Cardiovascular, Renal, and Endocrine Response to Atrial Natriuretic Peptide in Angiotensin II Mediated Hypertension


Studies done in vitro have demonstrated that atrial natriuretic peptide (ANP) antagonizes angiotensin II-mediated contraction of vascular smooth muscle. The present studies were designed to examine the in vivo actions of ANP in acute angiotensin II-mediated hypertension. The cardiovascular, renal, and hormonal effects of intravenous ANP were evaluated in anesthetized normotensive (n = 6) and hypertensive (n = 6) dogs. In both groups, ANP (3.0 µg/kg bolus, 0.3 µg/kg/min continuous infusion) reduced arterial pressure and cardiac output without changing systemic vascular resistance. ANP specifically reduced renal vascular resistance and increased sodium excretion. The natriuresis observed was greater in hypertensive than in normotensive dogs. This occurred without a significant change in glomerular filtration rate or aldosterone. The ANP-mediated reduction in arterial pressure was associated with an increase in circulating arginine vasopressin and catecholamines but not in renin. These studies demonstrate that (1) ANP-mediated hypotension results from a reduction in cardiac output without changing systemic vascular resistance, (2) ANP acts as a specific renal vasodilator, (3) ANP-mediated natriuresis can occur without alteration in glomerular filtration rate or aldosterone, and (4) ANP specifically inhibits the release of renin without inhibiting the release of other circulating vasoconstrictors. (Circulation Research 1986;59:663-667)

EXOGENOUS administration of atrial natriuretic peptide (ANP) results in multiple physiologic responses that include a reduction in arterial pressure, increase in sodium excretion, and inhibition of the renin–angiotensin–aldosterone axis. The mechanism of the ANP-mediated reduction in arterial pressure remains unclear. Studies have been reported that demonstrate that the reduction in arterial pressure results from either a decrease in cardiac output or a decrease in systemic vascular resistance.

In vitro studies of vascular smooth muscle have reported that administration of ANP results in a dose-dependent relaxation of vascular smooth muscle preconstricted with angiotensin II (All). Furthermore, pretreatment with ANP rendered vascular strips refractory to subsequent constriction by All or norepinephrine. In the whole animal, angiotensin II administration produces a model of hypertension characterized by intense systemic and renal vasoconstriction with enhanced release of aldosterone. While ANP infusion has been shown to reduce blood pressure in animals with systemic arterial hypertension, the mechanism of the reduction has not been defined. To date, no in vivo studies have investigated the integrated cardiovascular, renal, and endocrine responses in an acute pathophysiologic model of hypertension produced by fixed and elevated circulating angiotensin II. This study was undertaken with that objective. Based on in vitro studies, we hypothesized that in vivo ANP would antagonize All-mediated systemic and renal vasoconstriction and thereby reduce arterial blood pressure and increase renal blood flow.

Materials and Methods

The effect of ANP administration was studied in two groups of pentobarbital-anesthetized mongrel dogs of either sex. Group 1 consisted of six normotensive dogs and Group 2 of six dogs with acute hypertension produced by intravenous administration of All. After induction of the anesthesia, dogs in both groups were surgically prepared by selective cannulation of one femoral artery and both femoral veins. The right external jugular vein was isolated and a seven French balloon-tipped thermodilution pulmonary artery catheter (Model 93A-131 7F, American Edwards Laboratory, Santa Ana, Calif.) was advanced into the pulmonary artery. The trachea was intubated using a 9.5-mm endotracheal tube and the animal was mechanically ventilated (Large Animal Harvard Respirator, Harvard Apparatus, Millis, Mass.). The left kidney was exposed by a flank incision. The left ureter was isolated and cannulated for urine collection. An electromagnetic flow probe was placed around the left
renal artery and connected to a flowmeter (Model FM 501D, Carolina Medical Electronics, King, N.C.) for measurement of renal blood flow.

