Hemodynamic and Renal Responses to Physiological Levels of Atrial Natriuretic Factor in Conscious Dogs

Robert Pichet, Marc Cantin, Gaétan Thibault, and Michel Lavallée

The effects of increases in plasma atrial natriuretic factor (ANF) similar to those encountered after rapid volume expansion were examined in conscious dogs. Hemodynamics and renal function were continuously monitored during 30 minutes of human ANF infusion (10 ng/kg-min) and throughout a 30-minute recovery period. Ten minutes into the infusion period, plasma levels of ANF were elevated (p<0.01) by 34±9 from 36±5 pg/ml and sodium excretion increased (p<0.05) by 34±7 from 67±9 μeq/min. At that time, urine flow did not differ from baseline (0.25±0.03 ml/min). Renal blood flow velocity fell (p<0.01) by 5.0±0.5 from 42.3±3.7 cm/sec. Thirty minutes into the infusion period, plasma ANF levels were increased (p<0.01) by 61±9 pg/ml, similar to levels found after rapid volume expansion in conscious dogs. Urine flow and sodium excretion were elevated (p<0.01) by 0.35±0.06 ml/min and by 65±12 μeq/min, respectively. Renal blood flow velocity was reduced (p<0.05) by 4.4±1.5 cm/sec. Neither right atrial pressure, left ventricular end-diastolic pressure, mean arterial pressure, the first derivative of left ventricular pressure over time (dP/dt), nor heart rate were influenced by the elevated ANF plasma levels. Circulating levels of vasopressin and aldosterone were unaltered by these increases in plasma ANF. Thirty minutes into the recovery period, all variables were similar to the preinfusion baseline. Thus, in conscious dogs, physiologically relevant increases in plasma levels of ANF within physiological range had limited hemodynamic effects. (Hypertension 1989; 14:104-110)

After cardiac denervation, atrial distension with intracavitary balloons or volume expansion elicits substantial elevations of circulating atrial natriuretic factor (ANF). Whether these increases in ANF levels are sufficient to influence hemodynamic variables and renal function remains controversial. In a recent review, Goetz concluded that physiological levels of atrial peptides may not exert a significant effect on the kidney. However, the interpretation of several experimental reports is complicated by factors such as differences between the endogenous peptide sequence and the peptides administered intravenously, anesthesia of the animals under investigation, and administration of boluses rather than infusions.

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In a recent study conducted in conscious dogs,7 peak increases in plasma levels of ANF with rapid volume expansion averaged 61 ±13 from 34±5 pg/ml, consistent with previous reports.8,9,12 Therefore, the first goal of our study was to determine whether elevations of plasma human ANF similar to those found in conscious dogs with volume expansion reached natriuretic and diuretic thresholds. We also wished to determine whether these physiological levels of ANF were sufficient to influence hemodynamic variables in dogs. Because anesthesia dramatically alters cardiovascular regulation in general10 and the responses to atrial peptides in particular,21 our study was conducted in conscious animals.

Materials and Methods

Under general anesthesia with sodium pentobarbital (30 mg/kg i.v.), seven female dogs (20±2 kg) underwent a left thoracotomy at the fourth intercostal space. Aortic and right atrial pressures were monitored with implanted catheters connected to Bentley Trantec (model 800, Irvine, California) pressure transducers. Mean pressures were obtained with active filters having a time constant of 2 seconds. In six dogs, a miniature solid-state pressure gauge (model P.6.5, Konigsberg Instruments, Pasadena, California) was implanted in the left ventricular cavity through an apical stab wound to measure left ventricular systolic pressure, left ventricular end-diastolic pressure, and the first derivative of left ventricular pressure over time, left ventricular dp/dt. A catheter in the ventricle was used to cross-calibrate the pressure gauge. Through a flank incision, an ultrasonic Doppler flow probe (5 mm i.d.) was implanted around the left renal artery to measure renal blood flow velocity with a 10-MHz pulsed Doppler flowmeter. The linearity of the relation between blood flow velocity in kilohertz of Doppler shift and volume flow has been previously established for this type of instrument22 and confirmed in our laboratory.

