Persistent Hypertension in the Dog Following Disruption of the Carotid Sinus Nerves and Subsequent Unilateral Renal Artery Constriction

By Paul Kezdi, M.D.

Constriction of one renal artery in the dog does not as a rule produce sustained hypertension. Removal of the contralateral kidney, or bilateral renal artery constriction is necessary for the production of permanent hypertension. On the other hand, sustained hypertension may be produced regularly in the rat by unilateral renal artery constriction. It has been postulated that, in the rat, long standing hypertension damages the contralateral kidney which then maintains the elevated pressure by continued renin production. Another explanation attributes the persistence of hypertension to an extra-renal mechanism, initiated by the transient effect of unilateral renal ischemia and becoming self-perpetuating as a result of participation of the extra-renal mechanism. Still others have suggested that disturbance of a depressor function of the normal kidney necessary to maintain blood pressure within normal limits is responsible for the sustained hypertension.

Experiments have shown that baroreceptors are set at the high level in chronic renal hypertension and, thus, could participate in the maintenance of chronic hypertension.

In a previous paper we reported that disruption of the carotid sinus nerves and subsequent constriction of one renal artery in the dog resulted in persistent moderate hypertension. We concluded that carotid sinus disruption probably enhanced the development of hypertension in the dog following unilateral renal artery constriction. The dogs of the original experiment, therefore, were further observed and the experiment was extended to elucidate the mechanism of the combined carotid sinus and unilateral renal hypertension in the dog and to answer the following questions. Can this type of chronic hypertension be abolished by removal of the clamped kidney? Will carotid sinus nerve disruption alone lead to chronic hypertension? Will unilateral renal artery constriction, performed several months after carotid denervation, alter the course of hypertension? Does this type of hypertension alter renal function?

Methods

Mongrel dogs were used in which direct femoral artery blood pressure had been determined weekly for at least 2 months. In 1 group of dogs the carotid sinus nerves were isolated at their junction with the glossopharyngeal nerves and were crushed with an artery clamp several times. In another group, the nerves were cut and ligatures placed on both cut ends. The vago-noric nerves remained intact in all experiments. However, the buffer nerves of the thyroid-carotid junction were probably disrupted in most of the dogs at the time of the isolation of the common carotid artery.

A few days to a week later, a modified Goldblatt clamp was placed on 1 renal artery. However, in 5 dogs the clamp was applied 2 to 7 months after carotid sinus nerve disruption. The clamp was narrowed until a markedly decreased pulsation was felt in the distal portion. Blood pressure was measured with a mercury manometer weekly by direct femoral artery puncture. One year later the clamped kidney was removed in the surviving animals. The blood pressure in these animals was observed for at least another 6 months.

The function of the carotid sinus was tested in all of the dogs once or twice during the period of hypertension. For this purpose, the animals were anesthetized by Nembutal and the common carotid arteries were isolated. The effect of compression of the common carotids on femoral artery pressure was recorded. In some of the dogs, both common carotid arteries were explanted in a tube of skin.
Hypertension in the Dog

Table 1

Effect of Carotid Sinus Denervation and Unilateral Renal Artery Constriction on Blood Pressure in Dogs

