Enhanced Responsiveness to Carotid Baroreceptor Unloading in Conscious Dogs During Development of Perinephritic Hypertension

Debra A. Kirby and Stephen F. Vatner

The effects of unloading the carotid sinus baroreceptors before and during the development of perinephritic hypertension were studied in conscious dogs instrumented with aortic catheters to measure arterial pressure and heart rate, and electromagnetic flow probes to measure cardiac output and calculate total peripheral resistance. Prior to hypertension, bilateral carotid occlusion (BCO) increased mean arterial pressure by 38 ± 2 from 101 ± 2 mm Hg and total peripheral resistance by 19 ± 2 from 46 ± 3 mm Hg/l/min, while cardiac output and heart rate did not change from 2,299 ± 128 ml/min and 84 ± 4 beats/min, respectively. At 2 weeks after renal wrapping, there were significant increases in baseline mean arterial pressure, cardiac output, and total peripheral resistance and decreases in heart rate; BCO increased mean arterial pressure by 59 ± 5 from 130 ± 4 mm Hg, heart rate by 36 ± 5 beats/min from 69 ± 3 beats/min, and cardiac output by 458 ± 103 from 2,711 ± 239 ml/min. By 4 weeks after renal wrapping, heart rate and mean arterial pressure responses to BCO were approaching baseline levels. After β-adrenergic receptor blockade, responses to BCO of mean arterial pressure, cardiac output, and heart rate were no longer significantly enhanced during the development of hypertension. Thus, in conscious dogs, reflex pressor responses to baroreceptor unloading via BCO were enhanced during the development of hypertension but no longer present 3 weeks later. The augmented mean arterial pressor responses to BCO were mediated by increases in cardiac output and heart rate, which in turn, appeared to be controlled by β-adrenergic receptor mechanisms. (Circulation Research 1987;61:678-686)

It is widely held that arterial baroreflex sensitivity is depressed in hypertension. Reset baroreceptors or decreased baroreceptor sensitivity, usually evaluated by testing heart rate responses to acute increases in blood pressure, have been reported in many different models of hypertension, including humans with hypertension, renal hypertensive dogs and rabbits, and the spontaneously hypertensive rat. However, regulation of baroreceptor control of arterial pressure and vascular resistance during development of hypertension remains controversial. For example, Mancia et al reported normal baroreflex control of blood pressure in humans with hypertension, and Angell-James and George and Guo et al demonstrated baroreflex control of hind limb vascular resistance and sympathetic nerve activity were preserved in the early stages of hypertension despite impairment of baroreflex control of heart rate. However, relatively few studies have been conducted in which baroreceptor control of cardiac output has been measured, despite the importance of this variable in determining arterial pressure. Furthermore, most prior experimental studies have not examined the same animals before and after the development of hypertension or have been conducted in anesthetized, acutely prepared animals. This latter point is particularly important since it is well recognized that general anesthesia and recent surgery modify baroreflex control of the circulation.

Accordingly, the goal of the present study was to conduct a systematic evaluation of the effects of bilateral carotid occlusion on arterial pressure, cardiac output, heart rate, and total peripheral resistance in the same group of conscious, chronically instrumented dogs before and at weekly intervals during the development of perinephritic hypertension. Sensitivity of the heart rate component of the baroreflex was also examined weekly by determining the pulse interval/ systolic arterial pressure regression slope using bolus injections of phenylephrine (10 μg/kg i.v.) to raise arterial pressure acutely.

Materials and Methods

Mongrel dogs (n = 14) of either sex were tranquilized with xylazine (2 mg/kg i.m.) and anesthetized with sodium pentobarbital (30 mg/kg i.v.). Through a left thoracotomy at the fourth intercostal space, Tygon catheters were implanted in the aorta and left atrial appendage. An electromagnetic flow transducer (Zeppa Instruments, Seattle, Wash.) was implanted around the ascending aorta. In addition, hydraulic occluders (R.E. Jones, Silver Spring, Md., or Hazen-Evenett Co., Teaneck, N.J.) were placed around both
carotid arteries via a midline cervical incision. Animals were treated with prophylactic antibiotics and allowed to recover 2–3 weeks before experimentation. During that time, the animals were trained to lie quietly on their sides on a table. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the "Guide for the Care and Use of Laboratory Animals" [DHHS Publication No. (NIH) 85-23, revised 1985].

