Baroreflex Control of Renal Sympathetic Nerve Activity Is Potentiated at Early Phase of Two-Kidney, One-Clip Goldblatt Hypertension in Conscious Rabbits

Hiroo Kumagai, Hiromichi Suzuki, Munekazu Ryuzaki, Shigeaki Matsukawa, and Takao Saruta

Conscious normotensive and two-kidney, one-clip Goldblatt hypertensive rabbits were studied to determine the sensitivity of the arterial baroreflex control of renal sympathetic nerve activity (RSNA) and heart rate. The relations of the mean arterial pressure–RSNA and mean arterial pressure–heart rate were examined over a wide range of blood pressures produced by infusions of phenylephrine and nitroglycerin. The maximum slope obtained by logistic function analysis was considered to represent the baroreflex sensitivity. In the early hypertensive group (n=8; mean arterial pressure±SEM, 88±2 mm Hg) on day 5 after renal clip application, the maximum slope of the mean arterial pressure–RSNA relation was −11.3±1.2, which was significantly greater than that of the sham normotensive group (−6.9±0.3, p<0.05). The maximum slope (−4.3±0.2) of the mean arterial pressure–RSNA relation in the late hypertensive group (n=8; mean arterial pressure, 96±3 mm Hg) on day 21 after renal clipping was significantly smaller than that of another sham group (−7.2±0.2, p<0.05). In contrast to these changes in the baroreflex control of RSNA, the control of heart rate was attenuated according to the magnitude of mean arterial pressure. To elucidate the mechanisms underlying the potentiated baroreflex, the effects of endogenous neuropeptides were investigated. First, plasma concentrations of angiotensin II and arginine vasopressin that are known to affect the baroreflex were determined. Plasma concentrations of vasopressin (3.1±0.6 pg/ml) as well as of angiotensin II (34±7 pg/ml) were increased in the early hypertensive group, and the plasma vasopressin returned to a similar level to the sham group in the late hypertensive group (1.3±0.4 pg/ml). Second, to study endogenous effects of these neuropeptides on the baroreflex, the maximum slopes of the baroreflex curves during infusions of antagonists for the peptides were determined in the early hypertensive group. The maximum slope of mean arterial pressure–RSNA during intravertebral arterial [Sar⁴, Ala⁸]–angiotensin II (−16.4±1.5) was significantly greater (p<0.05), whereas the maximum slope during intravertebral arterial infusion of d(CH₂)₇Tyr(Me)arginine vasopressin (−4.7±0.5) was significantly smaller (p<0.05) than that during vehicle infusion (−11.3±1.2). These results suggest that the baroreflex control of RSNA was potentiated in the early phase of two-kidney, one-clip hypertension in conscious rabbits and that endogenous arginine vasopressin and angiotensin II, which counteract each other, were apparently involved in the potentiated baroreflex mechanism. (Circulation Research 1990;67:1309–1322)

Humoral factors such as angiotensin II (Ang II), arginine vasopressin (AVP), and nor-epinephrine (NE) are known to be involved in the development and maintenance of renovascular hypertension.¹⁻⁴ In addition to their actions on the heart, the kidneys, and the blood vessels, these peptides (Ang II and AVP) have been shown to modulate the arterial baroreceptor reflex through various mechanisms.⁵⁻⁹ For example, by exogenous administration of Ang II the sensitivity of the arterial baroreflex was found to be decreased, whereas it was increased by AVP administration. Some of these studies were performed as acute experiments under anesthesia. Since anesthesia and surgical stress have

From the Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.
Address for correspondence: Takao Saruta, MD, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan.
Received October 20, 1989; accepted July 19, 1990.
been demonstrated to affect the baroreflex,10–12 the precise roles of these peptides in the arterial baroreflex control remain unclear. In addition, only a few studies have examined the effects of endogenously elevated Ang II and AVP on the baroreflex in conscious animals.13

The arterial baroreflex has been shown to be blunted with the initiation of hypertension,14 and elevation of blood pressure has been considered as a major determinant of the sensitivity of the arterial baroreflex. On the other hand, a recent study has suggested that some compensatory mechanisms by the arterial baroreflex may operate to minimize the elevation of the blood pressure in the early developing phase of renal hypertension.15

It is therefore assumed that some endogenous neuropeptides could be involved in changing the baroreflex control of the peripheral sympathetic nerve activity and heart rate (HR) in renovascular hypertension in which these neuropeptides are known to be involved in regulating the blood pressure. The present study was undertaken to evaluate the effects of neuropeptides on the baroreflex control of the renal sympathetic nerve activity (RSNA) and HR in the early and late phases of two-kidney, one-clip Goldblatt hypertension (2K, 1C hypertension) in conscious rabbits.

Materials and Methods

General Preparations

Experiments were performed on 44 Japanese White rabbits weighing 2.5–3.0 kg in accordance with the guiding principles for research involving animals and humans. In all surgical procedures, anesthesia was induced by 30 mg/kg intravenous pentobarbital sodium and maintained by 6 mg/kg intravenous pentobarbital per hour. Four days before renal clip application, polyethylene catheters (0.76 mm i.d., 1.2 mm o.d., Clay Adams, Parsippany, N.J.) were placed in the left subclavian artery for measurement of arterial blood pressure and in the external jugular vein for drug administration. Further, 2 days after renal clipping (day 2), another polyethylene catheter of the same size for intravertebral arterial infusions of drugs was inserted in the right subclavian artery, and the tip of the catheter was placed at the origin of the right vertebral artery according to van Zwieten’s method.16 The catheters were exteriorized at the back of the neck. The arterial pressure (AP-611G, Nihon Kohden Co., Tokyo) and HR (AT-601G, Nihon Kohden) were recorded for 60 minutes daily in a sitting position to document the changes in mean arterial pressure (MAP) and HR before and after renal clip application.

Production of Two-Kidney, One-Clip Hypertension

On day 0, a stainless clip with a slit of 0.5 mm in width was placed on the right renal artery through a flank incision by using a dissecting microscope so as not to cause damage to the renal nerves. To compare with the early and the late renal hypertensive groups and eliminate the effects of time-dependent changes on hemodynamic parameters and the baroreflex sensitivity, we prepared two groups of sham-operated animals that corresponded to the respective phases of 2K, 1C hypertension (described below). The renal clip was placed close to the right renal artery in the sham-operated groups.

Recording and Quantification of Renal Sympathetic Nerve Activity

Through a retroperitoneal approach, the left renal artery and vein were exposed under the microscope. The renal nerves along the artery were carefully isolated and Teflon-coated stainless wire electrodes (0.05 mm i.d., 0.23 mm o.d., A-M System, Inc., Everett, Wash.) were implanted around the renal nerves. The nerves and the electrodes were covered and fixed together with silicone gel (Silgel 604A and 604B, Wacker Chemie, Munich).11,17 The electrodes were also exteriorized at the back of the neck. After the implantation of the renal electrodes, the rabbits were again kept in standard cages so that they could be given free access to chow and water.

