Significance of Renal Vasodilation After Administration of Atrial Natriuretic Factor in the Conscious Dog

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SUMMARY The contribution of alterations in renal hemodynamics to the diuretic and natriuretic actions of atrial natriuretic factor (ANF) was studied in chronically instrumented conscious dogs. Injection of ANF-(99-119), 10 μg/kg, had no effect on mean arterial pressure, heart rate, renal blood flow, or calculated renal vascular resistance; however, it increased urine flow rate (86 ± 20%) and sodium (118 ± 24%) and potassium (35 ± 22%) excretion (p < 0.05). In contrast, ANF-(99-122), 10 μg/kg, significantly increased renal blood flow (26 ± 4.5%), reduced renal vascular resistance (24 ± 2.9%) and arterial pressure (5.5 ± 1.9%), and markedly increased urine flow rate (198 ± 34%) and sodium (206 ± 32%) and potassium (104 ± 17%) excretion (p < 0.05), being almost twice as effective in the first 10 minutes as was ANF-(99-119) infusion. During a brief infusion, ANF-(99-122) (10 μg/kg/min for 4 minutes) increased renal blood flow (24 ± 2.7%), heart rate (18 ± 5.7%), urine flow rate (199 ± 25%), and sodium (290 ± 81%) and potassium (104 ± 17%) excretion. Injection of radioactive microspheres (15 or 9 μm) to measure intrarenal distribution of blood flow during the steady state increase in renal blood flow indicated that ANF-(99-122) infusion preferentially increased outer cortical blood flow. Blood flow in the four zones of the kidney cortex (Zone 1, outer, and Zone 4, inner) increased 96 ± 25% (Zone 1), 199 ± 87% (Zone 2), 139 ± 47% (Zone 3), p < 0.05, and 25 ± 28% (Zone 4, p = NS). Infusion of ANF-(99-119) did not lead to a redistribution of renal cortical blood flow as seen with ANF-(99-122). During a 1-hour infusion of ANF-(99-122), renal blood flow increased only transiently whereas glomerular filtration rate, urine flow rate, and sodium and potassium excretion increased 118 ± 15%, 104 ± 6.8%, 144 ± 24%, and 115 ± 26%, respectively. Following α₁-adrenergic receptor blockade, infusion of ANF-(99-122) resulted in renal vasodilation for the duration of the study. Therefore, in conscious dogs, ANF-(99-119) and ANF-(99-122) both enhance renal function while ANF-(99-122) also increases renal blood flow. Although not essential, the ANF-induced renal vasodilation accentuates and hastens the initial diuresis and natriuresis, thereby increasing the total salt and water excretion.

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KEY WORDS • atrial natriuretic factor • renal blood flow • radioactive microspheres • glomerular filtration rate • urine flow rate • sodium and potassium excretion • dogs

Atrial natriuritic factor (ANF) is a family of atrial peptides isolated from rat atria and purified and sequenced by Currie et al.1,2 as well as others.3–4 ANF-(99-119) relaxes intestinal but not vascular smooth muscle in vitro; ANF-(99-122) relaxes both intestinal and vascular smooth muscle.1–5 Recent work from a number of laboratories has indicated that the atrial peptides may prove to be part of a unique biological control mechanism crucial in the regulation of blood volume, and a defect in the synthesis or release of these peptides may be important in the development of disease states.6,7 The atrial peptides were shown to be powerful natriuretic and diuretic hormones when injected into rats8–10 and selectively increase renal blood flow.11,12 In the anesthetized dog, the atrial peptides increase renal blood flow on close arterial injection, reduce arterial pressure when injected intravenously, and with either method of delivery, cause a potent diuresis and natriuresis.12

However, a number of studies have shown that the increase in renal blood flow is only transient,13,14 that inner renal cortical blood flow, which only accounts for a small fraction of total renal blood flow, increases,15 that during a prolonged infusion
of ANF renal blood flow actually falls, and that the natriuretic ANF-(99–119) does not increase renal blood flow. These inconsistencies call into question the overall importance of renal vasodilation to the natriuresis and diuresis following ANF administration. The relationship between changes in renal blood flow and renal function induced by ANF may be due to a number of mechanisms, including 1) renal vasodilation, 2) a change in afferent or efferent arteriolar resistance (or both), 3) a redistribution of intrarenal blood flow. One purpose of the present study was to determine the effects of ANF-(99–122) on renal hemodynamics and function in chronically instrumented conscious dogs.

