Acute Effects of α- and β-Adrenoceptor Blockade on Plasma Atrial Natriuretic Peptides during Exercise in Elderly Patients with Mild Hypertension*

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In a randomized study in 26 elderly patients with mild essential hypertension, acute effects of α- and β-adrenoceptor blockade on plasma ANP levels were examined at rest and during ergometric exercise. Plasma ANP level and LVEF were measured before and after administration of prazosin (an α1-adrenergic blocker), atenolol (a cardioselective β-adrenergic blocker), or carteolol (a nonselective β-adrenergic blocker). Plasma ANP level was increased by exercise. Carteolol and atenolol increased plasma ANP levels at rest and during exercise, but the effect of atenolol was not statistically significant. Prazosin significantly suppressed the ANP values at rest and during exercise. The LVEF was increased by prazosin and decreased by β-blockers, especially by carteolol. Multivariate regression analysis showed that LVEF was the most significant predictor of the plasma ANP level at maximal exercise, the resting blood pressure and heart rate were not predictors of this value. The results showed that single administrations of an α-blocker and a nonselective β-blocker had opposite effects on the plasma ANP level both at rest and during exercise in elderly patients with mild essential hypertension. The observed difference in the ANP response seems to be related to changes in left ventricular function rather than changes in blood pressure or heart rate.

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Mammalian cardiac atria contain biologically active peptides that are capable of producing diuresis, natriuresis, and vasodilation.1-7 These ANPs also inhibit the actions of endogenous vasoconstrictors8 and reduce aldosterone synthesis.9 The plasma ANP level is increased by plasma volume expansion,10,11 and dietary sodium excess.12,13 Moreover, plasma ANP is high in patients with various pathologic conditions, including congestive heart failure,14-16 chronic renal failure,17 essential hypertension,18,19 and hyperthyroidism.20 A few recent reports suggest that the plasma ANP level increases after long-term treatment with β-blockers in patients with essential hypertension.21,22 This effect of β-blockers is clearer in elderly hypertensive patients.21 Here, we examined the effects of acute α- and β-adrenoceptor blockade on plasma ANP level and related humoral factors during ergometric exercise in elderly patients with mild essential hypertension. Plasma ANP and LVEF were measured before and after administration of the α1-adrenergic blocker prazosin, the cardioselective β-blocker atenolol, or the nonselective β-blocker carteolol.

Materials and Methods

Study Population

Twenty-six elderly patients with mild essential hypertension, 11 men and 15 women, aged 60 to 76 years (mean ± SD, 68 ± 5 years) took part in the study. Clinical evaluation indicated that all had stage 1-2 essential hypertension by World Health Organization criteria. They had a mean systolic blood pressure of 160 mm Hg or above, a diastolic blood pressure of 90 mm Hg or above, or both. Secondary hypertension was excluded by taking a clinical history, physical examination, routine laboratory tests including measurements of PRA, aldosterone, catecholamines, and cortisol, and an excretory urogram or renal arteriogram. None of the subjects was in the accelerated or malignant stage of hypertension. In addition, none had clinical evidence of pulmonary disease, anginal pain, myocardial infarction, or marked renal damage. All previous medication was discontinued for at least one week before the exercise study.

The patients were randomly assigned to one of the three following groups: the prazosin group, atenolol group, or carteolol group. Table 1 shows the baseline characteristics of the three study groups after previous medication had been discontinued for longer than one week. No significant differences were found among the three groups in age, sex, blood pressure, heart rate, blood urea nitrogen, serum creatinine, or serum electrolytes. The three groups were also similar in initial levels of PRA, plasma norepinephrine, and plasma ANP.

