Norepinephrine kinetics in dogs with experimentally induced renal vascular hypertension

Chollada Buranakarl, DVM, PhD; Chutamas Benjanirut, DVM; Somchai Pondeenana, MS; Kenneth C. Bovée, DVM, MMEdSc

Objective—To determine norepinephrine (NE) kinetics in dogs with experimentally induced renal vascular hypertension.

Animals—4 mixed-breed dogs.

Procedure—The study comprised a control and hypertensive period. The hypertensive period followed induction of renal vascular hypertension achieved by surgical placement of clips on both renal arteries to reduce diameter by approximately 80%. Arterial blood pressure, renal clearance, and NE kinetics were measured during each period while dogs were receiving a low-sodium diet. Measurements of NE kinetics and renal clearance during the hypertensive period were made 5 days after induction of hypertension.

Results—Five days after induction of hypertension, arterial blood pressure increased by 15 to 20 mm Hg. Mean (± SEM) plasma NE concentration and NE spillover rate increased significantly from 151.5 ± 14.1 pg/ml and 8.03 ± 0.62 ng/kg/min, respectively, during the control period to 631.4 ± 30.5 pg/ml and 54.0 ± 5.2 ng/kg/min, respectively, during the hypertensive period. Norepinephrine clearance rate also increased (54.0 ± 2.4 vs 86.0 ± 9.3 ml/kg/min). Positive associations between mean arterial pressure (MAP) and NE concentration and spillover rate were detected. However, MAP and NE clearance rate were not associated.

Conclusions and Clinical Relevance—Increased blood pressure during the hypertensive period was likely attributable to increased NE spillover rate, which resulted in a significant increase in plasma NE concentration. Analysis of these results suggests that central sympathetic outflow was increased and may be responsible for the pathogenesis of high blood pressure during the acute phase of renal vascular hypertension in dogs. (Am J Vet Res 2000;61:1534–1541)

Renal vascular hypertension is a rare syndrome and has not been reported clinically in dogs. This may be because of inadequate methods for measuring hypertension in dogs, the sudden reversal of hypertension, or rapid progression to malignant hypertension in dogs, the sudden reversal of hypertension. It is not clear from results of other studies whether blockade of the renin-angiotensin system or the sympathetic nervous system would be an effective treatment for this form of hypertension in dogs. Renal vascular hypertension can be experimentally induced in dogs, as first documented in 1934 by Goldblatt et al.1 Various methods of renal vascular constriction have been used to study the pathogenesis of this type of hypertension. The 2 kidney, 1 clip [2K1C] model of hypertension is defined as the constriction or clipping of 1 renal artery while the contralateral renal artery is left intact. Another model that can result in high blood pressure is referred to as the 1 kidney, 1 clip (1K1C) model in which 1 renal artery is clipped, and the contralateral kidney is removed. A third model in which both renal arteries are clipped is referred to as the 2 kidney, 2 clip (2K2C) model. Controversy exists regarding whether the methods used in each of these models induce hypertension as a result of the same or differing mechanisms. Although renal vascular hypertension can be induced in many species, pathogenesis may also differ among species.2 For example, in dogs, the response to renal artery stenosis differs from that in rats, rabbits, and humans.2

The importance of the renin-angiotensin system in the development and maintenance of renal vascular hypertension has long been recognized.3 In fact, renal vascular hypertension, especially that induced by use of the 2K1C model, has been referred to as renin-dependent hypertension.4,5 Compared with the prominent role of the renin-angiotensin system in induction of hypertension by use of the 2K1C model, the pathogenesis of hypertension induced by use of the 2K2C model remains unclear. In another study that evaluated dogs with renal vascular hypertension induced by use of this latter model, blood pressure was not correlated with increased activity of the renin-angiotensin system.6 Results of a number of studies indicate that blockade of the renin-angiotensin system does not normalize blood pressure in dogs with experimentally induced, or in humans with naturally developing, renal vascular hypertension.7,8 These findings suggest that other vasoconstrictor systems may participate in the development and...
Increased activity of the sympathetic nervous system has been suspected as an agent responsible for renal hypertension.\(^7\) Zimmerman et al\(^6\) reported that guanethidine decreased blood pressure in dogs with hypertension induced by use of the 2K1C model but not in normotensive dogs. The onset of renal vascular hypertension after bilateral clipping of the renal arteries is accompanied by increased activity of the sympathetic nervous system, which is reflected in the development of tachycardia and increases in plasma norepinephrine (NE) concentration.\(^3\) Similar results also were found in dogs with renal vascular hypertension induced by use of the 2K1C model.\(^8\) In the study that evaluated renal vascular hypertension induced by use of the 2K2C model,\(^5\) plasma epinephrine and NE concentrations increased immediately after renal arterial clipping but decreased gradually after 5 days until returning to preclipping values. However, if 1 renal artery was occluded completely in these dogs, malignant hypertension developed. Plasma NE concentrations increased dramatically during the malignant phase, compared with preclipping values.