The absence of vascular actions of ANF-(99–119) provided an ideal method for determining the contribution of changes in renal hemodynamics to the natriuresis and diuresis in response to ANF. Although in vitro studies have uniformly found that ANF-(99–122) relaxes vascular smooth muscle, recent studies including our own have shown that the renal vasodilation following ANF administration was only transient even if the infusion was maintained for 1 hour. Another goal of our study was to determine the possible role and importance of reflex mechanisms in the control of renal blood flow during ANF administration and therefore, indirectly, in the control of renal function. These studies were conducted in conscious dogs to avoid the effects of anesthesia on vascular smooth muscle, on reflex control, and on ANF-induced blood flow distribution.

Materials and Methods

Twenty-four female mongrel dogs were instrumented using sterile surgical techniques under sodium pentobarbital anesthesia. A Doppler ultrasonic flow transducer (Parks Electronics, Beaverton, OR, USA) was placed around the left renal artery, and a Tygon catheter (U.S. Stoneware, Akron, OH, USA) was positioned in the abdominal aorta through a midline laparotomy. The animals were allowed 10 days to 2 weeks to recover before experiments were begun. After the initial experiments, eight of the dogs underwent a left-sided thoracotomy, again using pentobarbital anesthesia and sterile surgical techniques to implant Tygon catheters in the left atrial appendage for the injection of 15-μm radioactive microspheres (3M, Minneapolis, MN, USA). An additional five female dogs were instrumented with Tygon catheters in the ascending aorta and left atrial appendage for the injection of 9-μm microspheres (3M). Renal function was not measured in these dogs. These dogs were allowed 10 days to 2 weeks to recover. During the training period, the dogs became accustomed to the placement of a urinary bladder catheter (Foley, 12F) for urine collection.

Arterial pressure was recorded using the implanted catheter attached to a Statham P23Db strain gauge transducer (Hato Rey, Puerto Rico). Renal blood flow was measured using an ultrasonic flowmeter (Model 806A, Parks Electronics) and the implanted Doppler flow transducer. Phasic arterial pressure and renal blood flow were recorded on magnetic tape (Model 3700B, Bell and Howell, Saddle Brook, NJ, USA) and played back on a direct writing oscillograph (Model 2800S, Gould-Brush, Saddle Brook, NJ, USA). Mean flow and pressure were derived using 2-Hz filters. Heart rate was calculated using a cardiotachometer (Model 80574, Beckman, Los Angeles, CA, USA) from the pressure-pulse interval. All of these techniques have been used previously.

From each urine sample, urine volume was measured and the concentration of urine and plasma sodium and potassium assayed using a flame photometer (Model 343, Instrumentation Laboratories, Chicago, IL, USA). Inulin was administered as a loading dose (3 ml/kg), followed by an infusion (2 ml/kg/hr) that lasted for the entire experiment. ANF-(99–122) infusion was begun 1 hour after the inulin loading dose. Plasma and urine samples were taken simultaneously for the analysis of inulin (American Critical Care, Chicago, IL, USA) concentration using a spectrophotometric assay. Hematocrit was also measured in each blood sample. Urine flow rate was calculated based on the volume of urine collected and the collection interval.

Intrarenal blood flow distribution was measured using the radioactive microsphere technique in eight of the dogs. Radioactive microspheres (15 μm) labeled with cerium-141, strontium-85, and scandium-46 were used. Due to difficulties inherent in measuring intrarenal blood flow with microspheres 9 ± 1 μm microspheres (3M) were also used to study renal blood flow in five additional dogs. The order of the isotopes was randomized. A reference arterial blood sample was taken at a fixed rate (10 ml/min) from a femoral arterial catheter, implanted on the day of the experiment using local anesthesia, starting just before the microsphere injection and continuing for 90 seconds. The animal was killed using an overdose of sodium pentobarbital. ANF-(99–122) or ANF-(99–119) was infused at 10 μg/kg/min for 4 minutes to achieve steady state changes in renal blood flow to allow use of radioactive microspheres.