RSNA was amplified with a differential amplifier (AVB-10, Nihon Kohden) with a bandpass filter of 50–3,000 Hz and made visible on an oscilloscope (VC-10, Nihon Kohden). The RSNA, after the passage through the differential amplifier, was rectified and integrated using a root mean square (RMS) integrator with a time constant of 28 msec (EI-601G, Nihon Kohden). We designated this as the "RMS of RSNA." This signal was further filtered at 0.08 Hz for quantification. We designated this as the "mean RSNA." The background noise was determined when the nerve activity had been eliminated by increasing MAP with phenylephrine infusion. The pulse pressure, MAP, HR, original neurogram of RSNA, RMS of RSNA, and mean RSNA were simultaneously recorded on a thermal array recorder (RTA-1300, Nihon Kohden) and stored in a multi-channel data recorder (A-89, Sony Inc., Tokyo).

Determination of the Baroreflex Sensitivity

On the day of determination of baroreflex sensitivity, conscious rabbits were placed in a shielded room. Before the experiment, the rabbits were allowed 60 minutes to become acclimatized to their environment.

The sensitivity of the baroreflex control of the RSNA and HR was determined as follows. Progressive infusion of phenylephrine (PE; 0.9–77.0 μg/kg/min, diluted in 0.9% NaCl) was performed at flow rates ranging from 0.0096 to 0.760 ml/min using a compact infusion pump (955-E, Harvard Apparatus, Millis, Mass.) for 2 minutes to induce 30 mm Hg of increase in MAP. Then, nitroglycerin (100 μg/kg, diluted in 0.9% NaCl) was infused at a flow rate of 0.068 ml/sec with the pump for 15 seconds to induce 25–30 mm Hg of decrease in MAP. In the present study, PE was infused first, and then at least 30
minutes elapsed before nitroglycerin was infused. Before infusions of PE and nitroglycerin, the levels of the MAP, HR, and RSNA values were ascertained to be within the same ranges. Because of these procedures, a wide range of changes in MAP (50–130 mm Hg) was obtained. For data analysis, RSNA and HR were plotted at 5 mm Hg intervals of MAP. The control values of MAP, HR, and RSNA were taken as their 3-minute averages before the infusion of PE. The value of the mean RSNA before the PE infusion was defined as 100%.

Data for the MAP-RSNA or MAP-HR relations during increases and decreases in MAP were collected and fitted to a logistic function curve. The equation used for the data analysis was based on the following mathematical model10,18:

\[
\text{RSNA or HR} = \frac{P_1}{1 + \exp[P_2(MAP - P_3) + P_4]}
\]

In this equation, \(P_1\) is the “range” of the response of RSNA or HR, \(P_2\) is the slope coefficient (but not the slope itself), \(P_3\) is the MAP at the midpoint of the curve (i.e., it corresponds to MAP at the midpoint of the RSNA or HR range), and \(P_4\) is the “lower plateau” of RSNA or HR. Data were fitted to the logistic function with a nonlinear regression program (NLMIN PROCEDURE, SAS Institute Inc., Cary, N.C.) on an IBM 3081 computer.

In the present study, the maximum slope \(S_{\text{max}} = \frac{-P_2 \times P_3}{4}\) calculated from the parameters of the logistic function curve18 was considered as the sensitivity of the baroreceptor reflex. Further, the slope of the logistic curve at any given MAP was calculated with the computer from the first derivative of the equation described above.19

To make the parameters physiologically meaningful and to avoid confusion in interpreting the data, we defined some more appropriate terms according to the studies of Head and McCarty20 and Verberne et al.21 “Upper plateau” of RSNA and HR was obtained as the sum of the range and the lower plateau. The reflex thresholds, upper threshold \((T_U)\) and lower threshold \((T_L)\), were obtained from the derivative of the equation

\[
T_U = P_3 - 1.317/P_2 - BP_{50} - 1.317\text{range}/4S_{\text{max}}
\]

\[
T_L = 1.317/P_2 + P_3 - 1.317\text{range}/4S_{\text{max}} + BP_{50}
\]

where \(BP_{50}\) is the MAP at the midpoint of the RSNA or HR range.

**Experimental Protocols**

We examined the relations of MAP-RSNA and MAP-HR in the following four groups of rabbits in the conscious state in a sitting position. In each group, the animals were allowed to recover for more than 3 days after the implantation of the renal electrodes before the determination of the baroreflex sensitivity to eliminate the effects of surgery, anesthesia, and dehydration. The infusion of PE was begun at least 15 minutes after the initiation of background infusion of vehicle.

**Early hypertensive group.** The clip was placed on the right renal artery on day 0, and the electrodes were implanted on day 2. On days 5 and 6, the sensitivity of baroreflex control of the RSNA and HR was determined during background intravertebral arterial infusions of Ang II analogue (Ang II A) and vehicle, or AVP antagonist (AVPX) and vehicle. Ang II A and AVPX were administered in the same rabbits on different days and designed in a random order. Background infusions of Ang II A or AVPX were initiated at least 180 minutes after the end of the infusion of vehicle.

The baroreflex sensitivity was first determined by PE and nitroglycerin with a background intravertebral arterial infusion of a vehicle \((n=8, 0.9\% \text{NaCl}, 30 \mu l/\min)\) with a microliter syringe pump (special model, Harvard Apparatus).

With background infusion of Ang II A \((n=8)\), the purpose of the experiment was to examine the modulatory action of endogenous Ang II on the baroreflex control of RSNA and HR. The dose of intravertebral arterial infusion of Ang II A \((0.25 \mu g/kg/\text{min})\) was predetermined in our preliminary pilot experiment to ensure that the pressor effect of 10 ng/kg/min of intravenous Ang II was blocked. The baroreflex sensitivity was determined by PE and nitroglycerin with a background intravertebral arterial infusion of [Arg, Ala]-angiotensin II (Ang II A; Peptide Institute, Inc., Osaka, Japan; 0.25 \(\mu g/kg/\text{min}, 30 \mu l/\text{min})\). On determination of the sensitivity of baroreflex during Ang II A infusion, even if RSNA was increased by Ang II A, we defined the level of mean RSNA recorded just before the PE infusion during the vehicle infusion as 100%.

