Low-Dose Infusion of Atrial Natriuretic Factor in Mild Essential Hypertension

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Intra-arterial blood pressure, cardiac output, heart rate, right heart indexes, urinary electrolytes, and urinary volume were monitored in eight patients with untreated (WHO Class I) essential hypertension. The patients were given synthetic atrial natriuretic factor (ANF) (99-126 α-human ANP) at 1 and 2 pmol/kg/min in series (phases 1 and 2, 2 hours each dose) or vehicle (hemaccel) in random order on two separate occasions while on their usual diet. Arterial plasma ANF levels increased significantly from basal and time-matched placebo values from 25±2 and 28±3 pmol/l to 50±4 and 83±9 pmol/l at the end of phases 1 and 2, respectively (p<0.001). After 30 minutes during phase 2, systolic blood pressure decreased significantly by 20±4 mm Hg (p<0.001) from basal and time-matched placebo values and remained significantly reduced (−17±4 mm Hg, p<0.001) by the end of the recovery period (2 hours after infusions were completed). Pulmonary systolic blood pressure decreased by 5±1 mm Hg (phase 2, p<0.05). Cardiac output decreased by 0.5±0.1 l/min below baseline at the end of phase 2 of ANF infusion, whereas it increased significantly (p<0.02) by 0.6±0.1 l/min during vehicle infusion. Systemic diastolic, pulmonary diastolic, right atrial, and wedge pressures were not significantly changed during ANF or vehicle infusions, nor were pulmonary vascular resistance or heart rate altered. Systemic vascular resistance did not change significantly during both infusions, whereas during recovery, systemic vascular resistance decreased significantly after ANF infusion was discontinued (p<0.05). Microhematocrit levels increased dose dependently during ANF. The maximum increase was observed at the end of phase 2 (+4.7±1.7%), whereas the microhematocrit level decreased to −2.4±0.6% with vehicle (p<0.001) at the end of phase 2. Urinary sodium excretion increased significantly (+38±15%), whereas it decreased (−10±6%) under placebo infusion by the end of phase 2. Urinary magnesium excretion was significantly increased during ANF infusion from phase 1 (p<0.02), whereas urinary potassium levels, calcium levels, creatinine levels, volume, and glomerular filtration rate did not differ significantly between the two infusions. Plasma renin, angiotensin II, aldosterone, and catecholamine concentrations did not change significantly during ANF or vehicle infusions. Our data suggest that increases in circulating arterial ANF levels to the upper limit of the ranges reported for humans with hypertension in absence of cardiac or renal failure reduce plasma volume and exert a selective lowering effect on systolic blood pressure without changing calculated peripheral vascular resistances. (Circulation 1989;80:893–902)

Atrial natriuretic factors (ANF) lower systemic blood pressure and reduce cardiac output in experimental hypertension.1,2 At present, little information is available on the effects of ANF in humans with hypertension. Most studies have reported the effects of ANF bolus injections or infusions for a limited period of time in doses that increase the circulating levels of the peptide to values equal to or higher than those found even in humans with severe cardiac failure.3–6 To our knowledge, the effects of ANF infusion for only 30 minutes at doses producing circulating levels slightly above the range reported for humans with hypertension have been reported only once in a limited series of three patients who were sodium depleted, but in that study, the actual plasma levels of ANF achieved were not reported.7 ANF may also suppress the renin-angiotensin-aldosterone system in normotensive humans and animals.8–10 In addition, administration of atrial extracts or pure synthetic ANF promotes diuresis,
increases urinary excretion of Na⁺ and Mg²⁺ in both normal humans and in animals,⁹–¹² and may reduce plasma volume by promoting a shift of fluids from the intravascular to the extravascular space by an extrarenal mechanism.¹³,¹⁴

Relaxation of vessels precontracted with norepinephrine or angiotensin II is another important physiologic effect of atrial natriuretic factors.⁹ Although the effects of synthetic ANF and of atrial extracts on large conduit arteries are well documented,⁹ less is known about the resistance vessels. A recent in vitro study¹⁵ showed that ANF has no effect on resistance arteries. On the other hand, another study¹⁶ has shown a decrease in forearm vascular resistance in normal humans by increasing the plasma levels of ANF within the upper limit of the “physiological range,” thus indicating a vasodilator effect in vivo.