Study Protocol

After informed consent was obtained, an indwelling intravenous catheter for blood sample collection was inserted into an antecubital vein. Before the exercise test, M-mode echocardiography was performed. Exercise was started 1 h after the patients had taken a

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\[\text{ANP} = \text{atrial natriuretic peptide; EDTA} = \text{ethylenediamine tetraacetic acid; LVEF} = \text{left ventricular ejection fraction; PRA} = \text{plasma renin activity; PA} = \text{pulmonary artery}\]
Table 1—Baseline Characteristics of the
Three Study Groups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prazosin (n = 10)</th>
<th>Atenolol (n = 7)</th>
<th>Carteolol (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>69 ± 6</td>
<td>69 ± 4</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>Sex</td>
<td>4M, 6F</td>
<td>3M, 4F</td>
<td>4M, 5F</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>162 ± 13</td>
<td>169 ± 17</td>
<td>161 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>90 ± 6</td>
<td>93 ± 4</td>
<td>91 ± 10</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>114 ± 6</td>
<td>118 ± 7</td>
<td>114 ± 11</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>82 ± 11</td>
<td>85 ± 9</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>18 ± 4</td>
<td>18 ± 3</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>142 ± 3</td>
<td>141 ± 1.3</td>
<td>141 ± 2</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.1 ± 0.3</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td>Serum chloride, mEq/L</td>
<td>105 ± 3</td>
<td>105 ± 2</td>
<td>105 ± 2</td>
</tr>
<tr>
<td>Plasma renin activity, ng/ml</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/ml</td>
<td>432 ± 91</td>
<td>481 ± 113</td>
<td>440 ± 107</td>
</tr>
<tr>
<td>Plasma ANP pg/ml</td>
<td>24 ± 3</td>
<td>96 ± 8</td>
<td>22 ± 4</td>
</tr>
</tbody>
</table>

*Values are means ± SD.

placebo tablet. The exercise protocol consisted of three fixed workloads on a bicycle ergometer in the sitting position. The initial work load was 20 W for 4 min, the second was 40 W for 4 min, and the third was 60 W for 4 min. Blood pressure and heart rate were measured at rest and at each exercise stage. Blood samples for PRA, norepinephrine, and ANP determinations were collected at rest and at maximal exercise from the indwelling intravenous catheter. Ten minutes after the control exercise study, the patients took either prazosin (1 mg), atenolol (50 mg), or carteolol (10 mg) orally. One hour later, M-mode echocardiography and the same exercise study were repeated under identical conditions. Blood pressure, heart rate, PRA, plasma norepinephrine, and plasma ANP level were also measured at rest and during exercise.

Hemodynamic and Hormonal Measurements

Blood pressure was measured by the standard cuff technique. All readings were made by the same investigator using the same calibrated mercury manometer. The heart rate was obtained from the electrocardiogram. The LVEF was measured according to the method of Pombo et al.10

Blood samples for ANP determinations were drawn immediately into ice-chilled siliconized disposable tubes containing Trasylol (500 KIU/ml) and EDTA (1 mg/ml). Plasma was separated by centrifugation for 10 min at 4°C, and then immediately frozen and stored at −80°C for several days. Immunoreactive ANP was extracted from plasma according to the method previously described.10 From each plasma sample, 2 ml was diluted with 5 ml of 4 percent acetic acid. After centrifugation, the solution was pumped at the rate of 1 ml/min through a Sep-Pak C18 cartridge (Waters Associates, Milford, Mass). After the cartridge was washed with 5 ml of distilled water, the adsorbed peptides were eluted with 96 percent ethanol in 4 percent acetic acid. After evaporation of the eluate by a centrifugal evaporator, (model RD-31, Yamato Scientific Co., Japan), the dry residue was dissolved in an assay buffer. The recovery rate was calculated by the addition of two different amounts of cold alpha human ANP(1-28) (50 or 100 pg/ml) to the plasma with dextran-coated charcoal. This rate was 62±3 percent.

Radioimmunoassay for ANP was performed as previously re-

![Graphs showing blood pressure and heart rate changes](image-url)

**Figure 1.** Systolic and diastolic blood pressure and heart rate at rest and during graded exercise before (control) and during treatment. Statistical analysis was performed by three-way analysis of variance. *F* is the effect of treatment; *Fl*, interaction between treatment and levels of activity. *p*<0.05, **p**<0.001.

