Chronic Angiotensin II Infusion Decreases Renal Norepinephrine Overflow in Conscious Dogs

ROBERT G. CARROLL, THOMAS E. LOHMEIER, AND ALISON J. BROWN

SUMMARY Sympathetic nerve activity and in particular renal sympathetic nerve activity were monitored in six conscious dogs subjected to 6 days of intravenous angiotensin (ANG II) infusion (20 ng/kg/min). This was accomplished by measurement of both arterial and renal venous plasma catecholamine concentration. During the initial 4 hours of ANG II infusion, mean arterial pressure (MAP) increased 35 ± 8 mm Hg from a control value of 101 ± 4 mm Hg. Although there were no significant changes in arterial plasma norepinephrine (NE) concentration at this time (control = 148 ± 40 pg/ml), arterial plasma epinephrine (E) concentration increased threefold (control 42 ± 15 pg/ml). After 24 hours of ANG II infusion, MAP remained elevated (132 ± 5 mm Hg), but plasma E concentration returned to control levels. From Days 2 through 6 of ANG II infusion, MAP was elevated approximately 40 mm Hg, but there were no chronic increases in either arterial plasma E or NE concentrations. In contrast to arterial plasma catecholamine concentration, renal vein plasma NE concentration (control = 216 ± 27 pg/ml) actually decreased during both the acute (122 ± 12 pg/ml) and chronic (103 ± 26 pg/ml) phases of ANG II infusion. Moreover, renal NE overflow (renal venous plasma NE concentration-arterial plasma NE concentration x effective renal plasma flow), an index of renal sympathetic nerve activity, was depressed during the chronic phase of ANG II hypertension. These results, therefore, do not support the contention that the sympathetic nervous system mediates the hypertension produced by elevated plasma levels of ANG II. In fact, the finding that renal NE overflow is chronically depressed during long-term ANG II infusion suggests that changes in renal sympathetic activity may serve to attenuate the development of elevated arterial pressure during ANG II hypertension. (Hypertension 6: 675-681, 1984)

KEY WORDS • epinephrine • catecholamines • hypertension • kidney • sympathetic nervous system

Numerous acute studies over the last 20 to 25 years have indicated that the pressor effects of angiotensin II (ANG II) are mediated, at least in part, by activation of the sympathetic nervous system. This activation of the adrenergic nervous system has been postulated to be produced by actions of ANG II on both the central and the peripheral nervous system. For example, many experiments suggest that ANG II receptors located in the circumventricular organs of the brain are particularly important in mediating the central actions of ANG II. The proposed peripheral actions of ANG II include: 1) facilitation of evoked norepinephrine (NE) release from adrenergic nerve endings; 2) inhibition of NE reuptake from adrenergic nerve terminals; and 3) potentiation of the vascular smooth muscle response to NE. Additionally, high doses of ANG II act directly on the adrenal gland to increase adrenal medullary catecholamine secretion. These acute observations have generated a great deal of interest regarding a possible physiological role of the sympathetic nervous system in mediating the actions of the renin-angiotensin system in both the regulation of arterial blood pressure and in the pathogenesis of hypertension.

Several theoretical analyses, as well as experimental studies, have indicated that the kidneys have a paramount role in the control of arterial pressure under chronic conditions. Accordingly, increases in renal sympathetic nerve activity and possibly plasma catecholamine concentration would be expected in forms of hypertension mediated by the sympathetic nervous system. Such apparently is the case in many instances of essential hypertension, according to much evidence that implicates the sympathetic nervous system in the pathogenesis of hypertension.

Difficulties in recording renal nerve activity, particularly in conscious animals, have limited direct assessment of renal sympathetic activity in hypertension. Recently, Oliver et al. have shown that under basal conditions there is a net addition of NE to renal venous plasma and that this renal NE overflow increases in direct proportion to the frequency of renal nerve stimu-
lulation. Similar results were reported by Kopp et al. Additionally, we have observed recently that occlusion of the common carotid arteries, which causes reflex activation of the sympathetic nervous system, increases both renal nerve activity and renal NE overflow (personal observations). Thus, measurement of renal NE overflow is believed to provide a sensitive indirect index of renal sympathetic nerve activity. In the present study, we employed this technique in chronically instrumented dogs to monitor changes in renal sympathetic nerve activity during the acute and chronic phases of ANGII hypertension.

