Role of Renal Nerves in the Potentiation of Atriopeptin-Induced Natriuresis by Vasopressin

Dale A. Hartuppee, Angelo J. Trapani, John P. Koepeke, and Edward H. Blaine

Previous studies have shown that vasopressin potentiates the natriuresis produced by atriopeptin. In five anesthetized dogs of this study, we found that the potentiation was proportional to the dose of vasopressin infused. Sodium excretion was 46±16 µeq/min with atriopeptin (103–126) (AP24) alone (0.36 nmol/kg • min), was increased to 127±29 by concomitant intravenous infusion of 0.4 mU/kg • min vasopressin, was further increased to 301±75 by 1.2 mU/kg • min vasopressin and leveled off at 328±37 with 3.6 mU/kg • min vasopressin. To investigate whether the potentiation by vasopressin was due to an intrarenal action, we infused three doses of vasopressin (0.04, 0.12, and 0.36 mU/kg • min) into the renal artery during intravenous AP24 infusion in a second group of five dogs. The natriuresis, 128±18 µeq/min, was unaffected by any intrarenal dose of vasopressin. In a third group, we determined whether the potentiation produced by vasopressin was mediated by a mechanism involving the renal nerves by denervating the left kidney before AP24 infusion. In the denervated kidneys, sodium excretion was increased from a control value of 33±5 µeq/min to 303±38 with AP24 alone and was unresponsive to subsequent intravenous vasopressin administration. The exaggerated natriuresis with AP24 alone was of the same magnitude as that produced by AP24 plus the highest doses of intravenous vasopressin in the innervated kidneys of the first group. From these results we conclude that the potentiation produced by vasopressin is mediated by a mechanism involving the renal nerves and probably results from the known effect of vasopressin to inhibit renal nerve activity. (Circulation Research 1989;64:370–375)

The mechanism by which atriopeptin (AP) induces increased urinary sodium excretion is poorly understood. We have been impressed by the variability of the natriuretic response of AP in dogs, rats, and monkeys and how alterations in volume status or renal perfusion pressure can markedly affect the natriuretic response.1,2 In a series of experiments conducted in rats3 and later in dogs,4 we observed that arginine vasopressin had a dramatic effect on the natriuresis induced by systemic AP infusion. We also studied the effects of the nonpressor analogue of arginine vasopressin, dDAVP, and observed no augmentation of the natriuretic response. These observations, along with our previous findings, led us to hypothesize that an intrarenal hemodynamic change mediated directly by volume expansion or intravenous pressor infusion resulted in the augmented natriuretic response. In the present study, we tested this hypothesis by comparing systemic to intrarenal artery infusion of arginine vasopressin to compare the route of administration on the potentiation of the AP-induced natriuretic response. If arginine vasopressin potentiated AP-induced natriuresis by a local intrarenal hemodynamic change, then intrarenal artery arginine vasopressin infusion should be equal to or perhaps more effective than intravenous arginine vasopressin.

These studies show that intrarenal administration of AVP does not potentiate AP-induced natriuresis and points to a systemic or perhaps central nervous system action of arginine vasopressin to explain the augmented natriuresis.

Another mechanism by which vasopressin might potentiate AP-induced natriuresis is through its modulation of renal nerve activity. Undesser et al5 reported that vasopressin causes significant inhibition of renal sympathetic nerve activity prior to any detectable increase in arterial pressure. Subsequent studies indicated that this action of vasopressin could be prevented by administration of a V1 receptor antagonist.6 Because stimulation of the renal...
nerves has been shown to decrease renal sodium excretion,7 we hypothesized that the potentiation of AP-induced natriuresis by vasopressin was mediated by the suppression of renal nerve activity. According to this hypothesis, the antinatriuretic effect of renal sympathetic nerve activity blunts the natriuresis caused by AP and vasopressin, by inhibiting renal nerve activity, permits a larger AP-induced natriuresis. In the present study, this hypothesis was tested by denervation of the left kidney before intravenous AP24 infusion. The finding that denervation was equieffective with arginine vasopressin to potentiate the natriuresis supports the idea that renal sympathetic nerve activity is a major determinant of the natriuretic action of AP.