With background infusion of AVPX \((n=8)\), the purpose of the experiment was to elucidate the effect of the endogenous AVP on the baroreflex control of RSNA and HR. \(d(\text{CH}_2)_3\text{Tyr(3Me)}\text{AVP} (\text{AVPX})\) is known to antagonize the vasoconstrictive \((V_c)\) effect of AVP.22 To exclude the direct vasodilating effect on the vascular smooth muscle, AVPX was infused into the vertebral artery instead of into a vein. The sensitivity was determined with a background intravertebral arterial infusion of AVPX (Sigma Chemical Co., St. Louis; 1.0 \(\mu g/kg/hr, 30 \mu l/min\)). This dose of AVPX infused into the vertebral artery had been found to eliminate the changes in MAP, HR, and RSNA induced by 3.0 \(\mu U/kg/min\) of intravenous AVP in our preliminary experiments. On determination of the sensitivity of the baroreflex during AVPX infusion, even if RSNA was increased by AVPX, we defined the mean RSNA recorded just before the PE infusion during the vehicle infusion as 100%. After the experiment, India ink was infused into the catheter and the distribution to the hindbrain area was confirmed.

Further, to evaluate the relative importance of the sympathetic and vagal systems in alteration in the baroreflex sensitivity and to determine the maximal
capability to activate or withdraw the sympathetic and vagal tone, the sensitivity of the baroreflex control of RSNA and HR was examined with administrations of methyl atropine (n=6), atenolol (n=6), and vehicle in other early hypertensive rabbits, according to the method of Head and McCarty.20

On days 5 and 6, 180 minutes after the end of the determination of the baroreflex sensitivity with the vehicle, the sensitivity was examined with either methyl atropine (0.5 mg/kg i.v., Sigma) or atenolol (1.0 mg/kg i.v., Sigma). To eliminate the effects of the cardiopulmonary reflex, 0.9% NaCl was infused at a rate of 30 μl/min after the injection of atropine and atenolol. Atropine and atenolol were administered in the same rabbits on the different days, and the order of the administrations was determined in a random manner.

Sham I group. In this group, sham clipping was performed on day 0, and the renal electrodes were implanted on day 2. On days 5 and 6, the baroreflex sensitivity was determined with background intravertebral arterial infusions of the vehicle, Ang II A, and AVPX (n=8). In other sham-clipped rabbits (n=6), the baroreflex sensitivity was determined with the administrations of vehicle, methyl atropine, and atenolol. The doses and rates of administrations of vehicle, Ang II A, AVPX, atropine, and atenolol were identical with the protocol in the early hypertensive group.

Late hypertensive group (n=8). The renal clip was put in place on day 0, and the renal electrodes were implanted on day 18. On day 21, the baroreflex sensitivity was determined by PE and nitroglycerin with a background intravertebral arterial infusion of the vehicle.

Sham II group (n=8). The sham operation was performed on day 0, and the renal electrodes were implanted on day 18. On day 21, the baroreflex sensitivity was determined with a background intravertebral arterial infusion of vehicle.

Plasma Concentrations of Vasoactive Substances

We withdrew 3 ml blood from each animal (in the sitting position) to determine the plasma concentrations of Ang II, AVP, and NE at least 3 hours before the determination of the baroreflex sensitivity. An equivalent dose of blood was infused into the venous catheter from donor rabbits. The plasma concentrations of Ang II and AVP were estimated by radioimmunoassay,23 and that of NE was measured by high-performance liquid chromatography.24 For these methods, the intra-assay coefficients of variation of Ang II, AVP, and NE were 8.6%, 4.7%, and 4.4%, respectively. The interassay coefficients of variation were 10.3%, 7.5%, and 7.5%, respectively.

Results

Figure 1 illustrates typical recordings obtained in the present study for the arterial pressure, MAP, HR, and RSNA in response to an increase in MAP produced with PE infusion (left panel) and to a decrease in MAP with nitroglycerin infusion (right panel) in a conscious rabbit of the early hypertensive group.

Baseline Data of Mean Arterial Pressure and Heart Rate

The MAP of the early hypertensive group (88±2 mm Hg) was significantly higher than that of the sham I group (76±1 mm Hg), and MAP of the late hypertensive group (96±3 mm Hg) was significantly higher than that of the sham II group (77±2 mm Hg). In the early and late hypertensive groups, HR (230±12 and 232±9 beats/min) did not reveal any significant changes compared with those of sham-operated groups.

Plasma Concentrations of Vasoactive Substances

In Figure 2, changes in the plasma concentrations of Ang II, AVP, and NE are shown. Ang II (34±7 pg/ml) and NE (361±34 pg/ml) were significantly elevated in the early hypertensive group compared with those in the sham I group (Ang II, 10±1; NE, 118±27). In the late hypertensive group, Ang II (17±4) and NE (174±32) were not statistically different from those in the sham II group (Ang II, 10±1; NE, 121±36). The plasma AVP concentration (3.1±0.6 pg/ml) in the early hypertensive group was also significantly higher than that in the sham I group (0.9±0.3). It was decreased to a similar level to that in the sham II group in the late hypertensive group (1.3±0.4).

Mean Arterial Pressure–Renal Sympathetic Nerve Activity Relations of the Sham I, Early Hypertensive, Sham II, and Late Hypertensive Groups

To investigate the differences in the MAP-RSNA and MAP-HR relation curves among each group by statistical analysis, the logistic function curve was used, and the parameters were obtained. Throughout the present study, over 90% of the data of the MAP-RSNA and MAP-HR relations fitted well to symmetric logistic curves (see correlation coefficients in Tables 1–6). This was confirmed by the small values
of the mean square root of the differences between
the measured and estimated RSNA and HR.

The effects of renal clipping on the baroreflex
control of RSNA are illustrated in Figure 3A. Although
the differences between the values below did
not reveal statistical significance, the $P_1$ value (slope
coefficient) of the early hypertensive group
(0.14±0.02) tended to be larger than that of the sham
I group (0.11±0.01), and $P_2$ of the late hypertensive
(0.08±0.01) tended to be smaller than that of
the sham II group (0.11±0.02). As shown in Table 1,
the range and upper plateau of RSNA of the early
hypertensive group were significantly larger than
those of the sham I group ($p<0.05$), whereas the
range of RSNA of the late hypertensive group
was slightly smaller than that of the sham II group but
without significance.

The calculated $S_{\text{max}}$ values are also presented in
Table 1. $S_{\text{max}}$ of the early hypertensive group
(−11.3±1.2) was significantly greater than that of
the sham I group (−6.9±0.3, $p<0.05$) and that of the late
hypertensive group (−4.3±0.2). In contrast, $S_{\text{max}}$ of
the late hypertensive group was significantly smaller
than that of the sham II group (−7.2±0.2).