We therefore investigated the hemodynamic and humoral effects of continuous infusion of ANF at two different doses on systemic and pulmonary blood pressures, cardiac output, and urinary and electrolyte volume, and on the renin-angiotensin-aldosterone system in humans with mild essential hypertension.

Based on preliminary personal observations, we chose two infusion rates that would modify the circulating levels of ANF within (the lower dose) or up to (the higher dose) the limit of the range reported in uncomplicated essential hypertension and in essential hypertension without cardiac or renal failure but with left ventricular hypertrophy.¹⁷

Methods

Patients

Eight patients with untreated, uncomplicated essential hypertension (mean age, 53±2 years) gave informed consent to the study protocol, previously approved by the clinical research committee of the Department of Internal Medicine of the Sassari University Medical School (Consiglio d’Istituto). The known duration of their hypertension ranged from 4 to 16 years, and they were either never treated (n=6) or treatment was withdrawn because of poor efficacy for at least 1 month before the studies (patients 2 and 3, enalapril 10 mg b.i.d.). Primary hypertension was diagnosed by exclusion of secondary forms of hypertension according to the diagnostic chart routinely applied in our hypertension center, which includes renal digital subtraction angiography as a diagnostic aid. According to electrocardiography, all patients had abnormalities without clinical signs of angina, and they had never received any coronary dilating drug. Patients underwent the study protocol before coronary angiography and renal digital subtraction angiography. Both of these studies with dyes were performed in the late afternoon. No significant lesions on either the coronary or the renal arteries were found.

Protocol

Patients were encouraged to continue their usual diet with constant sodium content throughout the studies. Serial 24-hour urine samples were collected for 3 days before each study day. Patients remained recumbent during infusions.

A peripheral venous line for ANF or placebo and intravenous infusion was inserted. A 4F Seldicap was inserted in the brachial artery of the nondominant arm for continuous blood pressure recording and blood sampling. A 7F Swan-Ganz balloon flotation catheter was inserted percutaneously through a brachial vein for measurements of right atrial, pulmonary arterial, and pulmonary wedge pressures and of cardiac output (triplicate thermodilution). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated from standard formulas: SVR=80 (Aom-RAm)/CO and PVR=80 (PAM-LAm)/CO, where Aom, RAm, PAm, LAm, and CO are aortic, right atrial, pulmonary artery, and left atrial (wedge) pressures in mm Hg and cardiac output in l/min, respectively.¹⁸

After overnight fasting, patients were given an oral water load (10 ml/kg) 2 hours before starting the study. Subsequently, they drank a fixed amount of water (200 ml/hr) throughout the study and ate no food. Urine was collected every 2 hours while avoiding any postural change. Glomerular filtration rate was monitored with a constant infusion of 10% inulin in saline (10 ml/hr) preceded by a bolus injection (25 ml 10% inulin in 5 minutes). The infusion was run for at least 1.5 hours before the first basal blood sample was obtained.

Sterilized atrial natriuretic peptide (99-126 α-hANP, Bachem, Torrance, California) dissolved in haemaccel, or haemaccel, 7 days apart, alone, was infused in a balanced random order starting at 9:00 AM (10 ml/hr). After a 2-hour run-in period, ANF (1 pmol/kg/min for 2 hours, phase 1, and then 2 pmol/kg/min for 2 additional hours, phase 2) or haemaccel was given. Monitoring continued for a “recovery period” of a further 2 hours.

The basal measurements were made at least 2 hours after the completion of the catheterization.

Cardiac output measurements (midthoracic level as zero reference) and blood samples for hormonal measurements and biochemistry profiles were obtained hourly. Heart rate (electrocardiography) and systemic and pulmonary pressures were monitored continuously (S&W recorder).

