Mechanism of the Carotid Sinus in Experimental Hypertension
By Paul Kezdi, M.D.

In recent years interest has been renewed in the role of baroreceptors in hypertension. It was emphasized again by Heymans and Neil that the baroreceptors function not only as regulators, but also as moderators, since they constantly decrease high central sympathetic vasoconstrictor and cardiac accelerator outflow to normal levels. Removal of this function by disruption of the buffer nerves results in the well-known experimental neurogenic hypertension. Despite their apparently important function in cardiovascular regulation, it is not clear what role they do play in the pathogenesis of hypertension. Since experimental neurogenic hypertension and human hypertension differ in several ways, any participation of the baroreceptors in the mechanism of either human or experimental non-neurogenic hypertension has been doubted by many investigators.

Any understanding of the mechanism of the baroreceptors in hypertension is related to the question of why the baroreceptors fail to counteract the elevated blood pressure. It has been suggested that the threshold of the baroreceptors is "set" to the higher blood pressure level in both human and chronic experimental renal hypertension, and instead of opposing the elevated pressure, they actually maintain it. The mechanism by which this "higher set" occurs is not understood. Heymans suggested that abnormal loss of tension within the arterial wall, resulting in decreased stimulation of the receptors, might be the cause of the "higher set" in hypertension. Whether this change in the arterial wall in the baroreceptor areas is the result of humoral factors produced in the course of experimental

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**Figure 1**
Sketch of the constricted carotid artery. C.S. = carotid sinus; E.C. = external carotid; I.C. = internal carotid; Occ. = occipital artery; S.T.A. = superior thyroid artery; C.S.N. = carotid sinus nerve; C.C.N. = common carotid nerve.
renal hypertension or of mechanical factors due to permanent distention by the elevated intra-arterial pressure is not known. The experiments reported here were designed to investigate this particular problem. The plan was to protect the wall of the carotid sinus from the increased arterial blood pressure of experimental renal hypertension by means of chronic constriction of the common carotid arteries. The major branches distal to the carotid sinus were tied to prevent backflow and retrograde elevation of the pressure through collaterals.

Methods

Surgery was performed using sodium pentobarbital (25 mg./Kg.) anesthesia. The common carotid artery was constricted bilaterally by a silver clip above the superior thyroid artery in the majority of the animals. In later animals the constriction was below the superior thyroid artery (fig. 1). Pressure was measured in the lingual artery before and after constriction of the common carotid artery and tying of its branches. The constriction was increased until pressure in the carotid sinus was significantly below systemic pressure.

Renal hypertension was produced by wrapping one kidney and removing the other. In some of the animals, Goldblatt clamps were used to constrict one renal artery. In a group of 10 dogs the opposite ("healthy") kidney was not removed. The animals were observed for a period of 5 to 11 months after production of unilateral or bilateral renal hypertension. Blood pressure was measured weekly in the conscious animal by direct femoral artery puncture. Six months after production of hypertension, the pressure in the carotid sinus was rechecked under pentobarbital anesthesia (fig. 2).

In eight animals with bilateral renal hypertension, carotid sinus nerve potentials were recorded before and after anastomosing the sinus with a systemic artery or perfusing the isolated sinus with arterial blood using a sine wave pump. Nerve potentials were recorded simultaneously with endosinus pressure by cathode ray oscillograph and photographed at paper speed of 75 mm./sec.

![FIGURE 2](image)

**Pressures in the constricted carotid sinus. Upper left=before constriction; upper right=after constriction; lower=systemic and carotid sinus pressure (lower tracing) after six months of hypertension.**