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Alpha- and Beta-Adrenoceptor Blockade in Mild Hypertension (Kohno et al)
The antibody used here (Peninsula Laboratories Inc., Belmont, Calif.) cross-reacts 100 percent with alpha human ANP(1-28) and alpha rat ANP(1-28), 57 percent with alpha human ANP(18-28), 27 percent with alpha rat ANP(5-27), and 3 percent with alpha rat ANP(5-25). The antibody does not cross-react with somatostatin, oxytocin, or vasopressin. The radioimmunoassay was performed in an assay buffer of 0.01M sodium phosphate, pH 7.4, containing 0.05M NaCl, 0.1 percent bovine serum albumin, 0.1 percent Nonidet NP-40, and 0.01 percent NaN3. The interassay variation was 12.6 percent and the intra-assay variation was 6.2 percent. Plasma norepinephrine was measured by high-pressure liquid chromatography. The PRA was measured by the solid phase radioimmunoassay of Ikeda et al.

Statistical Analysis

All values were expressed as means ± SD. The comparisons of baseline characteristics of the three study groups were analyzed by unpaired ANOVA, and significance was confirmed by Scheffe's method. The resting LVEF before and during the treatment was compared by paired ANOVA, and significance was confirmed by the method of Greenhouse and Geisser. Multivariate regression analysis was performed of plasma ANP levels at a workload of 60 W and of various clinical factors at rest to identify which measurements could be predictors of the plasma ANP level during exercise. To compare the data after treatment with control data within each of the three groups, three-way analysis of variance was used, considering levels of physical activity, subjects, treatments, and their interactions as sources of variance. Only the effect of treatment and interactions between treatment and the levels of physical activity are discussed here.

RESULTS

Figure 1 shows the effects of prazosin, atenolol, and carteolol on blood pressure and the heart rate at rest and with various workloads. At rest and during exercise, systolic and diastolic blood pressure were decreased by these three drugs. There were no significant interactions between treatment and physical activity for systolic or diastolic blood pressures. The heart rate at rest and during exercise was decreased by both β-blockers, but it was not affected by prazosin. The resting LVEF was increased by prazosin and was decreased by atenolol and carteolol (Fig 2). The decrease of LVEF by carteolol was greater than atenolol. The difference in the decreases was not statistically significant.

Figure 3 shows the effects of prazosin, atenolol, and carteolol on PRA at rest and at a workload 60 W. The PRA was increased by exercise (p<0.05). At rest and at a workload of 60 W, PRA was decreased by both β-blockers, but it was not affected by prazosin. There were no significant interactions between treatment and physical activity for PRA in the three groups.

Figure 4 shows the effects of prazosin, atenolol, and carteolol on plasma ANP levels at rest and at a workload of 60 W. The plasma ANP level was increased.
by exercise (p<0.01). Plasma ANP levels were decreased by prazosin. Carteolol and atenolol increased plasma ANP levels, but the effect of atenolol was not statistically significant. There were significant interactions between treatment and physical activity for ANP in the prazosin group, but were not in the atenolol or carteolol group.

Figure 5 shows the effects of prazosin, atenolol, and carteolol on plasma norepinephrine levels at rest and at a workload of 60 W. Plasma norepinephrine level was increased by prazosin and atenolol, but it was not affected by carteolol.

Table 2 shows the results of multivariate regression analysis of the plasma ANP level at maximal exercise and of clinical factors in the three groups. The resting LVEF was the most significant predictor of the ANP level at maximal exercise (Fig 6). The resting blood pressure and heart rate were not such predictors.

**DISCUSSION**

The present study showed that the plasma ANP level was increased by ergometric exercise in elderly patients with mild hypertension, and that a single administration of prazosin suppressed the plasma ANP level at rest and at maximal exercise. Single administrations of the cardioselective β-blocker atenolol and the nonselective β-blocker carteolol increased plasma ANP level, but the effect of atenolol was not statistically significant.