**Materials and Methods**

Conditioned dogs of either sex weighing 20–25 kg were anesthetized with sodium pentobarbital (30 mg/kg) and the plane of anesthesia maintained with supplemental doses as necessary. A femoral artery, both femoral veins, and a brachial vein were cannulated. Mean systemic arterial blood pressure was recorded from the arterial cannula, and the venous cannulas were used for infusions. The ureters of both kidneys were cannulated via a small incision and the incision subsequently closed with skin clips. The left kidney was isolated via a retroperitoneal flank incision, and an electromagnetic flow probe (Carolina Medical Electronic, King, South Carolina) was placed around the left renal artery. To measure glomerular filtration, a priming dose of polyfructosan (Inutest, Laevosan-Gesellschaft, Linz, Austria) was administered (0.5 ml/kg of a 10% solution), and an infusion into the brachial or femoral vein was begun at 1 ml/min in a dose calculated to give a steady plasma level of 0.25 mg/ml. Forty-five minutes were allowed for the plasma polyfructosan concentration to reach a constant level.

The dogs were divided into three groups, the intravenous, intrarenal, and denervated groups, which received both AP24 and vasopressin. A fourth group received vasopressin only. After an equilibration period in the intravenous group, isotonic saline infusions (0.5 ml/min) were begun into both femoral veins. Urine was collected for 15 minutes, and a blood sample was obtained at the midpoint of this control clearance measurement. One of the femoral vein saline infusions was replaced with an infusion of AP24 (atriopeptin numbered per prohormone sequence, 103–126) at 0.36 nmol/kg·min (0.5 ml/min), and a second urine collection was begun 5 minutes after the infusion was started. While the AP24 infusion continued, the second femoral vein saline infusion was replaced with an infusion of arginine vasopressin (Sigma Chemical Co, St. Louis, Missouri) at 0.4 mU/kg·min (0.5 ml/min). A third urine collection was begun 5 minutes after the vasopressin infusion was started. The vasopressin infusion was increased to 1.2 mU/kg·min (0.5 ml/min), and 5 minutes later, another urine sample was collected. Finally, the vasopressin infusion was increased to 3.6 mU/kg·min (0.5 ml/min), and a final collection was performed.

The protocol for the intrarenal group was the same as the intravenous group except that before the flow probe was put on the renal artery, a 23-gauge needle was placed in the renal artery for vasopressin administration, and the patency of the needle was maintained by an isotonic saline infusion at 0.5 ml/min. After the equilibration period, only one saline infusion was given into a femoral vein while the saline infusion into the left renal artery was continued. Subsequent vasopressin infusions were given into the left renal artery rather than a femoral vein at one tenth the dose of the intravenous infusions (i.e., 0.04, 0.12, and 0.36 mU/kg·min).

In the denervated group, the protocol was the same as that described for the intravenous group except that the left kidney was denervated before the flow probe was placed on the renal artery. The contralateral, right kidney was innervated for comparison. Acute denervation was accomplished by removal of all connective tissue attached to the kidney and renal pedicle and cutting of all visible nerves leading to the kidney. The adventitia surrounding a 0.25-inch length of the renal artery was removed, and a 10% solution of phenol in absolute ethanol was painted on the renal artery.

The fourth group (vasopressin) was studied to ascertain the effect of intravenous vasopressin administration without AP24 infusion. The protocol for this group was the same as that for the intravenous group except that isotonic saline was infused instead of AP24.