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**TABLE 1**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control period mean BP (range) mm. Hg</th>
<th>Hypertension mean BP (range) mm. Hg</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18*</td>
<td>118 (116-120)</td>
<td>184 (156-230)</td>
<td>11</td>
</tr>
<tr>
<td>9*</td>
<td>135 (125-140)</td>
<td>182 (164-230)</td>
<td>9</td>
</tr>
<tr>
<td>12*</td>
<td>115 (100-125)</td>
<td>188 (168-210)</td>
<td>6</td>
</tr>
<tr>
<td>21*</td>
<td>128 (124-130)</td>
<td>205 (185-245)</td>
<td>5</td>
</tr>
<tr>
<td>22*</td>
<td>127 (114-135)</td>
<td>190 (180-220)</td>
<td>5</td>
</tr>
<tr>
<td>25†</td>
<td>135 (120-150)</td>
<td>169 (140-168)</td>
<td>5</td>
</tr>
<tr>
<td>26†</td>
<td>150 (145-158)</td>
<td>155 (140-164)</td>
<td>5</td>
</tr>
<tr>
<td>15‡</td>
<td>122 (118-128)</td>
<td>167 (140-195)</td>
<td>6</td>
</tr>
<tr>
<td>13‡</td>
<td>126 (124-128)</td>
<td>159 (134-156)</td>
<td>5</td>
</tr>
<tr>
<td>19‡</td>
<td>108 (98-120)</td>
<td>119 (98-120)</td>
<td>5</td>
</tr>
<tr>
<td>Average</td>
<td>126 (118-134)</td>
<td>172 (155-200)</td>
<td>6</td>
</tr>
</tbody>
</table>

*Constriction above sup. thyroid artery.
†Constriction below sup. thyroid artery.
§Goldblatt clamp to one renal artery.
§§P < 0.01.
Results

Persistent Unilateral Renal Hypertension
in Carotid-Constricted Dogs

Following wrapping of one kidney or placing a Goldblatt clamp on one renal artery, the majority of the animals developed moderate to marked hypertension (table 1). This finding is similar to our previous observation that disruption of the carotid sinus nerves and narrowing of one renal artery resulted in moderate to marked hypertension in the great majority of animals (table 2). Hypertension persisted for a year under the latter conditions and was maintained even after removal of the kidney whose renal artery had been constricted. In a group of five control dogs, constriction of one renal artery alone led to transient blood-pressure elevation but not to permanent hypertension (table 3). We postulated an enhancing effect of carotid sinus nerve disruption on unilateral renal hypertension of the dog.

Carotid Sinus Nerve Potentials

When the sinus was connected to the systemic circulation, nerve potentials from the

TABLE 2
Comparison of Blood Pressure in Dogs with Carotid Denervation Plus Unilateral Goldblatt Clamp and Constriction of Common Carotid Plus Wrapping of One Kidney (or Goldblatt Clamp)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of dogs</th>
<th>Control mean BP (range) mm. Hg</th>
<th>Hypertension mean BP (range) mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid denervated</td>
<td>15</td>
<td>121 (119-130)</td>
<td>165* (148-188)</td>
</tr>
<tr>
<td>Common carotid constricted</td>
<td>10</td>
<td>180 (118-134)</td>
<td>1721 (155-200)</td>
</tr>
</tbody>
</table>

*P < 0.01.
1P < 0.01.
Carotid sinus nerve potential in the perfused sinus which was protected by constriction. Upper pressure is systemic, lower is perfusion pressure at levels between 50 to 240 mm Hg.

Carotid sinus showed increased, or almost continuous, firing (fig. 3). Perfusion of the chronically constricted carotid sinus at different pressure levels showed that firing of the sinus nerve became continuous usually below hypertensive systemic pressure levels (fig. 4). Some firing was present at pressure levels as low as 50 mm Hg mean. This is in contrast to the findings of McCubbin, Green, and Page in the unprotected carotid sinus of renal hypertensive dogs, where firing was still phasic at hypertensive blood pressure levels and ceased slightly below normotensive levels.3

Discussion
It was not surprising that chronic constriction of both common carotid arteries had the same enhancing effect on unilateral renal

TABLE 3
Effect of Unilateral Artery Constriction on Blood Pressure in Dogs††

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control period</th>
<th></th>
<th>First 6 weeks after unilateral Goldblatt clamp</th>
<th></th>
<th>After first 6 weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean BP (range) mm Hg</td>
<td>Duration</td>
<td>Mean BP (range) mm Hg</td>
<td>Duration</td>
<td>Mean BP (range) mm Hg</td>
<td>Duration</td>
</tr>
<tr>
<td>Average</td>
<td>126* (118-138)</td>
<td>2 mos.</td>
<td>145 (131-158)</td>
<td>7 mos.</td>
<td>132* (131-146)</td>
<td>7 mos.</td>
</tr>
</tbody>
</table>

*0.5 < P < 0.1.

