Hormonal and Renal Effects of Atrial Natriuretic Peptide in Patients With Secondary Hypertension

Yasunobu Hirata, MD, Masao Ishii, MD, Tokuichiro Sugimoto, MD, Hiroaki Matsuoka, MD, Kazushige Fukui, MD, Tsuneaki Sugimoto, MD, Minoru Yamakado, MD, Hitoshi Tagawa, MD, Atsuro Miyata, MD, Kenji Kangawa, PhD, and Hisayuki Matsuo, PhD

To investigate the involvement of atrial natriuretic peptide (ANP) in secondary hypertension, we examined hormonal and renal responses to ANP infusion (0.025 μg/kg/min) in 27 patients with renal parenchymal hypertension, 10 with primary aldosteronism, 8 with renovascular hypertension, and 15 normotensive subjects. The preinfusion plasma concentration of ANP was significantly higher in patients with renal parenchymal hypertension (120 pg/ml, p<0.01) and in patients with primary aldosteronism (98 pg/ml, p<0.05) than in the normotensive subjects (40 pg/ml), but it was not greater than in the patients with renovascular hypertension (73 pg/ml, NS). In the patients with renal parenchymal hypertension, plasma ANP correlated negatively with creatinine clearance (r=−0.76, p<0.001). Mean blood pressure (−5%, p<0.01) and plasma aldosterone (−40%, p<0.001) decreased to a similar degree in the four groups during ANP infusion. However, an increase in urinary sodium excretion caused by ANP was higher in the hypertensive than in the normotensive patients (+250% vs. +70%, p<0.01) and correlated positively with mean blood pressure during ANP infusion (r=0.47, p<0.001). The removal of adenomas in the patients with primary aldosteronism significantly lowered both plasma levels of ANP and cyclic guanosine 2′,3′-monophosphate and reduced an increase in sodium excretion during ANP infusion, whereas the responses of blood pressure and plasma aldosterone to ANP infusion were not altered by the operation. Thus, these results suggest that elevated ANP secretion and increased natriuretic responses to ANP may modify the blood pressure and body fluid volume status in some types of secondary hypertension. (Circulation 1988;78:1401–1410)

Because atrial natriuretic peptide (ANP), originally discovered from extracts of rat atrial tissue by de Bold et al., exerts potent natriuretic and blood pressure lowering effects, ANP has been considered to be involved in the regulation of body fluid volume and blood pressure.

In this context, its pathogenetic roles in both experimental and human hypertension have been extensively investigated. Although it is still uncertain whether or not the renal and vascular effects of ANP are physiological, animal experiments with specific antisera raised against ANP have suggested that ANP participates in the regulation of basal blood pressure and renal sodium handling. Accordingly, if ANP secretion is insufficient in some conditions, it may result in the expansion of body fluid volume and an elevation of blood pressure.

However, such pathological conditions have not yet been reported. Animal models for hypertension such as spontaneously hypertensive rats and DOCA salt-sensitive hypertensive rats have elevated plasma concentrations of ANP. Furthermore, both spontaneously hypertensive and DOCA salt-sensitive hypertensive rats are more responsive to ANP with regard to blood pressure and urinary...

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, the Department of Internal Medicine, Mitsui Memorial Hospital, and the Second Department of Biochemistry, Miyazaki Medical College, Tokyo and Miyazaki, Japan.

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Address for correspondence: Yasunobu Hirata, MD, The Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan.

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sodium excretion than the respective control animals. We have also reported that patients with essential hypertension have higher plasma concentrations of ANP and greater natriuretic responses to exogenously infused ANP compared with normotensive patients.8 Such enhanced ANP activity in essential hypertension may lead to the hypothesis that ANP plays a compensatory role for elevated blood pressure rather than a causative one. However, there are sharp differences of opinion concerning ANP activity in essential hypertension. The plasma concentration of ANP has been reported by several investigators to be elevated in patients with essential hypertension,9-12 whereas a similar number of investigations have not reported any differences in the plasma level of ANP between hypertensive and normotensive patients.13-16

The exact mechanisms of elevated ANP secretion in hypertension, if any, have not been elucidated. In some investigations that showed higher plasma ANP in hypertensive than in normotensive patients,9,10 plasma ANP correlated positively with blood pressure or negatively with plasma renin activity, suggesting that altered cardiovascular hemodynamics or the expansion of extracellular fluid volume might influence plasma ANP. Therefore, to examine which blood pressure or body fluid volume is more important in relation to an increase in the plasma ANP, it would be helpful to compare the plasma ANP levels in hypertensive patients with various statuses of blood volume, that is, volume-overload and non-overload types of hypertension.

