Atrial Natriuretic Factor in Mild to Moderate Chronic Renal Failure

SUSANNE SUDA, PETER WEIDMANN, HERMANN SAXENHOFER, CHRISTOPH COTTIER, SIDNEY G. SHAW, AND CLAUDIA FERRIER

SUMMARY The relationship between kidney function and plasma immunoreactive atrial natriuretic factor (irANF) levels as well as the effects of synthetic human ANF-(99-126) were investigated in 13 patients with mild to moderate chronic renal failure. Under basal conditions, glomerular filtration rate averaged 39 ± 5 (SEM) ml/min/1.73 m² and blood pressure (BP) averaged 166/107 ± 7/2 mm Hg; 12 patients were hypertensive. Plasma irANF levels were significantly increased (98 ± 16 vs 42 ± 4 pg/ml in healthy control subjects; p< 0.001) and correlated (p< 0.05-0.005) inversely with hematocrit (r = -0.65) and positively with systolic BP (r = 0.75) or fractional sodium excretion (r = 0.75). Human ANF-(99-126) infusion for 45 minutes at 0.034 μg/kg/min augmented (p< 0.05-0.01) diuresis and urinary sodium, chloride, calcium, phosphate, and magnesium excretion. During the subsequent 45 minutes of human ANF-(99-126) infusion at a rate of 0.077 μg/kg/min, diuresis and electrolyte excretion remained elevated (p<0.05-0.01). Glomerular filtration rate and effective renal plasma flow were not significantly modified, but filtration fraction rose progressively (p<0.01). Human ANF-(99-126) infusion decreased BP (p<0.05-0.01), produced hemoconcentration (hematocrit + 7%; p<0.01) without negative body fluid balance, and increased (p<0.01-0.001) plasma norepinephrine, insulin, and serum free fatty acids; plasma aldosterone and renin activity were unaltered during but rose after cessation of human ANF-(99-126) infusion. These findings indicate that circulating irANF increases in hypertensive patients with mild to moderate chronic renal failure and may support the homeostasis of sodium balance. Infused human ANF-(99-126) can acutely produce hemoconcentration, lower BP, induce sympathetic activation, stimulate plasma insulin, and augment the excretory function at least in part through tubular mechanisms.

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KEY WORDS • chronic renal failure • atrial natriuretic factor • sodium homeostasis • renal function • blood pressure • catecholamines • insulin • renin-angiotensin-aldosterone system

ATRIAL natriuretic factor (ANF) may play a complementary role in the regulation of blood volume, the overall body sodium-fluid volume state, and blood pressure (BP).1-3 Cardiac ANF secretion seems to be stimulated by atrial stretching1 and, perhaps, additional factors.2,3 In normal humans, circulating ANF consists largely of human ANF-(99-126), which has 28 amino acid residues.1,4 Plasma immunoreactive ANF (irANF) increases acutely in response to sodium-fluid volume loading,5 the central shift of circulatory volume when a person lies down,6,7 or a rise in systemic BP and, thus, afterload.8 On the other hand, synthetic human ANF-(99-126), at doses elevating plasma irANF within the physiological and pathophysiological range, augments the diuresis and natriuresis.9,10 Furthermore, human ANF-(99-126) may lower total peripheral vascular resistance, promote an extravascular shift of circulating fluid volume,4 decrease BP,6,9,11,12 and, through direct inhibition of steroidogenesis13 and renin production,14 reduce plasma aldosterone11,12 and renin9 levels.

Various kidney diseases are commonly complicated by sodium retention, activation of the renin-angiotensin-aldosterone system, and hypertension.15 These alterations may occur in the early stage of renal functional impairment.16,17 Nevertheless, except in patients with congestive heart failure or hypoproteinemia, severe sodium retention with edema is unusual before the preterminal stage of renal failure. In fact, with decreas-
ing functional renal mass, the fractional excretion of sodium per remaining intact nephron increases. Earlier observations suggested that this functional adaptation may be mediated by humoral natriuretic factor(s), whose chemical nature and pharmacological properties have not been clearly identified. The ANF system would appear to have the potential prerequisites for such an interaction. In rats with experimentally reduced renal mass (5/6 nephrectomy), fractional sodium excretion and plasma irANF levels were elevated, and both changes were mitigated by dietary sodium restriction. The few available reports on plasma irANF in patients with nonoliguric renal functional impairment variably described unaltered or increased plasma irANF levels and did not consider their relationship with fractional sodium excretion. Based on its diuretic, natriuretic, and renin- and aldosterone-inhibiting, and BP-lowering properties in normal humans, human ANF-(99-126) could also be of therapeutic interest. Effects of human ANF-(99-126) in patients with renal failure are unknown, but an infusion of the 24 amino acid compound atriopeptin III in 5/6 nephrectomized rats produced an acute fall in BP and rises in glomerular filtration rate (GFR), urine volume, and sodium excretion. Therefore, the present study was undertaken to investigate the relationship between circulating irANF and kidney function as well as the effects of synthetic human ANF-(99-126) on a spectrum of cardiovascular, endocrine, and renal variables in patients with mild to moderate chronic renal failure.