Plasma atrial natriuretic factor was measured after Sep-Pak C18 preextraction as previously described.¹⁹ Intra-assay and interassay coefficients of variation were 9.5% and 8.9%, respectively. Plasma renin, aldosterone, angiotensin II, catecholamines, and inulin concentrations were measured by established techniques.²⁰–²³ All samples from each patient were analyzed simultaneously in the same radioimmunoassay for both vehicle and ANF infusions. Urinary measurements included volume,
osmolality (freezing point depression), sodium and potassium (flame photometry), magnesium and calcium (atomic absorption), and creatinine concentrations (Jaffe method).

Microhematocrit (arterial blood) levels were collected in heparinized capillary tubes and measured after centrifugation.

For technical reasons, right atrial pressure and cardiac output were measured in only seven of the eight patients.

Statistical Analysis

Values are mean±SEM. Statistical analysis was performed with repeated measures analysis of variance with the Greenhouse-Geiser correction.

Results

Table 1 summarizes the characteristics of the patients included in the study. All the patients completed both studies without any side effect. In particular, we did not observe bradycardia or symptomatic hypotension because our patients were studied while in the recumbent position.

Arterial plasma levels of ANF showed a progressive decrease during placebo administration (from 28±3 to 19±2 pmol/l at the end of the study, p < 0.05). During active infusions, plasma levels of ANF rose dose dependently from the basal level of 25±2 pmol/l (NS vs. time-matched placebo values) to a twofold increase over baseline values during phase 1 (50±4 pmol/l, p < 0.001 vs. baseline values and time-matched placebo values) and to a 3.3-fold increase over baseline levels during phase 2 (83±9 pmol/l, p < 0.001 vs. basal levels and time-matched placebo levels). By the end of the recovery period, plasma ANF levels fell below the basal level (15±2 pmol/l, p < 0.02 vs. basal levels; NS vs. time-matched placebo levels) (Figure 1, top panel). The metabolic clearance rate (calculated from the plateau levels during ANF infusion, infusion rate/ [steady state—basal plasma concentrations of ANF]) was 2.90±0.46 l/min (phase 1) and 2.84±0.58 l/min (phase 2) (NS between phases). Change in percent microhematocrit levels (Figure 1, bottom panel) showed a slight progressive decrease during placebo infusion from 41±2% to 39.6±2% at the end of the recovery phase, whereas a dose-related increase was seen during ANF infusion from 41±2% to 42±2% after phase 1 and to 43±2% after phase 2 (p < 0.001); it returned to 41±2% at the end of recovery. Figure 1 shows the percent changes in microhematocrit levels from basal levels during ANF and placebo infusions. Thus, the effects of ANF infusion on microhematocrit levels became evident by the end of phase 1 with an increase of 2±1%, whereas the microhematocrit levels with the time-matched placebo infusion fell by 1±0.5% below the basal level. The peak of action was at the end of phase 2 when microhematocrit levels had risen by 4.6±1.5% above the basal level, whereas a decrease of 2.4±0.6% below the basal level was observed during time-matched placebo infusion. At the end of the recovery period, the microhematocrit level was back to basal levels after ANF infusion, whereas it was 3.5±0.6% below the basal level after placebo administration. Figure 2 illustrates the changes of systemic systolic and diastolic blood pressure during ANF or placebo infusions. During ANF infusion, systolic blood pressure fell nonsignificantly by the end of phase 1. During phase 2, systolic blood pressure was significantly decreased at 30 minutes (148±6 mm Hg compared with basal values of 168±7 mm Hg and time-matched placebo values of 167±6 mm Hg, p < 0.001 vs. both). These results were observed in every patient. At the end of the recovery period, systolic blood pressure was still lower than that with time-matched placebo or at baseline (152±5 vs. 166±6 and 167±7 mm Hg, p < 0.005 vs. both). Systolic blood pressure did not change significantly during placebo infusion.