Thus, to determine whether or not such elevated ANP secretion or increased renal responses to ANP or both are specific for essential hypertension, we measured plasma levels of ANP and examined the renal and endocrine responses to ANP infusion in patients with various types of secondary hypertension.

Subjects and Methods

Subjects

The subjects included 10 patients with primary aldosteronism (PA), 27 with renal parenchymal hypertension (RH), eight with renovascular hypertension (RVH), and 15 normotensive patients. These subjects were all hospitalized and placed on a diet containing NaCl 8 g/day. Eleven of the 43 hypertensive patients were treated before admission (four in the RH group received nifedipine or nicardipine and frusemide, three in the RH group received nifedipine or nicardipine, one in the RVH group received nifedipine and captopril, one in the RVH received nifedipine, one in the RVH group received captopril, and one in the PA group received spironolactone). Medication was withheld on the day of admission, except for three patients in the RH group. The combined therapy of nifedipine and frusemide in these three patients was discontinued 1 week before the ANP infusion study. The infusion study in the other previously treated patients was

Table 1. Background of Patients in the Four Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Primary aldosteronism</th>
<th>Renal parenchymal hypertension</th>
<th>Renovascular hypertension</th>
<th>Normotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44±3*</td>
<td>48±2†</td>
<td>45±7*</td>
<td>35±3</td>
</tr>
<tr>
<td>Men:women</td>
<td>3:7</td>
<td>19:8</td>
<td>6:2</td>
<td>11:4</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.59±0.07</td>
<td>1.67±0.03</td>
<td>1.64±0.08</td>
<td>1.74±0.04</td>
</tr>
<tr>
<td>Plasma sodium (meq/l)</td>
<td>141±2</td>
<td>137±1</td>
<td>135±1</td>
<td>138±1</td>
</tr>
<tr>
<td>Plasma potassium (meq/l)</td>
<td>3.1±0.3†</td>
<td>4.1±0.1*</td>
<td>3.3±0.2</td>
<td>3.5±0.1</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>0.8±0.2</td>
<td>4.3±0.7§</td>
<td>1.3±0.4</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>Basal blood pressure</td>
<td>159±4/96±3†</td>
<td>166±6/93±3†</td>
<td>184±13/102±4†</td>
<td>17±3/69±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.02, †p<0.001, §p<0.05, ‡p<0.01 vs. normotensive patients.

Figure 1. Bar graph of plasma atrial natriuretic peptide (ANP) concentrations during the control, ANP infusion, and recovery periods in the four groups. NT, normotensive group; PA, primary aldosteronism; RH, renal parenchymal hypertension; RVH, renovascular hypertension. *p<0.05, †p<0.01 vs. NT. Values during the infusion period are significantly higher than those during other periods (p<0.001, each group).
conducted at least 2 weeks after admission. One patient with PA treated with spironolactone was examined 1 month after cessation of the treatment. The patients were diagnosed as follows. The blood pressure in all patients had been higher than 160/95 mm Hg before receiving antihypertensive agents or before admission. Patients with RH showed either serum creatinine concentrations higher than 3 mg/dl or significant glomerular injury as proven by renal biopsy. Histological diagnoses were obtained in 20 of the 27 patients. The renal histological study could not be examined in the other patients because of their high serum creatinine levels. Serum creatinine concentrations in 12 patients with RH were higher than 3 mg/dl, and those concentrations in the other 15 patients with biopsy-proven glomerulonephritis averaged 1.3±0.1 (SEM) mg/dl (0.9–2.3 mg/dl). The RH group consisted of chronic glomerulonephritis in 23, diabetic nephropathy in two, renal tuberculosis in one, and polycystic disease in one. These diagnoses were based on histological findings and thorough clinical or laboratory examinations or both. None of these patients had received hemodialysis or peritoneal dialysis. The patients with RVH were diagnosed on the basis of renal arteriography and plasma renin activity in renal veins. The RVH group consisted of atherosclerosis in three, fibromuscular dysplasia in three, and renal infarction in two patients (one was postoperative, the other idiopathic). The lesions were all unilateral. Diagnoses of the patients with PA were based on computed tomographic scans, adrenal scintigrams, and hormonal examinations. Adenomas in all patients in the PA group were confirmed by surgery. No group of patients showed any signs of congestive heart failure. The normotensive control subjects were selected from patients who had been hospitalized because of chance hematuria and diagnosed as having idiopathic hematuria on the basis of renal histological studies and from patients who had been hospitalized for health checks. No abnormalities in laboratory examinations, including renal function and endocrine studies, were found in any of the normotensive subjects. Mean age, sex, body surface area, serum concentrations of sodium, potassium and creatinine levels, and blood pressure are shown in Table 1. After a detailed explanation of the study, informed consent was obtained from all subjects. Intravenous infusion of ANP was approved by the Ethical Committee for Clinical Research Trials, University of Tokyo Hospital, Tokyo, Japan.