Through a femoral vein catheter each dog received a priming dose of insulin (Nutritional Biochemicals, Cleveland, Ohio) and a continuous infusion at the rate of 1 ml/min in an effort to achieve a plasma steady-state insulin level of approximately 50 mg/dl. Additional venous cannulae in Groups 1 and 2 were used for infusion of ANP or of the vehicle (normal saline) at a rate of 1 ml/min and in Group 2 for administration of angiotensin II (1 ml/min).

Following preparation, the dog was suspended in the physiologic position and allowed to stabilize for 1 hour. In Group 1, a total of six periods were performed in each experiment. After two sequential control periods, the dog received a bolus infusion (3.0 μg/kg) of ANP (8-33 AA, Peninsula, Belmont, Calif.) followed by a constant infusion (0.3 μg/kg/min) at a rate of 1 ml/min. The lyophilized ANP was reconstituted and diluted in normal saline. After 15 minutes of ANP infusion, two sequential experimental periods were performed. Following completion of the second experimental period, the ANP infusion was stopped and replaced with normal saline. Beginning 45 minutes following discontinuation of ANP, two sequential recovery periods were performed.

In Group 2, after two sequential control periods, an intravenous infusion of angiotensin II (40 μg/kg/min, 1 ml/min) was begun. This infusion was continued for the duration of the study. Forty-five minutes after beginning All, data were collected during two baseline hypertensive periods. Following this, ANP was administered in the manner identical to that used in Group 1 and the same protocol was followed, with the single exception that the animal continued to receive All.

In both groups, each period consisted of a timed urine collection, hemodynamic assessment, and collection of blood for analysis of circulating hormones. Data collected during each pair of sequential periods were averaged and expressed as mean ± standard error. Hemodynamic data obtained included systemic and pulmonary arterial blood pressures (PAP), renal blood flow (RBF), right atrial pressure (RAP), pulmonary arterial capillary wedge pressure (PCWP), heart rate (HR), and cardiac output (CO), the latter determined by thermodilution (Model 9510-A, American Edwards Cardiac Output Computer). In each period, cardiac output was determined in triplicate and averaged.

At the midpoint of each period, arterial blood was collected for determination of sodium (Beckman System E2A, Brea, Calif.), osmolality (Wescor 5100C vapor pressure osmometer), and insulin,14 in addition to hormone analysis. Extracted plasma ANP concentration was measured by a sensitive and specific radioimmunoassay using a method previously reported by this laboratory.15 Plasma renin activity,16 aldosterone,17 and arginine vasopressin18 were determined for each period utilizing a specific radioimmunoassay. Plasma epinephrine and norepinephrine were determined in each sample by means of high performance liquid chromatography with two-column purification.19

Systemic vascular resistance (SVR) and renal vascular resistance (RVR) were calculated utilizing the following equations (mean arterial pressure = MAP):

\[
SVR = \frac{MAP - RAP}{CO} \times 80
\]

\[
RVR = \frac{MAP - RAP}{RBF} \times 80
\]

Data were analyzed using Student's paired and t test. Significance was achieved at the p < 0.05 level.

Results

Hemodynamics (Table 1)

Intravenous administration of ANP to both the normotensive (Group 1) and hypertensive (Group 2) dogs

| Table 1. Cardiac and Systemic Hemodynamic Effects of Atrial Natriuretic Peptide |
|---------------------------------|---------------|-----------|---------------|-----------|-----------|
| MAP (mm Hg) | HR (beats/min) | CO (l/min) | SVR (dyne-sec/cm²) | RAP (mm Hg) | PAP (mm Hg) | PCWP (mm Hg) |
| Group 1: Normotensive dogs (n = 6) |
| Baseline | 124 ± 6 | 158 ± 8 | 4.2 ± 0.19 | 2432 ± 108 | -0.6 ± 0.7 | 16.6 ± 1.6 | 4.3 ± 0.6 |
| ANP | 110 ± 5* | 160 ± 9 | 3.6 ± 0.18† | 2439 ± 90 | -1.1 ± 0.7 | 14.9 ± 1.2 | 3.6 ± 0.7 |
| Recovery | 124 ± 4 | 155 ± 9 | 3.7 ± 0.18‡ | 2853 ± 173 | -0.2 ± 0.8 | 15.9 ± 1.4 | 3.9 ± 0.4 |
| Group 2: Hypertensive dogs (n = 6) |
| Control | 117 ± 1 | 135 ± 7 | 4.0 ± 0.34 | 2512 ± 231 | 0.7 ± 0.7 | 14.7 ± 1.2 | 6.3 ± 0.4 |
| All-Baseline | 140 ± 3† | 128 ± 6 | 3.6 ± 0.44 | 3517 ± 308 | -0.5 ± 8.2 | 14.9 ± 1.2 | 7.1 ± 0.5 |
| All & ANP | 125 ± 2*‡ | 140 ± 3* | 3.2 ± 0.30# | 3458 ± 338# | -1.3 ± 0.7 | 14.6 ± 0.7 | 5.4 ± 0.6 |
| All-Recovery | 137 ± 3 | 129 ± 7 | 2.9 ± 0.30§ | 4344 ± 499** | 1.1 ± 0.9 | 15.0 ± 1.4 | 7.0 ± 0.7 |