The right and left kidneys were removed, weighed, and then sectioned into four cortical zones. Four samples were taken from each zone of the kidney and averaged in each animal. The number of counts in each sample was quantitated using a gamma spectrophotometer (Model 8500, Searle, Chicago, IL, USA) adjusted to separate the isotopes used. Microsphere blood flow was calculated using standard techniques as previously described. Comparisons were made between the right and left kidney (i.e., without and with an implanted flow transducer, respectively) to ensure that placement of the flow transducer did not alter left renal hemodynamics. Polysorbate 80 (Tween 80) was injected into
each dog 90 minutes before ANF infusion.27 All ANF injections or infusions were given intravenously. In five of the dogs plasma ANF levels were measured before and 3, 5, 10, 15, and 20 minutes after the bolus injection of ANF-(99-122) (10 μg/kg). Blood samples were taken in EDTA and aprotinin and immediately centrifuged in the cold. Plasma samples were stored at -80 °C. The antibody to ANF-(99-126) (Peninsula Laboratories, Los Angeles, CA, USA) was used following extraction of the plasma using a C-18 column. The percent recovery was calculated for each sample by adding 2000 cpm ANF-(99-126) to the original sample before extraction. ANF-(99-122) cross-reacts 100% with the Peninsula antibody for ANF-(99-126). Plasma ANF-(99-122) concentration was measured by standard radioimmunoassay techniques.

**Effects of ANF-(99-122) and ANF-(99-119) Injection on Renal Hemodynamics and Function**

ANF-(99-119) and ANF-(99-122) (10 μg/kg) were injected intravenously in each dog a minimum of 4 days apart. Plasma ANF-(99-122) was measured in five dogs.

**Effects of ANF Infusion (10 μg/kg/min) on Renal Hemodynamics and Function and Intrarenal Blood Flow Distribution**

In eight of the dogs, ANF-(99-122) was infused at a rate of 10 μg/kg/min for 4 minutes. Renal blood flow was measured continuously, using the previously implanted Doppler flow transducer, along with arterial pressure, heart rate, and renal function. Radioactive microspheres were injected into the left atrium prior to infusion of ANF-(99-122) and 3 minutes into the infusion, when steady state increases in renal blood flow were measured using the Doppler flowmeter. A third microsphere injection was made 10 minutes after cessation of the ANF-(99-122) infusion, when maximal increases in urine flow rate were achieved. In three separate male dogs, instrumented with left atrial and thoracic aortic Tygon catheters only, ANF-(99-119) was infused at 10 μg/kg/min for 4 minutes and radioactive microspheres injected as described for ANF-(99-122) to determine the role of intrarenal blood redistribution in the natriuresis and diuresis. Renal function was not measured in these three dogs.

In another five dogs, ANF-(99-122) was infused briefly and 9-μm microspheres used to measure intrarenal blood flow. Renal function and blood flow were not measured in these dogs. These small microspheres were used to avoid overestimation of renal cortical flow as seen with 15-μm spheres.

**Results**

**Effects of ANF-(99-119) and ANF-(99-122) (10 μg/kg) on Renal Hemodynamics and Function in Conscious Dogs**

Whereas ANF-(99-119) had no significant effect on mean arterial pressure, renal blood flow (6.3 ± 4.0%), calculated renal vascular resistance, or heart rate, ANF-(99-122) caused a marked initial increase in renal blood flow and fall in renal vascular resistance (Table 1). Renal blood flow, following injection of ANF-(99-122) increased 26 ± 4.5% from 296 ± 19 ml/min and renal vascular resistance fell 24 ± 2.9% from 0.35 ± 0.02 mm Hg/ml/min (p < 0.01).