Patients and Methods

We studied 13 patients with chronic mild to moderate impairment of renal function (7 women, 6 men), aged 22 to 65 years (mean ± SEM, 46.4 ± 4.1 years). GFR ranged from 11 to 66 ml/min/1.73 m² (mean, 39 ± 5 ml/min/1.73 m²), and untreated BP ranged from 131/87 to 217/119 mm Hg (mean, 166/107 ± 7/2 mm Hg). Twelve patients were hypertensive (diastolic BP >95 mm Hg), and one had values consistently below 140/90 mm Hg. The renal diagnosis, established by clinical, laboratory, and radiological criteria and renal biopsy results, was glomerulonephritis in four patients, interstitial nephritis in four, polycystic kidney disease in two, analgesic nephropathy in two, and medullary sponge kidney complicated by nephrocalcinosis and interstitial nephritis in one patient. Patients undergoing drug treatment of renal disease (e.g., corticosteroids, immune suppressants, nonsteroidal anti-inflammatory agents), patients with the nephrotic syndrome, congestive heart failure, edema of other cause, malignant hypertension with retinal hemorrhages or papilledema, previous stroke or myocardial infarction, diabetes mellitus, or endocrine or metabolic dysfunctions not related to renal failure, and alcohol or drug abusers were excluded from the study.

After the subjects had given their written consent, the following procedures were performed. The patients were instructed to eat a no-added-salt diet and to take no drugs for at least 14 days before the study. Thereafter, two consecutive 24-hour urine samples were collected for determination of sodium, potassium, chloride, calcium, phosphate, protein, uric acid, urea, and creatinine excretion rates. During the second night, the patients fasted and also avoided nicotine and caffeine after 2400, but they drank 200 ml of water or nonsweetened lime blossom tea and ate 60 g of bread without any additions before coming to the clinical study unit, where they arrived between 700 and 800. Fifteen minutes later, a bladder catheter was placed and plastic cannulas were inserted on each arm into an antecubital vein. Thereafter, renal function and a variety of additional factors were evaluated under steady state conditions with the patients in the supine position. GFR and effective renal plasma flow were determined by constant infusion clearance technique, using 51Cr-EDTA and p-aminohippuric acid (PAH), respectively. An intravenous priming dose of 30 µCi 51Cr-EDTA and 0.6 g PAH in 50 ml NaCl (0.9%) was administered, followed by a maintenance infusion (solution containing 18 µCi 51Cr-EDTA and 0.6 g PAH per 100 ml NaCl for patients with plasma creatinine levels <2.8 mg/dl, and 8 µCi 51Cr-EDTA and 0.3 g PAH per 100 ml NaCl for patients with creatinine levels >2.8 mg/dl, respectively) delivered by calibrated pump (infusion type 5094, sterile catgut, Gesellschaft, Neuhausen, Switzerland) at a rate of 1 ml/min.

For blood sampling, the venous access on the contralateral arm was used; the blood was aspirated by syringe. Urine was obtained by bladder catheter, which was rinsed twice with air and distilled water at the end of each period. Urine produced during an initial 60-minute equilibration period was discarded. Thereafter, two 15-minute clearance periods served as the control phase. During the 90 minutes of clearance periods 3 to 8, synthetic human ANF-(99-126) (Bisendorf Peptide, Wedemark, FRG) was infused intravenously at two different rates: 0.034 ± 0.005 (mean ± SEM) µg/min/kg body weight during the initial 45 minutes of human ANF-(99-126) infusion and 0.077 ± 0.008 µg/min/kg during the subsequent 45 minutes of this infusion. The human ANF-(99-126) infusion solutions (necessary amounts of human ANF-(99-126) added to 45 ml of 0.9% NaCl and 3 ml of 20% human serum albumin) were delivered by a calibrated pump (Perfusor V, B. Braun Apparatebau, Melsungen, FRG) at a rate of 1 ml/min; a similar rate of carrier solution only was infused during the control clearance periods 1 and 2 as well as during the 45 minutes of clearance periods 9 to 11 (recovery phase). The human ANF-(99-126) infusion rates were corrected for losses of human ANF-(99-126) during passage of the infusion solution through the infusion system; thus, human ANF-(99-126) concentrations at the outlet of the infusion system were determined in each subject at both infusion steps.