After baseline studies on the effects of bilateral carotid occlusion on hemodynamics were completed, a left flank incision was made and the kidney dissected free of its fat pad. The kidney was wrapped in sterile raw silk and then plastic sheeting to prevent adhesions, according to the method introduced by Page13 and modified by Overbeck16 and Ferrario et al.17 One week after the renal wrap procedure, the right kidney was removed under the conditions described above. A control group of sham wrapped animals (n = 3) was prepared similarly except the left kidney was dissected, plastic sheeting was laid beside the kidney, and the incision was closed. In these animals, nephrectomy was carried out 1 week later.

In 4 additional animals, to study carotid sinus baroreceptor control without the influence of the aortic baroreceptors, selective denervation of the aortic arch was performed. During the initial surgery, the aortic nerves were sectioned, and all nerve fibers and connective tissue were stripped free of the aortic arch and brachiocephalic and subclavian arteries. All stripped areas were painted with 2% phenol solution. The efficacy of the denervation was confirmed prior to killing the animal. At this time, using halothane 0.5 vol %, the carotid sinus nerves were sectioned bilaterally in the neck. After recovering from this procedure, elimination of the reflex heart rate responses to injections of phenylephrine (5 μg/kg) and nitroglycerin (10 μg/kg) confirmed complete baroreceptor denervation.

In a subgroup of the 14 animals, the changes in carotid sinus pressure (n = 5) and right atrial pressure (n = 3) were evaluated before hypertension and 2 weeks after renal wrapping, using catheters placed in the carotid artery via the thyroid artery and in the right atrium via the jugular vein. Catheters were removed after each measurement to prevent damage to the artery. Responses to bilateral carotid occlusion were tested before and after catheter placement on each occasion. Carotid artery and right atrial pressure were also measured in two of the aortic denervated dogs.

Arterial pressure was measured with a Statham P23 Db strain gauge (Statham Instruments, Oxnard, Calif.). Ascending aortic blood flow was measured with electromagnetic flowmeters (Benton Instruments, Cupertino, Calif.) that were calibrated in vitro using timed blood collections. Zero blood flow was assumed to occur in late diastole.

All pressure and flow data were recorded on magnetic tape (model 5600C, Honeywell, Denver, Colo.) and played back on a multichannel oscillograph (Gould Brush Mark 200, Cleveland, Ohio). Electronic resistance-capacitance filters with 2-second time constants were used to derive mean arterial pressure, while a filter with an 8-second time constant was used to derive mean ascending aortic blood flow, i.e., cardiac output minus coronary blood flow. Total peripheral resistance was calculated as the quotient of mean arterial pressure and mean aortic blood flow, and stroke volume was calculated as the quotient of mean aortic blood flow and heart rate.

In 14 dogs, the effects of 150–180-second periods of bilateral carotid occlusion were examined in the conscious, normotensive state 2–3 weeks after recovery from surgery. Data were analyzed 60–90 seconds into the response, when all parameters were stable. One to three bilateral carotid occlusions were carried out in each dog at 15-minute intervals, and responses were averaged. Dogs were studied in the normotensive state, one week after renal wrapping, and at weekly intervals following contralateral nephrectomy. In addition, at the same weekly intervals, bolus injections of phenylephrine (10 μg/kg i.v.) were administered in 6 of the 14 dogs, and the pulse interval/systolic arterial pressure (PI/SAP) slopes were determined according to the Smyth et al.14 method. Finally, to compare the effects of a different hypotensive stimulus, bolus injections of nitroglycerin (10 μg/kg i.v.) were administered to 9 dogs before and at weekly intervals during the development of hypertension. A separate group of 3 dogs was studied using the same protocols before and after sham wrapping followed one week later by contralateral nephrectomy.