All parameters were continuously recorded on an eight-channel tape recorder (model 3968A, Hewlett Packard, San Diego, California) and monitored on a direct ink-writing stripchart recorder (model 2800s, Gould, Cleveland, Ohio). Heart rate was measured using a cardiotachometer (model 9857, Sensor Medics, Anaheim, California) triggered by the phasic aortic pressure signal.

Protocols

Experiments were initiated in seven conscious dogs, 2 weeks to 2 months after surgery. Animals were fed a commercially available diet (Purina Dog Chow, Adult Formula, Ralston-Purina, Mississauga, Ontario, Canada) that provided ~70 meq/day sodium. Before experimentation, all dogs were made to fast for 14–16 hours with free access to water. Experiments were carried out in conscious dogs lying quietly on their right sides in a dimly illuminated laboratory. The urinary bladder was catheterized retrogradely with a Foley catheter allowing urine collection by gravity drainage. During continuous hemodynamic monitoring, 10-minute collection periods were made until urine volume in three consecutive samples reached a steady level. Synthetic human ANF (28a.a., Institut Armand Frappier, Laval, Quebec, Canada) in 0.1 M acetic acid was diluted in normal saline immediately before administration. The peptide was infused intravenously at a rate of 10 ng/kg-min for 30 minutes in a volume of 0.5 ml/min. This dose of human ANF was selected because preliminary experiments indicated that the resulting increases in plasma ANF levels approximated those reached after acute volume expansion in conscious dogs. Sham experiments in four dogs included in the analysis of ANF responses were conducted to verify the absence of significant changes in hemodynamics, renal function, and plasma levels of ANF during saline infusions at a rate of 0.5 ml/min. Right atrial pressure was not measured during these experiments.

Hemodynamics and renal function were continuously monitored for the duration of human ANF infusion and for a 30-minute recovery period. Urine samples were collected at 10-minute intervals to measure urine volume and to determine urine sodium concentration and osmolality. Blood samples were collected at 10-minute intervals to measure immunoreactive (ir) ANF plasma levels. Plasma sodium concentration, osmolality, vasopressin, and aldosterone levels were measured in samples obtained before the ANF infusion, 30 minutes into the infusion period, and 30 minutes into the recovery period.

In five additional dogs that were instrumented with left ventricular pressure gauges, aortic catheters, and renal flow probes, hemodynamic effects of human ANF infusions at 10 ng/kg-min for 30 minutes were evaluated before and after ganglionic blockade with hexamethonium bromide (40 mg/kg). Adequacy of autonomic blockade was confirmed by absence of reflex changes in heart rate to intravenous pressor doses of phenylephrine (3 μg/kg) and nitroglycerin (10 μg/kg). In addition, an infusion of human ANF (20 ng/kg/min) was performed in these animals before ganglionic blockade.

Biochemistry

Blood samples for irANF determinations were collected in ice-chilled tubes containing EDTA (1 mg), 10 μl phenylmethylsulfonyl fluoride (PMSF) 10−3 M, and 10 μl pepstatin A (500 μM/ml) blood to prevent degradation of irANF. Samples were spun for 20 minutes at 4° C, and the plasma was stored at −70° C until the day of the assay. Radioimmunoassay was performed as previously described for human ANF with prior extraction.23 The Sep-Pak cartridges (Waters Associates, Milford, Massachusetts) were activated by washing first with 8–10 ml acetonitrile and then with 8–10 ml ammonium acetate (0.2% at pH 4.0). The plasma samples (2 ml) were then applied on the cartridge and washed with...
5 ml ammonium acetate (0.2%, pH 4.0), and the adsorbed ANF was eluted with 3 ml acetonitrile (50%) in ammonium acetate (0.2%, pH 4.0). The organic solvent was evaporated under a nitrogen stream (about 50–60% of volume) and then lyophilized in a Speed-Vac. The residue was taken up in 500 µl radioimmunoassay buffer (phosphate buffer, pH 7.4, containing 0.2% NaCl, 0.1% bovine serum albumin, 0.1% Triton X-100, and 0.1% trifluoroacetic acid). Plasma extracts (50 and 100 µl) in duplicate were incubated overnight with antibodies (50 µl) and radioimmunoassay buffer for a total volume of 200 µl at 4° C. [125I]ANF (100 µl, 5,000 cpm) was then added, and incubation was continued overnight at 4° C. Separation of free from antibody-bound iodinated ANF was achieved with a second antibody precipitation by adding 100 µl goat anti-rabbit γ-globulin (1:50) and 100 µl normal rabbit serum (1:35). After 2 hours of incubation at room temperature, 1 ml 6.75% solution polyethylene glycol 8000 in water was added. The tubes were centrifuged for 20 minutes at 4,000 rpm at 4° C. The supernatant was then discarded, and the pellet was counted in a LKB gamma counter. The irANF values were not corrected for recovery, which was 78–80%. Vasopressin plasma levels were measured as previously described. Plasma aldosterone levels were determined by radioimmunoassay after extraction and paper chromatography.