The slopes of the curves of the MAP-RSNA rela-
tion at any given MAP obtained from the derivative
of the logistic curve equation are depicted in Figure
3C. This figure also demonstrates that the $S_{\text{max}}$ of the
baroreflex curve relating MAP-RSNA of the early
hypertensive group was larger than that of the sham
I group and that the $S_{\text{max}}$ of the late hypertensive
group was smaller than that of the sham II group.

**Mean Arterial Pressure–Heart Rate Relations of the
Sham I, Early Hypertensive, Sham II, and Late
Hypertensive Groups**

Figure 3B illustrates the average MAP-HR rela-
tion curves of each group. The parameters derived
from the logistic function and the $S_{\text{max}}$ are presented in
Table 2. The ranges of HR of the early hyper-
tensive group and the late hypertensive group were
significantly smaller than those of the sham I and
sham II groups, respectively. The lower plateaus of
the early and the late hypertensive groups were
significantly elevated compared with the lower plate-
aus of the sham I and sham II groups. The upper
plateaus of the early and late hypertensive groups
were not different from those of their sham groups.

Contrary to the unique changes in $S_{\text{max}}$ observed in
the MAP-RSNA relations (Table 1 and Figures 3A
and 3C), $S_{\text{max}}$ in the MAP-HR relation gradually
decreased according to the magnitude of the baseline
MAP of each group (Table 2). $S_{\text{max}}$ of the early
hypertensive group (−3.3±0.2) was significantly

---

**FIGURE 1.** Original recordings of arterial pressure, mean arterial pressure, heart rate, original neurogram of renal sympathetic nerve activity (RSNA, renal neurogram), mean RSNA, and RSNA integrated by a root mean square integrator (RMS of RSNA) in response to an increase in mean arterial pressure produced with phenylephrine infusion (left panel) and to a decrease in mean arterial pressure with nitroglycerin infusion (right panel) in a conscious rabbit.
FIGURE 2. Plasma concentrations of angiotensin II, arginine vasopressin, and norepinephrine of eight rabbits of the sham I, early hypertensive, sham II, and late hypertensive groups. Values are mean ± SEM. *p<0.05 vs. sham I group. Plasma concentrations of all vasoactive substances in the early hypertensive group were significantly greater than those in the sham I group. Plasma concentrations of all substances in the late hypertensive group were not statistically different from those of the sham II group.

FIGURE 3. Mean arterial pressure–renal sympathetic nerve activity (RSNA) (panel A) and mean arterial pressure–heart rate (panel B) relation curves in sham I, early hypertensive, sham II, and late hypertensive groups. Each curve represents an average value of eight conscious rabbits. The mean arterial pressure–RSNA curves in the early and late hypertensive groups are shifted to the right compared with those of respective sham groups. The slope of the mean arterial pressure–RSNA curve in the early hypertensive group seems to be greater than that in the sham I group. On the contrary, the slope of the mean arterial pressure–heart rate curve in the early hypertensive group is smaller than that in the sham I group and that of the late hypertensive group is also smaller than that of the sham II group. Panel C: Slopes of the baroreflex control of RSNA with variation of mean arterial pressure in each group. The slope at any given mean arterial pressure was obtained from the first derivative of the logistic curve equation. The maximum slope of the early hypertensive group is greater than that of the sham I group, and the maximum slope of the late hypertensive group is smaller than that of the sham II group.
smaller than that of the sham I group (−4.3±0.3, p<0.05), and \( S_{\text{max}} \) of the late hypertensive group (−2.1±0.3) was also significantly smaller than that of the sham II group (−4.4±0.4, p<0.05).

**Mean Arterial Pressure–Renal Sympathetic Nerve Activity Relations With Background Infusions of Angiotensin II Analogue and Arginine Vasopressin Antagonist in the Early Hypertensive and Sham I Groups**

During the infusion of Ang II A, MAP decreased significantly from 88±2 to 79±2 mm Hg (p<0.05), and HR increased from 230±11 to 245±10 beats/min (p>0.05). The mean value of mean RSNA before PE infusion during Ang II A infusion (146±21%) was significantly larger than that just before PE infusion during vehicle infusion (100% by definition). During the intravertebral arterial infusion of AVPX, MAP did not exhibit any significant change (from 88±2 to 86±3 mm Hg, p>0.05), and HR increased slightly but not significantly from 230±11 to 236±9 beats/min (p>0.05). The mean value of mean RSNA before PE infusion during AVPX infusion (118±9%) was significantly larger than that before PE infusion during vehicle (100%).

The MAP-RSNA relation curves during the background intravertebral arterial infusions of Ang II A, AVPX, and vehicle in the early hypertensive group are illustrated in Figure 4A. The parameters and calculated \( S_{\text{max}} \) are shown in Table 3. The range and upper plateau of RSNA during Ang II A infusion were slightly but not significantly larger than those during vehicle infusion, whereas the range and upper plateau during AVPX infusion were significantly smaller than those during infusion of vehicle.

The \( S_{\text{max}} \) of the MAP-RSNA relation during Ang II A infusion was significantly greater than \( S_{\text{max}} \) during vehicle infusion in the early hypertensive group (p<0.05). On the other hand, \( S_{\text{max}} \) during AVPX was significantly smaller than during Ang II A and vehicle.

Figure 4C illustrates the slopes of the baroreflex control of RSNA at any given MAP derived from the derivative of the logistic curve equation during infusions of the vehicle, Ang II A, and AVPX in the early hypertensive group. This figure also demonstrates that the \( S_{\text{max}} \) of the curve during Ang II A infusion was larger, whereas the \( S_{\text{max}} \) during AVPX infusion was smaller than that during the vehicle infusion.

In the sham I group, none of the parameters of the MAP-RSNA relation curve showed significant differ-

### Table 1. Parameters of Logistic Function Curves of Mean Arterial Pressure–Renal Sympathetic Nerve Activity

<table>
<thead>
<tr>
<th></th>
<th>Sham I (n=8)</th>
<th>Early hypertensive (n=8)</th>
<th>Sham II (n=8)</th>
<th>Late hypertensive (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum slope</td>
<td>−6.9±0.3</td>
<td>−11.3±1.2†</td>
<td>−7.2±0.2</td>
<td>−4.3±0.2‡</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>0±3</td>
<td>0±5</td>
<td>1±4</td>
<td>2±5</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>253±4</td>
<td>323±11†</td>
<td>261±9</td>
<td>217±10</td>
</tr>
<tr>
<td>Range of RSNA</td>
<td>253±8</td>
<td>323±11†</td>
<td>260±9</td>
<td>215±12</td>
</tr>
<tr>
<td>BP_{50}</td>
<td>75±1</td>
<td>82±2†</td>
<td>74±2</td>
<td>93±1‡</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>87±3</td>
<td>91±3†</td>
<td>86±2</td>
<td>109±3‡</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>63±2</td>
<td>73±2</td>
<td>62±2</td>
<td>77±3</td>
</tr>
<tr>
<td>r</td>
<td>0.94±0.02</td>
<td>0.95±0.02</td>
<td>0.92±0.01</td>
<td>0.90±0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM. RSNA, renal sympathetic nerve activity; BP_{50}, mean arterial pressure corresponding to the midpoint of the RSNA range.

