Effect of Vasopressors on Atrial Natriuretic Factor and Hemodynamic Function in Humans

YORAM SHENKER, ERIC R. BATES, BRENT H. EGAN, JAMAL HAMMOUD, AND ROGER J. GREKIN

SUMMARY To assess the effects of vasopressors on plasma levels of immunoreactive atrial natriuretic factor (ANF), 13 normal men were studied on two occasions. On the experimental day, subjects received sequential 15-minute intravenous infusions of angiotensin II in doses of 4, 8, and 16 pmol/kg/min. Following a 30-minute recovery period, subjects received sequential 15-minute infusions of phenylephrine in doses of 0.4 and 0.8 µg/kg/min. Right atrial pressure, mean pulmonary capillary wedge pressure, pulmonary artery pressure, mean systemic arterial pressure, and plasma levels of renin activity, aldosterone, angiotensin II, and immunoreactive ANF were obtained sequentially throughout the protocol. During the control day, vehicle was infused and plasma samples were obtained for hormone measurements. Infusion of angiotensin II and phenylephrine increased mean systemic arterial pressure in a stepwise fashion. Both right atrial pressure and pulmonary capillary wedge pressure increased significantly during both doses of phenylephrine, but only the highest dose of angiotensin II significantly increased atrial pressures. Plasma levels of immunoreactive ANF increased in parallel with the changes in right atrial pressure and pulmonary capillary wedge pressure, with significant increases occurring only at the highest dose of both pressors. Angiotensin II and aldosterone levels increased and renin activity decreased during infusion of angiotensin II. There were no significant changes in plasma levels of immunoreactive ANF during the control day. These studies demonstrate that infusion of vasopressors increases plasma levels of ANF, but only when the vasopressor effect is associated with significant increases in right atrial and pulmonary capillary wedge pressures. Atrial stretch is the most likely mediator of the increase in plasma levels of immunoreactive ANF during vasoconstriction. (Hypertension 12: 20-25, 1988)

KEY WORDS • atrial natriuretic factor • angiotensin II • vasopressors • atrial pressure

The regulation of atrial natriuretic factor (ANF) secretion appears to be achieved primarily by changes in atrial pressure, presumably mediated through direct alterations in the stretch of the atrial tissues. Conditions such as congestive heart failure and chronic renal failure are associated with increased plasma levels of immunoreactive ANF (irANF), probably due to increased atrial pressures. Previous studies have shown that plasma levels of irANF in patients with cardiac failure correlate closely with right atrial pressure and left atrial pressure as represented by pulmonary capillary wedge pressure. Rapid saline infusion or atrial distention in rats and saline infusion in humans cause increases in plasma levels of irANF, which also correlate with increases in atrial pressure. Infusion of vasopressors in rats has been reported to increase plasma irANF levels, apparently by increasing atrial stretch. Studies in humans have also shown stimulatory effects of pressors on ANF secretion, but the role of atrial distention has not been explored in these studies. In the present report, we describe the hemodynamic and hormonal effects of intravenous infusion of two vasopressors, angiotensin II (Ang II) and phenylephrine. The study was undertaken to examine the mechanisms of the stimulatory effects of vasopressors on the secretion of ANF in humans.

Subjects and Methods

Thirteen normal men aged 20 to 36 years were studied. All were within 10% of their ideal body weight and were found to be normotensive (supine
blood pressure < 135/85 mm Hg) on at least two occasions. None were taking any medication at the time of the study.

Protocol
Each volunteer was studied twice. Before each study, the subjects collected urine for 24 hours. On the day of the study, they ate breakfast as usual but did not eat lunch. All studies were performed between 1300 and 1800.

The experimental study was performed in the cardiac catheterization laboratory. Under fluoroscopic guidance, a thermodilution pulmonary artery catheter was inserted percutaneously through the femoral vein. Heart rate, right atrial pressure, pulmonary capillary wedge pressure, and mean pulmonary artery pressure were measured sequentially throughout the study. Blood pressure was measured using a sphygmomanometer, and cardiac output was measured using the thermodilution method.15

Forty-five minutes after the subject had assumed the recumbent position, and 15 minutes after placement of the catheter, Ang II, diluted in saline, was infused through an antecubital vein at a rate of 4 pmol/kg/min. After 15 minutes, the rate was increased to 8 pmol/kg/min, and after an additional 15 minutes, to 16 pmol/kg/min. At the end of this dose, the infusion of Ang II was discontinued and the intravenous catheter was kept open with a small amount of saline for the next 30 minutes. Following this recovery period, phenylephrine, diluted in saline, was infused at 0.4 µg/kg/min for 15 minutes and then at 0.8 µg/kg/min for 15 minutes. The infusion of phenylephrine was discontinued, and the pulmonary artery catheter was removed. The subjects were observed for 30 minutes after removal of the catheter.