Plasma NE concentration also increases in humans with renal vascular hypertension\(^1\) and in rats with hypertension induced by use of the 2K1C model.\(^4\) In rats with hypertension induced by use of the 2K1C model, Dargie et al\(^12\) reported that plasma NE concentration did not differ significantly from control values, and intracisternal injection of 6-hydroxydopamine did not affect hypertension. Therefore, the influence of NE on development of hypertension in rats depends on the model used to induce hypertension and may differ from results obtained with dogs.

Measurement of plasma catecholamine concentrations alone for evaluation of sympathetic nervous system activity can be misleading, because an increase in plasma NE concentration may be attributable to increased NE release from sympathetic nerve terminals, defective neuronal uptake, or decreased clearance or metabolism of NE. Determination of NE kinetics together with plasma NE concentrations may provide more information regarding sympathetic nervous system activity. Thus, the purpose of the study reported here was to use the 2K2C model to evaluate the role of the sympathetic nervous system in the developmental phase of renal vascular hypertension in dogs by determining plasma NE kinetics in dogs with experimentally induced renal vascular hypertension.

Materials and Methods

Animals—Four healthy mixed-breed male dogs that weighed between 15 and 24 kg were used in the study. Results of CBC as well as BUN and plasma creatinine concentrations were within reference ranges. The experimental procedures were in accordance with institutional guidelines and conformed to the National Science and Technology Development Agency, Thailand.

Experimental protocol—Dogs were acclimated to the investigators and the room in which measurements were obtained. Dogs also were trained to stand in a sling during the experiments and for recording of blood pressure. The study comprised a control and hypertensive period. During each period, dogs received a low-sodium (8 mEq/d) diet\(^1\) for 8 days before determination of NE kinetics. To ensure sodium depletion, furosemide (2 mg/kg of body weight) was injected subcutaneously at the initiation of the low-sodium diet during control and hypertensive periods. There was a several-month interval between control and hypertensive periods. On the third day that dogs received the low-sodium diet during the control period and at the initiation of the low-sodium diet during the hypertensive period, a catheter was surgically placed in a femoral artery for continuous determination of blood pressure; the catheter was removed between control and experimental periods. Five days before determination of NE kinetics during the hypertensive period (ie, on the third day that dogs received the low-sodium diet), both renal arteries were surgically clipped to induce renal vascular hypertension. Blood pressure was recorded on each dog on days that experiments on NE kinetics were not performed.

On the day of NE experiments, each dog had blood pressure recorded for a short duration (10 to 30 minutes) before infusion began, and blood pressure was recorded for the 55-minute duration of the kinetic study. Data collected during NE kinetic studies were used to calculate renal hemodynamics. During each period, measurements of NE kinetics and renal clearance were obtained on the eighth day that dogs received the low-sodium diet.

Surgical placement of femoral artery catheter—Dogs were anesthetized with pentobarbital sodium (25 mg/kg, IV). Using aseptic technique, a polyvinyl catheter (inner diameter, 0.05-inch) with a 20-gauge 1.25-inch-long Teflon-coated tip\(^4\) was inserted into the femoral artery and anchored with sutures into the femoral canal without placing sutures into the artery. The exit catheter was tunneled subcutaneously, anchored under the skin, and exteriorized over the back of each dog. The catheter was kept in a jacket and flushed and refilled with heparinized (1,100 U/ml) saline (0.9% NaCl) solution daily to prevent clotting.

Blood pressure measurements—Blood pressure was recorded from the femoral artery catheter by connecting the exit catheter with a pressure transducer connected to a physiograph.\(^4\) The signal was transformed by use of a specific software program and stored on a hard disk for subsequent analysis. Data were analyzed by use of a standard time series analysis technique. Signals were sampled (50 points/s) and digitized to provide a mean of 3,000 sample points/1 min. Further analysis was performed, using 1-minute averaging of data to yield true blood pressure and heart rate.