Pulmonary systolic pressure decreased progressively from basal values during ANF infusions and
reached a nadir at the end of phase 2 (23±1 vs. 28±2 mm Hg, p<0.05). During ANF and placebo infusions, no significant changes were seen for systemic or pulmonary diastolic, right atrial, and wedge pressures or heart rate (Table 2).

Mean arterial pressure ([Systolic−diastolic+diastolic]/3) is illustrated in Figure 3. The same pattern of systemic systolic blood pressure occurred; there was a slight, but not significant, decrease at the end of phase 1 of ANF infusion, whereas a greater decrease was observed at the end of phase 2 compared with basal values (115±5 vs. 122±3 mm Hg, p<0.001). At the end of the recovery period, mean blood pressure was still lower than that at baseline or with time-matched placebo infusion (110±5 vs. 122±3 and 120±4 mm Hg, respectively, p<0.001 for both). These changes were consistent in all the patients. No significant changes were seen during placebo infusions.

Cardiac output decreased by about 11% from the basal value at the end of phase 2 of ANF infusion. It increased slightly, but not significantly, over basal values at the end of recovery. At the end of phase 2, cardiac output was significantly below that at the time-matched placebo values (4.8±0.4 vs. 5.6±0.6 l/min, n=7, p<0.02) (Figure 3).

Systemic vascular resistances were not significantly different between the two studies, being 1,720±127 at time zero before ANF infusion and 1,845±213 dynes/sec/cm⁻² at time-matched placebo (NS). No significant changes were observed in systemic vascular resistance during ANF and placebo infusions (1,753±159 and 1,805±195 dynes/sec/cm⁻², respectively, at the end of phase 2 of ANF and placebo infusions, NS). During the recovery period, a significant decrease in systemic vascular resistance was observed after ANF and placebo infusions (1,433±126 and 1,645±136 dynes/sec/cm⁻², respectively, p<0.05, Figure 3). Pulmonary vascular resistance (Table 2) did not change significantly during the two studies. Basal values were 116±16 and 110±24 dynes/sec/cm⁻² before ANF and placebo infusions, respectively (NS). At the end of ANF infusions, pulmonary vascular resistances were 115±23 compared with time-matched placebo value of 119±20 dynes/sec/cm⁻² (NS). A slight, but not significant, change in pulmonary vascular resistance was observed at the end of the recovery period after ANF infusion (105±20 compared with time-matched placebo values 116±20 dynes/sec/cm⁻², NS).

Plasma renin, angiotensin II, aldosterone, and catecholamine concentrations did not change during ANF and placebo infusions (Table 3). During the recovery period, a transient increase in plasma angiotensin II concentration was observed in only one of eight patients. This one patient showed the highest basal value, which was 12 pg/ml, decreasing to 4 pg/ml by the end of ANF infusion, and increasing to 18 pg/ml at 1 hour of recovery and to 12 pg/ml at the end of the recovery period. In this same patient, plasma renin concentration showed the same pattern although to a lesser extent. The other hormonal and hemodynamic parameters of this patient did not differ from those observed in other patients of the group.

No significant changes between studies were seen in glomerular filtration rate. Basal values were 115±10 and 120±9 ml/min (NS) (ANF and vehicle, respectively). They increased slightly by the end of phase 2 (125±8 and 130±10 ml/min, NS), remaining at this level during the recovery phase.

Mean 24-hour urine sodium and potassium excretion in the day before ANF and placebo infusions was 168±8 and 45±4 mmol/day, respectively (n=8, NS) (Table 1). Urine samples were collected every...
FIGURE 2. Plot of changes is systemic systolic and diastolic blood pressures during atrial natriuretic factor (ANF) (●) and placebo (○) infusions in eight patients with essential hypertension. Systolic blood pressure decreased significantly during ANF infusions from the beginning of phase 2 (2 pmol/kg/min) (p<0.001, ANOVA). No significant changes in diastolic blood pressure were seen at any phase.