Methods

Six male dogs weighing 28.1 ± 1.3 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.), and chronic indwelling catheters made of Tygon microbore tubing (Norton Plastics, Akron, Ohio) were implanted in the femoral artery and the femoral vein. The tips of the femoral artery and vein catheters were positioned in the aorta below the origin of the renal arteries, and in the vena cava, respectively. Additionally, a catheter was inserted into the testicular vein and advanced 0.5 cm into the left renal vein. All catheters were tunneled subcutaneously and exteriorized in the posterior thoracic region. Patency of the renal vein catheters was maintained by flushing daily with sterile isotonic saline and by filling the catheters with heparin (1000 µl).

One week after surgery the dogs were placed in metabolic pens and fitted with an aluminum and canvas backpack containing a Statham arterial blood pressure transducer (Model P23ID, Statham Laboratories, Inc., Hato Rey, Puerto Rico) mounted at heart level. Mean arterial pressure (MAP) was recorded continuously from the femoral arterial catheter on a Grass polygraph (Model 7D, Grass Instruments Company, Quincy, Massachusetts). The dogs were allowed unrestricted access to water and were maintained on a fixed daily diet of two 15.5 oz cans of H/D prescription diet (Hills Pet Products, Topeka, Kansas) supplemented with 5 ml of vitamin syrup (vitamin 4X Hart-Delta, Inc., Baton Rouge, Louisiana). Two cans of H/D prescription diet provide about 45 to 50 mEq potassium and less than 5 mEq sodium per day. Isotonic saline (270 ml/day) was infused continuously through the femoral vein catheter by means of a Sage tubing pump (Model 375A, Sage Instruments, Cambridge, Massachusetts) so that sodium intake was about 45 mEq/day. When appropriate, ANG II ([ASP₁, NH₂, VAL₃] ANG II, Ciba Pharmaceutical Company, Summit, New Jersey) was added to the intravenous infusion. A millipore filter (Cathivex Millipore, Bedford, Massachusetts) was connected in series with the intravenous infusion line to prevent passage of bacteria and other contaminants. Body temperature was measured daily, and ampicillin (Principen, E.R. Squibb and Sons, Princeton, New Jersey) and a trimethoprim-sulfa-methoxazole combination (Bactrim, Roche Laboratories, Nutley, New Jersey) were given prophylactically.

After approximately 4 days of saline infusion, urinary bladders were catheterized daily at 11 a.m. with a sterile Bard ureteral catheter (C.R. Bard, Inc., Murray Hill, New Jersey). The urine collected from the bladder was added to that collected in the metabolic cage for determination of 24-hour urinary volume, sodium, and potassium excretion rates. Additionally, water intake was measured daily. After bladder catheterization, the dogs were trained to lie quietly, and, on appropriate days, arterial and venous blood samples (as described below) were taken 30 minutes into this quiet period. At this time, resting heart rates were measured for 1 minute in four dogs. On days when effective renal plasma flow (ERPF) was determined, this measurement was made during the 2 hours after blood sampling.

Exceptions to the above blood sampling schedule occurred on the day preceding (time control) and on the first day of ANG II infusion. On these 2 days, the initial quiet period was extended 1 extra hour for additional blood sampling (see below), and a second 30-minute quiet period preceded a final blood sample taken 4 hours after the first blood sample. The dogs were fed after blood sampling.

Experimental Protocol

After 7 to 10 days of saline infusion, a 2-day control period was begun. Subsequently, ANG II was infused continuously at 20 ng/kg/min for 6 days, and, finally, a 5-day recovery period was observed. This rate of ANG II infusion was expected to produce marked increases in plasma ANG II concentration (20 times normal) but to produce levels comparable to those reported in hypertensive dogs and humans. During each day of the control period, Days 1, 3, 5, and 6 of ANG II infusion, and Days 1, 3, and 5 of the recovery period, 7 ml arterial blood samples were taken for determination of hematocrit, plasma renin activity (PRA), and the plasma concentrations of NE, epinephrine (E), aldosterone, cortisol, sodium, potassium, and protein. Additionally, renal venous blood (3 ml) was sampled for determination of PRA, and plasma NE and E concentrations. Finally, ERPF (total blood sample = 18 ml) was measured on Day 1 of the control period and on Day 6 of ANG II infusion.