Blood pressure measurements were performed when each dog was standing in the sling during the NE kinetic study. Blood pressure also was recorded 1 day before surgical clipping of the renal arteries to ensure that blood pressure did not change from that measured during the control period. Rectal temperature was measured daily while catheters were in place, and blood was collected for hematologic analyses when rectal temperature was above the reference range.

Renal artery clip protocol—Dogs were anesthetized with pentobarbital sodium (25 mg/kg, IV), and a paracostal incision was made over both flanks, using aseptic technique, to approach the left and right renal arteries. A stainless-steel clip was applied to the renal artery on each side with pentobarbital sodium (25 mg/kg, IV). Using aseptic technique, a polyvinyl catheter (inner diameter, 0.05-inch) with a 20-gauge 1.25-inch-long Teflon-coated tip\(^4\) was inserted into the femoral artery and anchored with sutures into the femoral canal without placing sutures into the artery. The exit catheter was tunneled subcutaneously, anchored under the skin, and exteriorized over the back of each dog. The catheter was kept in a jacket and flushed and refilled with heparinized (1,100 U/ml) saline (0.9% NaCl) solution daily to prevent clotting.
position of the clips. Plasma creatinine or BUN concentrations were measured 4 days after surgery to ensure that dogs did not have serious impairment of kidney function. Plasma NE kinetics and renal clearance measurements were performed the fifth day after renal arteries were clipped.

**Determination of NE kinetics and renal clearance variables**—For measurement of NE kinetics and renal clearance variables, dogs were placed in a sling with minimal restraint. A urethral catheter was inserted into the bladder for urine collection. Catheters were inserted into both cephalic veins for collection of an arterial blood sample for determination of baseline plasma NE concentration, i-[3H]-norepinephrine (15.28 μCi/dog) dissolved in 5% dextrose in water containing ascorbic acid (2 mg/ml) was infused (rate, 0.760 ml/min) via a cephalic catheter for 5 minutes. Infusion of [3H]NE (dose, 0.764 μCi/min; rate, 0.191 ml/min) was maintained throughout the 55-minute data acquisition period.

To measure renal clearance variables, a priming dose of para-aminohippuric acid (PAH; 0.16 g/dog) and inulin (0.8 g/dog) dissolved in a mixture of 25 ml of a 25% mannitol solution and 30 ml of 5% dextrose in water was administered at the same time that [3H]NE was infused. The priming dose of PAH and inulin was infused intravenously at a rate of 7.64 ml/min for 6 minutes. The priming infusion was immediately followed by infusion at a rate of 3.82 ml/min of a sustaining solution that contained 1.2 g of PAH and 1.2 g of inulin dissolved in 75 ml of a 20% mannitol solution and 200 ml of 5% dextrose in water.

Three consecutive urine samples were collected from 25 to 55 minutes after initiating infusion of PAH and inulin; each urine sample was collected during a 10-minute period. The bladder was emptied at the beginning and the end of each collection period. Blood samples were obtained from the femoral artery catheter at the midpoint of each urine collection period (ie, 30, 40, and 50 minutes after initiating PAH and inulin infusions) for determination of osmolarity and plasma concentrations of NE, [3H]NE (ie, radioactivity), PAH, inulin, and electrolytes. Blood for determination of NE concentration was collected into tubes containing 0.02 vol of a solution comprising 90 mg of EGTA/ml and 60 mg of glutathione/ml. Plasma was separated and stored at −70 C for later analysis. The measurements of plasma NE concentration and [3H]NE radioactivity were performed in triplicate for each blood sample collected during the 10-minute period and averaged to yield the mean value of that 10-minute period.

Plasma NE concentrations were determined by use of high-performance liquid chromatography (HPLC) after alumina adsorption and extraction of plasma with perchloric acid (PCA). As described by Clemson et al., dihydroxybenzylamine was assayed simultaneously to determine standard recoveries. Plasma [3H]NE concentration was determined by use of alumina adsorption. Plasma extracted with PCA to release [3H]NE was added to scintillation vials containing 10 ml of scintillation cocktail. Radioactivity in samples was measured simultaneously to determine NE concentration. Quench correction was by use of an external standard. In this study, [3H]NE infuse was also collected to determine [3H]NE infusion rate. A portion of the infusate was added to 4 ml of the baseline plasma sample extracted with PCA and counted to determine [3H]NE recovery after alumina extraction. Urine and plasma PAH and inulin concentrations were determined by use of the ethylenediamine and anthrone methods, respectively. Packled cell volume was determined by use of the microcentrifugation method. Sodium and potassium concentrations in plasma and urine were determined by use of flame photometry. Plasma and urine chloride concentrations were measured, using a chloridometer, and plasma and urine osmolality were measured by use of an osmometer.