In a subgroup of 5 of the 14 dogs, responses to bilateral carotid occlusion were examined in the normotensive state and at 2 weeks after renal wrapping before and after β-adrenergic receptor blockade with propranolol (1.0 mg/kg i.v.; Ayerst Laboratories, New York), alone and in combination with atropine methyl bromide (0.1 mg/kg; Sigma Chemical Co., St. Louis, Mo.).

In the hypertensive dogs, weight decreased slightly by 2 weeks after renal wrapping, from normotensive values of 25.5 ± 1.6 to 24.3 ± 1.7 kg, and hematocrit decreased from 43 ± 1.6 to 34 ± 1.2%. Both blood urea nitrogen (BUN) and creatinine values were increased by 2 weeks, from 13 ± 2 to 34 ± 6 mg/dl and 0.8 ± 0.1 to 1.7 ± 0.2 mg/dl, respectively. Plasma Na⁺ (141 ± 1 meq/l) and plasma K⁺ (4.2 ± meq/l) values did not change significantly with the development of hypertension. Values for BUN, creatinine, and plasma Na⁺ and K⁺ were determined by commercial laboratory blood chemistry screening service (Tufts University, Boston, Mass.). Sham dogs also showed a slight increase in BUN from 17 to 21 mg/dl by 2 weeks after sham wrapping, while all other parameters remained stable.

Mean ± SEM for baseline values and changes from control were calculated. When one measurement was compared to control values, the paired t test was employed. For example, differences in baseline values and changes from baseline of each parameter between
Effects of Bilateral Carotid Occlusion Before and During the Development of Hypertension (Table 1)

Responses of a typical dog to bilateral carotid occlusion before and after hypertension are presented in Figure 1. In 14 normotensive, conscious dogs, 150-180 seconds of bilateral carotid occlusion increased mean arterial pressure significantly by 38 ± 2 from 101 ± 2 mm Hg (p < 0.05), heart rate by 6 ± 3 from 84 ± 4 beats/min and total peripheral resistance significantly by 19 ± 2 from 46 ± 3 mm Hg/l/min (p < 0.05). Cardiac output decreased nonsignificantly by 101 ± 56 from 2,299 ± 128 ml/min, and stroke volume decreased nonsignificantly by 3 ± 1 from 29 ± 3 ml (p < 0.05). Two weeks after renal wrapping, in the same dogs, there were significant increases in baseline mean arterial pressure, cardiac output, and total peripheral resistance (p < 0.05), while heart rate was significantly lower (p < 0.05) (Table 1). At 2 weeks after renal wrapping, bilateral carotid occlusion increased mean arterial pressure significantly by 59 ± 5 from 130 ± 4 mm Hg (p < 0.05), heart rate by 36 ± 5 from 69 ± 3 beats/min (p < 0.05), cardiac output by 458 ± 103 from 2,711 ± 239 ml/min (p < 0.05), and total peripheral resistance by 13 ± 3 from 52 ± 4 mm Hg/l/min (p < 0.05), while stroke volume decreased by 8 ± 1 from 40 ± 3 ml (p < 0.05). The responses of mean arterial pressure, heart rate, cardiac output, and stroke volume to bilateral carotid occlusion were all significantly greater (p < 0.05) at 2 weeks after renal wrapping than in normotension (Table 1). Before hypertension, mean right atrial pressure was −0.8 ± 1.8 mm Hg and in response to bilateral carotid occlusion, was −1.0 ± 1.4 mm Hg. Two weeks after renal wrapping, mean right atrial pressure in the same dogs was 0.3 ± 0.9 and −0.5 ± 1.0 mm Hg during bilateral carotid occlusion.

Although 14 dogs were studied in the normotensive state and at 2 weeks after renal wrapping, only 6 dogs were studied at every week of the 7-week protocol. Weekly sequential data from these 6 dogs from the normotensive state through 3 weeks of hypertension are presented graphically in Figures 2 and 3. In these dogs, the response of mean arterial pressure was significantly greater than normotension at renal wrap and 2 weeks after renal wrap (nephrectomy + 1 week). Cardiac output and heart rate responses to bilateral carotid occlusion were significantly greater than normotensive control at renal wrap, 2, 3, and 4 weeks after renal wrapping (p < 0.05). The response of total peripheral resistance to bilateral carotid occlusion did not increase during the development of hypertension. At 3 and 4 weeks after renal wrapping, the responses of total peripheral resistance were reduced, but these changes were not statistically significant.