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control period</th>
<th>Hypertension period</th>
<th>Postnephrectomy period</th>
<th>Remarks</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>
</tr>
<tr>
<td>35</td>
<td>122 (112-130)</td>
<td>2½ mos.</td>
<td>167 (140-188)</td>
<td>13 mos.</td>
</tr>
<tr>
<td>25</td>
<td>132 (118-142)</td>
<td>2 mos.</td>
<td>185 (170-230)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>18</td>
<td>132 (120-138)</td>
<td>2½ mos.</td>
<td>185 (160-208)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>22</td>
<td>111 (93-126)</td>
<td>2 mos.</td>
<td>183 (168-228)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>10</td>
<td>122 (112-130)</td>
<td>2 mos.</td>
<td>162 (154-188)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>40</td>
<td>100 (90-104)</td>
<td>2 mos.</td>
<td>136 (124-166)</td>
<td>15 mos.</td>
</tr>
<tr>
<td>26</td>
<td>130 (120-136)</td>
<td>2 mos.</td>
<td>187 (160-252)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>24</td>
<td>134 (118-140)</td>
<td>2 mos.</td>
<td>155 (136-178)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>60</td>
<td>109 (104-114)</td>
<td>1 mos.</td>
<td>154 (140-172)</td>
<td>12 mos.</td>
</tr>
<tr>
<td>25</td>
<td>131 (116-144)</td>
<td>2 mos.</td>
<td>156 (123-190)</td>
<td>8 mos.</td>
</tr>
<tr>
<td>41</td>
<td>128 (110-130)</td>
<td>3 mos.</td>
<td>160 (146-170)</td>
<td>8 mos.</td>
</tr>
<tr>
<td>16</td>
<td>106 (94-110)</td>
<td>1½ mos.</td>
<td>149 (136-172)</td>
<td>7 mos.</td>
</tr>
<tr>
<td>17</td>
<td>111 (100-128)</td>
<td>2 mos.</td>
<td>182 (166-196)</td>
<td>5 mos.</td>
</tr>
<tr>
<td>28</td>
<td>124 (112-134)</td>
<td>2 mos.</td>
<td>158 (144-182)</td>
<td>4 mos.</td>
</tr>
<tr>
<td>53</td>
<td>124 (120-134)</td>
<td>1½ mos.</td>
<td>162 (142-194)</td>
<td>3 mos.</td>
</tr>
<tr>
<td>Average</td>
<td>131 (120-130)</td>
<td>2 mos.</td>
<td>161 (148-188)</td>
<td>10 mos.</td>
</tr>
</tbody>
</table>

*p < 0.01
**p ≥ 0.05

Results

Carotid Sinus Disruption and Simultaneous Renal Artery Constriction

The mean and range of blood pressure before and after disruption of the carotid sinus nerves and narrowing of 1 renal artery in 15 dogs are shown in table 1. The duration of observation varied between 3 and 15 months following operation. In 5 of these dogs the ischemic kidney was removed 1 year after placing the Goldblatt clamp. The dogs then were observed for an additional 7 to 12 months. The remaining 10 dogs either died spontaneously before the end of the 1 year observation period, were sacrificed, or expired.
following operation on the carotid sinus or at the time of removal of the constricted kidney.

All 15 dogs developed significant hypertension following disruption of the carotid sinus nerves and narrowing of one renal artery. The blood pressure increase was moderate. The mean blood pressure increased from an average control value of 121 to 165 mm. Hg. The blood pressure increase was statistically significant (p < 0.01). The hypertension was usually more severe during the first 4 to 6 weeks. Subsequent pressures generally decreased but invariably remained above the control level throughout the observation period of 7 to 15 months. Significant changes in the pulse rate did not occur during the hypertensive phase.

Three of the 5 animals in which the clamped kidney was removed exhibited a subsequent slight decrease in blood pressure. The average decrease in the 5 animals was from 174 to 165 mm. Hg. The change was statistically not significant (0.1 > p ≥ 0.05).

Careful study of the constricted renal arteries at autopsy or after removal of the kidney showed that they were patent in all cases except in 1. No relation between the degree of narrowing the artery, atrophy of the kidney and the level of the blood pressure following renal artery constriction could be demonstrated.

**Table 2**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control period Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>First 6 weeks after Unilateral Goldblatt clamp Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>After first 6 weeks Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>120 (114-126)</td>
<td>3 mos.</td>
<td>132 (124-150)</td>
<td></td>
<td>130 (120-144)</td>
<td>12 mos.</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>31</td>
<td>133 (122-140)</td>
<td>2 mos.</td>
<td>150 (130-166)</td>
<td></td>
<td>134 (120-152)</td>
<td>7 mos.</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>32</td>
<td>121 (106-130)</td>
<td>2 mos.</td>
<td>146 (138-154)</td>
<td></td>
<td>136 (118-152)</td>
<td>7 mos.</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>33</td>
<td>135 (126-140)</td>
<td>2 mos.</td>
<td>146 (124-164)</td>
<td></td>
<td>131 (129-144)</td>
<td>5 mos.</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>34</td>
<td>129 (112-148)</td>
<td>2 mos.</td>
<td>151 (140-158)</td>
<td></td>
<td>133 (126-138)</td>
<td>5 mos.</td>
<td>Sacrificed</td>
</tr>
<tr>
<td>Average</td>
<td>126* (116-138)</td>
<td>2 mos.</td>
<td>145 (131-158)</td>
<td></td>
<td>132* (121-146)</td>
<td>7 mos.</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.2 > p > 0.1.