*\( p<0.05 \) vs. the sham I group.
†\( p<0.05 \) vs. the late hypertensive group.
‡\( p<0.05 \) vs. the late sham II group.

### Table 2. Parameters of Logistic Function Curves of Mean Arterial Pressure–Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Sham I (n=8)</th>
<th>Early hypertensive (n=8)</th>
<th>Sham II (n=8)</th>
<th>Late hypertensive (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum slope</td>
<td>−4.3±0.3</td>
<td>−3.3±0.2*</td>
<td>−4.4±0.4</td>
<td>−2.1±0.3†</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>89±16</td>
<td>153±16*</td>
<td>91±13</td>
<td>160±7†</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>376±24</td>
<td>299±21</td>
<td>384±19</td>
<td>297±12</td>
</tr>
<tr>
<td>Range of HR</td>
<td>287±35</td>
<td>146±26*</td>
<td>293±32</td>
<td>137±13†</td>
</tr>
<tr>
<td>BP_{50}</td>
<td>79±2</td>
<td>88±3</td>
<td>77±2</td>
<td>96±2‡</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>101±3</td>
<td>103±3</td>
<td>99±2</td>
<td>118±3†</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>57±2</td>
<td>73±3*</td>
<td>55±2</td>
<td>74±2‡</td>
</tr>
<tr>
<td>r</td>
<td>0.92±0.01</td>
<td>0.93±0.01</td>
<td>0.90±0.01</td>
<td>0.91±0.02</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HR, heart rate; BP_{50}, mean arterial pressure corresponding to the midpoint of the HR range.

*\( p<0.05 \) vs. the sham I group.
†\( p<0.05 \) vs. the sham II group.
FIGURE 4. Mean arterial pressure–renal sympathetic nerve activity (RSNA) (panel A) and mean arterial pressure–heart rate (panel B) relation curves during intravertebral arterial infusions of angiotensin II analogue (Ang II A), vasopressin antagonist (AVPX), and vehicle in the early hypertensive group. Each curve represents an average value of the same eight conscious rabbits. The maximum slope of the mean arterial pressure–RSNA curve during Ang II A infusion is greater than those during AVPX and vehicle infusions. The slope of the mean arterial pressure–RSNA curve during AVPX infusion is smaller than that during vehicle. The slope of the mean arterial pressure–heart rate curve during Ang II A infusion is greater than that during vehicle infusion. Panel C: Slopes of the baroreflex control of RSNA with variation of mean arterial pressure during Ang II A, AVPX, and vehicle infusions in the early hypertensive group. The slope at any given mean arterial pressure was obtained from the first derivative of the logistic curve equation. The maximum slope of the curve during Ang II A is greater, whereas that during AVPX is smaller, than that during vehicle infusion.

Table 3. Parameters of Logistic Function Curves of Mean Arterial Pressure–Renal Sympathetic Nerve Activity During Background Infusions of Vehicle, Angiotensin II analogue, and Vasopressin Antagonist in the Early Hypertensive Group

<table>
<thead>
<tr>
<th></th>
<th>Vehicle (n=8)</th>
<th>Ang II A (n=8)</th>
<th>AVPX (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum slope</td>
<td>-11.3±1.2</td>
<td>-16.4±1.5†</td>
<td>-4.7±0.5*</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>0±5</td>
<td>0±6</td>
<td>3±6</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>323±11</td>
<td>360±11</td>
<td>212±9*</td>
</tr>
<tr>
<td>Range of RSNA</td>
<td>323±11</td>
<td>360±12†</td>
<td>209±10*</td>
</tr>
<tr>
<td>BP&lt;sub&gt;50&lt;/sub&gt;</td>
<td>82±2</td>
<td>76±1*†</td>
<td>85±2</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>91±3</td>
<td>83±2†</td>
<td>100±3</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>73±2</td>
<td>69±2</td>
<td>70±2</td>
</tr>
<tr>
<td>r</td>
<td>0.95±0.02</td>
<td>0.93±0.01</td>
<td>0.92±0.02</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Ang II A, angiotensin II analogue; AVPX, arginine vasopressin antagonist; RSNA, renal sympathetic nerve activity; BP<sub>50</sub>, mean arterial pressure corresponding to the midpoint of the RSNA range.

* p<0.05 vs. during vehicle infusion.
† p<0.05 vs. during AVPX infusion.
sions of Ang II A (−5.9 ± 0.3) and AVPX (−6.0 ± 0.2) were not different from $S_{\text{max}}$ during vehicle infusion (−5.6 ± 0.3).

Mean Arterial Pressure–Heart Rate Relations With Background Infusions of Angiotensin II Analogue and Arginine Vasopressin Antagonist in the Early Hypertensive and Sham I Groups

The MAP-HR relations during the background infusions of Ang II A, AVPX, and vehicle are illustrated in Figure 4B. The parameters and $S_{\text{max}}$ are shown in Table 4. The range and upper plateau of HR during Ang II A infusion were slightly larger than those during vehicle, although there were no statistical differences. The lower plateau during Ang II A was significantly smaller than that during AVPX infusion. $S_{\text{max}}$ of the MAP-HR curve during Ang II A infusion was significantly larger than during vehicle, and $S_{\text{max}}$ during AVPX was not different from during vehicle.

In the sham I group, the MAP-HR relation curve during AVPX infusion was only slightly shifted to the right and upward, probably because of the increase in the basal HR without any decrease in MAP. There were no changes in the $S_{\text{max}}$ during infusions of Ang II A (−3.6 ± 0.2) and AVPX (−4.0 ± 0.2) compared with the $S_{\text{max}}$ (−4.2 ± 0.3) during vehicle infusion in the sham I group. Also, the ranges of HR during Ang II A (243 ± 15 beats/min) and AVPX (229 ± 17 beats/min) infusions were not significantly different from the range during the vehicle (246 ± 11 beats/min).