Effects of Bilateral Carotid Occlusion on Carotid Sinus Pressure (Table 2)

In 5 dogs, mean and phasic carotid sinus pressure were measured before and during bilateral carotid occlusion in normotension and again when the dogs were hypertensive, 2 weeks after renal wrapping. In normotension, mean carotid sinus pressure fell by 42 ± 4 from 98 ± 6 mm Hg, and carotid sinus pulse pressure decreased from 45 ± 4 to 3 ± 1 mm Hg during bilateral carotid occlusion. At 2 weeks after renal wrapping, the fall in mean carotid sinus pressure with bilateral carotid occlusion was similar to the fall that occurred in normotension, decreasing by 36 ± 8 from 120 ± 3 mm Hg. Carotid sinus pulse pressure in hypertension decreased from 58 ± 7 to 12 ± 3 mm Hg during bilateral carotid occlusion (Table 2). These data indicate that the enhanced responses of mean arterial pressure, heart rate, and cardiac output to bilateral carotid occlusion at 2 weeks after renal wrapping were not due to a greater fall in mean carotid sinus pressure or a greater drop in pulse pressure within the sinus. In fact, the decreases in both mean carotid sinus pressure

<table>
<thead>
<tr>
<th>Table 1. Responses to Bilateral Carotid Occlusion Before and After Hypertension in 14 Conscious Dogs</th>
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<tbody>
<tr>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/l/min)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
</tr>
</tbody>
</table>

*Significantly different from normotensive, p < 0.05.
and carotid sinus pulse pressure were similar despite the elevated baseline pressure at 2 weeks after renal wrapping.

**Table 2. Carotid Sinus Pressure Before and During Bilateral Carotid Occlusion at Normotension and 2 Weeks After Renal Wrapping in 5 Conscious Intact Dogs and 2 Aortic Baroreceptor Denervated Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Response</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean carotid sinus pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (n = 5)</td>
<td>98 ± 6</td>
<td>56 ± 4</td>
<td>-42 ± 4</td>
</tr>
<tr>
<td>Hypertensive (n = 5)</td>
<td>120 ± 3</td>
<td>84 ± 7</td>
<td>-36 ± 8</td>
</tr>
<tr>
<td>Aortic denervated dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (n = 2)</td>
<td>105</td>
<td>84</td>
<td>-21</td>
</tr>
<tr>
<td>Hypertensive (n = 2)</td>
<td>131</td>
<td>121</td>
<td>-10</td>
</tr>
<tr>
<td><strong>Carotid sinus pulse pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (n = 5)</td>
<td>45 ± 4</td>
<td>3 ± 1</td>
<td>-42 ± 4</td>
</tr>
<tr>
<td>Hypertensive (n = 5)</td>
<td>58 ± 7</td>
<td>12 ± 3</td>
<td>-46 ± 5</td>
</tr>
<tr>
<td>Aortic denervated dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (n = 2)</td>
<td>43</td>
<td>7</td>
<td>-36</td>
</tr>
<tr>
<td>Hypertensive (n = 2)</td>
<td>54</td>
<td>10</td>
<td>-44</td>
</tr>
</tbody>
</table>

**Sham Wrapped Dogs**

Three dogs were studied before and after sham wrapping followed by contralateral nephrectomy. Before sham wrapping, bilateral carotid occlusion increased mean arterial pressure by $23 \pm 7$ from $98 \pm 6$ mm Hg, heart rate by $3 \pm 1$ from $91 \pm 6$ beats/min, and cardiac output decreased slightly by $111 \pm 56$ from $2,467 \pm 251$ ml/min. Total peripheral resistance increased by $12 \pm 2$ from $40 \pm 2$ mm Hg/l/min, and stroke volume decreased slightly by $-2.4 \pm 0.4$ from $28.3 \pm 0.5$ ml. Two weeks after sham wrapping, bilateral carotid occlusion increased mean arterial pressure by $22 \pm 5$ from $95 \pm 8$ mm Hg, heart rate did not change from $90 \pm 8$ beats/min, cardiac output fell slightly by $65 \pm 117$ from $2,421 \pm 111$ ml/min, and total peripheral resistance increased by $11 \pm 3$ from $39 \pm 3$ mm Hg/l/min. There were no significant differences in any of the baseline hemodynamic parameters or in the responses to bilateral carotid occlusion between the normotensive state and 2 weeks after sham renal wrapping.