Norepinephrine kinetics were calculated according to the following formulas:

\[
\text{NE clearance rate} = \frac{\text{[3H]NE infusion rate}}{\text{Plasma [3H]NE concentration}}
\]

\[
\text{NE spillover rate} = \frac{\text{Plasma NE concentration } \times \text{NE clearance rate}}{\text{Plasma NE concentration}}
\]

**Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR)** were measured as the clearances of PAH and inulin, respectively. Effective renal blood flow (ERBF) was estimated as ERPF/(1−PCV). Filtration fraction (FF) was calculated as the ratio between GFR and ERPF. Renal vascular resistance (RVR) was calculated as the ratio between mean arterial pressure (MAP) and ERBF. The fractional excretion of electrolytes was calculated, using GFR and standard formulas.

Data for each dog were reported as the mean of measurements from 3 minutes of 10-minute collection period.

**Statistical analyses**—Data obtained during each period were reported as mean ± SEM. Values for NE kinetic and renal clearance variables determined during each period were compared by use of paired Student t-tests and Wilcoxon signed-rank tests. The association between MAP and NE kinetics was assessed by use of regression analysis. Significance was set at \( P < 0.05 \).

**Results**

**Arterial blood pressure**—Mean arterial pressure during the control period was not different from that measured a few months later immediately before the hypertensive period (101.7 ± 2.4 mm Hg vs 102.9 ± 3.5 mm Hg). Systolic, mean, and diastolic arterial pressures measured during the hypertensive period (ie, 5 days after clipping of the renal arteries) increased to a hypertensive range (increase of 17 to 20 mm Hg; Table 1). However, arterial blood pressures measured during this period did not differ significantly from those measured during the control period. Heart rate was significantly less during the hypertensive period, compared with the control period.

**Renal hemodynamics**—Bilaterally clipping the renal arteries resulted in a significant decrease in GFR and a 30 and 25% reduction in ERPF and ERBF, respectively (Table 2). The reduction in GFR was more pronounced than the reduction in ERPF, resulting in a decrease in FF. Calculated RVR doubled after renal arteries were clipped. However, induction of renal vascular hypertension did not affect PCV.

**Norepinephrine kinetics**—Plasma NE concentration increased significantly \( (P = 0.01) \) after induction of renal vascular hypertension (control period, 151.5 ± 14.1 pg/ml; hypertensive period, 631.4 ± 30.5 pg/ml; Fig 1). Norepinephrine clearance rate increased significantly from 53.00 ± 2.39 ml/kg/min during the control period to 86.03 ± 9.27 ml/kg/min during the hypertensive period. Finally, NE spillover rate also increased significantly after induction of hypertension (control period, 8.03 ± 0.62 ng/kg/min; hypertensive period, 53.97 ± 5.16 ng/kg/min).

We detected significant correlations between
MAP and plasma NE concentration ($r = 0.7524; P < 0.001$) and NE spillover rate ($r = 0.6375; P < 0.001; \text{Fig 2}$). However, a significant correlation was not found between MAP and NE clearance rate.

Urinary excretion of electrolytes—Five days after induction of renal vascular hypertension, absolute urinary excretion of all electrolytes decreased, compared with values determined during the control period (Table 3). Fractional excretion of sodium was unchanged, whereas that of chloride was increased slightly. Fractional excretion of potassium was reduced by 37% after renal arteries were clipped, compared with the value determined during the control period. Plasma concentrations of sodium, potassium, and chloride were within reference ranges during control and hypertensive periods (sodium, 140 vs 136 mEq/L; potassium, 4.3 vs 4.1 mEq/L; chloride, 106 vs 102 mEq/L).