**Study Protocol**

The examination was started by 8:30 AM after overnight fasting. A Ringer's solution containing

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**FIGURE 2.** Bar graph of plasma cyclic guanosine 2',3'-monophosphate (cGMP) concentrations during the control, atrial natriuretic peptide infusion, and recovery periods in the four groups. NT, normotensive group; PA, primary aldosteronism; RH, renal parenchymal hypertension; RVH, renovascular hypertension. *p<0.05, ‡p<0.01, §p<0.001 vs. NT. Values during the infusion period are significantly higher than those during other periods (p<0.001, each group).

**FIGURE 3.** Plot of time course of mean blood pressure (MBP) during the study in four groups. NT, normotensive group; PA, primary aldosteronism; RH, renal parenchymal hypertension; RVH, renovascular hypertension. *p<0.05, ‡p<0.01, §p<0.001 vs. control period. Values in hypertensive groups are significantly higher than those in the NT group at any period (p<0.001, each group).
p-aminohippuric acid (PAH) was infused into the right cubital vein of the supine subjects by an infusion pump (STC-503, Terumo, Tokyo, Japan). After a bolus injection of PAH (0.025 g/kg), the infusion rate was maintained at 100 ml/hr (0.94%) throughout the study. In patients with increased serum creatinine levels, infused PAH was reduced in proportion. After the 30-minute equilibrium period, urine was collected through the bladder catheter every 20 minutes. After two urine collections for baseline measurement, infusion of synthetic α-human ANP (α-hANP) solution was started at 0.025 μg/kg/min and continued for 40 minutes with another infusion pump (IVAC-700, IVAC, San Diego, California), connected to the PAH solution line. α-hANP was synthetized at the Protein Research Foundation (Osaka, Japan), and the purity was 99.9% as verified by chromatographic analysis. The ANP solutions were sterilized for clinical use by the Department of Pharmacy, University of Tokyo Hospital, Tokyo, Japan. One hundred micrograms of the peptide was dissolved in 50 ml isotonic saline. Recovery was observed for 40 minutes after cessation of ANP infusion. Blood was drawn from the indwelling cannula in the left cubital vein at the midpoint of each 20-minute urine collection period. Blood pressure was measured in the left arm by an automatic manometer every 5 minutes (ABPM-630, Nihoncolin, Aichi, Japan). The study was completed at about 11:00 AM.

In six of the 10 patients with PA, the ANP infusion study with the same protocol was repeated about 4 weeks after the adrenal operation. Their mean (±SEM) age was 45±4 years (two men and four women). Furthermore, in five healthy subjects (mean age, 37±2 years; mean body surface area, 1.84±0.09 m²), the time-course changes in blood pressure and renal and endocrine function with the above described protocol but with vehicle infusion instead of ANP infusion were also observed.

**Sample Measurements**

Sodium and potassium concentrations in the urine and plasma were measured with a flamephotometer (IL Autocal Flame Photometer G43, Instrumentation Laboratory, Lexington, Massachusetts). The glomerular filtration rate and effective renal plasma flow were estimated by measuring the renal clearance rates of endogenous creatinine and that of PAH, respectively. Creatinine and PAH in the plasma and urine were measured by Jaffe’s reaction and Marchall’s reaction, respectively, as previously reported.17 Renal blood flow was calculated from the clearance rate of PAH and hematocrit levels. The assay methods of plasma hormones were plasma aldosterone concentration and plasma renin activity (PRA) by standard radioimmunoassay,17 cGMP by radioimmunoassay after succinylation18 (cGMP assay kit, Yamasa, Chiba, Japan), immunoreactive ANP concentration by radioimmunoassay according to the method reported by Miyata et al.18,19 In this assay system, the intercept of 50% binding was about 13 pg/tube, and the sensitivity was less than 1 pg/tube. The intra-assay variation was 3.6% (n=10), and the interassay variation was 11.0% (n=11).