Body weight was recorded before and at completion of the test. BP and heart rate were measured at 1- to 3-minute intervals during clearance periods 3 to 11 and at 2- to 5-minute intervals during periods 1 and 2. Hematocrit, plasma irANF, glucose, urine volume, and plas-
ma and urinary sodium, chloride, potassium, calcium, phosphate, uric acid, urea, creatinine, \(^{51}\)Cr-EDTA, and PAH values were measured in each clearance period. Plasma renin activity, aldosterone, epinephrine, norepinephrine, dopamine, insulin, serum free fatty acids, plasma and urinary magnesium, and urine pH were determined in clearance periods 2 (control value), 5 (end of lower dose infusion), 8 (end of high dose infusion), and 11 (end of recovery phase), while urine and plasma osmolality were measured in clearance periods 2, 3, 5, 6, 8, and 11. All blood samples and urine losses were readily replaced by intravenous infusion of equal amounts of 0.9\% NaCl solution. Because of ethical restrictions, this experimental procedure with bladder catheterization in humans could not be repeated for a vehicle control.

To judge the basal plasma irANF values obtained in the renal patients, plasma irANF was also determined during the same period and under similar basal conditions in 18 healthy subjects of comparable age (40 ± 5 years).

BP was determined with standard cuff and the automatic device Tonoprint (Speidel & Keller, Jungingen, FRG); the mean reading over each 15-minute clearance period was used for analysis. Hematocrit was measured by the microhematocrit method, plasma and urinary \(^{51}\)Cr activity in a gamma counter (Tri-Carb-Scintillation spectrometer, Packard, Downers Grove, IL, USA), PAH by a standard photometric method, sodium and potassium by flame photometer, chloride, calcium, magnesium, phosphate, uric acid, urea and creatinine by autoanalyzer (Greiner SA, Langenthal, Switzerland), osmolality by freezing-point depression using a cryoscope with Peltier’s element, glucose by the hexokinase method, and serum free fatty acids by an enzymatic colorimetric method (Wako Pure Chemical Industries, Osaka, Japan). Plasma insulin, plasma renin activity, and aldosterone levels were measured by radioimmunoassay.\(^{23-25}\) Plasma norepinephrine, epinephrine and dopamine were determined with high performance liquid chromatography (HPLC) and electrochemical detection following extraction by a modification of the method of Smedes et al.\(^{26}\) as reported previously from this laboratory.\(^{11,27}\)

For determination of plasma irANF, 8 ml of blood was collected in polypropylene tubes containing EDTA (1 mg/ml). The blood samples were mixed, immediately centrifuged at 4\(^{\circ}\)C, and the plasma stored at -80\(^{\circ}\)C until assay. To eliminate variable lipid interference in the assay, plasma was acidified with 4 ml of 0.1\% hydrochloric acid, 3 ml of hexane was added, and the tubes were shaken and centrifuged for 5 minutes at 3000 rpm. All of the aqueous phase was then applied to a C\(_{18}\) octadecyl silica cartridge (Sep-Pak C\(_{18}\), Waters, Milford, MA, USA), washed with 2 ml of distilled water, and eluted with 2 ml of 0.1\% trifluoroacetic acid in 100\% ethanol. The efficiency of the extraction procedure was estimated by recovery of synthetic human ANF-(99-126) added to plasma. When synthetic human ANF-(99-126), 4 to 500 pg/ml, was added, plasma recovery was 91 ± 4\%(n = 8) after the extraction and radioimmunoassay procedures. Radioimmunoassay of ANF was performed using a rabbit anti-ANF antibody (Peninsula Laboratories Europe, Merseyside, UK).\(^{23}\) This antibody shows complete cross-reactivity with human ANF-(99-126) and rat atriopeptin III, but it has no cross-reactivity with somatostatin, oxytocin, or vasopressin. The standard buffer was 0.1 M Tris, pH 7.4, containing 0.1\% bovine serum albumin (radioimmunoassay grade), 0.1\% Triton X-100, and sodium azide. \(^{125}\)I-human ANF-(99-126) was used as the tracer (Amersham Buchler, specific activity, 2000 Ci/mmol), and synthetic human ANF-(99-126) was used to construct standard curves. Incubation was performed for 48 hours at 4\(^{\circ}\)C. Bound and free \(^{125}\)I-human ANF-(99-126) was separated by adding dextran-coated charcoal; the lowest concentration of human ANF-(99-126) detected was 4 pg/tube, and the 50% intercept was at 30 pg/tube. The interassay variation was 15.5\%(n = 6), and the intra-assay variation was 7.8\%(n = 6). All plasma values were calculated from an extracted standard curve after correction for nonspecific binding of tracer. In normal subjects, the ANF-like immunoreactive material in plasma has been characterized by reverse-phase HPLC and corresponds largely to human ANF-(99-126).\(^{21}\)