Mean systemic arterial blood pressure and renal blood flow were recorded continuously throughout each experiment, and mean values for each parameter were calculated for each clearance measurement by averaging each value at 1-minute intervals over the entire 15 minutes of the measurement period. Sodium excretion was calculated by multiplying urine flow and urine sodium concentration. Glomerular filtration was calculated as the clearance of polyfructosan (urine concentration/plasma concentration × urine flow rate). Sodium concentration in urine and plasma was measured with a flame photometer (Instrumentation Laboratories, Lexington, Massachusetts), and polyfructosan was assayed by the method of Fuhr et al.8

Statistical comparisons of mean arterial pressure, renal blood flow, glomerular filtration, and sodium excretion over time within the same group were made with analysis of variance for repeated measures. A one-way analysis of variance was used to test for significant differences between groups at each time point in the experiment. A paired t test was used to compare values of glomerular filtration and sodium excretion between the two kidneys of the same group.
Results

In the intravenous group, intravenous infusion of AP24 alone produced a natriuresis that was potentiated by subsequent intravenous vasopressin infusion (Figure 1). The magnitude of the potentiation was dose-dependent for the first two doses of vasopressin (0.4 and 1/2 mU/kg·min) but was not increased further by the highest dose (3.6 mU/kg·min) (Figure 1).

In the intrarenal group, on the other hand, intrarenal administration of vasopressin did not affect the AP-induced natriuresis (Figure 1).

In the denervated group, infusion of AP24 alone caused an exaggerated natriuresis in the denervated kidneys that was unresponsive to intravenous vasopressin infusion (Figure 1). The exaggerated natriuresis to AP24 alone was significantly greater (p<0.05) than the AP-induced natriuresis in the intravenous or intrarenal groups with innervated kidneys. The magnitude of the AP-induced natriuresis in the denervated kidneys was also greater than the AP-induced natriuresis in the contralateral innervated kidneys of the same animals (p<0.06).

Furthermore, the magnitude of the natriuresis to AP24 alone in the denervated group was the same as the potentiated natriuresis caused by concomitant administration of the highest doses of vasopressin and AP24 in the innervated kidneys of the intravenous group (Figure 1).

Mean arterial blood pressure in the intravenous group was decreased by AP24 alone and was increased toward control levels by subsequent vasopressin infusion (Table 1). AP24 alone decreased mean arterial blood pressure in the intrarenal group, but subsequent intrarenal infusion of vasopressin did not affect the lowered blood pressure (Table 2). In the denervated group, there were no significant changes in mean arterial blood pressure during the experiment (Table 3).

AP24 infusion alone did not alter renal blood flow in any group (Tables 1–3). Subsequent intravenous infusion of vasopressin in the intravenous and denervated groups increased renal blood flow (Tables 1 and 3), while intrarenal vasopressin infusion did not alter renal blood flow in the infused kidneys (Table 2).

Glomerular filtration was decreased by AP24 alone in the intravenous and denervated groups but not in the intrarenal group (Tables 1–3). Subsequent intravenous vasopressin infusion increased glomerular filtration to control levels in the denervated group and above control levels in the intravenous group (Tables 1 and 3). In the intrarenal group, there were no significant changes in glomerular filtration (Table 2).

In the vasopressin group, the same intravenous doses of vasopressin were infused without concomitant AP24 infusion. Mean blood pressure, renal blood flow, and glomerular filtration were not altered by the vasopressin infusions while sodium excretion was increased slightly by the two highest doses (Table 4).

Discussion

It has been shown previously that concomitant intravenous administration of vasopressin and AP in both the dog and rat greatly potentiates the natriuresis produced by AP. The current study confirms this observation in the dog and demonstrates a correlation between the magnitude of the natriuresis and the dose of vasopressin infused.

In a previous study in anesthetized rats, an intravenous dose of vasopressin that had no effect on arterial blood pressure caused potentiation of the AP-induced natriuresis, while intravenous administration of dDAVP, a nonpressor analogue of arginine vasopressin with antiuretic actions that stimulates the V2 receptor, did not. If atrial natriuretic peptide had a direct action within the kidney to potentiate AP-induced natriuresis, a lower dose of vasopressin should be effective. In the current study, intrarenal infusion of vasopressin during AP24 administration did not potentiate the AP-induced natriuresis. These data indicate that vasopressin does not act through a direct intrarenal action.