Plasma and urine osmolarity—Plasma osmolarity did not change significantly between the 2 periods (Table 4). Urine osmolarity decreased by 18%, and osmolar clearance was significantly reduced after induction of hypertension. The reduction in osmolar clearance corresponded to a significant decrease in
afferent arterioles and vascular resistance. Renal dogs indicated that NE caused vasoconstriction in investigators evaluated isolated blood vessels from suggests that afferent arteriolar vasoconstriction developmental decrease in GFR, more than ERPF, and ERPF, decreased after induction of hypertension. The pronounced decrease in GFR, more than ERPF, compared with the value for the control period. compared with the value for the control period. compared with the value for the control period.}

### Discussion

Blood pressure increased immediately after induction of renal vascular hypertension and was increased dramatically (by 20 mm Hg) through day 5. Heart rate decreased on the 5th day after induction of hypertension. These results are consistent with those of Suzuki et al. In that study, renal vascular hypertension was induced in dogs by use of the 2K2C model, the same model we used. Blood pressure increased (by 30 mm Hg) immediately after clipping of the renal arteries and stabilized at 110 mm Hg 2 days later. In that study, heart rate increased abruptly and returned to control values 5 days after renal surgery. The increase in MAP differed slightly between that study and the study reported here (30 vs 20 mm Hg), which may be attributable to the method of measurement and position of the dogs during measurement.

In our study, renal function, as measured by GFR and ERPF, decreased after induction of hypertension. The pronounced decrease in GFR, more than ERPF, suggests that afferent arteriolar vasoconstriction developed and decreased FF. Results of a study in which investigators evaluated isolated blood vessels from dogs indicated that NE caused vasoconstriction in afferent arterioles and vascular resistance. Renal hemodynamics were not measured in another study of dogs with renal vascular hypertension induced by use of the 2K2C model. Because both renal arteries were clipped in our study, compensatory vasodilation by the contralateral kidney could not develop. Therefore, the decrease in renal hemodynamics that we detected was relatively fixed and stable, compared with that determined in a study of dogs with hypertension induced by use of the 2K1C model.

In our study, mean (± SD) plasma NE concentration during the control period was 151.5 ± 28.3 pg/ml, which was similar to concentrations reported in studies of trained conscious dogs (145 ± 38 pg/ml and 120 to 145 pg/ml). Analysis of these data suggests that dogs in the study reported here were trained and acclimatized sufficiently to the laboratory environment such that NE concentrations did not increase as a result of necessary manipulations. Analysis of our results also indicated that hypertension 5 days after clipping both renal arteries was associated with significantly increases in sympathetic nervous system activity (ie, plasma NE concentration increased 6-fold, compared with the concentration for the control period). These results agree with those of Suzuki et al, who found increases in plasma epinephrine and norepinephrine concentrations in dogs during the first few days after induction of hypertension by use of the 2K2C model. In that study, however, values 5 days after induction of hypertension were only slightly higher than control values. The minor difference between results of that study and our study may be attributable to a higher degree of renal artery stenosis and a greater reduction in sodium intake in the study reported here. Suzuki et al found that further occlusion of the renal arteries induced malignant hypertension and caused a significant increase in plasma NE concentration.

Analysis of our data suggested that central sympathetic overdrive may be involved in dogs with renal vascular hypertension induced by use of the 2K2C model. This is supported by the increase in NE spillover and clearance rates that we detected. The increase in NE clearance rate was less than that of NE spillover rate, which resulted in a 6-fold increase in plasma NE concentration after induction of hypertension. It is known that removal of NE from plasma is the result of extraction by several organs. Fractional extraction of NE across the kidneys is about 35%: this represents 8% of total NE plasma clearance. Because the regional NE clearance rate is flow dependent, low renal plasma flow can cause a reduction in NE removal by the kidneys. However, in our study, total NE clearance rate increased significantly, indicating that other organs removed more NE from plasma after induction of hypertension.

Norepinephrine in plasma is derived mainly from transmitter released by sympathetic nerves with a minor contribution from the adrenal medulla.  