Osmolality of blood and urine were determined by the freezing point depression method on an Advanced Instruments Osmometer (model 68-31LAS, Needham Heights, Massachusetts) and are reported in milliosmoles per kilogram H2O. Sodium concentration measurements in plasma and urine were made with a flame photometer (model IL443, Instrumentation Laboratories, Lexington, Massachusetts).

Data Analysis
All values are mean±SEM. Urine volume is reported in milliliters per minute, and sodium excretion is reported in microequivalents per minute. Data sampling was made from recordings obtained during the last 150 seconds of each clearance period. Multiple readings of absolute values for each variable were made during this period and averaged to obtain time-integrated measurements. Left ventricular end-diastolic pressure was averaged over 15–20 consecutive beats under steady-state hemodynamic conditions. Data were analyzed with repeated-measures analysis of variance and Bonferroni's conversion for multiple comparisons over time. A p value of 0.05 or less after correction was considered significant.

All experimental procedures were performed in accordance with the guidelines of the Canadian Council on Animal Care.

Results
Neither plasma osmolality (291±3 mosm/kg H2O) nor sodium concentration (147±1 meq/l) changed significantly from baseline during human ANF infusion and recovery periods.

Plasma Levels of Immunoreactive Atrial Natriuretic Factor
In sham experiments (n=4), plasma levels of irANF after 30 minutes of saline infusion averaged 42±5 pg/ml, similar to preinfusion baseline levels (43±8 pg/ml) (Figure 1). Ten minutes after beginning administration of human ANF (10 ng/kg-min), plasma levels of irANF increased (p<0.01) by 34±9 from 36±5 pg/ml. At 30 minutes, plasma irANF levels were elevated (p<0.01) by 61±9 pg/ml. By 10 minutes into the recovery period, plasma levels of irANF had returned to preinfusion levels.

Hemodynamic Responses
In sham experiments, saline infusions did not alter baseline hemodynamic variables (Table 1). Neither mean arterial pressure, right atrial pressure, nor heart rate changed significantly from their preinfusion baseline values during human ANF infusion or the recovery period. Left ventricular pressure, left ventricular end-diastolic pressure, and left ventricular dp/dt also remained at preinfusion baseline levels during the infusion and recovery periods. In contrast, renal blood flow velocity fell significantly (p<0.01) by 5.0±0.5 from 42.3±3.7 cm/sec at 10 minutes into the infusion period. At 30 minutes, renal blood flow velocity was reduced (p<0.05) by 4.4±1.5 cm/sec. Renal blood flow velocity returned to preinfusion levels within 10 minutes after interrupting ANF delivery.

