Interaction between Sympathetic Nerve Activity and Atrial Natriuretic Peptide
with Respect to the Effects on Renal Hemodynamics in Patients
with Cardiovascular Diseases

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Since it is still controversial as to whether or not atrial natriuretic peptide (ANP) antagonizes norepinephrine (NE)-induced vasoconstriction, we examined the interactions of ANP and NE with respect to renal circulation. (I) Although ANP infusion at 25 ng/kg/min for 40 min caused a decrease in total peripheral resistance (−11%, p < 0.01) in 34 patients with cardiovascular disease and 15 normotensives (NTs), renal vascular resistance (RVR) was not reduced consistently by ANP. However, there was a negative correlation between changes in RVR and the preinfusion plasma NE level (r = −0.51, p < 0.001). (II) When NE infusion into 6 NTs at 100 ng/kg/min was followed by ANP infusion, urinary Na excretion was increased to a greater degree than that by ANP infusion alone (+234% vs +34%, p < 0.01). Furthermore, ANP brought about a recovery in NE-induced falls in renal blood flow (+40%) and glomerular filtration rate (+38%, both p < 0.05). These effects were attributed to both a decrease in calculated renal afferent resistance and an increase in efferent resistance (−43% and +17%, respectively, p < 0.05). Thus, increased sympathetic nervous activity seems to augment the renal effects of ANP, and the antagonistic effects of ANP to NE-induced preglomerular vasoconstriction may counteract Na retention caused by excessive sympathetic tone.

REGULATION of renal circulation greatly influences body fluid volume and blood pressure status. Neurohumoral factors such as sympathetic nerve activity, angiotensin and vasopressin are considered to play an important role in this regulation. Recent studies have suggested that atrial natriuretic peptide (ANP) is also involved because the peptide has potent cardiovascular and renal effects and the secretion of ANP is elevated in hypertension1,2 renal failure3,4 and congestive heart failure5,6 in which the regulation of blood pressure and body fluid volume are altered. Thus, it is conceivable that an interaction between ANP and these pressor systems may exist, especially in these disease

Key words:
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<table>
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<th>TABLE I  BASAL VALUES AND THE CHANGES IN SYSTEMIC AND RENAL HEMODYNAMICS DURING ANP INFUSION</th>
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<tr>
<td>NT</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>BSA (m²)</td>
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<tr>
<td>MBP (mmHg)</td>
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<td>%Δ</td>
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<tr>
<td>UNaV (µEq/min/m²)</td>
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<td>%Δ</td>
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<tr>
<td>CI (L/min/m²)</td>
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<td>%Δ</td>
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<tr>
<td>TPR (dyne·sec·cm⁻¹)</td>
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<td>RBF (ml/min·m²)</td>
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<td>GFR (ml/min·m²)</td>
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<td>FF</td>
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<td>%Δ</td>
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<tr>
<td>RBF/CO (%)</td>
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<tr>
<td>%Δ</td>
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<tr>
<td>PNE (pg/ml)</td>
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<tr>
<td>%Δ</td>
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<tr>
<td>RVr (10² dyne·sec·cm⁻³)</td>
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<tr>
<td>Raff (10² dyne·sec·cm⁻³)</td>
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<tr>
<td>Reff (10² dyne·sec·cm⁻³)</td>
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</tbody>
</table>

Values are means ± SE. NT = normotensive subjects; EH = essential hypertension; RH = renal parenchymal hypertension; CHF = congestive heart failure; BSA = body surface area; MBP = mean blood pressure; UNaV = urinary Na excretion; CI = cardiac index; TPR = total peripheral resistance; RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; RBF/CO = renal fraction of cardiac output; PNE = plasma norepinephrine concentration; RVr = total renal vascular resistance; Raff = renal afferent resistance; Reff = renal efferent resistance; Vascular resistance is corrected by 1.73 m² of BSA. 

<sup>a</sup>p < 0.05, <sup>b</sup>p < 0.02, <sup>c</sup>p < 0.01, <sup>d</sup>p < 0.001 vs preinfusion level.

conditions.

In the present study, in order to investigate the relationship between sympathetic nerve activity and ANP with regard to the regulation of renal circulation, we examined the effects of ANP and/or norepinephrine infusion on systemic and renal hemodynamics.

SUBJECTS AND METHODS

Study 1: ANP Infusion

In the first study, the systemic and renal effects of ANP were simultaneously examined in 14 patients with essential hypertension (EH), 11 with renal parenchymal hypertension (RH), 9 with congestive heart failure (CHF), and 15 normotensive subjects (NT). The patients were hospitalized and placed on a diet containing 8 g/day of NaCl for at least one week. Following overnight fasting, catheters were inserted into the left radial artery, veins and bladder. A lactate-Ringer's solution containing para-aminohippuric acid (PAH) was infused into the right cubital vein at 100 ml/hr. After a 30 min equilibrium...
determined by the trihydroxyindole method using high pressure liquid chromatography as previously reported.