The filtration fraction was calculated as the ratio of GFR/effective renal plasma flow. Fractional excretion rate was calculated as the ratio of clearance of excreted variable/GFR. Free water clearance was estimated as the difference between urinary volume and clearance of osmoles per minute.

Statistical analysis was performed with the help of the Statistical Analysis System software package (version 6.0, SAS Institute, Cary, NC, USA). Methods included analysis of variance complemented by Student-Newman-Keuls t test for comparison between repeated measurements and unpaired t test for comparison of some basal data between the renal patients and healthy control subjects. Values are given as means ± SEM. Since natural logarithmic transformation rather than absolute values followed a gaussian distribution, the natural logarithmic transformation of plasma renin activity, aldosterone, norepinephrine, epinephrine, dopamine, and irANF levels was used for statistical analysis.

Results

Clinical, Biochemical, and Endocrine Variables

Basal urinary sodium excretion rates in the renal patients were stable during the 2 days preceding the test, averaging 146 ± 18 and 145 ± 20 mmol/24 hr, respectively; potassium (67 ± 7 and 71 ± 6 mmol/24 hr) and creatinine excretion rates (1.17 ± 0.08 and 1.29 ± 0.09 g/24 hr) also were stable.

Basal plasma irANF concentrations were significantly higher (p < 0.001) in the renal patients (Table 1) than in the concomitantly analyzed healthy control subjects (n = 18) of similar age (40 ± 5 years) and on comparable sodium intake (urinary sodium, 127 ± 13 mmol/24 hr); mean irANF values in the two groups...
TABLE 1. Clinical, Biochemical, and Endocrine Variables in 10 Normal Subjects and in 13 Patients with Chronic Renal Failure Before, During, and After Human ANF-(99-126) Infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control*</th>
<th>Human ANF-(99-126) infusion</th>
<th>Low dose†</th>
<th>High dose‡</th>
<th>Recovery†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Systolic</td>
<td>166 ± 6</td>
<td>156 ± 5§</td>
<td>140 ± 6§</td>
<td>140 ± 7§</td>
<td></td>
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<tr>
<td>Diastolic</td>
<td>107 ± 2</td>
<td>97 ± 2§</td>
<td>90 ± 3§</td>
<td>89 ± 3§</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 3</td>
<td>74 ± 3‡</td>
<td>79 ± 3§</td>
<td>77 ± 3§</td>
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</tr>
<tr>
<td>Body weight (kg)</td>
<td>68 ± 3</td>
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<tr>
<td>Hematocrit (%)</td>
<td>35.2 ± 1.5</td>
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<td>36.1 ± 1.6</td>
<td>37.7 ± 1.5§</td>
<td>36.6 ± 1.4‡</td>
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<tr>
<td>Plasma</td>
<td></td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>2.5 ± 0.4</td>
<td>2.57 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>2.4 ± 0.4</td>
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<tr>
<td>Sodium (mmol/L)</td>
<td>141 ± 0.5</td>
<td>141 ± 0.4</td>
<td>142 ± 0.5</td>
<td>142 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>irANF (pg/ml)</td>
<td>98 ± 16</td>
<td>$ 2206 ± 302§$</td>
<td>5054 ± 374§</td>
<td>149 ± 13§</td>
<td></td>
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<tr>
<td>Renin activity (ng Ang I/ml/hr)</td>
<td>2.55 ± 0.5</td>
<td>2.88 ± 0.5</td>
<td>2.81 ± 0.5</td>
<td>3.36 ± 0.68</td>
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<tr>
<td>Aldosterone (ng/dl)</td>
<td>6.1 ± 1.5</td>
<td>5.0 ± 0.9</td>
<td>5.6 ± 1.1</td>
<td>15.5 ± 4.2‡</td>
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<tr>
<td>Epinephrine (ng/dl)</td>
<td>2.7 ± 0.9</td>
<td>2.5 ± 0.7</td>
<td>3.6 ± 1.2</td>
<td>5.5 ± 1.5‡</td>
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<tr>
<td>Norepinephrine (ng/dl)</td>
<td>31 ± 3</td>
<td>52.3 ± 8§</td>
<td>63.9 ± 13§</td>
<td>39.4 ± 7</td>
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<tr>
<td>Dopamine (ng/dl)</td>
<td>2.8 ± 0.5</td>
<td>3.3 ± 1.8</td>
<td>4.8 ± 1.1</td>
<td>3.3 ± 0.6</td>
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<tr>
<td>Insulin (µU/ml)</td>
<td>8.4 ± 1.2</td>
<td>12.2 ± 1.1§</td>
<td>14.6 ± 1.4§</td>
<td>9.8 ± 1.3</td>
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<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 0.1</td>
<td>4.9 ± 0.1</td>
<td>4.7 ± 0.2</td>
<td>4.7 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Serum free fatty acids (mmol/L)</td>
<td>1.53 ± 0.1</td>
<td>2.74 ± 0.2§</td>
<td>3.31 ± 0.2f</td>
<td>2.29 ± 0.2f</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM. irANF = immunoreactive ANF; Ang I = angiotensin I.
*Except for endocrine variables and fatty acids, mean values of clearance periods 1 and 2.
†Mean value of clearance periods 5, 8, or 11, respectively.
‡p<0.05, §p<0.01, \p<0.001, compared with control values.
\p<0.001, compared with values in normal subjects (n = 18; plasma irANF = 41.8 ± 4 pg/ml).