Five additional dogs were studied with infusions of human ANF (10 ng/kg-min) for 30 minutes before and after ganglionic blockade with hexamethonium (40 mg/kg). Human ANF (20 ng/kg-min) was also infused in these dogs before ganglionic blockade. Human ANF (10 ng/kg-min) for 30 minutes had no significant influence on baseline heart rate (82±4 beats/min), left ventricular pressure (121±7 mm Hg), left ventricular end-diastolic pressure (10.1±2.2 mm Hg), or left ventricular dp/dt (3,462±154 mm Hg/sec). Renal blood flow velocity fell (p<0.01) to 39.3±5.3 from 45.3±6.6 cm/sec at a time when
TABLE 1. Hemodynamics Under Baseline Conditions, During Saline, or Human ANF (10 ng/kg-min) Infusions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>Recovery (30 min)</th>
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<tr>
<td><strong>Heart rate</strong></td>
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<td>Sham</td>
<td>ANF</td>
<td>Sham</td>
<td>ANF</td>
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<tr>
<td>(beats/min)</td>
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<td><strong>Mean arterial</strong></td>
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<tr>
<td>pressure (mm Hg)</td>
<td></td>
<td>ANF</td>
<td>Sham</td>
<td>ANF</td>
<td>Sham</td>
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<tr>
<td></td>
<td></td>
<td>82±3</td>
<td>80±3</td>
<td>80±3</td>
<td>79±3</td>
</tr>
<tr>
<td><strong>Right atrial</strong></td>
<td></td>
<td>Sham</td>
<td>ANF</td>
<td>Sham</td>
<td>ANF</td>
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<tr>
<td>pressure (mm Hg)</td>
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<td>95±2</td>
<td>97±2</td>
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<tr>
<td><strong>Renal blood</strong></td>
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<td>ANF</td>
<td>Sham</td>
<td>ANF</td>
</tr>
<tr>
<td>flow velocity (cm/sec)</td>
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<td>(mm Hg)</td>
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<td></td>
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<td>1.1±0.7</td>
<td>3±3*</td>
<td>38±4*</td>
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<td>pressure (mm Hg)</td>
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<td></td>
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<td>115±1</td>
<td>117±2</td>
<td>119±3</td>
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<tr>
<td><strong>LV dP/dt</strong></td>
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<td>(mm Hg/sec)</td>
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<tr>
<td></td>
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<td>42±4</td>
<td>37±3*</td>
<td>38±4*</td>
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</tr>
<tr>
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<tr>
<td></td>
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<td>103±2</td>
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</table>

Sham, sham experiments with saline infusions; ANF, atrial natriuretic factor; LV, left ventricular; LV dP/dt, first derivative of LV pressure over time. */?<0.01, 1/>0.05 different from baseline.

mean arterial pressure averaged 96±5 mm Hg, similar to baseline levels (94±4 mm Hg). After ganglionic blockade, neither heart rate (131±6 beats/min), left ventricular pressure (108±6 mm Hg), left ventricular end-diastolic pressure (3.5±0.9 mm Hg), nor left ventricular dP/dt (2,742±171 mm Hg/sec) changed significantly from baseline during human ANF infusion. Renal blood flow velocity fell significantly (/?<0.01) from 46.9±6.5 to 43.1±6.1 cm/sec when mean arterial pressure averaged 92±5 mm Hg, similar to preinfusion levels (93±4 mm Hg).

Human ANF (20 ng/kg-min) for 30 minutes in absence of ganglionic blockade did not alter baseline heart rate (81±4 beats/min), left ventricular pressure (118±5 mm Hg), left ventricular end-diastolic pressure (9.8±1.9 mm Hg), or left ventricular dP/dt (3,459±198 mm Hg/sec). Renal blood flow velocity fell (/?<0.01) from 43.4±5.1 to 38.6±4.3 cm/sec when mean arterial pressure averaged 96±6 mm Hg, similar to baseline levels (93±5 mm Hg).

Renal Responses

In sham experiments, neither urine volume (0.25±0.03 ml/min) nor sodium excretion (67±7 μeq/min) at 30 minutes after the beginning of saline infusion differed from preinfusion levels (0.23±0.04 ml/min and 60±6 μeq/min, respectively). Ten minutes into the human ANF infusion period, urine volume was not significantly changed from baseline values. By 30 minutes, urine volume was increased (/?<0.01) by 0.35±0.06 ml/min. Ten minutes into the recovery period, urine volume remained elevated (p<0.01) by 0.25±0.11 ml/min but returned to preinfusion levels thereafter.

Sodium excretion increased (p<0.05) by 34±7 from 67±9 μeq/min at 10 minutes after the beginning of human ANF infusion (10 ng/kg-min). At 30 minutes, sodium excretion was elevated (p<0.01) by 0.35±0.06 ml/min. Ten minutes into the recovery period, sodium excretion did not differ from preinfusion levels.