In spite of the lack of renal hemodynamic effects, ANF-(99-119) increased urine flow rate, and sodium and potassium excretion. Hematocrit did not change from 39 ± 1.8%. Plasma sodium did not change from 144 ± 6.3 mEq/L, and plasma potassium did not change from 4.15 ± 0.16 mEq/L.

On the other hand, ANF-(99-122) increased renal blood flow, urine flow rate, and sodium and potas-
In the five dogs studied, plasma immunoreactive ANF-(99-126) level increased from 156 ± 41 to 43,264 ± 12,781, 10,166 ± 2437, 3316 ± 545, 1255 ± 211, and 799 ± 69 pg/ml (p < 0.05, compared with control) at 3, 5, 10, 15, and 20 minutes after injection, respectively.

Effects of ANF Infusion (10 μg/kg/min) on Renal Hemodynamics and Function and the Intrarenal Distribution of Blood Flow

The time course of changes in renal blood flow, arterial pressure, heart rate, urine flow rate, and sodium and potassium excretion for the first 10 minutes following ANF-(99-122) infusion is similar to that shown for injection in Table 1. Briefly, ANF-(99-122) infusion increased renal blood flow by 24 ± 2.7% and reduced renal vascular resistance by 24 ± 1.4%. Heart rate increased (18 ± 5.7%), and mean arterial pressure fell (5.1 ± 0.9%). There was a marked increase in urine flow rate (199 ± 25%), sodium excretion (290 ± 82%), and potassium excretion (104 ± 17%). Hematocrit did not change from 36 ± 2.0%. Plasma sodium and potassium did not change from 144 ± 1.0 and 4.16 ± 0.13 mEq/L, respectively.

Radioactive microspheres were injected prior to ANF-(99-122) infusion, during the steady state effects on blood flow, and 10 minutes after stopping the ANF-(99-122) infusion, at a time when urine flow rate was maximal. These data are presented in Table 2. During the steady state effects of ANF-(99-122), blood flow increased in the outer cortical zones by 26 ± 25% from 3.37 ± 0.42 ml/min/g in the left and by 76 ± 22% from 3.78 ± 0.61 ml/min/g in the right kidney, whereas flow did not change in the inner cortical zone (see Table 2).

In three dogs, infusion of ANF-(99-119) (10 μg/kg/min) had no effect in either the left or right kidney on intrarenal blood flow distribution. For instance, in Zone 1, 2, 3, or 4 of the left kidney, renal blood flow did not change from 3.90 ± 0.71, 3.52 ± 0.35, 2.07 ± 0.17, and 0.85 ± 0.16 ml/min/g, respectively, during the infusion of ANF-(99-119). Intrarenal blood flow distribution did not vary in these dogs 10 minutes after the infusion of ANF-(99-119). In dogs in which 9-μm microspheres were used to measure intrarenal blood flow,
outer cortical blood flow increased (Table 3), as seen with 15-μm microspheres.

**Effects of a 1-Hour Infusion of ANF-(99-122) (5 μg/kg/min) on Renal Blood Flow and Renal Function**

The increase in renal blood flow and fall in renal vascular resistance was only transient and was followed by a reduction in blood flow and increase in renal resistance (Figure 1 and Table 4). Despite the transient renal vasodilation, urine flow rate, GFR, and sodium and potassium excretion remained elevated at 30 minutes (Figure 2) respectively. Hematocrit increased, whereas plasma sodium (145 ± 1.5 mEq/L) and potassium (3.75 ± 1.3 mEq/L) did not change.

**Effects of α1-Adrenergic Receptor Blockade on Renal Function and Blood Flow During ANF-(99-122) Infusion**

In contrast to the transient renal vasodilation, after α1-adrenergic receptor blockade renal blood flow remained elevated for the duration of the ANF-(99-122) infusion. The increase in GFR and urine flow rate developed slowly but increased to the same degree in the presence of α1-adrenergic receptor blockade (see Figure 2) as in the unblocked state.