The lack of effect of intrarenal vasopressin administration cannot be attributed to subthreshold doses since the highest intrarenal dose (0.36 mU/kg·min) was similar to the lowest intravenous dose (0.40...
sympathetic nerve activity on intrarenal hemodynamics or on tubular sodium reabsorption to cause antinatriuresis. Subsequent systemic administration of vasopressin enhances the function of baroreflexes to produce an inhibition of renal nerve activity, allowing a larger natriuretic response to AP24. Renal denervation acts in the same manner as vasopressin by eliminating neural influences on renal hemodynamics or tubular sodium reabsorption to unmask a greater response to AP24.

Studies in conscious rats have found that renal denervation does not affect the AP-induced natriuresis,9,14 These results are not consistent with the results of this study in which renal denervation caused an exaggerated natriuresis to AP24, and the inconsistency may reflect species differences and/or the difference between anesthetized and conscious animals. It is noteworthy that the ability of vasopressin to enhance cardiovascular reflex inhibition of sympathetic nerve activity has been demonstrated in dogs9,11,12 and rabbits5,6,15,16 but not in rats.15

Inhibition of renal sympathetic nerve activity by vasopressin or denervation could augment the AP-induced natriuresis by acting through changes in glomerular filtration, renal blood flow, or intrarenal distribution renal blood flow, or in tubular sodium reabsorption. The augmentation does not appear to be related to changes in renal blood flow or glomerular filtration since the intravenous and denervated groups have very different natriuretic responses to AP24 and to subsequent administration vasopressin administration but exhibit similar changes in renal blood flow and glomerular filtration. In both groups, there was no change in renal blood flow with AP24 alone while concomitant vasopressin administration significantly increased renal blood flow. Glomerular filtration was slightly decreased by AP24 alone in both groups and then was returned to or above control levels by concomitant intravenous vasopressin administration. Thus, the augmentation of the AP-induced natriuresis by vasopressin or renal denervation does not appear

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**Table 1. Renal Hemodynamic Parameters During Intravenous Infusions of Vasopressin and AP24 in the Dog (n=5)**

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>132±7</td>
<td>161±25</td>
<td>42.9±1.9</td>
</tr>
<tr>
<td>AP24</td>
<td>120±7*</td>
<td>167±16</td>
<td>36.7±2.8*</td>
</tr>
<tr>
<td>AP24 and vasopressin (0.4 mU/kg · min)</td>
<td>123±7*</td>
<td>185±20</td>
<td>58.3±2.4*†</td>
</tr>
<tr>
<td>AP24 and vasopressin (1.2 mU/kg · min)</td>
<td>128±5†</td>
<td>196±27*</td>
<td>53.3±4.8†</td>
</tr>
<tr>
<td>AP24 and vasopressin (3.6 mU/kg · min)</td>
<td>128±4†</td>
<td>203±28†</td>
<td>47.2±2.8††</td>
</tr>
</tbody>
</table>

AP24, atriopeptin (103–126); MAP, mean systemic arterial blood pressure; RBF, renal blood flow; GFR, glomerular filtration rate. Values are mean±SEM. AP24 was infused intravenously at 0.36 nmol/kg · min.

* p<0.05 vs. control.
† p<0.05 vs. AP24.
‡ p<0.05 vs. AP24 and vasopressin at 0.4 and 1.2 mU/kg · min.

mU/kg · min), which potentiated the AP-induced natriuresis.

A direct effect of intravenously administered vasopressin on sodium excretion was ruled out in the group in which vasopressin was administered without concomitant AP24 administration. In these animals, sodium excretion was increased modestly by the two highest doses of vasopressin. The magnitude of the increase in sodium excretion was minimal in comparison to that which occurred when AP24 was administered concomitantly.

Renal denervation before AP24 infusion unmasked an exaggerated natriuretic response to AP24 that was unresponsive to subsequent intravenous vasopressin administration. The magnitude of this enhanced natriuresis was indistinguishable from the natriuresis produced by the highest doses of intravenous vasopressin and AP24 in innervated kidneys (intravenous group). These results support the hypothesis that the potentiation caused by vasopressin is mediated by suppression of renal nerve activity. Several reports have demonstrated that increased activity of the renal nerves promotes sodium retention.7–10 Studies in conscious rabbits by Undesser et al12 showed that vasopressin sensitized the arterial baroreflex to produce decreases in renal sympathetic nerve activity that were greater than could be accounted for by the increase in arterial pressure. Other studies in the dog show a similar interaction between vasopressin and cardiovascular reflexes.11,13 Furthermore, this interaction of vasopressin with cardiovascular reflexes to inhibit renal sympathetic nerve activity was prevented by administration of V1 receptor antagonist.6 Thus, this action of vasopressin to suppress renal nerve activity before detectable increases in arterial pressure could explain the present observations.