Ten minutes after the beginning of human ANF, urine osmolality did not change from preinfusion levels but decreased (p<0.01) by 390±97 mosm/kg H2O at 30 minutes. Ten minutes into the recovery period, urine osmolality remained decreased (p<0.01) by 390±97 mosm/kg H2O but returned to preinfusion levels after 30 minutes of recovery.

Hormonal Responses

Neither aldosterone nor vasopressin plasma levels changed from their preinfusion baseline values.
(10.1±0.7 ng/ml and 1.12±0.42 pg/ml, respectively) during human ANF infusion or the recovery period.

Discussion

The present study demonstrates that elevations of ANF plasma levels within physiological range exert substantial influences on the kidney. Urine volume and sodium excretion increased with elevated plasma ANF levels and returned to baseline when plasma ANF levels declined. Concomitantly, renal blood flow fell and remained depressed throughout the infusion period. Cardiac filling pressures, aortic pressure, left ventricular contractility, and heart rate did not change from baseline values. Circulating levels of vasopressin and aldosterone were not altered by these elevated plasma levels of ANF.

In the present study, we administered an exogenous synthetic atrial peptide similar to the endogenous peptide of the dog.27 Furthermore, the elevations of plasma levels of ANF were comparable with those achieved through endogenous mechanisms.7 Also, conscious dogs were used to exclude the complicating influences of anesthesia on cardiovascular control in general20 and on the responses to atrial peptides in particular.21 Taken together, these important features of the present study may explain why our conclusions regarding hemodynamic and renal effects of ANF differed from most previous studies.

Under the present experimental conditions, substantial natriuretic and diuretic responses were found in our conscious dogs. At 10 minutes into the infusion period, increases in sodium excretion were already significant despite increases in plasma levels of irANF by only 34±9 pg/ml, half the peak increases found in conscious dogs with volume expansion. Later, urine volume and sodium excretion doubled and increases in plasma irANF levels averaged 61±9 pg/ml, similar to changes elicited with rapid volume expansion in conscious dogs.7 Therefore, natriuretic and diuretic thresholds were reached at physiological plasma levels of ANF. On a speculative basis, if we assume that renal responsiveness to ANF is not altered by volume expansion and is similar in normal and cardiac denervated dogs, 12% of increases in urine flow and 23% of sodium excretion within 30 minutes after volume expansion could be accounted for by increases in plasma ANF levels in normal dogs. In cardiac denervated dogs, changes in ANF levels could explain 23% of urine excretion and 39% of sodium excretion over the same period of time. Given the limitations of such a speculation, the extent to which ANF contributed to renal responses after volume expansion could not be accurately established from the present observations. Nevertheless, our data indicate that increases in plasma ANF levels within physiological range could lead to significant renal effects.

Bie et al16 reported that threefold increases in plasma levels of atrial peptides, which is similar to increases reported in the present study, resulted in modest increases in sodium excretion only after 40–60 minutes of continuous infusion in conscious dogs. Also, significant reductions of right and left atrial pressures occurred before the end of the infusion period. The reason for these delayed renal responses and the fall in cardiac filling pressures is not apparent; a slight difference in the experimental procedure might be the cause. Bie et al16 performed their experiments in dogs standing in a sling, while the present study was conducted in conscious dogs lying on their sides. Although postural-related translocation of blood between peripheral and central locations in quadrupeds is expected to be limited, this factor may conceivably alter the response to atrial peptides. Differences in the vehicle used to administer ANF should also be considered. Of greater significance, sodium excretion in the study of Bie et al16 was less than in the present study under baseline conditions. Baseline sodium balance has been reported to influence the amplitude of renal responses to atrial peptides.28,29 Therefore, a greater baseline sodium excretion, such as in the present study, might explain enhanced diuretic and natriuretic responses.