Renal Artery Constriction Without Disruption of the Carotid Sinus

Data from 5 dogs in which 1 renal artery was narrowed without operation on the carotid sinus nerves are shown in table 2. A slight increase in blood pressure was observed in all animals during the first 6 weeks after narrowing of the renal artery. However, the blood pressure returned to the control level in 2 of the animals, while in 3 it remained slightly increased. The change between the average control blood pressure and the pressure in the period after 6 weeks following narrowing of 1 renal artery (126 and 132 mm. Hg) was not significant (0.2 > p > 0.1). The animals were sacrificed after an observation period of 5 to 12 months following narrowing of the renal artery.

Carotid Sinus Denervation

Hypertension developed in 7 of 9 dogs following carotid sinus denervation alone (table 3). The blood pressure increase was usually gradual following carotid sinus denervation with the maximum increase 2 to 6 weeks after operation. The average increase was +26 mm. Hg (125 and 151 mm. Hg of columns 1 and 2 of table 3). The increase was less than in the combined carotid sinus and unilateral renal group (+44 mm. Hg of table 1). This difference in the average blood pressure increase of the carotid sinus denervated alone and the
HYPERTENSION IN THE DOG

combined carotid sinus unilateral group was statistically significant (p < .01).

Superimposed Later Renal Artery Constriction

Two to 7 months after bilateral carotid sinus denervation, 1 renal artery was narrowed in 5 dogs (table 3). A further blood pressure increase occurred in the 5 dogs (from 145 to 167 mm. Hg). The p value was 0.1 > p > 0.05. The total pressure increase was about the same, irrespective of whether the renal artery was narrowed soon after carotid denervation, or the clamp was placed several months later (+44 and +42 mm. Hg of table 1 and table 3 respectively).

Test of Carotid Sinus Function

The function of the carotid sinus was tested in all animals one or more times during the hypertensive phase (table 4).* Crushing the carotid sinus nerves rather than complete disruption was done in some of the animals on the basis that prolonged but temporary suspension of the buffer function might lead to the same enhancement of hypertension in dogs with unilateral renal artery constriction as permanent disruption.

In the dogs in which the nerves were only crushed, tests for carotid sinus function were negative or partially negative when performed between 1 and 6 months after crushing. However, the carotid sinus regained its function after 6 months in most of the animals. The average blood pressure increased following bilateral common carotid occlusion in 10 dogs in which the carotid sinus function later returned was +46 mm. Hg during the control period and +40 mm. Hg during the hypertensive phase. The level of hypertension did not change when carotid sinus function returned. In 5 dogs the function of only 1 of the carotid sinus nerves returned. Some tendency for the blood pressure to decrease was observed in dogs (16, 24 and 53) in which an early return of the carotid sinus function was detected. In dogs in which the carotid sinus nerves were permanently disrupted between ligatures, the occlusion test remained negative as expected.

Tetraethylammonium Chloride Test (Table 5)

The decrease in mean blood pressure following tetraethylammonium chloride (TEAC) in the combined carotid sinus and unilateral renal hypertensive dogs was similar to that found in normal controls.11 In 5 control dogs the decrease was -26 mm. Hg, while in 10 combined carotid sinus unilateral renal hypertensive animals the decrease was -23 mm. Hg. In contrast, dogs with neurogenic hypertension have been reported to exhibit an exaggerated response to TEAC.12

Renal Clearance

Creatinine and PAH clearances were measured in 3 dogs before and after the production of hypertension by carotid sinus denervation and unilateral renal artery constriction and again following removal of the clamped kidney in 2 dogs (table 6). Glomerular filtration rate and renal plasma flow decreased in all 3 animals when hypertension became established. Average creatinine clearance was 78 ml./min. before and 51 ml./min. after production of hypertension. The average PAH clearance decreased from 288 ml./min. to 145 ml./min. The renal plasma flow decreased relatively more than the glomerular filtration rate, as reflected by increased filtration fraction (29 before, 35 after). After removal of the constricted kidney a further slight decrease in the glomerular filtration rate and renal plasma flow occurred in 1 of 2 dogs.