In relation to this study, the natriuretic response to AP24 may be blunted by the effects of renal sympathetic nerve activity on intrarenal hemodynamics or on tubular sodium reabsorption to cause antinatriuresis. Subsequent systemic administration of vasopressin enhances the function of baroreflexes to produce an inhibition of renal nerve activity, allowing a larger natriuretic response to AP24. Renal denervation acts in the same manner as vasopressin by eliminating neural influences on renal hemodynamics or tubular sodium reabsorption to unmask a greater response to AP24.

Studies in conscious rats have found that renal denervation does not affect the AP-induced natriuresis,9,14 These results are not consistent with the results of this study in which renal denervation caused an exaggerated natriuresis to AP24, and the inconsistency may reflect species differences and/or the difference between anesthetized and conscious animals. It is noteworthy that the ability of vasopressin to enhance cardiovascular reflex inhibition of sympathetic nerve activity has been demonstrated in dogs9,11,12 and rabbits5,6,15,16 but not in rats.15

Inhibition of renal sympathetic nerve activity by vasopressin or denervation could augment the AP-induced natriuresis by acting through changes in glomerular filtration, renal blood flow, or intrarenal distribution renal blood flow, or in tubular sodium reabsorption. The augmentation does not appear to be related to changes in renal blood flow or glomerular filtration since the intravenous and denervated groups have very different natriuretic responses to AP24 and to subsequent administration vasopressin administration but exhibit similar changes in renal blood flow and glomerular filtration. In both groups, there was no change in renal blood flow with AP24 alone while concomitant vasopressin administration significantly increased renal blood flow. Glomerular filtration was slightly decreased by AP24 alone in both groups and then was returned to or above control levels by concomitant intravenous vasopressin administration. Thus, the augmentation of the AP-induced natriuresis by vasopressin or renal denervation does not appear

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**Table 2. Renal Hemodynamic Parameters During Intrarenal Infusion of Vasopressin and Intravenous Infusion of AP24 in the Dog (n=5)**

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>135±5</td>
<td>217±27</td>
<td>44.8±5.6</td>
</tr>
<tr>
<td>AP24</td>
<td>121±4*</td>
<td>204±21</td>
<td>47.7±11.5</td>
</tr>
<tr>
<td>AP24 and vasopressin (0.04 mU/kg · min)</td>
<td>122±4*</td>
<td>214±18</td>
<td>35.6±4.0</td>
</tr>
<tr>
<td>AP24 and vasopressin (0.12 mU/kg · min)</td>
<td>121±3*</td>
<td>216±17</td>
<td>43.0±6.5</td>
</tr>
<tr>
<td>AP24 and vasopressin (0.36 mU/kg · min)</td>
<td>119±3*</td>
<td>210±17</td>
<td>38.2±5.1</td>
</tr>
</tbody>
</table>

AP24, atriopeptin (103–126); MAP, mean systemic arterial blood pressure; RBF, renal blood flow; GFR, glomerular filtration rate. Values are mean±SEM. AP24 was infused intravenously at 0.36 nmol/kg · min.

* p<0.05 vs. control.
to act through changes in renal blood flow or glomerular filtration. The renal nerves alter renal blood flow distribution or affect tubular sodium reabsorption. The current study cannot distinguish between these two possible mechanisms.