In a recent study, Zimmerman et al15 examined the effects of human ANF in anesthetized dogs in a dose range consistent with plasma levels after volume expansion. Aside from the obvious differences between conscious and anesthetized dogs, our conclusions are consistent with this study with respect to renal function. In both studies, increases in irANF levels secondary to infusions of human ANF (10 ng/kg-min) resulted in significant diuretic and natriuretic responses. Hemodynamic responses differed; Zimmerman et al15 found decreases in right atrial pressure, whereas renal blood flow remained at preinfusion baseline. In contrast, in conscious animals neither central venous pressure nor left ventricular pressure was reduced, but renal blood flow fell consistently. This reduction of renal blood flow persisted when a dose of 20 ng/kg-min ANF was administered. Experiments performed after ganglionic blockade further indicate that decreases in renal blood flow were not of reflex origin.

Seymour et al30 examined the effects of human ANF (10 pmol/kg-min) in conscious dogs (standing in a sling), which is roughly threefold the amount we administered but failed to report significant diuretic and natriuretic responses despite increases in urine volume by 100% under these conditions. The reason for the low sensitivity of their analysis is not apparent.

Benjamin et al31 failed to detect a specific contribution of elevated plasma levels of ANF on renal function in anesthetized, vagotomized dogs with volume expansion. Therefore, the increases in ANF levels with volume expansion were subnatriuretic. An alternate explanation is that the dramatic increases in vasopressin secondary to sectioning the vagi31 could have masked the effects of elevated atrial peptide levels after volume expansion.
It is not clear why Goetz et al\textsuperscript{1} could not demonstrate renal responses to atrial distension in dogs with cardiac denervation despite significant elevations of plasma irANF levels. They suggested that the effects of ANF on the kidney might require neurohormonal influences that were blocked by cardiac denervation.

Elevated levels of atrial peptides have resulted in inconsistent effects on plasma renin activity and circulating levels of vasopressin and aldosterone, as recently reviewed by Goetz.\textsuperscript{11} Plasma levels of vasopressin and aldosterone did not change from baseline values during ANF infusion in our conscious dogs. In the present study, the close parallel between changes in sodium excretion and ANF plasma levels might reflect a direct effect of ANF on the kidney.

Elevations of plasma ANF within physiological range modestly but consistently reduced renal blood flow velocity. Therefore, diuretic and natriuretic effects of human ANF were not secondary to changes in renal hemodynamics as previously suggested.\textsuperscript{32-34} Renal vasodilation,\textsuperscript{21,32-34} no change in renal blood flow,\textsuperscript{32} and decreases in renal blood flow\textsuperscript{2} have all been reported with atrial peptide administration. In the present study, the decrease in renal blood flow was not of reflex origin because cardiac filling pressures and mean arterial pressure were not reduced during ANF infusions. Furthermore, the decrease in renal blood flow persisted after ganglionic blockade, which is consistent with a direct influence of ANF on renal hemodynamics.

Increases in plasma levels of ANF within physiological range had no significant effect on cardiac filling pressures, mean arterial pressure, or left ventricular contractile state. Also, after autonomic blockade, mean arterial pressure, left ventricular end-diastolic pressure, and left ventricular dP/dt did not change from baseline. In contrast, reductions of mean arterial, central venous, left atrial, and left ventricular end-diastolic pressures have been reported in anesthetized and conscious dogs.\textsuperscript{2,15,16,35,36} Differences in doses and sequences of peptides administered could potentially explain why several of these studies differed from the present study. However, it is not clear why the present findings concerning cardiac filling pressures differed from those of Bie et al.\textsuperscript{16}

In conclusion, elevations of plasma ANF to levels below or similar to those achieved during volume expansion in conscious dogs reached diuretic and natriuretic thresholds. These changes in renal function were independent of alterations of circulating levels of vasopressin and aldosterone and occurred despite reduced renal blood flow. In contrast, cardiac filling pressures, mean arterial pressure, left ventricular contractility, and heart rate were not influenced by these increases in plasma ANF levels. When the present findings are examined in the perspective of earlier studies performed under slightly different experimental conditions, it becomes apparent that it is not yet possible to accurately define and control the necessary conditions that determine the physiological threshold of atrial peptides.

References


**Key Words** • atrial natriuretic factor • renal function • hemodynamics • dog studies
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