**Statistical Analysis**

Variables are expressed as mean±SEM. Two preinfusion measurements were averaged for the values of the control period, and values for the infusion and recovery periods were taken as those during the second urine-collecting periods of the respective phase. Urine volume, urinary sodium excretion, renal blood flow, and creatinine clearance were corrected with respect to body surface area. Differences between groups were assessed by the modified t test based on one-way analysis of variance. Effects of ANP infusion and those of surgery in the patients with PA were estimated by paired t test. Correlation coefficients were calculated by the least-squares method. Levels of significance were set at a p value less than 0.05.

**Results**

**Plasma Levels of Atrial Natriuretic Peptide and cGMP**

Plasma concentrations of ANP in the PA and RH groups during the control period were significantly
higher than those in the normotensive group (Figure 1). The average plasma ANP was also higher in the RVH group than that in the normotensive group, but the difference did not reach significance. ANP infusion at 0.025 μg/kg/min increased the plasma ANP concentration by about eight times in each group, and plasma ANP in the RH group during the infusion period was significantly higher than in the other three groups. The plasma ANP concentration during the recovery period returned to the preinfusion level. Basal plasma concentrations of cGMP in the PA and RH groups were also higher than that in the normotensive group (Figure 2) and closely correlated with those of ANP in the four groups (r=0.84, p<0.001). The plasma cGMP concentration was markedly increased during ANP infusion, with the changes in plasma cGMP not being different among the groups. In contrast to plasma ANP, the plasma cGMP concentration 30 minutes after cessation of ANP infusion was still higher than that during the control period.

**Effects of Atrial Natriuretic Peptide on Blood Pressure, Plasma Renin Activity, and Plasma Aldosterone Concentration**

Mean blood pressure, which was obviously higher in the hypertensive groups than in the normotensive group throughout the study, was significantly lowered by ANP infusion to a similar degree in the four groups (Figure 3). Figure 4 demonstrates the plasma renin activity and plasma aldosterone concentration before, during, and after ANP infusion. The plasma renin activity was stimulated in the RVH group, whereas it was suppressed in the PA group during the control period, and it was not affected by the infusion. In contrast to the plasma renin activity, ANP infusion significantly reduced the plasma aldosterone concentration. Although basal plasma aldosterone concentration was very high in the PA and RVH groups, the levels of reduction in plasma aldosterone concentration were comparable in the four groups (about −40% each, p<0.001). The plasma aldosterone concentration returned to basal levels during the recovery period.

**Renal Responses to Atrial Natriuretic Peptide**

Table 2 summarizes the urine volume, urinary sodium excretion, renal blood flow, and creatinine clearance before, during, and after ANP infusion, and changes in urinary sodium excretion are presented in Figure 5. Although significant ANP diuretic and natriuretic effects were observed in the four groups, changes in the urinary sodium excretion were greater in the hypertensive groups than in the normotensive group. The average creatinine clearance was markedly reduced in the RH group during the control period compared with that in other groups (p<0.05), but it was significantly increased.

### Table 2. Time-Course Changes in Renal Function of the Four Groups Before, During, and After Atrial Natriuretic Peptide Infusion