hour. Pooled results for each 2-hour period are presented. Urinary volume decreased progressively throughout the study, and no significant differences between ANF and placebo infusions were seen (Figure 4). As expected, urinary sodium excretion increased by the end of phase 2 during ANF infusion (38±15%, p<0.001), whereas no significant differences compared with placebo infusion were seen during phase 1 (Figure 4). Urinary magnesium excretion was significantly higher during ANF infusion by the end of phases 1 and 2 compared with the basal values (15±3%, p<0.02, Figure 4). Con-

<table>
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<tr>
<th>Table 2. Pulmonary, Wedge, Right Atrial Pressures; Pulmonary Vascular Resistance; and Heart Rate During ANF and Placebo Infusions in Patients With Mild Essential Hypertension</th>
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<tr>
<td>Pulmonary vascular resistance (dynes/sec/cm²)</td>
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<td>Basal (hr) ANF and placebo infusions</td>
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<tr>
<td>Phase 1 (hr) Phase 2 (hr) Recovery (hr) ANF Placebo</td>
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<tr>
<td>Pulmonary systolic blood pressure (mm Hg)</td>
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<td>Placebo</td>
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<tr>
<td>Pulmonary diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
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<td>ANF</td>
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<td>Right atrial pressure (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>ANF</td>
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<td>Placebo</td>
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Data are mean±SEM; n=8 in each group.
*p<0.05.
versely, progressive and significant decreases in urinary sodium (10±6%, p<0.05) and magnesium excretion (27±7%, p<0.02) were seen at the end of phase 2 of placebo infusion. At the end of the recovery phase, no significant differences in urinary volume or sodium and magnesium excretion were observed between the ANF and placebo studies. No significant differences were seen for urinary potassium, phosphorus, calcium, and creatine excretion throughout both studies (Table 4).

Discussion

In this study, the plasma levels of ANF were kept within or up to the upper limit we have observed in untreated human hypertension in the absence of severe cardiac or renal impairment.17 Arterial levels of ANF are 1.5-2.0-fold higher than the venous levels,24 so the peak values during the second dose of ANF correspond to 40-60 pmol/l in venous plasma. Our results provide evidence that under these conditions ANF infused throughout a period of 4 hours exerts a hypotensive effect in human essential hypertension. This hypotensive effect was not accompanied by reflex tachycardia, which is atypical for a "vasodilator" but similar to the action of angiotensin converting enzyme inhibitors.25 Because the heart rate was continuously monitored (electrocardiographically), we did not miss any transient rise. During the second dose of ANF infusion, mean arterial pressure decreased significantly by 8-10 mm Hg mainly because of a significant reduction in systolic blood pressure of about 20 mm Hg and a nonsignificant increase in heart rate of about 8 beats/min. During placebo infusion, a nonsignificant increase in heart rate of about 6 beats/min was observed, whereas blood pressure did not change significantly. Thus, during the ANF study, the increase in heart rate in response to a decrease in systolic blood pressure of about 20 mm Hg appears to be inadequate. These data therefore suggest that the baroreceptor reflex was in some way inhibited. A direct inhibitory effect of ANF on baroreceptors per se could be another possible explanation. This is in accordance with the already reported "vagomimetic effect" of ANF.7

The hypotensive effect of ANF was limited to systolic blood pressure, which decreased by about
20 mm Hg after 30 minutes of infusion at the higher dose. This effect lasted throughout the recovery period. Thus, despite the reported short half-life of ANF in plasma,13,26 its effects on systolic blood pressure were long lasting. Diastolic blood pressure was decreased only slightly. The lack of a clear effect on diastolic blood pressure or on calculated systemic vascular resistance stands against a vasodilatory action of ANF on the resistance vessels. Moreover, a vasorelaxant effect on the resistance vessels has been recently denied in vitro.15 Conceivably, an angiotensin II or norepinephrine precontracted state of the vasculature is needed for ANF to exert a vasodilatory effect in vivo as described in vitro.8,9 Our patients were in the higher part of the range of the normal sodium diet (about 170 meq/24 hr) and studied while in the recumbent position. Therefore, neither the renin-angiotensin system nor the sympathetic nervous system was particularly activated. Recently, Cusson et al27 showed no effect of infused ANF on blood pressure even at plasma levels 20-fold greater than basal level. However, differences in the protocol design and the mild degree of hypertension of our patients could account for our results. We did not experience any sudden hypotension with bradycardia in our patients throughout the infusion period. Others have described the possibility of symptomatic hypotension with bradycardia with doses 10- to 20-fold higher than those used in our study or in a state of sodium depletion.7