**Aortic Denervated Dogs**

In 4 dogs, the aortic arch was surgically denervated during the initial surgery. In these dogs, in which the response to bilateral carotid occlusion was not buffered by aortic arch baroreceptors, the responses of mean...
arterial pressure, heart rate, and cardiac output to bilateral carotid occlusion in normotension were greater than in intact normotensive dogs. In normotensive, aortic baroreceptor denervated dogs, mean arterial pressure increased by 101 ± 10 from 105 ± 2 mm Hg, heart rate increased by 81 ± 21 from 82 ± 9 beats/min, cardiac output increased 175 ± 97 from 2,897 ± 479 ml/min, total peripheral resistance increased by 31 ± 2 from 40 ± 7 mm Hg/l/min, and right atrial pressure in 2 dogs did not change from −1 mm Hg in response to bilateral carotid occlusion. At 2 weeks after renal wrap, bilateral carotid occlusion increased mean arterial pressure by 124 ± 8 from 120 ± 7 mm Hg, heart rate by 102 ± 12 from 80 ± 8 beats/min, and cardiac output by 623 ± 200 from 3,146 ± 764 ml/min, while the response of total peripheral resistance was unchanged from normotension, increasing 29 ± 12 from 50 ± 15 mm Hg/l/min, and right atrial pressure in 2 dogs rose from 2 to 3 mm Hg. In aortic denervated dogs, changes in carotid sinus pulse pressure and mean carotid sinus pressure during bilateral carotid occlusion in hypertension were not exaggerated compared to those that occurred in response to bilateral occlusion in normotension (Table 2).

Effects of β-Adrenergic and Cholinergic Receptor Blockades (Table 3)

In a subgroup of 5 of the 14 animals, responses to bilateral carotid occlusion were evaluated in normotension and at 2 weeks after renal wrapping using β-adrenergic blockade with propranolol (1.0 mg/kg) alone and in combination with cholinergic receptor blockade with atropine (0.1 mg/kg). Increased pressor responses to bilateral carotid occlusion, mediated by increases in heart rate and cardiac output, were present 2 weeks after renal wrapping. After β-adrenergic and β-adrenergic plus cholinergic blockades, there were no longer any statistically significant differences in the response of mean arterial pressure, heart rate, or cardiac output to bilateral carotid occlusion between normotension and hypertension.

Table 3. Effects of β- and Cholinergic-Receptor Blockade on Hemodynamic Responses to Bilateral Carotid Occlusion Before and After Hypertension in 5 Conscious Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Response</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>104 ± 2</td>
<td>142 ± 2</td>
<td>38 ± 2*</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>122 ± 4</td>
<td>185 ± 8</td>
<td>63 ± 4*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>74 ± 6</td>
<td>85 ± 8</td>
<td>11 ± 3*</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>65 ± 7</td>
<td>97 ± 11</td>
<td>32 ± 5*</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>2,639 ± 177</td>
<td>2,601 ± 224</td>
<td>−37 ± 136</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2,831 ± 391</td>
<td>3,458 ± 477</td>
<td>627 ± 95*</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>40 ± 3</td>
<td>56 ± 5</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>46 ± 5</td>
<td>57 ± 8</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>36 ± 4</td>
<td>32 ± 4</td>
<td>−5 ± 1</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>43 ± 3</td>
<td>36 ± 2</td>
<td>−8 ± 2</td>
</tr>
</tbody>
</table>

*Significantly different from change from control in normotensive, p<0.05.
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bilateral carotid occlusion), responses to a transient unloading using a pharmacologic stimulus were unchanged by the development of hypertension.