Contributions of Sympathetic and Vagal Nerve Activity to Alterations in Baroreflex Sensitivity

Figures 5A and 5B demonstrate the MAP-RSNA relation curves and Figures 5C and 5D show the MAP-HR relation curves with vehicle, atenolol, and methyl atropine in the sham I and early hypertensive groups. In the sham I group (Figure 5A, Table 5), the upper plateau and the range of RSNA were slightly increased by methyl atropine compared with those by vehicle. The $S_{\text{max}}$ of the MAP-RSNA curve with atropine (−7.6 ± 0.3) was slightly increased compared with $S_{\text{max}}$ with vehicle (−5.9 ± 0.2), but there was no statistical significance. The upper plateau, range, and $S_{\text{max}}$ by atenolol did not reveal any significant differences from those by vehicle. As shown in Table 6, the upper and lower plateaus of the MAP-HR curves (Figure 5C) were elevated by methyl atropine in comparison with those by vehicle, and the converse was true for the curve by atenolol in the sham I group.

In the early hypertensive group (Figures 5B and 5D), by the administration of methyl atropine, the HR and RSNA were increased to 295 ± 6 beats/min and 121 ± 4% without significant alteration in MAP (88 ± 2 mm Hg). After atenolol, HR and MAP were reduced to 205 ± 7 beats/min and 79 ± 2 mm Hg, and the RSNA showed a significant increase of 130 ± 5%. The upper plateau and range of RSNA were significantly increased by atropine compared with those by vehicle ($p<0.05$). The $S_{\text{max}}$ of the curve was also increased by administration of atropine (−12.6 ± 0.6, Table 5). The upper plateau, range, and $S_{\text{max}}$ of the MAP-RSNA curve by atenolol were not significantly different from those by vehicle. As shown in Figure 5D and Table 6, the upper and lower plateaus of the MAP-HR curve with methyl atropine were different from those with vehicle. The upper and lower plateaus with atenolol were not different from those with vehicle, and the $S_{\text{max}}$ (−1.6 ± 0.2) with atenolol were significantly smaller than with vehicle.

As shown in Table 5 and Figures 5A and 5B, the range and $S_{\text{max}}$ of the MAP-RSNA with methyl atropine in the early hypertensive group were significantly greater than those with atropine in the sham I group. In contrast, as shown in Table 6 and Figures 5C and 5D, the range and $S_{\text{max}}$ of the MAP-HR relation curve with atenolol in the early hypertensive group were significantly smaller and the lower plateau was significantly larger than those with atenolol in the sham I group. On the other hand, the range and $S_{\text{max}}$ of the MAP-HR curves with methyl atropine treatment did not show significant differences between the early hypertensive and sham I groups.

### Table 4. Parameters of Logistic Function Curves of Mean Arterial Pressure–Heart Rate During Background Infusions of Vehicle, Angiotensin II Analogue, and Vasopressin Antagonist in the Early Hypertensive Group

<table>
<thead>
<tr>
<th></th>
<th>Vehicle (n=8)</th>
<th>Ang II A (n=8)</th>
<th>AVPX (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum slope</td>
<td>−3.3±0.2</td>
<td>−4.3±0.2*</td>
<td>−3.5±0.3</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>153±16</td>
<td>126±11†</td>
<td>171±5</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>299±21</td>
<td>371±19</td>
<td>344±9</td>
</tr>
<tr>
<td>Range of HR</td>
<td>146±21</td>
<td>245±24</td>
<td>173±11</td>
</tr>
<tr>
<td>$BP_{50}$</td>
<td>88±3</td>
<td>78±2*</td>
<td>81±2</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>103±3</td>
<td>97±3</td>
<td>97±3</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>73±3</td>
<td>59±2*</td>
<td>65±2</td>
</tr>
<tr>
<td>$r$</td>
<td>0.93±0.01</td>
<td>0.91±0.02</td>
<td>0.91±0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Ang II A, angiotensin II analogue; AVPX, arginine vasopressin antagonist; HR, heart rate; $BP_{50}$ mean arterial pressure corresponding to the midpoint of the HR range.

*p<0.05 vs. during vehicle infusion.

†p<0.05 vs. during AVPX infusion.

Downloaded from http://circres.ahajournals.org/ by guest on July 10, 2017
FIGURE 5. Mean arterial pressure–renal sympathetic nerve activity (panel A) and mean arterial pressure–heart rate (panel relation curves after the administration of atenolol, methyl atropine, and vehicle in the sham I group, and mean arterial pressure–renal sympathetic nerve activity (panel B) and mean arterial pressure–heart rate (panel D) relation curves in the ex hypertensive group. Each curve represents an average value of six conscious rabbits. The maximum slope and the range of the mean arterial pressure–renal sympathetic nerve activity curve treated with methyl atropine in the early hypertensive group were larger than those in the sham I group (panels A and B). The $S_{max}$ and the range of the mean arterial pressure–heart rate curve treated with atenolol in the early hypertensive group were smaller than those in the sham I group (panels C and D).

**Discussion**

The present study, which was performed in conscious rabbits, is the first to demonstrate an increase in the sensitivity of the arterial baroreflex control of RSNA but not of HR during the development phase of 2K, 1C hypertension. The major findings of the study indicate that this potentiation of the baroreflex was closely related with the endogenous AVP and Ang II in these animals.

Ang II exerts a diverse action including the following: 1) increases the central sympathetic outflow, raises peripheral resistance, and 3) stimulates secretion of AVP and aldosterone. As for the effect of exogenously administered Ang II on the baro

**TABLE 5. Parameters of Logistic Function Curves of Mean Arterial Pressure–Renal Sympathetic Nerve Activity After Administration of Vehicle, Atenolol, and Methyl Atropine**

<table>
<thead>
<tr>
<th></th>
<th>Sham I</th>
<th>Early hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle $(n=6)$</td>
<td>Atenolol $(n=6)$</td>
</tr>
<tr>
<td>Maximum slope</td>
<td>$-5.9\pm0.2$</td>
<td>$-7.0\pm0.2$</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>$0\pm2$</td>
<td>$2\pm3$</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>$238\pm7$</td>
<td>$234\pm10$</td>
</tr>
<tr>
<td>Range of RSNA</td>
<td>$238\pm6$</td>
<td>$232\pm10$</td>
</tr>
<tr>
<td>$BP_{50}$</td>
<td>$74\pm1$</td>
<td>$70\pm1$</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>$87\pm2$</td>
<td>$81\pm1$</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>$61\pm2$</td>
<td>$59\pm1$</td>
</tr>
<tr>
<td>$r$</td>
<td>$0.92\pm0.02$</td>
<td>$0.92\pm0.02$</td>
</tr>
</tbody>
</table>

Values are mean±SEM. RSNA, renal sympathetic nerve activity; $BP_{50}$, mean arterial pressure corresponding to the midpoint of RSNA range.

$p<0.05$ vs. respective value in the sham I group.