The results of our experiment show that renal denervation augments the natriuresis produced by AP24 in the dog, suggesting that enhanced renal nerve activity may effectively blunt AP-induced natriuresis. The ability of renal nerve activity to blunt AP-induced natriuresis might explain the decreased natriuretic response to APs in certain disease states such as congestive heart failure, cirrhosis and nephrotic syndrome.9 18 These disease states are associated with a high level of sympathetic nerve activity9 17 and the resulting increased renal component might blunt the "normal" natriuretic response to AP. Consistent with this possibility, Koepke et al found that renal denervation restored the ability of the kidney to respond to AP in cirrhotic10 and nephrotic rats.9

In summary, we found that intravenous vasopressin administration augments AP-induced natriuresis in a dose-dependent manner. Intrarenal administration of vasopressin does not produce this effect, eliminating an intrarenal mechanism of action for vasopressin. Renal denervation before AP24 administration unmasks an exaggerated natriuresis of the same magnitude as that caused by vasopressin in the innervated kidney but which is unresponsive to subsequent intravenous vasopressin administration. Thus, the effect of vasopressin appears to be mediated via the renal nerves and may result from the action of vasopressin to inhibit renal sympathetic nerve activity.

Acknowledgments

We thank Dr. Vernon S. Bishop for suggesting the possible mechanism of vasopressin action. We also thank Dr. Jeanne Sebaugh for her help in the statistical analysis of the data. Lesley Graczak provided excellent technical assistance and Irene Ulsaker provided skillful secretarial help.

References


TABLE 3. Renal Hemodynamic Parameters in Denervated Kidneys During Intravenous Infusions of Vasopressin and AP24 in the Dog (n=5)

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>150±11</td>
<td>194±22</td>
<td>44.1±4.4</td>
</tr>
<tr>
<td>AP24</td>
<td>142±10</td>
<td>210±32</td>
<td>35.3±5.3</td>
</tr>
<tr>
<td>AP24 and vasopressin</td>
<td>146±9</td>
<td>218±36*</td>
<td>49.6±5.4†</td>
</tr>
<tr>
<td>AP24 and vasopressin (0.4 mU/kg·min)</td>
<td>145±8</td>
<td>220±37*</td>
<td>48.5±2.6†</td>
</tr>
<tr>
<td>AP24 and vasopressin (1.2 mU/kg·min)</td>
<td>144±8</td>
<td>216±33*</td>
<td>47.8±3.6†</td>
</tr>
<tr>
<td>AP24 and vasopressin (3.6 mU/kg·min)</td>
<td>144±8</td>
<td>216±33*</td>
<td>47.8±3.6†</td>
</tr>
</tbody>
</table>

AP24, atriopeptin (103-126); MAP, mean systemic arterial blood pressure; RBF, renal blood flow; GFR, glomerular filtration rate. Values are mean±SEM. AP24 was infused intravenously at 0.36 nmol/kg·min.

* p<0.05 vs. control.
† p<0.05 vs. AP24.
‡ p<0.05 vs. control-2.

TABLE 4. Renal Hemodynamic Parameters During Intravenous Infusion of Vasopressin Alone in the Dog (n=5)

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>UnV (μEq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control-1</td>
<td>143±4</td>
<td>224±59</td>
<td>43.2±6.8</td>
<td>26.7±8.6</td>
</tr>
<tr>
<td>Control-2</td>
<td>146±4</td>
<td>228±59</td>
<td>42.9±6.7</td>
<td>29.2±8.8</td>
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<tr>
<td>Vasopressin</td>
<td>0.4 mU/kg·min</td>
<td>146±6</td>
<td>232±61</td>
<td>49.6±4.0</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1.2 mU/kg·min</td>
<td>148±6*</td>
<td>236±60</td>
<td>47.6±9.2</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>3.6 mU/kg·min</td>
<td>144±4</td>
<td>241±56</td>
<td>45.4±13.8*</td>
</tr>
</tbody>
</table>

AP24, atriopeptin (103-126); MAP, mean systemic arterial blood pressure; RBF, renal blood flow; GFR, glomerular filtration rate; UnV, sodium excretion. Values are mean±SEM.

* p<0.05 vs. control-1.
† p<0.05 vs. control-2.


**KEY WORDS** • atrial natriuretic peptide • renal denervation • sodium excretion • renal function • dogs
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Circ Res. 1989;64:370-375
doi: 10.1161/01.RES.64.2.370

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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