**Discussion**

The concept that the baroreflex is reset and its sensitivity reduced in hypertension is based primarily on studies of heart rate responses to intravenous injections of pharmacologic agents that acutely raise or lower arterial pressure and has been reviewed by Kirchheim and Krieger et al. Most studies have used the method of evaluation of baroreflex sensitivity developed by Smyth et al. The present study also found a decrease in the sensitivity of the heart rate component of the baroreflex to increased arterial pressure in hypertension. The decreased slopes were apparent at 2 weeks after renal wrapping, somewhat in advance of the maximum developed elevations in arterial pressure.

The technique of Smyth et al provides information about only one aspect of baroreceptor function, i.e., control of heart rate, in response to baroreceptor hypertension, which is regulated primarily by the parasympathetic nervous system. We examined responses of arterial pressure, cardiac output, and total peripheral resistance to baroreceptor hypotension during the development of perinephritic hypertension, which also examines the sympathetic component of the reflex. In contrast to the PI/SAP data, which indicated a reduction in baroreceptor sensitivity, experiments utilizing bilateral carotid occlusion indicated significantly enhanced baroreflex responses of mean arterial pressure, which occurred early in the development of hypertension (Figure 2). Normal responses of arterial pressure to baroreflex stimulation have been observed in hypertensive dogs, humans, and rabbits. However, the present study is unique in demonstrating consistent and significantly enhanced pressor responses to baroreceptor unloading. Ueda et al noted a resetting toward more sensitive baroreflex control during the development of renal hypertension. The enhanced pressor responses seen during the development of hypertension were no longer observed by 3 weeks after renal wrapping in our experiments. The enhanced response appears transient and would not have been observed if different groups of dogs were studied just prior to and after hypertension was fully established. This may explain why in a preliminary report from Stephenson and Tagett the gain of baroreflex control of arterial pressure was reduced in response to both increases and decreases in carotid sinus pressure in a group of conscious dogs with perinephritic hypertension.

To investigate the mechanism of the enhanced responses to bilateral carotid occlusion in mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) in 6 conscious dogs before (normotensive) and at weekly intervals during the development of hypertension.

![Figure 2](image-url)
were felt to be due to increased responses of total peripheral resistance rather than cardiac output. However, these conclusions are based on two separate groups of patients reported in two different publications. In our experiments, the same animals were studied using direct and continuous measurement of cardiac output before and during the development of hypertension.

It is also important to note that when the dogs in the present study were normotensive, the mean arterial pressure increases that occurred in response to bilateral carotid occlusion were due to increases in total peripheral resistance, and cardiac output was unchanged. These results are in agreement with other studies of responses of cardiac output and total peripheral resistance to bilateral carotid occlusion in normotension.

The state of the peripheral resistance component of the baroreceptor reflex in hypertension is a more controversial issue. Gordon and Mark found impaired baroreflex control of hind limb vascular resistance in prehypertensive rats, while Angell-James and George found increased peripheral resistance and lumbar sympathetic nerve activity, respectively, to be increased during baroreceptor stimulation in renal hypertensive rabbits. It is important to recognize that the responses of one bed may not reflect the responses of the total systemic vasculature. In the current experiments, responses of total peripheral resistance during the development of hypertension were similar to those observed in the normotensive state and then appeared to decrease later in the development of the disease state (Figure 3).

The increased cardiac output observed in the present study support the contention that responsiveness to norepinephrine is enhanced during the development of hypertension. From this study suggest that responsiveness to norepinephrine is enhanced during the development of perinephritic hypertension. Furthermore, other preliminary data from our laboratory suggest that responsiveness to norepinephrine is enhanced during the development of perinephritic hypertension.