Discussion

The experiments presented indicate that long standing moderate to marked hypertension can be produced in the dog by constriction of one renal artery if combined with bilateral disruption of the carotid sinus nerves. In animals in which the carotid sinus nerves were crushed, no relation between the return of the carotid sinus function and blood pres-

*Tables 4, 5 and 6 of this paper have been deposited as Document number 6324 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. Copies may be obtained by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.
Table 3

Effect of Bilateral Carotid Sinus Denervation and Subsequent Narrowing of One Renal Artery on Blood Pressure in Dogs

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>Mean BP (range) mm. Hg</th>
<th>Duration</th>
<th>Mean BP (range) mm. Hg</th>
<th>Postnephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122 (112-130)</td>
<td>2 mos.</td>
<td>133 (114-162)</td>
<td>4 mos.</td>
<td>172 (156-208)</td>
<td>13 mos.</td>
<td>170 (154-204)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>116 (104-126)</td>
<td>2 mos.</td>
<td>126 (118-136)</td>
<td>2 mos.</td>
<td>165 (156-196)</td>
<td>13 mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>119 (108-126)</td>
<td>1½ mos.</td>
<td>120 (118-122)</td>
<td>2 mos.</td>
<td>152 (140-172)</td>
<td>12 mos.</td>
<td>151 (140-170)</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>144 (140-150)</td>
<td>1½ mos.</td>
<td>184 (166-200)</td>
<td>7 mos.</td>
<td>185 (166-194)</td>
<td>3 mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>125 (120-130)</td>
<td>1 mos.</td>
<td>157 (132-160)</td>
<td>3 mos.</td>
<td>163 (166-167)</td>
<td>3 mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>194 (120-140)</td>
<td>2 mos.</td>
<td>102 (140-192)</td>
<td>6 mos.</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>124 (120-130)</td>
<td>2 mos.</td>
<td>155 (136-172)</td>
<td>6 mos.</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>140 (138-140)</td>
<td>1 mos.</td>
<td>182 (100-200)</td>
<td>6 mos.</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>105 (90-115)</td>
<td>2 mos.</td>
<td>140 (125-152)</td>
<td>3 mos.</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>125 (118-133)</td>
<td>1½ mos.</td>
<td>151 (137-166)</td>
<td>4½ mos.</td>
<td>167 (156-189)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Renal artery was not constricted.

\*p < 0.01.

\*0.1 > p ≥ 0.05

sure level was observed if recovery of the carotid sinus function took place several months after disruption. Early return of the function could be correlated in 3 animals with some amelioration of the hypertension.

Unilateral renal artery constriction did not lead to significant permanent hypertension. This is an agreement with the findings of others. The early transitory blood pressure increase following unilateral narrowing of the renal artery probably indicates that a renal hypertensive mechanism is active in the early phase of renal ischemia only. The blood pressure increase is eliminated either by counterregulatory changes or cessation of the renal mechanism.

In contrast to data in the literature, our observations indicate that carotid sinus nerve disruption alone can lead to a mild hypertension in some animals. The fact that the carotid sinus hypertension in our animals developed gradually several weeks after the disruption may explain this discrepancy. Other investigators did not state how long they followed their animals. The mechanism of this delayed hypertension in animals with the carotid sinus nerve disrupted is not clear. The observation of Thomas that the sudden increase of blood pressure after cutting all 4 buffer nerves temporarily declines 1 to 2 weeks and that permanent hypertension develops only thereafter is of interest in this connection. Heymans and Neil speculate that this may be explained by temporary control exerted by pulmonary and mesenteric baroreceptor mechanisms until they are overwhelmed by the absence of restraint of the medullary centers. The development of hypertension following carotid sinus nerve disruption alone would indicate that even the presence of functioning aortic nerves is not sufficient to prevent such hypertension in the long run.