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hypertension of the dog as did disruption of the carotid sinus nerves. The effect of chronic hypotension in the carotid sinus is physiologically the same as disruption of the carotid sinus nerves, namely decreased inhibition of central sympathetic outflow. Recent studies by others have indicated, however, that the problem is a complicated one. Bartter, Mills, and Gann have suggested that aldosterone production is influenced by baroreceptor nerves originating in the common carotid artery at the junction of the superior thyroid artery. Since we probably disrupted these nerves during dissection of the carotid artery, it is entirely possible that decreased buffering of sympathetic outflow as well as decreased buffering of aldosterone regulating centers is involved in the enhancement of unilateral renal hypertension by chronic carotid artery constriction. Confirmation of the experiments of Bartter and co-workers must be awaited before the mechanism of this enhancing effect can be fully understood.

Although the number of carotid sinus nerve potential recordings in this experiment is not sufficient, they do suggest that the “higher set” is due to the hypertension itself rather than to some humoral agent. The continuously increased arterial stretch in hypertension probably results in some damage of the stretch-sensitive arterial walls, thus decreasing stimulation and promoting “higher set” of the carotid sinus.

This increased stretch of the carotid sinus is prevented by constriction of the common carotid artery. If humoral factors or electrolyte changes in the arterial wall are responsible for the “higher set,” they would reach the sinus irrespective of constriction of the carotid artery. Heymans’ theory of an abnormal state of contraction, namely a decreased intramural tone of the barosensitive arterial
walls, implicates a humoral factor as a cause. Epinephrine locally on the carotid sinus will increase the nerve potential while phenolamine will decrease nerve potential from the sinus nerve. Increased concentration of circulating pressor substances in renal hypertension would, if anything, increase the tone of the sinus wall, increase carotid sinus sensitivity, and decrease blood pressure. Electrolyte changes and water logging as shown by Tobian and Redleaf would explain such a defect in stretchability of the barosensitive arterial wall; however, it would not explain why the "higher set" does not take place in the protected sinus.

This adaptation or "higher set" requires time. In acute experiments the carotid sinus resists adaptation, since its response does not diminish after hours of distention, as shown by Koch. If systemic pressure is increased to extremely high levels for one or two hours by infusion of intravenous norepinephrine, the increased potentials in the carotid sinus nerve persist without diminishing (fig. 5). Whether the prolonged stretch produced by the chronic hypertension affects the barosensitive arterial walls or the receptors themselves cannot be decided by these experiments. The occurrence of some damage to the receptor endings under these conditions has been reported by Hilgenberg, who found degenerative changes and even complete destruction of some receptor endings in the carotid sinus area in hypertensive humans.

It is possible that primary changes in the barosensitive arterial wall can initiate a "higher set" of the carotid sinus and thereby the increased sympathetic outflow in primary or essential hypertension. If future experiments confirm the findings that not only sympathetic outflow, but also aldosterone production, is regulated by the baroreceptors, both the tendency to increased sympathetic outflow and increased aldosterone production might be attributed to a "higher set" of this mechanism. This is the challenge for further investigation of baroreceptor function in hypertension.

References
CAROTID SINUS IN EXPERIMENTAL HYPERTENSION

Discussion

Dr. Sjoerdsm: Is there any evidence that systematically administered norepinephrine has a direct effect on the carotid receptors independent of blood pressure? There is some discussion about whether tumors of this area may contain norepinephrine on occasion. Could this amine actually be involved at an afferent receptor level in addition to being a neuromediator on the effector side?