Abbreviations: MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; RAP, right atrial pressure; PAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

Paired t test baseline vs. ANP or All ANP *p < 0.005, †p < 0.05.
Paired t test baseline vs. recovery #p < 0.05, §p < 0.02, **p < 0.005.
Paired t test control vs. All and ANP (Group 2) tp < 0.005, #p < 0.05.
Paired t test control vs. baseline All ||p < 0.005.
resulted in a reduction in systemic arterial pressure (124 ± 6 to 110 ± 5, p < 0.005 and 140 ± 3 to 125 ± 2 mm Hg, p < 0.005, respectively). In Group 1, cardiac output decreased significantly during administration of ANP (4.2 ± 0.2 to 3.6 ± 0.2 l/min (p < 0.05). In Group 2, the cardiac output further decreased (3.6 ± 0.4 to 3.2 ± 0.3 l/min); thus, the absolute decrease in cardiac output during ANP administration was -0.4 ± 0.1 l/min (p < 0.02). In neither the normal group nor the All group with increased systemic vascular resistance did ANP administration result in a change in systemic vascular resistance (Group 1, 2432 ± 108 to 2439 ± 90; Group 2, 3517 ± 308 to 3458 ± 338 dyne-sec/cm²). In neither group did ANP result in a significant change in right atrial, pulmonary arterial, or pulmonary capillary wedge pressure. In Group 2, ANP administration was associated with a significant increase in heart rate (128 ± 6 to 140 ± 3 beats/min, p < 0.005).

In both the normotensive and hypertensive animals, discontinuation of the ANP infusion resulted in a return in systemic arterial pressure to control values (110 ± 5 to 124 ± 4 and 125 ± 2 to 137 ± 3 mm Hg, respectively). The restoration in arterial pressure resulted from an increase in systemic vascular resistance (Group 1, 2432 ± 108 to 2439 ± 90; Group 2, 3517 ± 308 to 3458 ± 338 dyne-sec/cm²). In neither group did ANP result in a significant change in renal blood flow (250 ± 20 to 259 ± 23 ml/min), while in the group with acute angiotensin-II-mediated hypertension, ANP administration was associated with a sustained and significant increase in renal blood flow (115 ± 10 to 153 ± 11 ml/min, p < 0.005). Renal vascular resistance decreased in Group 1 (59.8 ± 8.1 to 50.1 ± 7.0 dyne-sec/cm², p < 0.005) and in Group 2 (109.2 ± 13.0 to 68.1 ± 5.0 dyne-sec/cm², p < 0.005). Glomerular filtration rate did not change significantly when ANP was administered to either group (Group 1, 34.1 ± 3.9 to 42.2 ± 2.9 ml/min, p < 0.064; Group 2, 38.5 ± 2.8 to 34.5 ± 2.9 ml/min, p < 0.084).