**Discussion**

ANF-(99-119) and ANF-(99-122) both cause natriuresis and diuresis in the conscious dog, whereas only ANF-(99-122) has a significant, although transient, effect on renal blood flow. Injection of equal doses of ANF-(99-119) and ANF-(99-122) caused increases (86 ± 20 and 198 ± 34%) in urine flow rate initially. While ANF-(99-119) had no significant effect on renal blood flow, ANF-(99-122) increased renal blood flow markedly, but only briefly. This increase in renal blood flow was associated with a reduction in renal vascular resistance and an increase in blood flow to the outer cortical zones of the kidney. In the three outer cortical zones, blood flow increased, whereas there was no significant change in blood flow to the inner cortical zone. In contrast, ANF-(99-119) had no effect on intrarenal blood flow distribution.

In further support of the concept of a blood flow-independent mechanism are the data comparing the changes in renal blood flow and renal function 10 minutes after injection of either ANF-(99-119) or ANF-(99-122). At that time, neither drug caused a significant increase in renal blood flow; nonetheless, urine flow rate and sodium excretion were

### Table 3. Left Renal Blood Flow Distribution During Infusion of ANF-(99-122) as Measured with 9-μm Microspheres

<table>
<thead>
<tr>
<th>Area</th>
<th>Control (ml/min/g)</th>
<th>Steady state (ml/min/g)</th>
<th>10 min (ml/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1 (outer cortex)</td>
<td>3.21 ± 0.34</td>
<td>2.31 ± 0.61*</td>
<td>0.25 ± 0.81</td>
</tr>
<tr>
<td>Zone 2</td>
<td>2.64 ± 0.25</td>
<td>2.01 ± 0.52*</td>
<td>0.32 ± 0.78</td>
</tr>
<tr>
<td>Zone 3</td>
<td>1.71 ± 0.30</td>
<td>1.73 ± 0.59*</td>
<td>0.27 ± 0.19</td>
</tr>
<tr>
<td>Zone 4 (inner cortex)</td>
<td>0.76 ± 0.13</td>
<td>0.36 ± 0.18</td>
<td>0.04 ± 0.21</td>
</tr>
</tbody>
</table>

Values are means ± SEM of five dogs. Values were not statistically different from those measured with 15-μm microspheres in the left kidney in Table 2.

*p < 0.05, compared with control.
Figure 1. Effect of a 60-minute infusion of ANF-(99–122), 5 μg/kg, before (•) and after (▲) α₁-adrenergic receptor blockade in five dogs. The initial renal vasodilation in response to ANF-(99–119) was prolonged following α₁-adrenergic receptor blockade, indicating that the secondary vasoconstriction was most likely reflex. Asterisk indicates significant difference compared with control (p < 0.05). AP = arterial pressure; RBF = renal blood flow; HR = heart rate.

Although there was no significant increase in renal blood flow 10 minutes after the infusion of ANF-(99–122), an increase in outer cortical blood flow was seen using the 15-μm radioactive microspheres. This effect was not observed when small 9-μm microspheres were used and may support the contention that the use of 15-μm microspheres overestimates renal cortical blood flow.²⁵ There was no change in intrarenal blood flow distribution during ANF-(99–119) infusion; thus, there was no systematic error in using microspheres.

Our results with 15-μm microspheres are supported by data with 9-μm spheres; thus, it is unlikely that we overestimated outer cortical blood flow during the initial vasodilation. Radioactive microspheres, as used in our study, do not discriminate between an increase in the number of glomeruli perfused and an increased perfusion of each individual glomerulus. During the initial transient vasodilation the actions of ANF-(99–122) on GFR can be explained by an initial increase in renal blood flow, by an effect on the filtration properties of the glomerulus, and by a possible perfusion of normally unperfused glomeruli in the cortex. Alternatively, an alteration in efferent (constriction) and afferent (vasodilation) arteriolar resistance may occur. However, this occurrence is unlikely during the initial acute renal vasodilation since microsphere-measured blood flow increased and all of the excess blood flow would have to have been filtered. The effects of ANF on renal tubules are more controversial and as yet unsettled;³⁰ a direct tubular action could not be defined by our studies.