Acute responses to saline and ANG II infusion were measured on Day 2 of the control period (time control) and during the initial 4 hours of ANG II infusion, respectively. Arterial (3 ml) and renal venous (3 ml) blood samples were taken at 5, 20, 60, and 240 minutes and were assayed for PRA and plasma catecholamine concentration.

Analytical Methods

Commercially available radioimmunoassay kits were used to measure plasma aldosterone concentration (Diagnostic Products, Los Angeles, California), plasma cortisol concentration (Diagnostic Products), and PRA (Angiotensin I [125I] RIA Kit, New England Nuclear, North Billerica, Massachusetts). The PRA was expressed as nanograms of angiotensin I (ANG I)
generated per milliliter of plasma per hour of incubation (ng ANG I/ml/hr). Plasma catecholamine concentration was measured by a commercially available radioenzymatic assay (Cat-A-Kit, Upjohn Diagnostic, Kalamazoo, Michigan). Plasma and urine concentrations of sodium and potassium were determined by flame photometry (IL 343, Instrumentation Laboratories, Watertown, Massachusetts), plasma protein concentration by refractometry (American Optical, Buffalo, New York), and hematocrit by a micromethod (Autocrit II, Clay Adams, New York). The ERPF was calculated from the clearance of \([^{131}I]\) iodohippurate (Hippuran, Mallinckrodt Nuclear, St. Louis, Missouri) by methods previously described in detail. 20 Finally, the continuous MAP tracings for the period from 6 p.m. to 8 a.m. were analyzed for determination of MAP.

All values presented are means ± standard error of the mean (SEM). Statistical significance (p < 0.05) was determined by using a one-way analysis of variance (ANOVA) and the Tukey test (significant differences). Experimental values that differed from all control values were considered significant. Values for the left kidney renal NE overflow \((V_{NE} - A_{NE\text{-}left\text{ kidney}}\text{ERPF})\) were calculated for the control period and for Day 6 of ANG II infusion, and were compared by a t test for paired observations. In this formula, \(V_{NE}\) = renal venous plasma NE concentrations; \(A_{NE}\) = arterial plasma NE concentration; and ERPF for the left kidney = \(\frac{1}{2}\) ERPF for both kidneys.

**Results**

The effects of ANG II infusion of MAP, sodium and potassium excretion, urine volume, and water intake are shown in Figure 1. The MAP was elevated approximately 30 mm Hg after 24 hours of ANG II infusion and about 40 mm Hg from Days 2 through 6. However, in marked contrast to the effects of lower rates of ANG II infusion (0.5 to 5 ng/kg/min), 21, 22 urinary sodium excretion actually increased during the initial 2 days of ANG II infusion. During these days, urinary sodium excretion was about 2 times control. Also, urinary potassium excretion was elevated during the first 24 hours of ANG II administration. Due to the large interanimal variation, the increases in urine volume and water intake were not statistically significant during ANG II infusion. Additionally, during ANG II infusion, there were no consistent changes in heart rate (control = 61 ± 2 bpm). By the end of the 6-day recovery period, all variables had returned toward control values.

The effects of ANG II on plasma aldosterone and cortisol concentration, plasma electrolyte concentration, plasma protein concentration, and hematocrit are shown in Figure 2. As expected, during ANG II infusion there was a sustained increase in plasma aldosterone concentration (about eightfold) and a decrease in plasma potassium concentration. 22 Hemoconcentration during ANG II infusion was reflected by the increases in plasma protein concentration and hematocrit.

Changes in plasma E and NE concentrations and PRA in the arterial and renal venous plasma during saline infusion (time control) or during the initial 24 hours of ANG II infusion can be seen in Figure 3. During the initial 4 hours of ANG II infusion, MAP increased 35 ± 8 mm Hg from a control value of 101 ± 4 mm Hg. The control value for arterial plasma E concentration was 42 ± 15 pg/ml, and, consistent with the findings of others, arterial plasma E concentration increased transiently (two- to threefold) during ANG II
infusion. However, this increase was not sustained, and within 24 hours arterial plasma E concentration was similar to the control value. Control renal venous plasma E concentration (7 ± 6 pg/ml) was lower than arterial plasma levels and was unchanged during ANG II infusion.