Intravenous ANP resulted in an increase in sodium excretion in the normotensive group (29 ± 10 to 240 ± 47 mEq/min, p < 0.005) and in the group with acute hypertension (88 ± 32 to 586 ± 54 µEq/min, p < 0.005). The fractional excretion of sodium also increased significantly in both groups (Group 1, 0.53 ± 0.12 to 3.9 ± 0.73%, p < 0.005; Group 2, 1.60 ± 0.60 to 12.81 ± 1.60%, p < 0.005). The natriuresis that resulted from ANP administration in the hypertensive animals was significantly greater (p < 0.005) than that which occurred in the normotensive group.

Circulating Hormones (Table 3)

Administration of intravenous ANP resulted in a similar increase in immunoreactive ANP in the normotensive (102 ± 20 to 414 ± 25 pg/ml, p < 0.005) and in the hypertensive (118 ± 20 to 460 ± 7 pg/ml, p < 0.005) animals. In Group 1, ANP significantly suppressed plasma renin activity (4.0 ± 0.6 to 2.8 ± 0.5 ng/ml/hr, p < 0.005), while in Group 2 plasma renin activity, was previously suppressed by the infusion of angiotensin II. Arginine vasopressin increased in both the normotensive (3.7 ± 0.6 to 5.8 ± 0.4 pg/ml, p < 0.05) and the hypertensive (5.8 ± 0.9 to 10.1 ± 0.9 pg/ml, p < 0.05) animals during intravenous infusion of ANP. In both groups of animals, intravenous ANP increased plasma epinephrine and norepinephrine.

In the normal dog, plasma levels of aldosterone declined during ANP administration (15.3 ± 3.2 to 10.7 ± 3.9 ng/ml), but this did not reach significance.

**Table 2. Renal Hemodynamic and Excretory Effects of Atrial Natriuretic Peptide**

<table>
<thead>
<tr>
<th></th>
<th>GFR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>RVR (dyne-sec/cm²)</th>
<th>UₐₙV (mEq/min)</th>
<th>FEₐₙ (ml/min)</th>
<th>OSM (Mosl/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1. Normotensive dogs</strong> (n = 6)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>34.1 ± 3.9</td>
<td>250 ± 20</td>
<td>59 ± 8</td>
<td>29 ± 10</td>
<td>0.53 ± 0.12</td>
<td>0.21 ± 0.03</td>
</tr>
<tr>
<td>ANP</td>
<td>42.2 ± 2.9</td>
<td>259 ± 23</td>
<td>50 ± 7*</td>
<td>240 ± 47*</td>
<td>3.9 ± 0.73*</td>
<td>1.4 ± 0.25*</td>
</tr>
<tr>
<td>Recovery</td>
<td>43.3 ± 3.3†</td>
<td>260 ± 12</td>
<td>54 ± 6</td>
<td>65 ± 15†</td>
<td>1.0 ± 0.20§</td>
<td>0.38 ± 0.05§</td>
</tr>
<tr>
<td><strong>Group 2. Hypertensive dogs</strong> (n = 6)</td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>38.9 ± 3.0</td>
<td>176 ± 13</td>
<td>55 ± 9</td>
<td>20 ± 4</td>
<td>0.38 ± 0.08</td>
<td>0.17 ± 0.2</td>
</tr>
<tr>
<td>All-Baseline</td>
<td>38.5 ± 2.8</td>
<td>115 ± 10</td>
<td>109 ± 13</td>
<td>88 ± 32</td>
<td>1.6 ± 0.63</td>
<td>0.62 ± 0.22</td>
</tr>
<tr>
<td>All &amp; ANP</td>
<td>34.5 ± 2.9</td>
<td>153 ± 11*</td>
<td>68 ± 5*</td>
<td>586 ± 54*#</td>
<td>12.8 ± 1.60*#</td>
<td>4.16 ± 0.49*#</td>
</tr>
<tr>
<td>All-Recovery</td>
<td>32.2 ± 4.1</td>
<td>111 ± 9</td>
<td>102 ± 8</td>
<td>67 ± 20</td>
<td>1.4 ± 0.34</td>
<td>0.62 ± 0.15</td>
</tr>
</tbody>
</table>

**Abbreviations:** GFR, glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance; UₐₙV, sodium excretion; FEₐₙ, fractional excretion of sodium; V, urine flow; OSM, osmolality.