**Study II: ANP and NE Infusion**

The effects of concomitant infusion of NE and ANP on renal hemodynamics were examined in 6 NTs. Following a 40 min control period, NE infusion at 100 ng/kg/min was started and continued for 120 min. ANP infusion was added during the second 40-min period of NE infusion. After cessation of ANP infusion, NE infusion was continued for a further 40 min. Throughout the infusion, urine collection was repeated every 20 min and blood was collected at the mid point of each urine collection period. MBP, UV, U\textsubscript{Na}V, GFR and RBF were measured and FF, total and segmental RVR were calculated as in Study I. Informed consent was obtained from all subjects in Studies I and II after detailed explanation of the procedures.

**Statistics**

Values are expressed as means ± SE. Comparisons among groups were assessed on the basis of one-way analysis of variance. Changes in measured variables during the infusions were tested by the paired t-test. Correlation coefficients were obtained by the least square method. Values were considered to be statistically significant if $p < 0.05$.

**RESULTS**

**Study I**

ANP lowered MBP by 5%. Although the degrees of changes in MBP were comparable among the groups, U\textsubscript{Na}V values were greater in EH and RH than in NT. Table I lists the effects of ANP infusion on systemic and renal circulation. ANP decreased TPR and somewhat increased CO in the NT, EH and RH groups. The effects of ANP on renal circulation were variable among the groups. RBF was significantly increased in CHF and RH, unchanged in EH and somewhat decreased in NT. GFR was significantly increased in all groups except the NT group. The effects of ANP on RBF/CO differed among the groups. Fig. 1 shows the effects of ANP on RVR. RVR was significantly reduced in the CHF and RH groups. This reduction was attributable to a decrease in the $R_{\text{eff}}$. In patients with EH in whom total RVR was not influenced by ANP, the $R_{\text{eff}}$ was significantly decreased.
Fig. 2. Relationship between the preinfusion plasma level of norepinephrine and the changes in renal vascular resistance during ANP infusion. NT = normotensive subjects, EH = essential hypertension, RH = renal parenchymal hypertension, CHF = congestive heart failure.

| TABLE II BLOOD PRESSURE AND RENAL FUNCTION BEFORE AND DURING NE AND ANP INFUSION |
|--------------------------------------------------|------|----------------|----------------|----------------|
|                                    | Control | NE (1) | NE (2) + ANP | NE (3)         |
| MBP (mmHg)                          | 85 ± 5  | 102 ± 6d | 97 ± 5d       | 103 ± 6        |
| \( U_{Na}V \) (μEq/min/m²)          | 83 ± 17 | 62 ± 13a | 171 ± 45a     | 131 ± 31a      |
| RBF (ml/min/m²)                     | 540 ± 56| 331 ± 35b | 462 ± 67e     | 414 ± 36a      |
| GFR (ml/min/m²)                     | 69 ± 3  | 53 ± 6a  | 73 ± 8e       | 59 ± 7         |
| FF                                  | 0.23 ± 0.02| 0.30 ± 0.03a | 0.30 ± 0.02b | 0.26 ± 0.02c  |

Values are means ± SE. MBP = mean blood pressure; \( U_{Na}V \) = urinary Na excretion; RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; \(^d\) p < 0.01 vs control period, \(^c\) p < 0.05 vs NE infusion period.

while the \( R_{\text{eff}} \) was increased. The \( R_{\text{eff}} \) was significantly increased in NT. Since such a variety of changes in total and segmental RVR among the underlying pathological states was observed, we assessed the determinants of the renal vasodilatory activity of ANP. Overall, a significant negative correlation between the preinfusion plasma NE level and the changes in RVR was observed (Fig. 2). However, such a relationship between the basal plasma NE level and changes in TPR was not found. Plasma NE concentration was significantly increased in NT, EH and RH, although decreased in CHF during ANP infusion.

**Study II**

Table II and Fig. 3 demonstrate the effects of concomitant infusion of ANP with NE. MBP was elevated by 20% during NE infusion and
hypothesis and in normal subjects. The renal vasodilatory effects of ANP were, however, inconsistent. In vitro studies have shown that ANP or atrial extracts relax arterial strips derived from various organs. However, the results from in vitro studies do not seem to predict the in vivo effects of ANP in animals as well as in humans. Although administration of ANP always causes BP reduction, variable changes in TPR have been reported: decreased or unchanged or somewhat increased. Concerning renal circulation, several reports have demonstrated that ANP selectively dilates renal vessels. Nonetheless, ANP infusion did not change or occasionally decreased renal blood flow. The reason for these controversies is unknown. However, most hemodynamic studies found that ANP decreased cardiac output, probably due to a decrease in venous return. The decrease in CO and accompanying neurohumoral reflex may modulate the vasodilatory effects of ANP. Furthermore, ANP seems to be a partial agonist of vasoconstriction. When ANP was infused into the isolated rat kidney, renal vascular resistance was somewhat elevated. However, renal vasorelaxant activity of ANP becomes apparent with angiotensin or norepinephrine pretreatment. Thus, these findings indicate that the cardiovascular effects of ANP may depend upon basal vascular tone.