Several possible mechanisms should be considered in the explanation of the opposite effect of single administrations of an α-blocker and a nonselective β-blocker on the plasma ANP level. When a β-blocker, especially the nonselective β-blocker propranolol, is given once or for a short term to patients with essential hypertension, the typical response is a decrease in the

**Table 2—Multivariate Regression Analysis of Plasma ANP Levels at Maximal Exercise and Clinical Measurements in the Three Study Groups Before and During Treatment**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Beta Weight</th>
<th>Significant Level, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP vs LVEF</td>
<td>-0.238</td>
<td>85.7</td>
</tr>
<tr>
<td>ANP vs systolic blood pressure</td>
<td>0.067</td>
<td>29.1</td>
</tr>
<tr>
<td>ANP vs diastolic blood pressure</td>
<td>-0.025</td>
<td>9.7</td>
</tr>
<tr>
<td>ANP vs heart rate</td>
<td>0.010</td>
<td>4.0</td>
</tr>
<tr>
<td>ANP vs PRA</td>
<td>-0.150</td>
<td>63.9</td>
</tr>
<tr>
<td>ANP vs norepinephrine</td>
<td>-0.146</td>
<td>58.7</td>
</tr>
</tbody>
</table>
 heart rate and cardiac output and an increase in total peripheral resistance above the pretreatment levels, although these hemodynamic changes gradually decrease with continued treatment. Our subjects were elderly hypertensive patients. One characteristic hemodynamic change in such patients is a fall in cardiac output, which is probably due to impaired myocardial contractility, increased left ventricular wall thickness, and decreased cardiac compliance. Therefore, short-term administration of a nonselective β-blocker to elderly hypertensive patients may further reduce cardiac output and prevent the normal augmentation of myocardial contractility during exercise. Actually, LVEF was decreased by both β-blockers we used, especially by the nonselective β-blocker carteolol. These hemodynamic changes caused by acute β-adrenoceptor blockade may increase the left ventricular filling pressure, and thereby cause atrial overload, which in turn stimulates ANP release from the atrium into the general circulation. This hypothesis may be supported by the findings that LVEF is a predictor of the ANP level at maximal exercise and that the resting blood pressure and heart rate are not such predictors. On the other hand, a single administration of prazosin can decrease left ventricular filling pressure and PA wedge pressure and increase cardiac output. The present study also showed that LVEF was slightly but significantly increased by prazosin in elderly hypertensive patients. Previously, we found that the plasma ANP level and PA wedge pressure were increased by ergometric exercise in patients with essential hypertension and with valvular heart disease, and that plasma ANP during exercise was correlated with PA wedge pressure. The PA wedge pressure and right atrial pressure regulate the release of ANP from the atrium. Therefore, the decrease in the plasma ANP level observed in patients given prazosin appears to be related to the declines in PA wedge pressure and right atrial pressure induced by prazosin. Our results failed to demonstrate such a causal relationship between the plasma ANP level and cardiopulmonary hemodynamics. Measurements in the second exercise period may be influenced by familiarity with the bicycle test.

Another possible explanation for the raised plasma ANP level in patients given carteolol may be a change in sympathetic activity. However, carteolol did not affect the plasma norepinephrine level at rest or at maximal exercise. It seems unlikely, therefore, that changes in sympathetic activity are directly related to the alterations in the ANP levels. Nakaoka et al also
did not find a significant relationship between the plasma ANP and catecholamine levels in patients receiving β-blockers. Furthermore, the decline in the plasma ANP level that we observed in patients given prazosin might be, in part, associated with α-adrenoceptor blockade itself, as α-adrenergic stimulation triggers ANP release in vitro. The exact mechanism by which prazosin suppresses and carteolol facilitates the ANP release from the atrium at rest and during exercise in elderly hypertensive patients is not known.

Plasma renin activity was suppressed by β-blockers at rest and during exercise. The ANP suppresses renin release, but whether the elevated plasma ANP level in patients receiving carteolol is directly related to the observed decline of PRA remains to be determined.

In conclusion, the present study showed that single administrations of the α-blocker prazosin and the nonselective β-blocker carteolol have opposite effects on the plasma ANP level in elderly patients with mild essential hypertension. The observed difference in the ANP response appears to be related to changes in left ventricular function rather than changes in blood pressure or heart rate.
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