) to peak velocity of late filling (A) (E/A ratio: < 1 being indicative of diastolic dysfunction), measured by transmitral pulsed Doppler echocardiography.

Four different patterns of LV geometry were identified by categorizing patients according to values of LVMI and RWT. The cutoff value for LVMI was 111 g/m² for men and 106 g/m² for women, and that of RWT was 0.44 for both. These LV geometric patterns include normal LV, with normal LVMI and RWT, concentric remodeling, with normal LVMI and normal RWT, eccentric hypertrophy, with increased LVMI and normal RWT, and concentric hypertrophy, with both increased LVMI and increased RWT.

Statistical Analysis Data are expressed as mean ± SEM. Differences among the groups were analyzed by one-way analysis of variance followed by Bonferroni’s test. Relationships between variables were assessed using linear regression analysis. Prevalence was compared with χ² test. The differences were considered statistically significant when a P value was < 0.05.

RESULTS

Clinical and Echocardiographic Characteristics Of 84 patients with essential hypertension, 34 patients (41%) were categorized as normal LV, seven patients (8%) as concentric remodeling, 21 patients (25%) as eccentric hypertrophy, and 22 patients (26%) as concentric hypertrophy. There was no significant difference among the four groups in terms of age, gender, duration of hypertension, BSA, and DBP. However, SBP was significantly higher in the concentric hypertrophy group as compared with normal LV and eccentric hypertrophy groups (P < .01 and P < .05, respectively). As compared with normal LV geometry, concentric remodeling was characterized by increased TPR and decreased CI, eccentric hypertrophy by increased CI and decreased %FS, and concentric hypertrophy by increased SBP and decreased E/A.

Relations of Natriuretic Peptides and Neurohumoral Factors to LV Anatomical and Functional Variables There was a positive correlation between plasma BNP and ANP levels after logarithmic transformation (r = 0.51, P < .01). A significant positive correlation was found between plasma ANP levels and LVMI (r = 0.33, P < .05), but not between plasma BNP levels and LVMI (r = 0.21, P < .1). There was no correlation between peptide levels and other echocardiographic variables. Neurohumoral factors (PNE, PE, PRA, and PAC) did not show any significant correlation between LV anatomical variables (LVMI and RWT).

The mean plasma BNP level in the concentric hypertrophy group was significantly higher than in the normal LV group (34 ± 9 v 14 ± 3 pg/mL, P < .05, Figure 1). This was also true for plasma ANP level (32 ± 5 v 21 ± 2 pg/mL, P < .05). These were, however, no significant differences in PAC, PNE, and PE among the four groups, although PRA in the eccentric hypertrophy and concentric remodeling groups tended to be suppressed.

DISCUSSION

Major Findings Plasma ANP level was associated with LVMI, but BNP was not. However, increased
BNP was associated with the concentric hypertrophy group, characterized by both increased LVMI and RWT. Patients with this specific LV geometric pattern had increased SBP and decreased LV diastolic function.

Natriuretic Peptides in Hypertension ANP is released by atrial myocytes in response to stretching, e.g., increased atrial pressure, and is also released by ventricular myocytes only in the presence of ventricular hypertrophy. In contrast, recent studies have shown that BNP is predominantly released to ventricles in response to pressure or volume overload. Production of BNP is greatly enhanced as compared with ANP in the presence of chronic congestive heart failure or moderate to severe LVH. In hypertensive patients with LVH, both plasma BNP and ANP levels were higher than in patients without LVH. In patients with mild to moderate hypertension, however, the diagnostic usefulness of plasma BNP and ANP levels in detection of LVH or LV dysfunction is still unclear. In the present study, a positive correlation was found between plasma ANP levels and LVMI, but not between plasma BNP levels and LVMI. This result suggests that linkage between plasma BNP level and LVMI in mild to moderate essential hypertension is weak as compared with plasma ANP level. This result is not consistent with the previous study in hypertensive patients with WHO stage II and III, possibly due to different extents of organ damage between the present study and the previous study.

Association Between Natriuretic Peptides and LV Geometry Concentric Hypertrophy In the present study, plasma BNP and ANP levels were increased in the concentric hypertrophy group, in which LVMI was the greatest and E/A ratio was the smallest among the four study groups, although serum creatinine levels were less than 1.2 mg/dL in the entire cohort of subjects. In previous studies on LV geometry in hypertension, subjects with elevated serum creatinine were included, which might lead to a higher prevalence of concentric hypertrophy with accentuated volume overload. There were no differences in either plasma BNP or ANP levels among the other three groups. Thus, at the early or subclinical stage of hypertensive heart failure, as demonstrated by a depressed E/A ratio, LV diastolic dysfunction may precede LV systolic dysfunction, as detected through elevated plasma BNP and ANP levels. Recently, Nishikimi et al documented that plasma BNP levels in hypertensive patients with concentric hypertrophy were markedly increased as compared with those with other LV geometric patterns, a finding consistent with the present result. However, they found that plasma ANP levels were not elevated. The concentric hypertrophy patients had the greatest LV afterload (SBP), LV wall thickening (LVMI and RWT), and smallest LV diastolic function (E/A) among the four study groups in the present study. Thus, it could be a reflection of the link between BNP production and LV systolic overload or depression of diastolic function in concentric hypertrophy.

Eccentric Hypertrophy The tendency towards suppressed PRA in the eccentric hypertrophy group may indicate that volume overload could be present in this geometric pattern. Naruse et al suggested that elevated plasma ANP levels were induced by volume expansion and that factors other than volume expansion may be responsible for the increased plasma BNP levels in patients with chronic renal failure requiring maintenance hemodialysis. However, both plasma BNP and ANP levels in the eccentric hypertrophy group were not different from those of the normal LV geometry group in the present study. Thus, the contribution of volume overload might be small in the genesis of eccentric hypertrophy in mild to moderate essential hypertension.

Concentric Remodeling The group of patients with concentric remodeling was characterized by decreased

![FIGURE 1. Plasma brain natriuretic peptide (BNP) levels, plasma atrial natriuretic peptide (ANP) levels, plasma renin activity (PRA), and plasma aldosterone concentration (PAC) in essential hypertensive patients with different left ventricular geometric patterns. Values are mean ± SEM. *P < .05 vs normal left ventricle.](image-url)
CI, increased TPR, and normal LV systolic and diastolic function, a consistent finding with the result obtained by Ganau et al. A plausible mechanism for LV concentric remodeling is a natriuresis-induced contraction of the intraventricular volume, which might account for the relatively mild BP elevation despite severely increased TPR. In the present study, both plasma BNP and ANP levels in this group were elevated, but not significantly, as compared with those in the normal LV and eccentric hypertrophy groups. Accordingly, it is possible that BNP or ANP as well as the elevated pressure per se could contribute to the genesis of LV concentric remodeling, although the number of patients was too small to reach that conclusion.

Clinical Implications The present results indicate that measurements of plasma BNP and ANP levels could give us insights into the pathogenesis of different LV geometry in patients with mild to moderate essential hypertension. Further, we found that BNP production is associated with LV systolic overload or diastolic dysfunction. Measurements of plasma BNP level could be a useful tool to identify the early stage of LV dysfunction in patients with mild to moderate essential hypertension.

REFERENCES