Serum electrolytes were measured at the start of the study. Femoral blood was drawn for irANF, aldosterone, and plasma renin activity before beginning the Ang II infusion, at the end of each 15-minute infusion period, and following each recovery period. Samples were drawn for measurement of plasma levels of Ang II before, during, and after Ang II infusion. Hemodynamic measurements were obtained at the same times as blood sampling.

The control study was performed 1 to 14 days after the experimental study. During this study blood sampling and volume infusion with normal saline were performed in the same fashion as during the experimental day. Antecubital veins in both arms were used for saline infusion and blood sampling. Blood pressure and heart rate were monitored throughout. Following 45 minutes of recumbency, an initial blood sample for serum electrolytes was obtained and samples were drawn throughout the study for plasma irANF levels.

The total volume of saline infused, including 30 to 50 ml of saline for each determination of cardiac output, was approximately 300 ml for each day of the study. The total volume of blood drawn was 240 ml for the experimental day and 120 ml for the control day. No side effects of any kind were observed. The study was approved by the Human Studies Committees of the University of Michigan and the Veterans Administration Medical Center (Ann Arbor, MI, USA), and informed consent was obtained from each subject.

Assays
Urinary and serum electrolytes were measured by flame photometry (Klina-A, Beckman Instruments, Fullerton, CA, USA), and urinary creatinine was measured by autoanalyzer (Astra-8, Beckman Instruments). Plasma levels of aldosterone, renin activity, and Ang II were measured by radioimmunoassay.16-18 Plasma irANF levels were measured by radioimmunoassay following an extraction step as previously described.1 Intra-assay and inter-assay variations for immunoreactive human ANF were 8.5 and 12.6%, respectively. The lower limit of detectability of the assay was 3.4 pmol/L.

Statistical Analysis
Results are expressed as means ± SE. The data were analyzed using repeated-measures analysis of variance (ANOVA). A two-tailed paired t test with Bonferroni protection was used to compare individual measurements during the experimental day with corresponding control measurements. Fisher’s modified least significant difference test was used to compare individual measurements with basal levels. For urinary excretion and serum electrolyte data, a two-tailed paired t test was used to compare the experimental and control measurements.

The data were stored, processed, and analyzed using the CLINFO computer system at the Clinical Research Center of the University of Michigan Hospitals.

Results
Urinary measurements and serum electrolytes are shown in Table 1. Urinary volume, urinary creatinine, urinary electrolytes, and serum electrolytes were similar during the experimental and the control studies, and there were no significant differences for any of these data. The high urinary sodium excretion of 167 and 180 mEq/24 hr is compatible with the high sodium diet typical for the United States.

Figure 1 shows the results of mean arterial pressure and heart rate monitoring. Mean arterial pressure increased significantly during the lowest infusion rate of Ang II and continued to increase in response to the higher infusion rates. After infusion of Ang II, 16 pmol/kg/min, for 15 minutes, arterial pressure was 23 mm Hg higher than basal pressure. Mean arterial pressure returned to the basal level after the 30-minute recovery period and responded to phenylephrine infusion with progressive, significant increases, which reached 18 mm Hg following the higher infusion rates. Thirty minutes after the
termination of the protocol, the arterial pressure was still slightly but significantly elevated (98 ± 1 mm Hg; data not shown).

There was a significant decrease in heart rate during the lowest infusion rate of both vasopressors and further significant slowing with the higher doses. Following the highest dose of both Ang II and phenylephrine, heart rate was decreased by 9 beats/min compared with basal or recovery values (see Figure 1).

During the infusion of both vasopressors, mean arterial pressure was significantly higher than at corresponding times during the control day. Neither arterial pressure nor heart rate changed significantly during the control day (see Figure 1).