In contrast to arterial plasma E concentration, arterial plasma NE concentration actually tended to decrease (control = 148 ± 20 pg/ml) during ANG II infusion; however, this decline was not statistically significant (Figure 3). Control renal venous NE concentration (216 ± 27 pg/ml) was higher than arterial plasma NE concentration, and it was depressed significantly throughout the initial 24 hours of ANG II infusion. In fact, during ANG II infusion, the arterial and renal venous plasma levels of NE were actually comparable. Finally, as expected, both arterial and renal venous PRA decreased progressively during the initial hours of ANG II infusion. Control values for arterial and renal venous PRA were 0.40 ± 0.08 and 0.54 ± 0.09 ng ANG I/ml/hr, respectively. Both arterial and renal venous plasma levels of E, NE, and PRA were unchanged during the time control study on control Day 2.

**FIGURE 2.** Effect of intravenous angiotensin II infusion on arterial plasma aldosterone concentration, plasma cortisol concentration, plasma sodium concentration, plasma potassium concentration, plasma protein concentration and hematocrit. All values are means ± se for six dogs.

**FIGURE 3.** Acute changes in arterial and renal venous plasma epinephrine concentration, plasma norepinephrine concentration, and plasma renin activity during saline (○) or angiotensin II (●) infusions. All values are means ± se for six dogs.
The chronic changes in arterial and renal venous plasma E and NE concentrations and PRA during the 6 days of ANG II infusion are shown in Figure 4. In contrast to the acute increase in arterial plasma E concentration observed during the first 4 hours of ANG II infusion (Figure 3), there were no significant changes in arterial plasma E concentration during chronic ANG II infusion. Additionally, there were no significant changes in renal venous E concentration during chronic ANG II infusion. On the other hand, plasma NE concentration actually decreased throughout the entire 6-day period of ANG II administration, although only the decrease in renal venous plasma NE concentration was statistically significant. As in the acute study shown in Figure 3, renal venous plasma NE concentration was greater than arterial plasma NE concentration during the control period, but not during ANG II infusion. Both arterial and renal venous PRA were suppressed to undetectable levels during ANG II infusion. During the recovery period, all variables returned to control levels.

Table 1 shows the calculated values for renal NE overflow in the three dogs in which ERPF was determined. In all three dogs, both ERPF and renal venous plasma NE concentration were lower than control levels on Day 6 of ANG II infusion. Moreover, in all three dogs the calculated values for renal NE overflow were suppressed during chronic ANG II infusion.

**Discussion**

In the present study, chronic ANG II infusion at 20 ng/kg/min produced approximately a 40 mm Hg increase in MAP. In one of our earlier studies, MAP increased about 30 mm Hg when ANG II was infused chronically at 5 ng/kg/min in dogs maintained on a comparable sodium intake. At these two infusion rates of ANG II, one would expect plasma concentrations of ANG II to increase from control levels of about 20 pg/ml to about 100 pg/ml (at 5 ng/kg/min) and 400 pg/ml (at 20 ng/kg/min). Increases in plasma ANG II concentration of this magnitude have been reported in both hypertensive dogs and humans. Interestingly, in these two ANG II infusion studies, all of the changes in the variables measured were qualitatively similar with the exception of sodium and water balance: in dogs infused at 5 ng/kg/min, sodium and water balance was positive, whereas in the present study in which ANG II was infused at a rate four times greater, salt and water balance was negative, and hemoconcentration occurred.