Averaged 98 ± 16 and 42 ± 4 pg/ml, respectively. Individual plasma irANF values in the renal patients correlated positively with systolic BP (r = 0.75, p < 0.005) and inversely with hematocrit (r = -0.65, p < 0.05; Figure 1); a trend for positive correlations with mean BP (r = 0.54) or age (r = 0.52) did not achieve statistical significance, and no relationship between plasma irANF and aldosterone, renin activity, epinephrine, norepinephrine, or dopamine levels, or 24-hour urinary sodium excretion was apparent.

During human ANF-(99-126) infusion, plasma irANF increased about 20-fold with the low infusion rate and about 50-fold with the high infusion rate; thereafter, plasma irANF fell rapidly, almost reaching control values 37.5 minutes into the recovery phase (Figure 2; see Table 1).

Compared with control values, BP decreased (p < 0.05–0.01) an average 6% during the lower human ANF-(99-126) infusion rate and 12% during the high infusion rate (see Table 1); heart rate rose progressively. During the recovery phase, BP remained low and heart rate returned only partly toward control values.

Hematocrit tended to rise during the lower human ANF-(99-126) infusion rate, increased significantly during the high infusion rate (an average 7%; p < 0.01), and tended to fall again during the recovery phase (see Table 1). The rise in hematocrit was not due...
to diuresis, since it occurred despite isovolemic replacement of all blood samples and urine losses with 0.9% saline.

Plasma norepinephrine increased \((p<0.001)\) progressively during the human ANF-(99–126) infusion phase; a similar tendency for epinephrine and dopamine did not reach statistical significance (see Table 1). At the end of the recovery phase, plasma norepinephrine was restored toward control values, but epinephrine tended to be elevated with a marked interindividual splay \((p<0.05)\).

Plasma renin and aldosterone levels (see Table 1) were not significantly modified during human ANF-(99–126) infusion, but they rose significantly \((p<0.01\) and \(p<0.05\), respectively) during the recovery phase. Conversely, serum free fatty acid and plasma insulin concentrations rose progressively during human ANF-(99–126) infusion \((p<0.01\)–0.001), then returned partly toward control values after the infusion ceased (see Table 1). Plasma glucose levels were largely unaltered.

Renal Function and Plasma and Urinary Electrolytes

Under basal conditions, fractional sodium excretion in the renal patients correlated positively with plasma irANF levels \((r=0.75, p<0.005; \text{Figure} 3)\). Relationships between basal plasma irANF and GFR \((r=-0.29; \text{Figure} 4)\) or creatinine clearance \((r=-0.02)\) did not achieve statistical significance. During the low human ANF-(99–126) infusion rate, the rise in plasma irANF values correlated inversely with the initial GFR \((r=-0.61, p<0.05; \text{see Figure} 4)\). A similar tendency during the high infusion rate \((r=-0.50)\) did not achieve statistical significance. Rises in plasma irANF values correlated during the whole infusion phase with the human ANF-(99–126) infusion rates \((r=0.54, p<0.01)\).

Compared with the mean value of the two control clearance periods, GFR and effective renal plasma flow were not significantly modified by analysis of variance during the human ANF-(99–126) infusion (Table 2). However, filtration fraction increased progressively, reaching 30% at the end of the high infusion rate \((p<0.01)\), and it returned partly toward control values at the end of the recovery phase.