Figure 2 represents the results of mean levels of aldosterone, Ang II, and renin activity. As expected, Ang II levels rose sharply following increasing infusion rates of Ang II and returned to basal levels after 30 minutes of recovery. Aldosterone levels increased by almost 100% during infusion of the highest dose of Ang II. Following the recovery period, aldosterone decreased to levels close to basal and continued to decrease during phenylephrine infusion. Basal renin activity was low and decreased even further during the Ang II infusion. Renin activity remained stable during recovery and phenylephrine infusion.

The systemic and pulmonary vasoconstriction achieved by both vasopressors resulted in concomitant decreases in cardiac output (Table 2). Calculated values for systemic and pulmonary vascular resistance increased sharply following both vasopressor infusions.

Figure 3 shows right atrial pressure and pulmonary capillary wedge pressures as well as plasma irANF levels during pressor infusions. The increases in both pressures were nearly parallel and reached statistical significance following the highest dose of Ang II. Right atrial and pulmonary capillary wedge pressures were also significantly increased following the low dose infusion of phenylephrine and increased even further during the higher infusion rate. The maximal increases in both pressures were 3 and 4 mm Hg during phenylephrine infusion and only 2 mm Hg during Ang II infusion.

Levels of irANF increased significantly following the highest infusion rate of both Ang II and phenylephrine (from 9.1 ± 2.1 to 17.1 ± 3.1 pmol/L for Ang II and from 10 ± 2 to 14 ± 2 pmol/L for phenylephrine). During the control period, the levels did not change (Table 3). Basal levels during the control day were higher than basal levels during the experimental day (p < 0.05).

Discussion

During these studies, the volunteers maintained their usual dietary habits. Sodium and potassium

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**TABLE 1. Urinary Measurements and Serum Electrolytes**

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume (ml/24 hr)</th>
<th>Creatinine (g/24 hr)</th>
<th>Sodium (mEq/24 hr)</th>
<th>Potassium (mEq/24 hr)</th>
<th>Sodium (mEq/L)</th>
<th>Potassium (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>1131±123</td>
<td>1.7±0.1</td>
<td>167±17</td>
<td>59±6</td>
<td>143±2</td>
<td>4.1±0.1</td>
</tr>
<tr>
<td>Control</td>
<td>1397±171</td>
<td>1.8±0.1</td>
<td>180±23</td>
<td>53±6</td>
<td>143±1</td>
<td>4.3±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE.
TABLE 2. Cardiac Output, Pulmonary Artery Pressure, and Systemic and Pulmonary Vascular Resistances During the Experimental Day of Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Ang II (pmol/kg/min)</th>
<th>Phenylephrine (/tg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>7.6±0.4</td>
<td>6.3±0.3*</td>
<td>5.9±0.3*</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>18±1</td>
<td>17±1</td>
<td>18±1</td>
</tr>
<tr>
<td>SVR (dyn-sec-cm⁻⁵)</td>
<td>866±43</td>
<td>1145±86*</td>
<td>1338±110*</td>
</tr>
<tr>
<td>PVR (dyn-sec-cm⁻⁵)</td>
<td>45±5</td>
<td>56±5</td>
<td>62±6*</td>
</tr>
</tbody>
</table>

Values are means ± SE. CO = cardiac output; PAP = pulmonary artery pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

ANOVA for all the variables: \( p < 0.0001 \).

* \( \alpha = 0.05 \), compared with basal values (Fisher's test).

\( \alpha t = 0.05 \), compared with recovery values (Fisher's test).

intake, as reflected by urinary excretion data, did not change from the experimental to the control day. A relatively high sodium intake, as reflected by urinary sodium measurements, probably explains the low basal renin levels.

Both Ang II and phenylephrine are potent vasoconstrictors, each acting by different mechanisms. Phenylephrine primarily activates vascular \( \alpha \)-adrenergic receptors, whereas Ang II acts through the angiotensin receptor. Both directly constrict vascular smooth muscle.

As a result of these mechanisms, both agents cause a rapid and prominent elevation of blood pressure, as shown in Figure 1. The blood pressure-elevating effects of Ang II are more prominent under sodium-replete conditions, which apply to our volunteers. \(^{19}\) The significant decrease in heart rate observed after infusion of both pressors was expected on the basis of baroreceptor reflex brady-cardia. During the control stage both blood pressure and heart rate remained stable.