Crandall and co-workers showed that con-
striction of the carotid sinus by a plastic cast leads to moderate hypertension. They assumed that altered cerebral hemodynamics was the cause of this hypertension. It may be argued that hypertension in our experiments is also the result of such altered cerebral hemodynamics due to scar tissue after the operation around the carotid arteries. However, in another experiment, narrowing of the external and internal carotid arteries by silver clips did not lead to hypertension until later disruption of the carotid sinus nerve. In 10 dogs the average pressure before operation on the neck was 119 mm Hg, while after operation it was 121 mm Hg during an observation period of 4 to 8 months postoperatively. This experiment is believed to be sufficient evidence to refute such arguments and can be considered as a control or sham operation on the neck.

It is unlikely that carotid sinus disruption alone is responsible for the chronic hypertension in the combined group of the experiment presented here, since in most of the animals blood pressure increased further when carotid sinus nerve disruption was followed by renal artery constriction several months later (dogs no. 1, 3, 8 and 75 of table 3). The mean blood pressure in the group with carotid sinus disruption and unilateral renal artery constriction was significantly higher than in the animals with carotid sinus disruption only. This would indicate that at least in some instances the 2 mechanisms are superimposable. McCubbin and Kezdi and Wennemark showed that the carotid sinus mechanism may be "set" at a higher level and may participate in the maintenance of the hypertension, or may be part of the extra-renal mechanism by which chronic hypertension is maintained in dogs whose 1 kidney is wrapped with cellophane, while the other is removed. The experiment presented here may bear out the fact that carotid sinus disruption enhances the extra-renal or renal mechanism by which chronic renal hypertension is maintained.

Page and McCubbin showed that disruption of the buffer nerves markedly enhances TEAC response. Chronic renal hypertensive dogs, on the other hand, were reported to show the same response to TEAC as normal dogs. In the experiments presented here, the response to TEAC was the same as in the normal controls. It appears that neurogenic factors play no more role in the maintenance of unilateral renal carotid sinus hypertension than of the chronic renal hypertension produced by other methods. How carotid sinus disruption enhances the renal or extra-renal mechanisms concerned with maintenance of hypertension, deserves further investigation.

Hypertension persisted following removal of the offending kidney in most of the animals. In some, a moderate decrease of pressure was observed suggesting in these dogs a continued influence of the constricted kidney on the chronic hypertensive blood pressure level. However, extra-renal, rather than renal factors, are probably important in this phase.

The renal function changes in the combined carotid sinus renal hypertensive group showing an increased filtration fraction were typical of those observed in hypertension in man. Glomerular filtration rate, renal plasma flow and filtration fraction changed very little after removal of the clamped kidney in 2 dogs. This observation lends no support to the suggestion that the unclamped kidney participates in the maintenance of hypertension in our experiments.

Summary

Constriction of 1 renal artery in combination with disruption of the carotid sinus nerves resulted in moderate chronic hypertension in dogs. Hypertension persisted at the same level in some of the animals after removal of the kidney 1 year later, while in others blood pressure decreased somewhat though not to the prehypertensive control level. Narrowing of 1 renal artery without carotid nerve disruption did not lead to significant chronic hypertension. Disruption of the carotid sinus nerves alone, on the other hand, produced mild to moderate hypertension. Constriction of 1 renal artery, if performed several months after carotid nerve disruption, further increased the blood pres-
sure in these animals. Tests of the carotid sinus nerves function by the occlusion reflex of the common carotids indicated a return of function several months after disruption in animals in which the carotid sinus nerves were only crushed. Hypertension persisted in these animals despite the return of the carotid sinus function. Tetraethylammonium chloride given intravenously to combined carotid sinus-unilateral renal hypertensive dogs resulted in blood pressure decrease similar to that produced in normal animals. Glomerular filtration rate and renal plasma flow decreased, and filtration fraction increased in 3 dogs following production of the combined type of hypertension.

**Summario in Interlingua**

Le constriiction de un arteria renal en combination con le disparation del nervus del sino carotic resultava in cases in grades moderate de hypertension chronic. Post le ablation del ren un anno plus tarde, le hypertension persisteva in certes del animates ill mesme del altere latere, produceva—mesmo in le absentia chronice del nervus del sino carotic, resultava in grados significative de hypertension. Lo constriction del nervus del sino carotic, del altere latere, proce-quadra—mesmo in le absen-865

**References**


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