Dr. Kezdi: It would be quite difficult to differentiate the systemic effect of norepinephrine from the effect on the arterial wall of the carotid sinus. However, the amount of norepinephrine injected into the arterial wall of the sinus by Heymans is probably much higher than the concentration attained locally when norepinephrine is infused systemically. Increased firing of the carotid sinus nerve during infusion of norepinephrine is probably due entirely to the increased intra-arterial pressure.

Dr. Neil: If you infuse norepinephrine through the isolated sinus up to concentration $10^{-8}$, which would be higher than anything that would happen in life, the sinus nerve ending response is not affected. Secondly, as regards the carotid body tumor, it is an interesting idea, but the carotid body has a fantastic blood flow of 2,000 ml. per 100 Gm. per minute. According to Dixon Boyd of Cambridge and his colleagues, LeVer and Lewis, the epitheloid cells of glomus contain inclusion structures in the cytoplasm which are of catecholamine nature. I doubt you could conceivably get, acting on the sinus (which is headstream of the carotid body), any local effects of norepinephrine on the structure.

Dr. Freis: Professor Hauss has inserted electrodes in the carotid sinus area of conscious human patients and has recorded action potentials which look somewhat like carotid sinus potentials. He finds he can divide his patients into (a) normotensives, (b) those with what he calls secondary hypertension, that is, renal hypertension, and (c) patients with long-standing essential hypertension. In the so-called renal hypertensives, he found increased activity of the carotid sinus and in the long-standing essential hypertensives, decreased activity in the carotid sinus, which may be due to the stretching of the walls, as you say.

Dr. Kezdi: I am aware of this study of Dr. Hauss and his associates. What I could not explain is that their recordings show no pulse-related fluctuations. We know from animal experiments that potentials from the sinus are related to the pulsatile changes in pressure, increasing during systole and decreasing during diastole. Their recordings were continuous, both in hypertensive and normotensive subjects. I do not know what physiologists would say about the published recordings. Dr. McCubbin has recorded carotid nerve potentials directly in human beings. Maybe he can tell us whether the same phasic nerve potentials occur in man as in experimental animals. The validity of the study of Hauss et al. in regard to the relation of the carotid sinus to hypertension rests entirely on the question of whether they recorded the baroreceptor potentials.

Dr. McCubbin: I was puzzled by the lack of pulse-synchronous firing in Hauss' recordings. As I recall them, there was steady firing throughout. In a limited number of experiments, we have found the same rhythmic firing in man as in dogs.

Dr. Neil: I would inject a note of warning: the carotid sinus nerve contains at least as many chemoreceptors as does baroreceptors. In animals breathing room air, the chemoreceptors are firing tonically although, admittedly, not very much. Firing profoundly depends on the flow through the chemoreceptors; thus, in renal hypertension arteriolar narrowing may have occurred in vessels supplying the carotid body and, despite the sustained rise in pressure, may result in the recording of chemoreceptor firing. To be convincing, one would have to show that these effects in hypertension were quite independent.
of the oxygen content of the blood. This would require only that the individual breathe pure oxygen to minimize any chemoreceptor contribution. The multifiber carotid nerve which contains baroreceptors and chemoreceptors also contains sympathetic components from the neighboring superior cervical ganglion, as shown very convincingly in Salt Lake City.

Dr. Tuttle: The 24-hour period that Dr. McCubbin indicated was necessary for carotid sinus adaptation is shorter than we usually think is required for hypertrophy of arterial muscles to develop. However, if you have ever ridden horseback, you know that, within 24 hours, the skeletal muscles have a marked response to increased exercise. I wonder if the change in the modulus of viscosity and elasticity mentioned by Dr. Peterson might be due to an early change in the direction of hypertrophy of the muscle wall within the 24-hour period in which it is observed.

Dr. Kezdi: This is a very difficult question to answer. Perhaps in the early phase of strain on the smooth muscle, there is a change in the chemical property of the muscle which alters its elasticity and response to stretch.
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