Infusion of Ang II caused a rapid increase in circulating plasma levels of Ang II (see Figure 2), and the two higher infusion rates (8 and 16 pmol/kg/min) caused significant increases in plasma aldosterone levels. The stimulation of aldosterone secretion was quite modest: The levels doubled following the highest infusion rate. This limited increase probably occurred because glomerulosa cells are relatively resistant to Ang II in sodium-replete subjects.\(^{19}\) The decrease in renin activity during Ang II infusion is probably a result of direct suppressive effects of Ang II on renin secretion.\(^{20}\)

As expected, both pressor agents caused increases in systemic and pulmonary vascular resistance associated with elevations in mean arterial and pulmonary artery pressures. The effects of both pressor agents on right atrial and pulmonary capillary wedge pressures were very similar (see Figure 3). In each instance, the changes in atrial pressures were almost completely parallel. The highest infusion rate of angiotensin was needed to cause significant increases in atrial pressures, but both the low and the high infusion rates of phenylephrine caused significant increases. The plasma level of Ang II required to significantly increase atrial pressures was above the normal range for healthy subjects (20-83 pg/ml), but well within the range seen during diuretic therapy or in patients with congestive heart failure.\(^{18,21,22}\)

The highest infusion rate of Ang II caused almost a doubling of irANF levels, whereas the higher

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>irANF (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>14.7±2.6</td>
</tr>
<tr>
<td>15</td>
<td>15.7±3.2</td>
</tr>
<tr>
<td>30</td>
<td>13.7±2.7</td>
</tr>
<tr>
<td>45</td>
<td>11.2±3.1</td>
</tr>
<tr>
<td>90</td>
<td>13.5±2.7</td>
</tr>
<tr>
<td>105</td>
<td>11.8±3.0</td>
</tr>
<tr>
<td>120</td>
<td>13.7±2.7</td>
</tr>
</tbody>
</table>

ANOVA not significant
infusion rate of phenylephrine caused an increase of 40% (see Figure 3). During the control day, irANF levels were stable throughout the study. The increase in irANF levels during the experimental day cannot be attributed to the modest volume infusion because the same volume was infused during the control day. Our own and other studies with hemodynamic monitoring during saline infusion suggest a 2- to 15-minute lag period. Based on the finding that significant changes in atrial pressures are closely associated with small changes in atrial pressure, increases in atrial pressure (as small as 2 mm Hg) is enough to stimulate ANF secretion. Based on the finding that significant changes in atrial pressures achieved by the low infusion rate of phenylephrine were not accompanied by an increase in irANF, we would postulate that the increased secretion of ANF has a lag period after a pressure increase of at least 4 minutes and perhaps as much as 15 minutes. Our studies with hemodynamically monitored rapid saline infusions suggest a 2- to 15-minute lag period, and Anderson et al. reported a 10- to 30-minute delay using a similar protocol.

The results also suggest the possibility that angiotensin is a more potent stimulator of ANF secretion than phenylephrine is, since greater increments in irANF levels occurred in response to smaller increases in atrial pressure during Ang II infusions. These differences between the two agents were not statistically significant.

The present studies do not exclude a direct effect of Ang II or α-adrenergic agents on ANF secretion. Uehlinger et al. however, recently reported that nopepinephrine-induced secretion of ANF was abolished by concurrent infusion of nitroprusside to titrate arterial pressure to control levels.

Of interest is the finding that basal plasma irANF levels during the control stage were higher than those seen during the experimental stage. One difference between the control and experimental studies that may explain these higher basal levels is that blood was drawn from the antecubital vein during the control day, whereas blood was drawn from the femoral vein during the experimental day. Although metabolism of ANF liver, kidney, and lower limb is approximately equal, no information has been reported concerning metabolism of this peptide in the upper extremity. The rapid metabolism and prominent arteriovenous difference in irANF levels suggest that regional differences might result in consistently higher irANF levels in antecubital venous blood as compared with femoral venous blood.

In conclusion, this study demonstrates that infusion of vasopressors in humans increases plasma levels of irANF and that the increase is temporally associated with small changes in atrial pressures. The ability of pressors to increase plasma irANF levels is probably mediated by atrial stretch.

Acknowledgments

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