<table>
<thead>
<tr>
<th>Phase</th>
<th>Control (min)</th>
<th>Infusion (min)</th>
<th>Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-20</td>
<td>20-40</td>
<td>40-60</td>
</tr>
<tr>
<td></td>
<td>Urine volume (ml/min/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>2.3±0.4</td>
<td>2.1±0.4</td>
<td>3.0±0.7</td>
</tr>
<tr>
<td>Renal parenchymal hypertension</td>
<td>1.7±0.3</td>
<td>1.5±0.1</td>
<td>2.2±0.2*</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>2.5±0.6</td>
<td>2.7±0.7</td>
<td>3.7±0.6*</td>
</tr>
<tr>
<td>Normotension</td>
<td>2.9±0.4</td>
<td>1.8±0.3</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td></td>
<td>Urinary sodium excretion (μeq/min/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>107±21</td>
<td>113±24</td>
<td>178±34*</td>
</tr>
<tr>
<td>Renal parenchymal hypertension</td>
<td>77±9</td>
<td>78±10</td>
<td>126±17‡</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>87±24</td>
<td>96±33</td>
<td>164±46*</td>
</tr>
<tr>
<td>Normotension</td>
<td>110±12</td>
<td>117±13</td>
<td>150±23†</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance (ml/min/m²)</td>
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<tr>
<td>Primary aldosteronism</td>
<td>57.7±5.5</td>
<td>60.0±7.4</td>
<td>65.4±6.6</td>
</tr>
<tr>
<td>Renal parenchymal hypertension</td>
<td>23.5±4.0</td>
<td>25.5±4.0</td>
<td>24.5±3.7</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>41.4±6.3</td>
<td>40.8±5.6</td>
<td>45.3±5.5</td>
</tr>
<tr>
<td>Normotension</td>
<td>65.8±2.8</td>
<td>66.7±4.9</td>
<td>58.5±3.9</td>
</tr>
<tr>
<td></td>
<td>Renal blood flow (ml/min/m²)</td>
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<tr>
<td>Primary aldosteronism</td>
<td>404±57</td>
<td>429±46</td>
<td>447±58</td>
</tr>
<tr>
<td>Renal parenchymal hypertension</td>
<td>174±38</td>
<td>187±34</td>
<td>183±35</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>300±50</td>
<td>301±50</td>
<td>324±45</td>
</tr>
<tr>
<td>Normotensive</td>
<td>454±27</td>
<td>497±38</td>
<td>445±26</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.01, †p<0.02, ‡p<0.001, §p<0.05 vs. control periods.
in the RH group by ANP infusion. The other two hypertensive groups showed a similar tendency with respect to creatinine clearance changes, whereas the creatinine clearance in the normotensive group was not influenced, resulting in significantly greater increases in the creatinine clearance in the RH, RVH, and PA groups than in the normotensive group (Figure 5). The renal blood flow in the RH group was also much less than in the other groups and did not change in any group. When the relation between renal function and plasma ANP concentration was analyzed in the RH group, plasma ANP concentration increased exponentially with a decrease in creatinine clearance. Thus, within the RH group, the plasma concentration of ANP was negatively correlated with creatinine clearance (Figure 6). However, the plasma ANP concentration was not correlated with the mean blood pressure within any group or in all. When factors involving natriuretic responses were assessed, changes in urinary sodium excretion significantly correlated with the mean blood pressure during ANP infusion and changes in creatinine clearance by ANP (Figure 7).

**Effects of Removal of Adrenal Tumors in Patients With Primary Aldosteronism**

Figures 8 and 9 show blood pressure, hormonal, and urinary variables before and after the adrenal operation in the PA group. Figure 8 describes the effects of ANP on blood pressure and urinary sodium excretion. Although the blood pressure level during the control period after surgery was much lower than that before surgery, the levels of decreases in mean blood pressure by ANP infusion were similar (−4.4±1.1% vs. −3.1±1.2%, NS). On the other hand, the natriuretic effects of the peptide were significantly attenuated by the surgery. Preoperative increases in urinary sodium excretion were greater than postoperative increases (+370±100 vs. +129±51 µeq/min/m², p<0.05). Figure 9 shows plasma concentrations of ANP, cGMP, and aldosterone before, during, and after ANP infusion. Adenoma removal caused a signifi-

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**Figure 5.** Bar graphs of level of changes in urinary sodium excretion ($U_{NaV}$) and creatinine clearance ($C_{Cr}$) induced by atrial natriuretic peptide infusion in the four groups. NT, normotensive group; PA, primary aldosteronism; RH, renal parenchymal hypertension; RVH, renovascular hypertension. *p<0.02, †p<0.01, §p<0.001 vs. control period.

**Figure 6.** Linear regression plot of relation between creatinine clearance ($C_{Cr}$) and plasma atrial natriuretic peptide (ANP) concentration in the patients with renal parenchymal hypertension during the control period. Both values are expressed on a logarithmic scale.