In vitro, ANP antagonizes almost all vasconstrictors, such as angiotensin, norepinephrine, vasopressin, and potassium; however, this finding is not necessarily applicable to in vivo studies. In particular, it is still unclear whether or not ANP antagonizes NE-induced vasoconstriction. Kleinert et al. showed that partially purified atrial factor relaxed NE-induced vasoconstriction in aortic strips, but that its degree was less than that induced by angiotensin. Trippodo et al. also showed that angiotensin and vasopressin rather than norepinephrine enhanced the renal effects of ANP in rats. Furthermore, Proctor et al. demonstrated that ANP only antagonized angiotensin-induced vasoconstriction in skeletal muscle and the small intestine of rats, but not norepinephrine-induced vasoconstriction. Although in the present study ANP showed different vascular effects in systemic and renal vessels, the renal vasodilatory effects of ANP were augmented in patients with elevated sympathetic nerve tone. As described in the reports mentioned above, since ANP did not exert vasodilatory effects until the vessels were pharmaco-

Fig. 3. Total and segmental renal vascular resistance during ANP and/or norepinephrine infusion. RVR = total renal vascular resistance, Raff = renal afferent resistance, R eff = renal efferent resistance.

DISCUSSION

In the present study, ANP infusion uniformly caused systemic vasodilation in patients with lowered by 5% during the concomitant ANP infusion. After cessation of ANP infusion, MBP increased again to the level before ANP infusion. ANP markedly increased U, by 234%, a value which was significantly greater than that in NT during ANP infusion alone (+34%, p < 0.05). The decreased RBF brought about by NE infusion recovered to the control level with ANP infusion (+40%). Similarly, GFR was increased by 38%. FF remained elevated throughout the infusion. As shown in Fig. 3, ANP infusion decreased NE-induced renal vasoconstriction. Renal vasodilatation caused by ANP was preferentially observed in the renal afferent vessels while the efferent vascular resistance remained elevated.

logically constricted in the isolated kidney, these findings can be interpreted to mean that ANP dilates sympathetically constricted renal vessels.

However, the renin-angiotensin system and vasopressin may also have been activated in patients with elevated sympathetic nerve activity in the present study. To examine the specificity of the interaction between ANP and the sympathetic nerve system and the mechanism of the interaction, NE was infused concomitantly with ANP and the changes in renal hemodynamics were determined. It was found that ANP infusion increased both RBF and GFR in normotensive subjects pretreated with NE infusion. These effects were different from those in normotensive subjects who received ANP infusion alone, suggesting that ANP brought about the recovery of NE-induced renal vasoconstriction.

In the present study, segmental RVR was obtained using Gomez's equation. Although it has several limitations, relatively accurate values can be obtained when comparisons are made serially in the same subjects. Actually, in Study II, NE increased the calculated afferent and efferent RVR values. This is compatible with previous reports which found that NE constricts both preglomerular and postglomerular arterioles. The changes in total RVR during ANP infusion differed among the groups, i.e., slightly increased in NT, unchanged in EH and decreased in RH and CHF. The increase in total RVR in NT was attributed to that in glomerular efferent resistance and the decreases in total RVR in RH and CHF to those in afferent resistance. With regard to segmental RVR in patients with EH, ANP infusion caused renal afferent vaso- dilatation and efferent vasoconstriction at the same time. Summation of these effects led to unchanged total RVR. These findings are consistent with the results of renal micropuncture studies in which ANP dilates afferent vessels while it constricts efferent ones. Thus, ANP antagonizes NE at the renal afferent arteries and enhances NE's actions at the efferent arteries. Such differential effects of ANP on renal vessels attached to the glomeruli may help to facilitate the elevation of intraglomerular pressure, leading to the observed marked natriuresis when NE is infused concomitantly.

Excessive sympathetic nerve activity, especially in the kidney, causes sodium retention directly and indirectly. Considering the cardiovascular and renal effects of ANP, increased secretion of ANP in patients with high blood pressure, renal failure or congestive heart failure may be a compensatory phenomenon for altered blood pressure — body fluid volume status. Moreover, augmented renovascular responses to ANP in patients with elevated sympathetic nerve tone are beneficial in terms of eliminating sodium retention.

In summary, ANP showed natriuretic and blood pressure lowering effects in patients with various types of cardiovascular disease and normal subjects. The antihypertensive effects were mainly due to systemic vasodilatation. In contrast, the renal vascular dilatory effects of ANP were observed only in patients with increased sympathetic nerve tone. This was confirmed by the NE infusion study in which pretreatment with NE augmented the preglomerular vasodilatory effects of ANP in normal subjects, resulting in marked natriuresis. Thus, sympathetic nerve tone seems to play a modulatory role in the renal effects of ANP.

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