*P < 0.05
**P < 0.005
†P < 0.005
‡P < 0.05
§P < 0.02
Table 3. Neurohumoral Effects of Atrial Natriuretic Peptide

<table>
<thead>
<tr>
<th>Group</th>
<th>Neurohumoral Effects</th>
<th>ANP (pg/ml)</th>
<th>PRA (ng/ml/hr)</th>
<th>AVP (pg/ml)</th>
<th>Epi (pg/ml)</th>
<th>NE (pg/ml)</th>
<th>Aldo (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normotensive dogs (n = 6)</td>
<td><strong>Baseline</strong></td>
<td>102.3 ± 20.1</td>
<td>4.0 ± 0.6</td>
<td>3.7 ± 0.6</td>
<td>30.4 ± 9.7</td>
<td>147.3 ± 25.2</td>
<td>15.3 ± 3.2</td>
</tr>
<tr>
<td></td>
<td><strong>ANP</strong></td>
<td>413.6 ± 25.3*</td>
<td>2.8 ± 0.5*</td>
<td>5.8 ± 0.4†</td>
<td>54.3 ± 13.4*</td>
<td>189.6 ± 26.5†</td>
<td>10.7 ± 3.9</td>
</tr>
<tr>
<td></td>
<td><strong>Recovery</strong></td>
<td>216.6 ± 31.1‡</td>
<td>4.7 ± 0.6§</td>
<td>4.7 ± 1.2</td>
<td>23.6 ± 8.1</td>
<td>151.8 ± 20.1</td>
<td>25.1 ± 5.6</td>
</tr>
<tr>
<td>2. Hypertensive dogs (n = 6)</td>
<td><strong>Control</strong></td>
<td>81.2 ± 16.0</td>
<td>3.8 ± 0.5</td>
<td>8.9 ± 1.3</td>
<td>90.6 ± 21.0</td>
<td>145 ± 13.0</td>
<td>9.9 ± 1.0</td>
</tr>
<tr>
<td></td>
<td><strong>All-Baseline</strong></td>
<td>117.7 ± 20.0</td>
<td></td>
<td></td>
<td>1.2 ± 0.25</td>
<td>5.8 ± 0.99#</td>
<td>59.7 ± 13.0</td>
</tr>
<tr>
<td></td>
<td><strong>All &amp; ANP</strong></td>
<td>460.0 ± 7.0* **</td>
<td>1.0 ± 0.2**</td>
<td>10.1 ± 0.95*</td>
<td>109.8 ± 30.0*</td>
<td>87.1 ± 12.7‡‡</td>
<td>20.8 ± 2.0**</td>
</tr>
<tr>
<td></td>
<td><strong>All-Recovery</strong></td>
<td>193.0 ± 23.0</td>
<td>0.6 ± 0.1</td>
<td>6.8 ± 0.73</td>
<td>71.5 ± 20.0</td>
<td>68.3 ± 15.0</td>
<td>26.8 ± 3.4</td>
</tr>
</tbody>
</table>

Abbreviations: ANP, atrial natriuretic peptide; PRA, plasma renin activity; AVP, arginine vasopressin; Epi, epinephrine; NE, norepinephrine; Aldo, aldosterone.

Paired test baseline vs. ANP or All & ANP *p < 0.005, †p < 0.05, ††p < 0.02.
Paired test baseline vs. recovery $p < 0.05, ‡p < 0.005
Paired test control vs. All & ANP (Group 2) **p < 0.005
Paired test control vs. baseline All $p < 0.005, ||p < 0.02, #p < 0.05

In the group with All-mediated hypertension, aldosterone was stimulated by All administration (9.9 ± 1.0 to 20.2 ± 2.2 ng/ml, p < 0.005), and this did not change during ANP administration.

Discussion

In the model of angiotensin-II-mediated hypertension, ANP significantly modulates cardiovascular function, renal hemodynamic and excretory function, and circulating hormones. Administration of ANP in both the normotensive and hypertensive dog resulted in a significant reduction in systemic arterial pressure. This study for the first time demonstrates in a hypertensive model that the ANP-mediated reduction in systemic arterial pressure results from a decrease in cardiac output from control levels without altering systemic vascular resistance.