**Figure 7.** Linear regression plots of relation between changes in urinary sodium excretion ($U_{NaV}$) and mean blood pressure (MBP) during atrial natriuretic peptide (ANP) infusion or changes in creatinine clearance ($C_{Cr}$).
cant reduction in these plasma hormones; however, the surgery did not alter the degree of ANP-induced aldosterone suppression (-39.5±12.4% vs. -49.6±17.0%, NS). Although plasma potassium increased from 3.0 to 4.0 meq/l (p<0.05) and plasma renin activity increased from 0.2 to 0.9 ng/ml/hr (p<0.02), they were not influenced by ANP infusion before or after surgery.

**Adverse Reaction of Atrial Natriuretic Peptide Infusion**

There were no significant adverse effects in any group during or after ANP infusion.

**Effects of Vehicle Infusion**

Table 3 summarizes the time-course changes in blood pressure, plasma hormones, and renal function during vehicle infusion in the healthy subjects. None of the variables changed significantly.

**Discussion**

In the present study, we measured the plasma ANP concentration in patients with three types of secondary hypertension and analyzed the relation between the plasma ANP level and renal function or blood pressure. As a result, the plasma concentrations of ANP in the PA and RH groups of patients were significantly higher than that in the normotensive subjects. The RH group, with lower creatinine clearance, showed higher plasma ANP levels compared with the normotensive group despite comparable blood pressure, suggesting that body fluid expansion resulting from reduced renal function may elevate ANP secretion, at least in the RH group. This is compatible with the findings that very high plasma ANP concentrations in renal failure are markedly lowered by body fluid volume reduction with hemodialysis.20

Plasma ANP concentration was also significantly higher in the patients with PA than in the normotensive patients. Moreover, the successful surgical removal of adenomas lowered the plasma concentration of ANP in all of the patients with PA that were examined. It has been reported that plasma ANP in patients with PA is decreased by spironolactone treatment.13,21 Furthermore, the DOCA-salt-sensitive hypertensive rat, which is considered to be an animal model for human PA, also exhibits high plasma ANP concentration.5 These findings suggest that ANP secretion is enhanced in hypertension caused by hyperaldosteronism.

In contrast to the RH and PA groups, patients with RVH did not show a significantly higher plasma concentration of ANP than the normotensive patients. It is known that plasma volume in patients with RVH decreases somewhat.22 This may explain the lack of significant differences in plasma ANP concentration of the RVH from that of the normotensive patients, though this group of patients had very high blood pressure and slightly reduced renal function. However, it has been reported that human RVH and its animal model, 2-kidney, 1-clip Goldblatt rats have increased plasma ANP concentrations.14,23 Furthermore, Garcia et al23 demonstrated that unclipping of the Goldblatt rats resulted in a significant reduction in plasma ANP concentration along with a decline in blood pressure. Because the average plasma ANP level in the RVH group

**FIGURE 8. Plot and bar graph of mean blood pressure (MBP) and urinary sodium excretion (\(U_{NaV}\)) before and after removal of adenomas in the patients with primary aldosteronism.**

- **Table 3** summarizes the time-course changes in blood pressure, plasma hormones, and renal function during vehicle infusion in the healthy subjects. None of the variables changed significantly.

**FIGURE 9. Plots of plasma concentrations of atrial natriuretic peptide (ANP), cyclic guanosine 2',3'-monophosphate (cGMP), and plasma aldosterone concentration (PAC) before and after removal of adenomas in the patients with primary aldosteronism. Former two values are plotted on a logarithmic scale.**

- **Table 3** summarizes the time-course changes in blood pressure, plasma hormones, and renal function during vehicle infusion in the healthy subjects. None of the variables changed significantly.
was substantially higher than in the normotensive patients in the present study, it is possible that the state of RVH may raise plasma ANP. Further studies are needed to clarify this.

The most important stimulus for ANP secretion has been considered to be the extension of atrial walls. Both blood pressure elevation and plasma volume expansion are capable of increasing plasma ANP concentration.\textsuperscript{24,25} We could not specify whether volume expansion or high blood pressure was more important in relation to increases in the plasma ANP concentration of the PA group because the surgery probably corrected both hypervolemia and hypertension. However, blood pressure was not related to the plasma ANP concentration within any group or in the whole. Moreover, the average plasma ANP level in the PA group was slightly higher than in the RVH group, despite the lower blood pressure and higher creatinine clearance. Thus, although we did not measure plasma volume in the present study, these results suggest that the increase in ANP secretion may be more importantly related to increased body fluid volume rather than to high blood pressure.