Our data are supported by a number of studies in dogs,¹³ ¹⁹–⁴¹ in which the renal vasodilation during ANF infusion or injection is only transient while the natriuresis and diuresis persist. On the other hand, our data with radioactive microspheres are at odds with an early report by Borenstein et al.¹⁵ In that study an extract of atrial tissue increased inner cortical blood flow, as measured using radioactive microspheres or albumin uptake.¹⁵ These studies reported a 29% increase in inner cortical blood flow, the portion of the kidney that has the lowest baseline blood flow. This increase was accompanied by a reduction in mean arterial pressure from 122 ± 3 to 109 ± 4 mm Hg or 126 ± 2 to 107 ± 4 mm Hg during studies using radioactive microspheres or albumin, respectively. McNay and Abe⁴² reported that aortic constriction-induced systemic hypotension caused a shift in renal blood flow to the inner cortex. Perhaps the discrepancy between the study by Borenstein et al.¹⁵ in rats and our study in dogs can be explained by the differences in species used or by the degree of hypotension. One obvious additional difference, however, is that the study by Borenstein et al.¹⁵ was conducted in the anesthetized rat using a crude extract and ours was performed in the conscious dog using a purified peptide. There are species differences, as seen with heart rate regulation; in the rat, for instance, ANF-
Table 4. Effects of a 60-Minute Infusion of ANF-(99–122) (5 μg/kg/min) on Renal Hemodynamics and Function Before and After α1-Adrenergic Receptor Blockade

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unblocked</td>
<td>97 ± 7.7</td>
<td>-15 ± 1.7*</td>
<td>-10 ± 2.4*</td>
<td>-10 ± 3.6*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>88 ± 5.4</td>
<td>-10 ± 0.5*</td>
<td>-7.5 ± 0.9*</td>
<td>-9.0 ± 1.3*</td>
</tr>
<tr>
<td>Mean renal blood flow (ml/min)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unblocked</td>
<td>270 ± 33</td>
<td>33 ± 3.0*</td>
<td>-21 ± 10*</td>
<td>-15 ± 11*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>275 ± 9.6</td>
<td>42 ± 2.7*</td>
<td>37 ± 4.4*</td>
<td>38 ± 6.9*</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/ml/min)</td>
<td>0.39 ± 0.09</td>
<td>-0.11 ± 0.03*</td>
<td>-0.04 ± 0.03</td>
<td>-0.03 ± 0.03</td>
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<tr>
<td></td>
<td>0.32 ± 0.03</td>
<td>-0.11 ± 0.01*</td>
<td>-0.06 ± 0.01*</td>
<td>-0.07 ± 0.01*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unblocked</td>
<td>80 ± 2.8</td>
<td>5.0 ± 6.6</td>
<td>8.0 ± 3.7</td>
<td>3.0 ± 4.0</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>87 ± 4.4</td>
<td>16 ± 4.0*</td>
<td>13 ± 3.9*</td>
<td>12 ± 2.7*</td>
</tr>
<tr>
<td>Urine flow rate (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unblocked</td>
<td>0.53 ± 0.02</td>
<td>0.54 ± 0.09*</td>
<td>0.52 ± 0.03*</td>
<td>0.51 ± 0.09*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>0.65 ± 0.10</td>
<td>0.43 ± 0.14*</td>
<td>0.61 ± 0.17</td>
<td>0.58 ± 0.09*</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unblocked</td>
<td>72 ± 14</td>
<td>82 ± 7.7*</td>
<td>79 ± 13*</td>
<td>57 ± 14*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>41 ± 11</td>
<td>26 ± 8.0*</td>
<td>36 ± 7.4*</td>
<td>44 ± 13*</td>
</tr>
<tr>
<td>Sodium excretion (μEq/min)</td>
<td></td>
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<tr>
<td>Unblocked</td>
<td>106 ± 65</td>
<td>129 ± 19*</td>
<td>152 ± 17*</td>
<td>147 ± 31*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>84 ± 13</td>
<td>73 ± 11*†</td>
<td>123 ± 39*</td>
<td>122 ± 22*</td>
</tr>
<tr>
<td>Potassium excretion (μEq/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unblocked</td>
<td>64 ± 12</td>
<td>74 ± 12*</td>
<td>68 ± 10*</td>
<td>66 ± 5.1*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>73 ± 12</td>
<td>42 ± 15*</td>
<td>45 ± 23*</td>
<td>52 ± 11*</td>
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<tr>
<td>Hematocrit (%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Unblocked</td>
<td>41 ± 0.8</td>
<td>0.5 ± 0.3</td>
<td>1.0 ± 0.4*</td>
<td>1.0 ± 0.4*</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>42 ± 0.9</td>
<td>-0.5 ± 0.3</td>
<td>0.8 ± 0.3*</td>
<td>0.8 ± 0.3*</td>
</tr>
</tbody>
</table>