---

### Table 3—Urinary and fractional excretion of electrolytes in 4 dogs before (control) and 5 days after (hypertensive) experimental induction of renal vascular hypertension

<table>
<thead>
<tr>
<th>Period</th>
<th>U NaV (mEq/min)</th>
<th>Fe Na (%)</th>
<th>U K (mEq/min)</th>
<th>Fe K (%)</th>
<th>U ClV (mEq/min)</th>
<th>Fe Cl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>77.9 ± 22.2</td>
<td>1.98 ± 0.34</td>
<td>79.7 ± 25.5</td>
<td>64.3 ± 11.2</td>
<td>25.4 ± 5.3</td>
<td>0.78 ± 0.07</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>37.2 ± 8.1</td>
<td>1.99 ± 0.69</td>
<td>27.1 ± 9.6</td>
<td>40.5 ± 8.2</td>
<td>12.9 ± 3.3</td>
<td>1.17 ± 0.07</td>
</tr>
</tbody>
</table>

Data reported as mean ± SEM.

### Table 4—Plasma and urine osmolality in 4 dogs before (control) and 5 days after (hypertensive) experimental induction of renal vascular hypertension

<table>
<thead>
<tr>
<th>Period</th>
<th>P osm (mosm/L)</th>
<th>U osm (mosm/L)</th>
<th>C osm (ml/min)</th>
<th>C H2O (ml/min)</th>
<th>V (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>292.5 ± 2.3</td>
<td>605.1 ± 29.4</td>
<td>3.05 ± 0.46</td>
<td>-1.59 ± 0.31</td>
<td>1.46 ± 0.1</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>296.2 ± 7.6</td>
<td>498.9 ± 89.8</td>
<td>1.66 ± 0.26*</td>
<td>-0.57 ± 0.23</td>
<td>1.02 ± 0.1*</td>
</tr>
</tbody>
</table>

Data reported as mean ± SEM. P osm = Plasma osmolality, U osm = Urinary osmolality, C osm = Osmolar clearance, C H2O = Free water clearance, V = Urinary flow rate.
Norepinephrine spillover rate provides the rate at which released NE enters plasma. It was reported that low intake of sodium increases the rate of NE spillover. In the study reported here, dogs received a low-sodium diet before and after induction of hypertension. Thus, the effect of surgically narrowing the renal arteries on NE spillover rate was compared between dogs in a uniform sodium state.

The rate of NE spillover into plasma and NE clearance in healthy dogs has been reported. Values for NE spillover and clearance rates in a study of NE kinetics in awake dogs were comparable to results of our study. Deegan et al reported higher control values even though plasma NE concentrations were comparable to those reported here. These minor differences can result from differences in analytic procedures.

The net spillover of total NE in the plasma is the sum of NE spillover from many organs. The overflow of NE from the kidneys accounts for approximately 25% of the total NE spillover to plasma in healthy humans at rest. This NE is derived from sympathetic nerve firing and is increased during periods of sodium depletion. Moreover, development of renal vascular hypertension is believed to involve activity of afferent renal nerves, because renal denervation delays the development of hypertension in rats with hypertension induced by use of the 2K1C model and in dogs with chronic coarctation of the aorta. It was suggested that an increase in afferent renal nerve signals from an ischemic kidney enhances sympathetic activity in animals with established renal vascular hypertension. Adenosine, which is released by proximal tubular cells of ischemic kidneys directly into tubular fluid and stimulates chemoreceptive nerve endings located in the renal pelvis, was proposed as the possible stimulus. Evidence to support this hypothesis was provided by results of the study of Katholi et al, who reported that intrarenal infusion of adenosine in uninephrectomized conscious dogs caused increases in MAP, heart rate, cardiac output, renal blood flow, and plasma NE concentration. After renal denervation, intrarenal infusion of adenosine did not have an effect on these variables. These data suggest that adenosine can cause hypertension associated with increased activity of renal sympathetic nerves.

Numerous factors other than firing rate of sympathetic nerves could influence the rate at which renal NE spills into the plasma. The possible influence of blood flow on NE washout is of particular concern. In other reports, it was suggested that NE spillover rate depended on regional blood flow. Esler et al studied the effects of blood flow on NE clearance and spillover rate at various degrees of reduction of renal blood flow in uninephrectomized dogs. These results indicate that only a high degree of flow reduction (ie, 50%) resulted in reduced NE clearance and spillover rates. In the study reported here, renal plasma flow was reduced by only 30%, which would not likely affect renal NE spillover rate.

Despite the reduction in renal blood flow, other investigators found an increased NE concentration in the renal vein of patients with unilateral and bilateral renal stenosis with a higher renin release. The NE concentration in the renal vein may be increased because of an increase in sympathetic activity to the kidneys or a decrease in renal blood flow, but it would not play an important role in inducing an increase in plasma NE concentration. However, in our study, renal venous blood was not obtained for measuring NE concentration. Although plasma NE concentration and NE spillover rate were increased 6-fold in our study, it is unlikely that the source of excessive NE in the plasma was the kidneys, because they account for only 25% of NE spillover into the plasma without taking into consideration the reduction of renal plasma flow that resulted from clipping both renal arteries.