Urine flow and sodium, chloride, calcium, phosphate, and magnesium excretion rates rose during human ANF-(99–126) infusion \((p<0.05–0.01; \text{Figure} 5; \text{see Table} 2)\), reached a maximum during the low infusion rate, and were already less pronounced toward the end of the high infusion rate. Potassium excretion increased minimally \((p<0.01\) during clearance period 4). Maximal percent increases of absolute excretion rates were 181% for urine flow, 217% for sodium, 217% for chloride, 134% for calcium, 108% for phosphate, 70% for magnesium, 40% for potassium, and 103% for osmolar excretion. Maximal percent increases of fractional excretion rates were 152% for sodium, 153% for chloride, 94% for calcium, 87% for phosphate, 39% for magnesium, and 63% for osmoles.

Compared with control conditions, urinary osmolality, free water clearance (see Table 2), and urinary pH were not significantly modified during human ANF-(99–126) infusion. Plasma sodium (see Table 1), potassium, chloride, calcium (2.19 ± 0.02 mmol/L), magnesium (0.81 ± 0.02 mmol/L), and phosphate (0.89 ± 0.06 mmol/L) were also unaltered.

Discussion

These findings demonstrate that plasma irANF levels are on average higher in hypertensive patients with mild to moderate chronic renal failure than in healthy humans and correlate positively with fractional renal sodium excretion. In addition, a further marked rise in plasma irANF concentrations, induced by intravenous infusion of synthetic human ANF-(99–126), produced a decrease in BP and hemoconcentration, increases in circulating norepinephrine and free fatty acid levels, an elevation in plasma insulin concentration, and in-

![Figure 3. Relationship between urinary fractional sodium excretion and plasma immunoreactive ANF (irANF) levels under basal conditions in 13 patients with mild to moderate chronic renal failure and seven normal subjects. The data in normal subjects are from C. Cottier, L. Matter, P. Weidmann, unpublished studies, 1987.](http://hyper.ahajournals.org/)