The increased cardiac output observed in the present investigation in response to bilateral carotid occlusion in hypertension could have been due to either increased heart rate or stroke volume. We observed that the enhanced cardiac output response to bilateral carotid occlusion in the hypertensive dogs in the present study was mediated entirely by increased heart rate (Figures 2 and 3, Table 1). This evidence of enhanced sensitivity of the heart rate component of the baroreceptor reflex in the hypertensive dogs appears initially to conflict with the evidence of decreased heart rate sensitivity suggested by the PI/SAP slope data, which show a reduction in slope, indicating a reduction in sensitivity. However, Thames et al. found baroreflex control of heart rate to be preserved during transient decreases in arterial pressure in the renin hypertensive rabbit, while baroreceptor control of heart rate during transient increases in arterial pressure was impaired. Our data on responses to bolus injections of nitroglycerin concur with those of Thames et al. West and Korner also found preserved responses of heart rate at low levels of arterial baroreceptor pressure. Thus, the results of the present study support the contention that vagally mediated responses to transient stimuli may be more likely to be compromised by the development of hypertension. In contrast, steady-state baroreceptor stimuli, which evoke sympathetically mediated responses, appear to be enhanced as the data from the current study suggest.

To determine the role of the autonomic nervous system in the enhanced pressor response to bilateral carotid occlusion in hypertension, the responses were studied following beta-blockade with propranolol, as well as combined β-adrenergic and cholinergic receptor blockade. In the absence of blockade, increased pressor responsiveness to bilateral carotid occlusion in hypertension was mediated by cardiac output and heart rate. After β-adrenergic blockade, there were no longer any statistically significant differences between responses of mean arterial pressure, cardiac output, or heart rate to bilateral carotid occlusion between normotension and hypertension (Table 3). These results indicate that the enhanced responses of arterial pressure to bilateral carotid occlusion are mediated primarily by β-adrenergic mechanisms. The elimination of the enhanced heart rate response in hypertension via β-receptor blockade is consistent with the observation made earlier in this laboratory of increased β-receptor density in dogs with perinephritic hypertension. Furthermore, other preliminary data from our laboratory suggest that responsiveness to norepinephrine is enhanced during the development of perinephritic hypertension.

The data from the three sham-operated, nephrectomized dogs studied indicated that nephrectomy or surgical procedures did not play a role in the enhanced responses to bilateral carotid occlusion observed in the
hypertensive dogs. Furthermore, data from the hypertensive dogs with aortic denervation indicated that the enhanced responsiveness present at 2 weeks after renal wrapping in the hypertensive dogs was not due to decreased buffering from the aortic receptors because the aortic denervated dogs showed enhanced mean arterial pressure, heart rate, and cardiac output changes during the development of hypertension comparable to the intact hypertensive dogs.

It was possible that the differences observed in the responses to bilateral carotid occlusion before and after hypertension may have been due to a difference in the magnitude of the stimulus presented to the carotid sinus baroreceptors during bilateral carotid occlusion. However, in both intact and aortic denervated dogs in which carotid sinus pressure was measured, the magnitude of the fall in mean carotid artery pressure at 2 weeks after renal wrapping was not exaggerated compared to that observed in normotension (Table 2). The decrease in pulse pressure in response to bilateral carotid occlusion was also similar. The change in pulse pressure may be an important aspect of the stimulus to the baroreceptors in the conscious hypertensive dog, and perhaps is involved in the difference between the results of the present study and the Stephenson and Tagett study in which the pressure stimulus presented to the carotid sinus was constant.

In summary, the present study demonstrates increased sensitivity of the arterial pressure component of the baroreceptor response to carotid sinus hypertension in conscious dogs during the development of hypertension. These enhanced responses were no longer present 3 weeks later. The enhanced response of arterial pressure to bilateral carotid occlusion was mediated by increases in cardiac output that were primarily due to increases in heart rate. Pressor, heart rate, and cardiac output responses to bilateral occlusion were no longer enhanced following \( \beta \)-adrenergic blockade, indicating that enhanced responses to carotid baroreceptor unloading in conscious dogs with peri-nephritic hypertension are mediated primarily by \( \beta \)-adrenergic mechanisms. These mechanisms, i.e., either enhanced sensitivity of the baroreflex to hypertension or enhanced \( \beta \)-adrenergic responsiveness, may be important in the development of hypertension.

Acknowledgment

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Key Words • hypertension • baroreflex • conscious dogs • cardiac output • carotid sinus
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