The cardiac output decreased during ANF infusion. This could be a consequence of a reduction in plasma volume, indirectly suggested by the observed increase in microhematocrit, and of a decreased venous return; both effects are able to reduce the preload. The lack of a significant reduction in atrial pressures does not rule out a reduction of venous return because our patients were recumbent and because neither measurement is sensitive enough to evaluate what may be a very subtle change in the central blood pool.28 Thus, the fall in blood pressure in our study could be most likely the result of a decrease in cardiac output without significant changes in systemic peripheral resistances. Moreover, the decrease in cardiac output was most likely due to a reduction in stroke volume because the heart rate did not change significantly. ANF receptors have been found in rabbit and rat aorta.9 The physiologic role of these receptors is still uncertain.

ANF infusion had a significant blood pressure lowering effect also in the pulmonary circulation, though this effect was not prolonged during the recovery. In our patients, basal systemic vascular resistances were higher than normal, whereas pulmonary vascular resistances were normal.18 The mechanisms underlying the vasodilatory effect of ANF on resistance arteries in essential hypertension may be rather complex and, as discussed above, may be dependent on the preexisting hemodynamic status. Thus, ANF could act in vivo as a vasodilator when blood pressure is mainly sus-
tained by angiotensin II or other vasoconstrictor agents. The patients investigated in the study were mildly hypertensive, and higher blood pressures could lead to different results.

The changes in microhematocrit were progressive and dose dependent. This effect was significant even with the lower dose of ANF; we have previously found that this effect is present in humans independent from renal function.13,29 Our present results confirm these previous reports. Microhematocrit was increased significantly during ANF infusion, whereas no significant change in urine volume was evident. This effect previously postulated in dogs30 and described in rats14 appears to be an important mechanism in regulating blood volume. Thus, our results on microhematocrit indicate that circulating levels of ANF fluctuating within the “physiologic range” may cause a shift of fluids from the intravascular to the extravascular space and reduce the preload by a decreased venous return to the heart. This mechanism could be physiologically important when considering the combined effects on the heart and kidneys in any situation involving acute increases in blood volume. Thus, this reduction in plasma volume could con-

### Table 4. Urinary Potassium, Phosphorus, Calcium, and Creatinine Concentrations During ANF and Placebo Infusions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal (hr)</th>
<th>Phase 1 (hr)</th>
<th>Phase 2 (hr)</th>
<th>Recovery (hr)</th>
</tr>
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<tr>
<td>Time (hr)</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Urinary potassium (μmol/min)</td>
<td>64±10</td>
<td>60±9</td>
<td>58±8</td>
<td>59±6</td>
</tr>
<tr>
<td>ANF</td>
<td>72±12</td>
<td>69±1</td>
<td>64±9</td>
<td>60±8</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary phosphorus (μmol/min)</td>
<td>20±3</td>
<td>18±2</td>
<td>22±4</td>
<td>20±3</td>
</tr>
<tr>
<td>ANF</td>
<td>18±4</td>
<td>21±3</td>
<td>24±5</td>
<td>19±4</td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
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</tr>
<tr>
<td>Urinary calcium (μmol/min)</td>
<td>5±2</td>
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<td>7±2</td>
<td>4±1</td>
</tr>
<tr>
<td>ANF</td>
<td>5±1</td>
<td>4±2</td>
<td>4±1</td>
<td>5±1</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Urinary creatinine (μmol/min)</td>
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<td>11±2</td>
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<tr>
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<td>Placebo</td>
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Data are mean±SEM.
ANF, atrial natriuretic factor.
No significant changes occurred for any of the parameters.
ceivably lead to a reduction in venous return to the heart and in turn to a reduction on stroke volume. As discussed before, the lack of change in right atrial end-wedge pressures does not stand against this effect. From our data, we cannot exclude a possible negative inotropic effect of ANF, although convincing data are lacking in the literature concerning this effect in vivo, at least to our knowledge. Recently, a possible negative inotropic effect (mediated by reduction of calcium current) of rat ANF on isolated frog cardiac cells has been postulated.31 In that study, nanomolar concentrations of ANF were used, and by allowing for dose, species, and methodologic differences, the possibility of a negative inotropic effect of ANF in our study remains purely speculative.