![Figure 4. Relationship between plasma immunoreactive ANF (irANF) levels before or during human ANF-(99–126) infusion and glomerular filtration rate in 13 patients with mild to moderate chronic renal failure.](http://hyper.ahajournals.org/)
TABLE 2. Renal Function and Electrolyte Excretion in 13 Patients with Mild to Moderate Chronic Renal Failure Before, During, and After Human ANF-(99–126) Infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control*</th>
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<th>Low dose†</th>
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<th>Recovery†</th>
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<tr>
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<tr>
<td>Effective renal plasma flow (ml/min/1.73 m²)</td>
<td>198 ± 30</td>
<td>192 ± 31</td>
<td>146 ± 26</td>
<td>149 ± 24</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min/1.73 m²)</td>
<td>39 ± 5</td>
<td>45 ± 6§</td>
<td>39 ± 7</td>
<td>33 ± 5</td>
<td></td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>22.7 ± 2</td>
<td>26.9 ± 2§</td>
<td>28.5 ± 2§</td>
<td>25.3 ± 2§</td>
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<tr>
<td>Urinary excretion rate</td>
<td></td>
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<tr>
<td>Fluid volume (ml/min)</td>
<td>3.1 ± 0.5</td>
<td>7.4 ± 1.3§</td>
<td>5.4 ± 1.2</td>
<td>2.2 ± 0.4</td>
<td></td>
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<tr>
<td>Sodium (µmol/min)</td>
<td>277 ± 66</td>
<td>599 ± 109§</td>
<td>629 ± 158</td>
<td></td>
<td>236 ± 47</td>
</tr>
<tr>
<td>FE sodium (%)</td>
<td>5.8 ± 1.0</td>
<td>10.2 ± 1.4§</td>
<td>10.7 ± 1.7§</td>
<td>6.4 ± 1.7</td>
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<tr>
<td>Chloride (µmol/min)</td>
<td>272 ± 62</td>
<td>600 ± 109§</td>
<td>658 ± 160§</td>
<td>223 ± 52</td>
<td></td>
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<tr>
<td>FE chloride (%)</td>
<td>7.8 ± 1.4</td>
<td>12.9 ± 1.8§</td>
<td>14.2 ± 2.2§</td>
<td>8.1 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Potassium (µmol/min)</td>
<td>62.1 ± 6.2</td>
<td>74.1 ± 7.8</td>
<td>53.7 ± 8.2</td>
<td>43.6 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>FE potassium (%)</td>
<td>49.1 ± 8.3</td>
<td>50.2 ± 7.9</td>
<td>47.9 ± 7.9</td>
<td>42.1 ± 6.9</td>
<td></td>
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<tr>
<td>Calcium (µmol/min)</td>
<td>3.4 ± 0.8</td>
<td>6.6 ± 1.4§</td>
<td>6.3 ± 1.5§</td>
<td>2.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>FE calcium (%)</td>
<td>4.5 ± 0.9</td>
<td>7.1 ± 1.2§</td>
<td>7.2 ± 1.2§</td>
<td>4.3 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Phosphate (µmol/min)</td>
<td>10.6 ± 1.8</td>
<td>15.8 ± 2.4</td>
<td>13.3 ± 2.4</td>
<td>9.8 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>FE phosphate (%)</td>
<td>37.3 ± 6.1</td>
<td>46.3 ± 6.6</td>
<td>46.6 ± 6.1</td>
<td></td>
<td>40.4 ± 6.9</td>
</tr>
<tr>
<td>Magnesium (µmol/min)</td>
<td>4.5 ± 0.5</td>
<td>6.6 ± 0.7</td>
<td></td>
<td>5.8 ± 1.0</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>FE magnesium (%)</td>
<td>17.5 ± 2.7</td>
<td>21.3 ± 2.7</td>
<td></td>
<td>20.8 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Uric acid (µmol/min)</td>
<td>2.0 ± 0.2</td>
<td>2.4 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>1.0 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>FE uric acid (%)</td>
<td>17.7 ± 2.0</td>
<td>18.5 ± 2.4</td>
<td>16.0 ± 2.3</td>
<td>11.9 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>FE urea (%)</td>
<td>69.6 ± 3.7</td>
<td>67.6 ± 3.7</td>
<td>67.3 ± 4.2</td>
<td>59.2 ± 5.7</td>
<td></td>
</tr>
<tr>
<td>FE creatinine (%)</td>
<td>130 ± 7.4</td>
<td>116 ± 6.9</td>
<td>123 ± 5.2</td>
<td>124 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Osmoles (µosm/min)</td>
<td>950 ± 134</td>
<td>2011 ± 509</td>
<td></td>
<td>1479 ± 387</td>
<td>704 ± 109</td>
</tr>
<tr>
<td>Urine osmolality (mosmol/L)</td>
<td>351 ± 50</td>
<td>263 ± 24</td>
<td>295 ± 15</td>
<td>351 ± 32</td>
<td></td>
</tr>
<tr>
<td>Free water clearance (ml/min/1.73 m²)</td>
<td>36.1 ± 5.5</td>
<td>38.6 ± 5.7</td>
<td>32.1 ± 6.6</td>
<td>30.7 ± 4.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM. FE = fractional excretion rate.

*Except for osmolality, free water clearance, and magnesium, mean values of clearance periods 1 and 2.
†Mean values of clearance periods 5, 8, 11, respectively.
§p < 0.01, ||p < 0.05, compared with control values (by paired t test).

FIGURE 5. Effect of human ANF-(99–126) infusion on diuresis and monovalent electrolyte excretion in 13 patients with mild to moderate chronic renal failure. Values are means ± SEM.

Increases in the renal filtration fraction and excretion of water and various electrolytes.

The significant relationship between fractional sodium excretion rates and circulating irANF concentrations (r = 0.75, p < 0.005) in our patients with renal disease is consistent with, although not proof of, a regulatory interaction. Although earlier observations suggested an important homeostatic role of humoral natriuretic factors,18 a structural identification has been lacking. Attention focused particularly on suspected digitalislike substances with Na⁺,K⁺-adenosine triphosphatase (ATPase)-inhibiting properties,18 but their relationship with fractional sodium excretion in the presence of impaired renal function has not been clarified.24 Human ANF-(99–126) does not act by inhibiting Na⁺,K⁺-ATPase. Moreover, human ANF-(99–126) is structurally identified, is thought to represent the biologically active moiety of the ANF system in humans,1,3 and occurs as the predominant circulating moiety in patients with renal failure.29,30 As our patients, plasma irANF levels were also elevated in rats with 5/6 nephrectomy,19 and dietary sodium restriction mitigated the increases in irANF and fractional sodium excretion in this experimental model. It follows that human ANF-(99–126) may well emerge as a hormone that helps to adapt renal excretion and thereby maintain sodium balance with decreasing kidney function.
Several mechanisms could mediate a compensatory rise in circulating human ANF-(99–126) with progressive nephron loss. Based on observations in healthy humans, general blood volume expansion, a central shift of circulatory volume, or increased systemic BP and, thus, afterload deserves particular consideration. In the course of kidney disease, measurable sodium retention may occur at a GFR of 65 ml/min/1.73 m² or lower; each of the present patients belonged to this functional category, although body sodium and fluid spaces were not determined. Moreover, an initial rise in blood volume and cardiac output, subsequent arteriolar and venous vasoconstriction and increase in BP, and a pressure (or hormone?)-mediated restoration of normovolemia were described as a characteristic sequence in the pathogenesis of hypertension accompanying renal parenchymal diseases. Twelve of our 13 patients were hypertensive. The significant correlations between their basal supina plasma irANF and systolic BP (r = 0.75, p < 0.005) or hematocrit (r = -0.65, p < 0.05) may be consistent with a stimulatory influence of hypertension or of its own determinants, such as sodium-fluid volume retention and severity of renal functional impairment, or of both. A positive correlation between basal circulating irANF and creatinine clearance was noted in one of the previous reports of high irANF values in mild to advanced chronic renal failure, while a tendency for a relationship with GFR in the present study did not reach statistical significance.

