ACUTE HYPERTENSION IN DOGS WITH CEREBRAL ISCHEMIA

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CUSHING (1) demonstrated in 1903 that increased intracranial pressure can cause hypertension in dogs. Many years later Nash (2) and Volhard (3) independently showed in heart-lung-brain preparations that there is definitely a vasopressor reflex originating within the cerebral vault, and McDowall (4) demonstrated that complete cerebral anemia causes a powerful pressor response. Yet it has been the tendency by many to believe that the body’s pressor receptors are located strictly in peripheral areas (5). Experiments with sympathectomy in hypertensive patients indicate that these patients have a hyper-reactive nervous system, and there are many reasons for believing that essential hypertension is possibly neurogenic in origin (6). For this reason the present study was undertaken to elucidate the nature of the central vasopressor reflex.

METHODS

The purpose of the surgical procedures in these studies was to abolish all reflexes originating in the carotid and aortic sinuses and thereafter to study the central vasomotor reflex resulting from ischemia of the brain. This was accomplished by two methods. In the first set of animals, all of the blood supply to the brain except that through the carotid arteries was occluded. Through an incision on each side of the neck immediately above the first rib the subclavian artery was tied at its junction with the axillary artery, and all branches from the subclavian artery were independently tied and cut. The costocervical, thyrocervical, internal mammary and vertebral arteries were occluded by this procedure. The carotid sinuses were stripped without obstructing the blood flow through the internal and external carotids, and the vagi were cut at a point approximately one inch below the carotid sinuses to denervate the aortic arch. Central vasopressor reflexes were then studied by compression of the common carotid arteries. In the second series of animals the entire bifurcation of each carotid artery, including the carotid sinus and the internal carotid up to the point of its entrance into the skull, was actually removed, and the common carotids, internal carotids and external carotids were ligated. The subclavian arteries were then isolated and tied in the neck as described for the first series of animals, and all branches of the subclavian were tied except the vertebrals. There-
fore, the remaining blood supply to the brain flowed entirely through the vertebral arteries except for collateral supply through spinal and muscular channels. The cerebral reflexes were then studied by compression of these vertebral arteries. A special screw clamp was devised for this purpose so that the incisions could be closed except for the projection of a small brass tube and screwing mechanism.

Because the respiration of the animals often ceased when the brain became ischemic, it was necessary to insert an intratracheal cannula for artificial respiration. The animals were anesthetized with sodium pentobarbital to a stage of medium surgical anesthesia. The experiments progressed over a period of 4 to 7 hours. During this time, approximately one half of the animals suffered a reduction in blood pressure below normal because of the extensive operative procedures. Nevertheless, these animals had essentially the same responses found in the other animals though quantitatively smaller. To insure that the carotid sinus areas were completely denervated, they were painted after stripping with a 1 per cent solution of phenol and electrically stimulated to prove that no further neurogenic connections existed from these areas. Blood pressure was recorded from a femoral cannula.

RESULTS

After standardizing the surgical procedures, various studies of the vasopressor reflexes were made in 16 animals as follows:

A. Acute occlusion of the common carotids with the remaining cerebral circulation intact produced the well-known results which are generally ascribed to the carotid sinus reflex. Clamping of either one of the common carotids produced a rise in blood pressure of approximately 6 to 10 mm. Hg. Occlusion of both carotids simultaneously produced an average rise in 12 animals of 26 mm. Hg. This rise in blood pressure was maintained for the duration of carotid occlusion regardless of how long the carotids were compressed, and the blood pressure returned to normal immediately after release of the clamps.

B. Acute occlusion of the common carotids after the vertebrals and other branches of the subclavian had been tied produced, in 8 animals, an average rise of blood pressure of 57 mm. Hg. The character of this rise in blood pressure was slightly different from that obtained before the vertebrals and accessory circulation had been occluded. In general, the blood pressure rose rapidly for 15 seconds, then slowly for approximately one minute, after which time there was a slow fall over a period of 8 to 15 minutes back to normal or below normal. At the end of each period of occlusion there was usually a 30-second period of compensatory subnormal pressure ranging 20 to 30 mm. below normal. Cerebral ischemia in these experiments was complete except for minor blood flow through collateral channels. For this reason, even the vasopressor centers probably became functionally inactivated after a few minutes, resulting in the slowly falling pressure. The greater rise in blood pressure after the vertebrals had been ligated than before could be explained by two possible mechanisms. First, there is the possibility that back pressure in the carotid sinuses, from the circle of Willis, was less in the second case. Second, there is possibly a pressureresponsive area located in the brain in addition to those in the peripheral circulation.

C. Acute occlusion of the common carotids with the vertebrals tied and carotid
sinuses denervated still caused a rise of blood pressure averaging 30 mm. Hg in 7 animals. In this instance the carotid sinuses were completely inoperative and the aortic sinuses, though still intact, were actually opposing the rise in blood pressure. The character of the blood pressure response was essentially the same as that noted before the carotid sinuses were denervated, though the height was less and the rapidity of rise was slightly decreased. Likewise when the clamps on the carotids were removed, the blood pressure fell rapidly and markedly to a level 20 to 30 mm. below normal, returning thereafter to normal in approximately 15 to 30 seconds.