Depletion of catecholamine stores in the brain by intracisternal injection of 6-hydroxydopamine diminished the increase in arterial pressure in rabbits with renal hypertension experimentally induced by wrapping both kidneys with cellophane. Moreover, in rats with hypertension induced by use of the 1K1C model, NE concentrations in peri- and paraventricular, anterior, and posterior hypothalamic nuclei were reduced, compared with sham-operated controls. Reductions in central NE concentrations were directly responsible for increased activity in peripheral sympathetic nerves. Activities of tyrosine hydroxylase in the brainstem and hypothalamic nuclei of these rats decreased within 72 hours after induction of hypertension. Reduction in brain NE content, therefore, is accompanied by decreased activity of tyrosine hydroxylase in certain hypothalamic nuclei. However, results of a study by Winternitz et al indicated that NE concentration in the hypothalamus of rats with hypertension induced by use of the 1K1C model increased 3 weeks after surgery. Renal denervation resulted in a significant reduction in blood pressure and hypothalamic NE concentration. Analysis of results of that latter study suggests that renal nerves contribute to maintenance of hypertension by modulating central sympathetic nerve activity. The difference in brain NE content between these 2 studies may be explained by differences in location of neurons evaluated and duration of each study. Changes in brain NE content after induction of hypertension imply enhanced central sympathetic activity, as supported by detection of increased NE spillover rate after induction of renal hypertension in dogs in our study.

The renin-angiotensin system may be involved in an early phase of hypertension (ie, when sodium is depleted) in dogs with renal vascular hypertension induced by use of the 2K2C model. In that study, plasma renin activity as well as concentrations of plasma angiotensin I and II increased significantly 2 days after induction of hypertension but decreased slightly after 3 days and became stable for the duration of the 3-week study. These results raised the question as to whether intrarenal angiotensin II may be responsible for afferent arteriolar vasoconstriction on the fifth day after induction of hypertension.

Interactions between angiotensin and sodium in the maintenance of blood pressure in normotensive rats and rats with renal vascular hypertension was studied. An angiotensin-II inhibitor induced a substantial decrease in blood pressure in hypertensive rats only when they were sodium-depleted but not after...
sodium repletion. Moreover, neither sodium depletion nor angiotensin blockade alone prevented the development of hypertension in rats with hypertension induced by use of the 1K1C model. Therefore, an increase in renin activity as a result of sodium depletion, but not as a result of volume expansion, may be a key component for early development of hypertension.

Sodium and water retention were not responsible for the hypertension we detected in dogs during the study reported here. Plasma osmolarity and electrolyte concentrations after induction of hypertension did not differ from control values. Furthermore, free water clearance was increased, and urine osmolarity was decreased. Urinary excretion of all electrolytes was decreased, with a corresponding reduction in urine flow after induction of hypertension. Fractional excretion of sodium and chloride did not change significantly, whereas that of potassium decreased in a manner dependent on urine flow rate. These data do not support a role of the renin-angiotensin-aldosterone system and antidiuretic hormone on water retention in hypertensive dogs that are sodium-depleted. Instead, these dogs can maintain sodium balance by decreasing the rate of sodium filtration rather than increasing hypertensive dogs that are sodium-depleted. Instead, support a role of the renin-angiotensin-aldosterone system for the hypertension we detected in dogs during the use of the 1K1C model. Therefore, an increase in NE spillover rate in dogs with renal vascular hypertension.

Analysis of our results suggested that activity of the sympathetic nervous system increased as a result of an increase in NE spillover rate in dogs with renal vascular hypertension induced by use of the 2K2C model. Increased central sympathetic activity may be responsible for development of hypertension in these dogs. Because the renin-angiotensin system does not appear to play a role in this form of hypertension, pharmacologic blockade of angiotensin II is unlikely to benefit affected dogs. However, analysis of our results and results of others suggests that an increase in activity of the sympathetic nervous system does play a role. Thus, the use of β-blockers or other agents that affect the sympathetic system may be beneficial for treatment of dogs in the early stages of renal vascular hypertension.

References