$\dagger p<0.05$ vs. after vehicle.
ceceptor reflex, controversy exists whether Ang II has inhibitory effects on the baroreflex control of the sympathetic nerve activity.5,6,27 Moreover, few data on the role of endogenous Ang II in the modulation of the baroreflex have been presented.28,29 Our data in the present study demonstrated that the sensitivity of the baroreflex control of RSNA was increased accompanied by simultaneous elevations of the blood pressure and plasma concentration of Ang II in the early phase of 2K, 1C hypertension. These results may contradict a previous study in which the sensitivity of the arterial baroreceptor was decreased with the initiation of hypertension.14 However, several studies performed in the early and developmental stages of hypertension in experimental animals with high renin support our present data. Ueda et al30 reported that the baroreflex was transiently potentiated in the early phase of renal hypertension. Kirby and Vatner15 recently found that the sensitivity of the arterial pressure component of the baroreceptor response to carotid sinus hypotension was increased in conscious dogs during the development stage of one-kidney, one-wrap hypertension. According to these experiments, endogenously elevated Ang II is suggested to play some roles in modifying the baroreflex control, although the precise mechanisms remain unclear. To clarify the role of the endogenous Ang II in the baroreflex regulation, we infused Ang II A in the early hypertensive group with measurements of the sensitivity of the baroreflex. The ranges and sensitivities of the baroreflex control of both RSNA and HR during the Ang II A infusion were found to be significantly increased. Thus, the present results strongly suggest that increased endogenous Ang II caused by renal clipping blunted the baroreflex control of RSNA. These results indicated that mechanisms other than Ang II may contribute to the potentiation of the baroreflex control of RSNA observed in the early hypertensive group.

A number of previous studies have shown that intravenous administration of AVP facilitates the arterial baroreflex, acting in the central nervous system7,8 or on the baroreceptors.9 Imaizumi and Thamess31 observed that intracerebroventricularly administered AVP induced an increase in the sensitivity of the baroreflex control of RSNA. On the other hand, both MAP and HR were increased with administration of intracerebroventricular AVP because of the increased sympathetic nerve outflow.32 These studies imply that actions of AVP may be different in the peripheral circulation and in the central nervous system. In contrast to these results of exogenously administered AVP in the cardiovascular regulation, very few data concerning the effects of endogenous AVP on the baroreflex have been reported. In the present study, plasma concentration of AVP increased threefold to fourfold in the early hypertensive group, suggesting that endogenous AVP is a possible candidate for potentiation of the baroreflex control of RSNA.

To examine the role of endogenously elevated AVP in the modulation of baroreflex, we used AVPX, which antagonizes the vasoconstrictive effect of AVP via V1 receptors. AVPX was infused into the vertebral artery, because an earlier experiment has shown that AVP exerts its effect in the hindbrain.8 During the intravertebral arterial infusion of AVPX, the maximum slope and the range of the baroreflex control of RSNA were significantly decreased compared with those during the vehicle infusion in the early hypertensive group. Endogenous AVP may therefore be responsible for the potentiation of the baroreflex control of RSNA in this model. Recently, controversy has arisen over what types of receptors are involved in the potentiating effect of AVP on the baroreflex. Matsuguchi and Schmid33 found that dPVDAVP (another type of V1 receptor antagonist) blocked the central inhibitory neural influence of AVP when the perfusion pressure of the hindquarters of rats was examined. Hassler et al34 demonstrated that the inhibitory effect on RSNA induced by volume expansion was augmented by AVP infusion through the V1 receptor in the area postrema. The above studies may thus support our finding that

### Table 6. Parameters of Logistic Function Curves of Mean Arterial Pressure–Heart Rate After Administration of Vehicle, Atenolol, and Methyl Atropine

<table>
<thead>
<tr>
<th></th>
<th>Vehicle (n=6)</th>
<th>Atenolol (n=6)</th>
<th>Atropine (n=6)</th>
<th>Vehicle (n=6)</th>
<th>Atenolol (n=6)</th>
<th>Atropine (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum slope</td>
<td>-4.3±0.3</td>
<td>-3.3±0.3</td>
<td>-3.1±0.2*</td>
<td>-2.7±0.2†</td>
<td>-1.6±0.2†</td>
<td>-2.2±0.3†</td>
</tr>
<tr>
<td>Lower plateau</td>
<td>77±4</td>
<td>63±2</td>
<td>260±2*</td>
<td>132±5†</td>
<td>132±5†</td>
<td>266±1*</td>
</tr>
<tr>
<td>Upper plateau</td>
<td>363±10</td>
<td>250±4*</td>
<td>350±5</td>
<td>285±7†</td>
<td>242±7</td>
<td>347±4*</td>
</tr>
<tr>
<td>Range of HR</td>
<td>286±11</td>
<td>187±5</td>
<td>90±4*</td>
<td>153±7†</td>
<td>110±9†</td>
<td>81±3*</td>
</tr>
<tr>
<td>BP 50</td>
<td>79±1</td>
<td>83±1</td>
<td>71±2</td>
<td>100±2†</td>
<td>85±2</td>
<td>85±2</td>
</tr>
<tr>
<td>Upper threshold</td>
<td>101±3</td>
<td>102±2</td>
<td>80±2*</td>
<td>119±3†</td>
<td>107±3</td>
<td>97±3</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>57±3</td>
<td>64±3</td>
<td>62±3</td>
<td>81±2†</td>
<td>63±3</td>
<td>73±2</td>
</tr>
<tr>
<td>r</td>
<td>0.93±0.02</td>
<td>0.94±0.02</td>
<td>0.94±0.01</td>
<td>0.92±0.02</td>
<td>0.95±0.01</td>
<td>0.94±0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HR, heart rate; BP 50, mean arterial pressure corresponding to the midpoint of the HR range. *p<0.05 vs. after vehicle. †p<0.05 vs. respective value in the sham I group.
endogenously elevated AVP was involved in potentiation of the baroreflex control of RSNA through V₁ receptors in the early phase of 2K, 1C hypertension in conscious rabbits. It is enigmatic that Sₘₐₓ of the MAP-RSNA curve with AVPX in the early hypertensive group was smaller compared with that with the vehicle in the sham I group. In interpreting the exaggerated potentiation of the baroreflex control of RSNA, we have to consider the site(s) of action of AVP. Abbad et al³⁰ and Guo et al³⁰ have demonstrated that the sites at which AVP facilitates the baroreflex are located in the afferent limb of the baroreceptor reflex and the central nervous system. Further, Undesser et al⁸ emphasized the importance of the area postrema in facilitation of arterial baroreflex function by AVP. Taken together, it is suggested that in the present study the exaggerated potentiation of the arterial baroreflex control of RSNA by elevated endogenous AVP in 2K, 1C hypertensive rabbits is at least in part attributable to the action of AVP on both the afferent limb of the baroreflex and the area postrema. Therefore, we speculate that the sensitivity of the baroreflex was substantially suppressed because the actions of AVP on both sites were abolished by AVPX infusion.