It is now well established that ANG II acutely stimulates the release of adrenal catecholamines. However, there is some question as to the physiological significance of this interaction since in previous studies very high infusion rates of ANG II have been required to achieve this effect. Further, one can only speculate as to potential importance of increased plasma levels of E as a mediator of ANG II hypertension since little data are available regarding the chronic effects of ANG II on adrenal medullary catecholamine secretion. In the present study in conscious dogs, the two- to threefold increase in plasma E concentration seen during the initial 4 hours of ANG II infusion

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**Table 1. Left Kidney Norepinephrine Overflow During Chronic Angiotensin Infusion**

<table>
<thead>
<tr>
<th>Dog</th>
<th>ERPF/2 (ml/min)</th>
<th>V&lt;sub&gt;NE&lt;/sub&gt;-A&lt;sub&gt;NE&lt;/sub&gt; (pg/ml)</th>
<th>NE overflow (pg/min/kidney)</th>
<th>ERPF (ml/min)</th>
<th>V&lt;sub&gt;NE&lt;/sub&gt;-A&lt;sub&gt;NE&lt;/sub&gt; (pg/ml)</th>
<th>NE overflow (pg/min/kidney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ign</td>
<td>96</td>
<td>(204-133)</td>
<td>6816</td>
<td>85</td>
<td>(27-39)</td>
<td>-1020</td>
</tr>
<tr>
<td>Jas</td>
<td>85</td>
<td>(280-124)</td>
<td>13260</td>
<td>70</td>
<td>(65-125)</td>
<td>-4200</td>
</tr>
<tr>
<td>Leo</td>
<td>147</td>
<td>(264-222)</td>
<td>6174</td>
<td>125</td>
<td>(104-82)</td>
<td>+2750</td>
</tr>
</tbody>
</table>

V<sub>NE</sub> = renal venous plasma norepinephrine (NE) concentration; A<sub>NE</sub> = arterial plasma NE concentration; ERPF = effective renal plasma flow for both kidneys; NE overflow = (V<sub>NE</sub> - A<sub>NE</sub> x ERPF/2).

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Figure 4. Chronic changes in arterial and renal venous plasma epinephrine concentration, plasma norepinephrine concentration, and plasma renin activity, during angiotensin II infusion. All values are means ± se for six dogs.
indicates that high physiological levels of ANG II are capable of increasing adrenal catecholamine secretion. This adrenal medullary stimulation, however, was not sustained, and within 24 hours of ANG II infusion, plasma E concentration was similar to control levels. This finding is consistent with reports of normal or even suppressed levels of E concentration in patients with high renin forms of primary and secondary hypertension. Thus, it is unlikely that enhanced secretion of adrenal catecholamines is involved in any important way in mediating the chronic hypertensive effects of ANG II.

Although many acute studies have indicated that circulating ANG II acts both centrally and peripherally to activate the sympathetic nervous system and increase arterial pressure, the importance of this interaction in the pathogenesis of hypertension remains to be elucidated. Sympathetic nerve activity, as assessed by measurement of plasma catecholamine concentration, may or may not be elevated in high-renin forms of human and experimental hypertension. Further, it is difficult in many of these studies to determine cause-effect relationships between the renin-angiotensin system and the sympathetic nervous system, particularly since the sympathetic nervous system activates renin release. In the present study, we determined both the acute and long-term effects of ANG II on the sympathetic nervous system more directly by infusing ANG II intravenously and by measuring plasma catecholamine concentration. The present data provide no support for the hypothesis that the long-term hypertensive effects of high plasma levels of ANG II are mediated via activation of the sympathetic nervous system.

In the present study, although not statistically significant, arterial plasma NE concentration actually tended to decrease during the entire period of ANG II infusion. Although this finding does not support the contention that the sympathetic nervous system mediates ANG II hypertension, a caveat in the interpretation of these data is that peripheral catecholamine concentration may not be a reliable index of sympathetic nervous system activity because of differential activation of the sympathetic nervous system. For example, in essential hypertension, sympathetic activity to the large skeletal muscle vascular bed is frequently not increased or may even be reduced with increased sympathetic activity occurring mainly in the heart, renal, and splanchnic vascular beds. However, since the liver has a great capacity to clear plasma NE, little of the NE released by the splanchnic vascular bed would be expected to enter the systemic circulation. Therefore, in circumstances such as essential hypertension characterized by differential activation of the sympathetic nervous system, it is doubtful whether peripheral plasma NE concentration would reliably reflect the sympathetic pattern: little NE would come from the gastrointestinal area and perhaps even reduced amounts from skeletal muscle, which would tend to cancel out increased NE overflow from, for example, heart and kidneys. Thus, a better index of sympathetic activity in hypertension would involve regional NE overflow estimations from venaarterial differences and local blood flows.