Antihypertensive agents might affect the plasma ANP concentration in the present study, particularly in three patients with marked renal failure in whom medication was discontinued 1 week before the study. These patients were given nifedipine and frusemide. Although calcium antagonists cause a transient increase in plasma ANP concentration,\textsuperscript{26} a 1-week washout period is long enough to eliminate the effects of nifedipine. On the other hand, frusemide could still decrease the plasma concentration of ANP 1 week after its cessation.\textsuperscript{27} However, the plasma ANP concentration in these patients remained extremely high (477, 386, and 222 pg/ml). Furthermore, the converting enzyme inhibitor, which two patients with RVH were given, has been reported not to change the plasma ANP level.\textsuperscript{28} Thus, the treatments before the examination did not appear to have a major influence on the plasma concentration of ANP in the present study.

It has been well established that ANP has potent depressor, natriuretic, and aldosterone suppressing effects. In this regard, primary aldosteronism is an important disease to investigate the pathophysiological roles of ANP. Several in vitro studies have suggested that adenoma cells from patients with PA are devoid of intact ANP receptors.\textsuperscript{29,30} However, Naruse et al\textsuperscript{31} demonstrated that ANP suppressed aldosterone secretion from aldosterone-producing cells of five patients. Furthermore, Jungmann et al\textsuperscript{32} reported that subcutaneous injection of ANP decreased urinary excretion of aldosterone from an aldosteronoma-implanted nude mouse. Although we have not directly examined the ANP receptors, our data can be interpreted to mean that aldosterone-producing adenoma cells are responsive to ANP in vivo. Thus, ANP seems to suppress the secretion of aldosterone even in patients with PA. From a teleological point of view, elevated plasma ANP may be one of the compensatory responses to hyperaldosteronism and related to a so-called "escape phenomenon" from body fluid retention.\textsuperscript{21}

In the present study, the plasma concentration of cGMP was positively correlated with that of ANP. This is not specific for patients with secondary hypertension because we have already reported a close correlation between plasma ANP concentration and plasma cGMP in heart disease.\textsuperscript{18} It is well known that exogenously administered ANP markedly increases the plasma concentration of cGMP.\textsuperscript{33} However, the present study has revealed that endogenous ANP also has some influence on the plasma concentration of cGMP, suggesting that the plasma cGMP level is a consistent functional indicator of endogenous ANP activity.

The exact mechanisms of the natriuretic effects of ANP are still unclear, but one of the characteristic facets is that the renal effects of ANP are influenced considerably by renal hemodynamics.\textsuperscript{34--36} Davis and Briggs\textsuperscript{36} have shown that reduction in renal perfusion pressure remarkably attenuated ANP-induced natriuresis in dogs. The natriuretic responses to ANP in patients with secondary hypertension were greater than those in the normotensive patients. Moreover, the higher the mean blood pressure during ANP infusion, the greater was the natriuretic response. Together with the finding that patients...
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with essential hypertension are more responsive to ANP in natriuresis,8,37,38 high blood pressure itself seems to contribute to the renal effects of ANP. We have observed that the natriuretic responses to ANP in patients with uremic or advanced heart failure also depend in part on the blood pressure during ANP infusion.39 If ANP increases the glomerular filtration rate primarily by some mechanism, such as vasodilatation of the afferent arterioles or an increase in permeability of the glomerular capillary,41 high renal perfusion pressure may promote the natriuretic effects of ANP.

Facial flushing, hypotension, and bradycardia have been reported as the side effects of ANP infusion.43-45 In the present study, such signs or symptoms were not found. This seems to be attributable to the relatively low dose infused in the current study because we have observed hypotension and bradycardia during ANP infusion or immediately after cessation of ANP infusion only at a rate greater than 0.05 μg/kg/min in healthy subjects.44

In conclusion, ANP secretion in patients with secondary hypertension is enhanced. Although this mechanism remains to be clarified, body fluid volume expansion together with high blood pressure may contribute to plasma ANP elevation. In addition, increased natriuretic responses to ANP observed in patients with secondary hypertension may also modify the blood pressure and body fluid volume status in these disease conditions.

References


**Key Words** • cGMP • renal parenchymal hypertension • primary aldosteronism • renovascular hypertension
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