While ANP does not alter overall systemic vascular resistance, this peptide hormone does specifically reduce renal vascular resistance in both normotensive and hypertensive dogs. This finding supports the in vitro studies in which the renal artery has been demonstrated to be sensitive to the spasmolytic actions of ANP.\(^9\) This study extends to the hypertensive dog the observations made by others that ANP acts as a specific renal vasodilator.\(^20,21\) It is of interest to note that in the in vitro studies of Garcia and associates,\(^9\) pretreatment of vascular strips with ANP rendered them resistant to subsequent contraction by All. In the present in vivo study, when the ANP infusion was discontinued, the renal vasculature was not protected and rapidly reconstricted under the continuing stimulation of All.

Atrial natriuretic peptide has potent natriuretic actions in the normotensive dog. In the present hypertensive model, the natriuretic actions of ANP are markedly enhanced as compared to the normotensive dog. The remarkable increase in sodium excretion occurred without significant alterations in glomerular filtration rate or plasma levels of aldosterone. This suggests that the natriuresis observed in the hypertensive animal may be largely related to alterations in intrarenal Starling forces independent of glomerular filtration rate. Such an observation is consistent with preliminary studies in the rat reported by Mendez and associates.\(^22\)

In the normotensive and hypertensive animal, ANP administration is known to reduce systemic arterial pressure. The mechanism responsible for the hypotension has been attributed by some to a reduction in systemic vascular resistance.\(^6,8\) In the dog\(^23\) and sheep,\(^4\) others have reported that ANP-induced hypotension results from a reduction in cardiac output. Our study supports the hypothesis that ANP-induced hypotension in the normotensive animal results from a reduction in cardiac output. The current study extends this observation to the All model of hypertension in which ANP reduced arterial blood pressure without a decrease in systemic vascular resistance.

The role of ANP in modulating circulating vasoconstrictors was also evaluated in the present investigation. This study confirms previous reports that ANP is a specific inhibitor of renin secretion.\(^12\) In the normotensive animal, ANP reduced renin despite a decrease in renal perfusion pressure. In the All-induced hypertension model, renin was suppressed by fixed and elevated circulating All. Importantly, however, in the hypertensive animal, ANP administration resulted in a reduction of renal perfusion pressure without a significant compensatory increase of renin secretion. The observed natriuresis in both normotensive and hypertensive animals supports the recent observation of Ogrenorth and associates\(^24\) that the mechanism of ANP-mediated inhibition of renin release is mediated through a macula densa mechanism.

Previous in vitro and in vivo studies have demonstrated that ANP inhibits aldosterone synthesis.\(^25\) In the current study, plasma aldosterone levels did not significantly decrease during ANP infusion in either group. This does not imply that ANP does not modulate aldosterone synthesis. Because of the short duration of ANP infusion employed in the present study
and the long half-life of circulating aldosterone, one might not expect to demonstrate an acute alteration in circulating aldosterone.

A reduction in systemic arterial pressure is a known stimulus for secretion of arginine vasopressin and catecholamines. Previous studies utilizing bolus ANP administration in the rat have reported that ANP may inhibit arginine vasopressin release. In the current study, continuous infusion of ANP was associated with a reduction in systemic arterial pressure and a significant increase in arginine vasopressin. Thus, we cannot demonstrate that ANP inhibits arginine vasopressin either in the normal dog or in the hypertensive animal. Furthermore, during a reduction in arterial pressure mediated by ANP, circulating catecholamine plasma levels were significantly increased.

In conclusion, these studies report important actions of ANP in both the normal and All-hypertensive dog. Administration of ANP is shown to 1) reduce arterial pressure by decreasing cardiac output without changing systemic vascular resistance, 2) selectively vasodilate the renal circulation and reverse All-mediated renal vasoconstriction but not protect against subsequent constriction by All, 3) selectively inhibit the renin-angiotensin system without suppressing vasopressin or catecholamines, and 4) cause a marked diuresis and natriuresis that are exaggerated by All-induced hypertension.

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