Plasma ANF concentrations depend partly on the rate of clearance from the circulation. In our renal patients, plasma levels achieved during the low human ANF-(99–126) infusion rate correlated inversely with basal GFR (r = -0.61, p<0.05), and a similar although statistically insignificant trend (r = -0.50) was noted during the high human ANF-(99–126) infusion rate. During passage of the blood through normal kidneys, about 50% of irANF is eliminated from the plasma. Considering that normal humans have a renal plasma flow of about 600 ml/min and a total circulatory plasma irANF clearance of 1.5 to 2.4 L/min, even bilateral nephrectomy could elevate plasma irANF levels by at least 20% in rats, the half-life of exogenously administered ANF was slightly prolonged in the nephrectomized as compared with the normal state.

Since the present investigation involved a bladder catheterization in humans, the effects of infused synthetic human ANF-(99–126) had to be evaluated without vehicle control. Synthetic human ANF-(99–126) in the hypertensive patients with mild to moderate renal failure rapidly enhanced the diuresis and excretion of various electrolytes, which often reached a maximum during the low human ANF-(99–126) infusion rate; free water clearance was unchanged. In rats, atriopeptin III was found to exert potent excretory effects, even in the presence of 5/6 nephrectomy. Possible mechanisms mediating excretory action of ANF include an elevated GFR with its attendant rise in filtered load of fluid and solutes, redistribution of blood flow to the renal medulla, altered peritubular Starling forces along the medullary collecting ducts, and perhaps, an additional indirect or even direct influence on the distal nephron.

GFR could not be an indispensable sole mechanism for the diuretic and natriuretic effects of ANF in our patients with mild to moderate renal failure, in previously studied normal subjects, or in patients with essential hypertension. In the renal patients, GFR and effective renal plasma flow were not significantly modified during the human ANF-(99–126) infusion. However, the filtration fraction rose progressively by up to 30%, as noted previously in normal subjects, hypertensive patients, and experimental animals.

When possible humoral mediators were considered, plasma renin and aldosterone levels were largely unchanged during human ANF-(99–126) infusion, but they rose (p < 0.05–0.01) during the recovery phase in the renal patients. The latter reaction probably reflects overshoot following a human ANF-(99–126)-induced inhibition of renin secretion and adrenocortical function. Nevertheless, a direct inhibitory influence of human ANF-(99–126) on renin release probably can be counterbalanced by stimulatory signals resulting from hemoconcentration, decreased BP, and sympathetic activation. The latter is probably baroreceptor reflex-mediated and evidenced by indices such as increased plasma norepinephrine, heart rate, and serum free fatty acid levels during human ANF-(99–126) infusion in the present and earlier studies. The human ANF-(99–126)-induced increase in plasma insulin in the renal patients complements similar findings in normal subjects and patients with essential hypertension. The magnitude of this change is obviously below the range of insulin concentrations that would modify plasma glucose. Nevertheless, considering its renal sodium-retaining properties, insulin could partially antagonize the human ANF-(99–126)-mediated natriuresis.

Human ANF-(99–126) may acutely lower BP in humans by decreasing both total peripheral vascular resistance and intravascular volume. The rise in hemoconcentration indices during human ANF-(99–126) infusion in our patients with renal failure or in previously studied normal or hypertensive subjects could not be accounted for by renal fluid losses, thus pointing to an extravascular shift of fluid. Taken together, these observations suggest that, in hypertensive patients with chronic nonoliguric renal failure, the ANF system contributes to sodium homeostasis, and synthetic human ANF-(99–126) infused in pharmacological doses may at least acutely enhance the excretory function and decrease BP.

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