Values are means ± SEM of five dogs. Plasma potassium = 3.75 ± .13 μEq/L and did not change. Plasma sodium = 145 ± 1.5 μEq/L and did not change. GFR = glomerular filtration rate. *p < 0.05, compared with control; †p < 0.05, compared with unblocked value.

(99–122) causes bradycardia while in the conscious dog ANF-(99–122) causes mild tachycardia. Finally, it could be argued that radioactive microspheres cannot be used to measure intrarenal blood flow; however, McNay and Abe went to great extremes in the dog to prove their validity and the authors most often quoted in this respect, defended the use of 15 ± 3 μm microspheres, especially within the same animal.

In a recent study using a Doppler laser technology, Hansell and Ulfendahl have also reported an increase in outer cortical blood flow (22%) following ANF infusion in the rat. These authors reported an increase in inner cortical blood flow (99%) as well as only a 12 mm Hg fall in arterial pressure. Again, the percent increase in inner cortical blood flow was significant, however, the absolute increase in outer cortical blood flow was much greater. As in our study, ANF-(99–119) had no effect on renal blood flow distribution. It is also interesting and consistent with our data that the majority of binding sites for ANF in the kidney are in the glomeruli, which are located predominantly in the cortex, not in the medulla. The exact site of peptide binding—whether on glomerular membranes or glomerular blood vessels—is not known. Since a number of authors believe that the increase in GFR following ANF injection is due to efferent arteriolar constriction, a significant increase in vasa recta blood flow seems unlikely.

Our data are consistent with the natriuresis and diuresis described by others in the rat and anesthetized or conscious dog. Furthermore, the lack of vascular action of ANF-(99–122) is supported by the observations of Currie et al., who found no relaxation of isolated vascular smooth muscle strips in vitro. Our data also support the conclusions of Wakitani et al., who at least a portion of the diuresis and natriuresis is blood flow-dependent. This conclusion is further substantiated by the initial increase in perfusion, as measured by radioactive microspheres, in the outer cortex of the kidney and by the transient dramatic increase in renal blood flow during a 1-hour infusion. Prolonged infusion of ANF-(99–122) resulted in sustained increases in renal function despite the...
transient nature of the increase in renal blood flow; however, GFR remained elevated, possibly reflecting the role of efferent arteriolar constriction in normalizing renal blood flow and increasing intraglomerular pressure.

α₁-Adrenergic receptor blockade prolonged the renal vascular effects of ANF-(99-122) infusion by eliminating the renal vasoconstriction. Table 4 shows a clear fall in renal vascular resistance after α₁-adrenergic blockade during ANF-(99-122) infusion. Before α-blockade renal resistance did not change, most likely because of the contribution of reflex α-adrenergic constriction and renal autoregulation. After α₁-adrenergic blockade, a prolonged dilator effect of ANF-(99-122) infusion was uncovered, as shown by significant sustained increases in renal blood flow and a fall in renal vascular resistance. This effect resulted in a more slowly developing natriuresis and diuresis that increased to the same degree, indicating that renal vasodilation is unnecessary. Na = urinary sodium excretion; K = urinary potassium excretion.

FIGURE 2. Following α₁-adrenergic blockade (△) in five dogs, ANF-(99-122) infusion resulted in a more slowly developing diuresis and increase in glomerular filtration rate (GFR) than before blockade (●). However, GFR and urine flow rate (UF) increased to the same degree, indicating that renal vasodilation is unnecessary. Na = urinary sodium excretion; K = urinary potassium excretion.

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