We found significant increases in sodium and magnesium excretion, whereas potassium and phosphorus excretions were unchanged as previously reported in normal humans.10 This increase in urinary Na+ excretion by about 30% is similar to that recently described in normal volunteers with an induced increase of plasma ANF twofold.32 The lack of effects on Ca++ excretion could be due to a different protocol design or to a different mechanism of action of ANF in essential hypertensive patients and normotensive volunteers.

ANF has been shown to be natriuretic in animals and humans, but the mechanism of action is not clear. ANF could act through an increase in glomerular filtration rate, either by a direct tubular action,9 by a modulation of the intrarenal circulation, or by inhibition of aldosterone synthesis.33 In our study, we observed a slight increase in glomerular filtration rate (measured by inulin clearance) not significantly different from that during placebo administration and no inhibition of plasma aldosterone levels. In any case, even meticulously conducted inulin clearance studies may have an error as high as 10%. Smaller modifications of the glomerular filtration rate (1–2%) could account for the natriuretic effect in the absence of increased tubular reabsorption. The lack of changes in plasma renin, angiotensin II, and aldosterone concentrations despite a decrease in blood pressure and despite an increase in sodium excretion may suggest a relative suppression of the renin-angiotensin-aldosterone system by ANF. From our data, we cannot rule out a possible contribution to natriuresis by this effect. We did not measure effective renal plasma flow, but in previous studies in normal volunteers, we found a nonsignificant change in glomerular filtration rate accompanied by a significant decrease in effective renal plasma flow.10

Because our patients were similarly hydrated during the two studies, the lack of effects on urinary volume may be explained by the concurrent decrease in systolic blood pressure during the ANF study.

Previously, we showed a significant inhibitory effect of ANF on the renin-angiotensin-aldosterone system in normal volunteers who were studied while seated and with the system partially activated.10 In the present study, patients were recumbent, and the basal renin-angiotensin-aldosterone system activity was already very low. Either suppression or stimulation of the renin-angiotensin system by ANF has been described in humans and animals, depending on the experimental design and on the circulating levels of ANF.12,34,35 The ability of ANF to inhibit the renin system has been shown to depend on the levels of its activation and on the sodium balance.36,37 Needless to say, despite a prolonged and consistent decrease in systemic blood pressure, we did not observe the expected rise in plasma renin concentration. No significant changes in plasma catecholamines were seen either during placebo or ANF infusions. However, an increase in plasma catecholamine levels has been reported during ANF infusion with doses much higher than those used in our study possibly as a result of reflex stimulation of the baroreceptors.6

In summary, our results suggest that an increase in arterial plasma levels of ANF from twofold to threefold basal values in humans with essential hypertension can cause 1) a clear and prolonged effect on systolic blood pressure mainly due to a reduction in the cardiac output, 2) a shift of fluids from the intravascular to the extravascular space, evident at circulating levels of ANF higher than basal but still within the range of values commonly seen in uncomplicated, untreated human hypertension, 3) an early significant increase in sodium and magnesium excretion together with negligible effects on glomerular filtration rate and urine volume, and 4) a lack of response of the renin-angiotensin-aldosterone system to the hypertensive and natriuretic effects. Altogether, our data suggest that ANF plays an important role in the circulatory and renal homeostasis in humans with mild essential hypertension.

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References


**KEY WORDS** • atrial natriuretic factor • cardiac output • hypertension • blood pressure, pulmonary
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