Because of the importance of the kidneys in the chronic regulation of arterial pressure, we emphasized changes in renal NE overflow during ANG II hypertension. Recently, Oliver et al. concluded that measurements of NE overflow into the renal vein may be used as an index of renal nerve activity. In these experiments, Oliver et al. observed a baseline overflow of NE into the renal venous blood of the dog that increased with increasing frequency of electrical stimulation of the renal nerves. Similar results were reported by Kopp et al. Additionally, we have observed recently increased renal nerve activity and renal NE overflow during reflex activation of the sympathetic nervous system by bilateral carotid occlusion (personal observations). Therefore, in the present study, to assess the activity of the renal sympathetic nervous system in conscious dogs during both the acute and chronic phases of ANG II hypertension, we monitored renal NE overflow throughout the 6 days of ANG II infusion. Our results from measurements of both renal venous NE concentrations as well as renal NE overflow suggest that there is an immediate (as early as 5 minutes) and a sustained (lasting for the entire 6 days) decrease in renal sympathetic nerve activity during ANG II hypertension. Our acute observations are consistent with those of Ferrario and associates who measured renal nerve activity directly in anesthetized dogs infused with ANG II into the vertebral circulation. In a related study that further discounts the importance of the sympathetic nervous system in mediating the renal actions of ANG II, Oliver et al. reported that converting enzyme blockade with captopril (although presumably blocking the rise in plasma ANG II concentration) did not attenuate either the renal venous NE or the renal hemodynamic response to direct nerve stimulation. Thus, enhanced renal nerve activity does not appear to contribute either acutely or chronically to the elevation in arterial pressure caused by high plasma levels of ANG II. In fact, our data indicate both acute and chronic changes in renal nerve activity that would be expected to attenuate the development of elevated arterial pressure during ANG II hypertension.

It is important to note that the present study examined only changes in renal NE overflow (an indirect index of renal nerve activity) during ANG II hypertension. Although most studies indicate that the predominant peripheral adrenergic potentiating effect of ANG II is mediated via facilitation of neurotransmitter release, there are reports that ANG II enhances smooth muscle responsiveness to NE. Therefore, it is conceivable that although renal nerve activity may have been depressed during ANG II hypertension, the high plasma levels of ANG II may have produced such a marked increase in renal vascular sensitivity to NE that even the reduced levels of neurotransmitter were adequate to produce increased renal sympathetic tone. Studies by Oliver et al. and Zimmerman et al. in the dog do not support such a contention, however.
Additionally, it is possible that the fall in renal venous NE concentration during ANG II infusion was a result of increased renal metabolism of NE due to some physiological action of ANG II, such as diminution or redistribution of renal blood flow. However, since the renal extraction of E (which is not produced in the kidney) and NE is apparently comparable, the following factors argue against such a hypothesis: 1) renal nerve stimulation (which increases renin release) does not alter the renal extraction of E; and 2) in the present study, the renal extraction of E (the venoarterial difference) was unchanged during chronic ANG II infusion.

Finally, although the changes in plasma NE concentrations as well as renal NE overflow indicate chronic (as well as acute) suppression of the sympathetic nervous system during ANG II hypertension, the peripheral and central mechanisms that mediate this apparent compensatory response are unknown. Acutely, one would expect a general decrease in activity of the sympathetic nervous system following a 30 to 40 mm Hg increase in MAP due to activation of the sinoaortic baroreceptors. However, it is well established that these receptors adapt to a given arterial pressure level within 36 hours. Similarly, since atrial stretch receptors also apparently adapt to increased arterial pressure levels, they would not be expected to contribute to the chronic suppression of renal nerve activity during prolonged ANG II hypertension. Therefore, the nature of the feedback control mechanism that chronically suppresses renal sympathetic nerve activity (and possibly sympathetic nerve activity in general) during ANG II hypertension remains to be determined. It will be most interesting to ascertain whether this renal sympathetic response observed during chronic ANG II infusion occurs in other forms of hypertension as well.

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