In assessing the results of the present study, interactions between endogenous Ang II and AVP exerting complex modulations on the baroreflex should be taken into account. Circulating Ang II stimulates AVP secretion,¹⁴ and AVP, in turn, acts on the kidney to inhibit renin secretion.³⁶ According to the present results for which antagonists to the neuroptides were used, elevated Ang II caused by renal clip application seemed to attenuate the baroreflex control of RSNA, whereas endogenously elevated AVP potentiated the baroreflex. Thus, the facilitated baroreflex control of RSNA in the early hypertensive group may reflect a countercation between endogenous Ang II and AVP in regulating the baroreflex. Alternatively, Ferrario et al³⁷ contended that circulating Ang II might act through AVP to cause inhibitory effects on the sympathetic outflow in the central nervous system or AVP may modulate the interplay between Ang II and the sympathetic nervous system. Thus, it seems possible that the endogenous Ang II and AVP interact with or counteract each other, modifying the baroreflex.

Although in the present study and many previous studies PE has been used as a tool for increasing the MAP, a recent paper by Keast et al³⁸ has indicated that the use of PE to test the baroreflex may be complicated by a direct influence of PE on neurotransmission. In this paper, they clearly demonstrated that neurotransmission in ganglia was facilitated by PE. In this regard, a possibility that PE affects the neurotransmission under the influences of either Ang II or AVP must be taken into account. However, this poses a few problems in the interpretation of the present data, because the infusion of PE was conducted in the identical manner throughout all experiments in the present study.

Plasma concentration of NE has been used as an index of the sympathetic nervous system. The sympathetic nerve activity was reported to be high in the early phase of renovascular hypertension.³⁰ In the present study, plasma NE concentration in the early hypertensive group was higher than that in the sham-operated group, while the sensitivity of the baroreflex control of RSNA was increased. This phenomenon seems curious. However, the baroreflex control of RSNA might be potentiated to attenuate the facilitated sympathetic nervous system in the early phase of hypertension, or other mechanisms may exist.

In 2K, 1C hypertension, the nonstenosed kidney is well known to compensate for the decreased function of the stenosed kidney. It is thus likely that the elevated renal blood flow and glomerular filtration rate of the intact nonstenosed kidney may reflect a decrease in the magnitude of RSNA caused by the potentiated baroreflex. Faber and Brody⁴⁰ found that the afferent renal nerve-dependent pressor reflex was revealed after renal artery stenosis in conscious rats and that this pressor reflex was opposed by the arterial baroreflex or the contralateral intact kidney, at least in the acute phase. From these previous experiments, the possibility cannot be excluded that potentiation of the arterial baroreflex control of RSNA observed in our study was caused by compensation of the intact kidney.

The present results indicate a discrepancy between the baroreflex control of RSNA and HR in the early phase of 2K, 1C hypertension. This finding is supported by a hypothesis presented by Kirby and Vater¹⁵ that the vagally mediated responses may be more likely to be compromised than the sympathetically mediated responses during the development phase of renal hypertension. Various previous studies have revealed that the baroreflex control of HR in hypertensive animals is impaired with the progression of hypertension.⁴¹–⁴₃ In 2K, 1C hypertension in dogs, Suzuki et al³ noted that elevation of the blood pressure in 2–3 days after renal clipping was associated with tachycardia. Recently, Moreira et al⁴⁴ reported that impaired baroreflex control of HR was observed from the initial phase in high-renin renal hypertension. In the present study, the decrease in sensitivity of the baroreflex control of HR in the early hypertensive group resembles the results of these earlier studies.

To evaluate the mechanisms of the discrepancy in the regulations of the baroreflex control of RSNA and HR, we sought to assess the sympathetic and vagal components of the baroreflex curve separately based on the earlier studies of Korner et al⁴₅ and Head and McCarty.²⁰ We therefore tried to differentiate the sympathetic and vagal activity contributing the baroreflex responses by administrations of atenolol and methyl atropine. The MAP-RSNA curves with methyl atropine to assess the sympathetic element in the early hypertensive group revealed that the sympathetic nerve component would be accentuated in the early hypertensive group, since the upper
plateau, range, and S_{max} of the relation curve were greater than those with methyl atropine in the sham I group. This may contribute to the facilitated baroreflex control of RSNA recognized in the early hypertensive group. In contrast, the MAP-HR curves with atenolol in the early hypertensive and sham I groups suggested that the vagal component of HR responses might be impaired in the early hypertensive group, which is indicated by reductions in the range and upper plateau, and elevation of the lower plateau of the curve by atenolol. This probably contributed to the attenuated baroreflex regulation of HR in the early hypertensive group. Therefore, these approaches, which differentiate the sympathetic and vagal contributions, could clarify the reason for the discrepancy of the baroreflex control of RSNA and HR observed in the early hypertensive group.

In agreement with previous reports,^{46} the baroreflex controls of RSNA and HR in the late hypertensive group of the present study were both blunted in comparison with those of the corresponding sham-operated (sham II) group. In the late hypertensive group, we did not determine the sensitivity of baroreflex during Ang II A and AVPX infusions, because the plasma concentrations of both Ang II and AVP were not increased compared with those of the sham II group and significant decrease in MAP was not observed by infusion of Ang II A (data not shown).

In summary, we have determined baroreflex sensitivity in the early and late phases of 2K, 1C hypertension in conscious rabbits. In the early phase of hypertension, the baroreflex control of RSNA was potentiated, and in contrast, the control of HR was attenuated. The plasma concentrations of AVP as well as Ang II increased significantly in the early hypertensive phase. During intravertebral arterial infusion of vasopressin vascular antagonist, the baroreflex sensitivity was significantly decreased. On the contrary, it was increased during infusion of Ang II A. These findings suggest that a buffering action of the arterial baroreceptor reflex might operate to prevent the elevation of the blood pressure in the early developing stage of hypertension and that significantly elevated, endogenous AVP and Ang II, which counteract each other in the central nervous system, may be involved in the facilitated baroreflex mechanism. In this regard, further precise study to investigate the control mechanisms of this counteraction on the baroreflex control will be needed.

References


Baroreflex control of renal sympathetic nerve activity is potentiated at early phase of two-kidney, one-clip Goldblatt hypertension in conscious rabbits.

H Kumagai, H Suzuki, M Ryuzaki, S Matsukawa and T Saruta

doi: 10.1161/01.RES.67.6.1309

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/67/6/1309

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/