D. Acute occlusion of the common carotids with the vertebrals tied, the carotid sinuses denervated and both vagi cut caused a rise in blood pressure averaging 46 mm. of mercury in 6 animals as shown in table 1. The blood pressure, after the vagi were cut, rose much more rapidly than before, reaching a maximum in approximately 30 seconds rather than in one minute and 15 seconds. The height of the pressure was approximately one and one-half times the blood pressure rise before the vagi were cut. Cutting the vagi removed two factors in the neurogenic control of blood pressure. First, it removed the tonic and reflex effect of the vagi on the heart. This caused a variable rise in blood pressure at the time of cutting the vagi. Second, cutting the vagi denervated the aortic arch. This removed the buffering action of the pressoreceptors of the aortic arch and resulted in a higher and more rapid rise in pressure after carotid occlusion. Blood pressure readings in this category were often over 200 and, in one animal, reached a mean pressure of 260 mm.

E. Acute occlusion of the vertebrals with the carotid sinuses totally ablated and the carotids, subclavians, costocervicals, and thyrocervicals all tied produced an average rise in blood pressure in 4 animals of 15 mm. Hg. In this instance the carotid sinuses had been completely removed and, therefore, could have had no effect whatsoever in producing this rise in blood pressure. The character of the rise in blood pressure was the same as that previously described when the brain was almost completely ischemic except that the total rise was less than that previously discussed.

F. Acute occlusion of the vertebrals in the 4 animals noted in paragraph E after both vagi had been cut caused a rise in blood pressure averaging 32 mm. Hg. In this set of observations, in which both the action of the vagi on the heart and the buffering action of the aortic arch had been removed, the result was an exaggeration of the central vasopressor response.

G. The entire neck except the spinal column was sectioned in two of the animals which already had both carotid sinuses ablated, the carotids, subclavians, costocervicals and thyrocervicals all tied, and the vagi cut. After this procedure, the average rise in blood pressure on occlusion of the vertebrals was 76 mm. Hg as noted in table 1. It appeared that the collateral circulation increased much more rapidly when the experiment was carried out by ablating the carotid sinuses first rather than by tying the vertebrals first. This is reasonable because the small vertebrals could not adequately supply the entire head with blood. While sectioning the neck, even though the carotids had been tied and the vertebrals clamped, numerous small but profusely bleeding arteries were found throughout the muscles.

H. Control observations. After the buffering action of the carotid sinuses and the aortic arch had been removed, it would be possible for the increase in peripheral
resistance upon clamping the carotids to be partly responsible for the rise in blood pressure. Therefore, in 4 of the animals which had had the carotid and aortic sinuses denervated, one femoral artery was suddenly occluded. In not one of these 4

### Table I. Effect of Occluding the Cerebral Blood Supply after the Carotid Sinuses and the Aortic Arch Had Been Denervated

<table>
<thead>
<tr>
<th>DOG NO.</th>
<th>VESSELS OCCCLUDED</th>
<th>DURATION OF OCCLUSION</th>
<th>D. P. BEFORE OCCLUSION</th>
<th>MAXIMUM LEVEL OF B. P. DURING PERIOD OF CEREBRAL ISCHEMIA</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>carotids</td>
<td>13</td>
<td>140</td>
<td>166</td>
<td>Pressure had fallen to 105 at 13 min.</td>
</tr>
<tr>
<td>6</td>
<td>carotids</td>
<td>4</td>
<td>156</td>
<td>206</td>
<td>Pressure fell to 110 on release of occluding clamps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>150</td>
<td>226</td>
<td>Pressure had fallen to 70 at 14 min.</td>
</tr>
<tr>
<td>7</td>
<td>carotids</td>
<td>3</td>
<td>154</td>
<td>184</td>
<td>Fell to 130 on release of clamps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>160</td>
<td>214</td>
<td>Pressure maintained, respiration did not cease</td>
</tr>
<tr>
<td>8</td>
<td>carotids</td>
<td>5</td>
<td>104</td>
<td>140</td>
<td>Rapid fall to 70 after release</td>
</tr>
<tr>
<td>9</td>
<td>carotids</td>
<td>2</td>
<td>166</td>
<td>234</td>
<td>Rapid fall to 130 after release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3½</td>
<td>154</td>
<td>224</td>
<td>Same rapid fall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>184</td>
<td>260</td>
<td>Sustained blood pressure rise and sustained respiration</td>
</tr>
<tr>
<td>10</td>
<td>carotids</td>
<td>2</td>
<td>174</td>
<td>234</td>
<td>Rapid fall to 130 after release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>154</td>
<td>220</td>
<td>Same rapid fall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>170</td>
<td>200</td>
<td>After tying external carotids. Sustained rise in blood pressure and sustained respiration</td>
</tr>
<tr>
<td>14</td>
<td>vertebrals</td>
<td>3</td>
<td>100</td>
<td>150</td>
<td>Slow fall back to normal after release of clamps</td>
</tr>
<tr>
<td>15</td>
<td>vertebrals</td>
<td>1½</td>
<td>60</td>
<td>168</td>
<td>Slow fall after release of clamps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>104</td>
<td>170</td>
<td>Slow fall after release of clamps</td>
</tr>
</tbody>
</table>

In animals 5, 6, 7, 8, 9, and 10, the vertebrals, costocervical, thyrocervical and subclavian arteries had been ligated. In animals 14 and 15, the carotid bifurcations had been removed and the necks had been entirely sectioned except the vertebral arteries and the spinal column. The blood pressure levels reached their maximum height between 30 sec. and 5 min. after which they usually began to fall at a very slow rate.

animals was there a perceptible rise in blood pressure although the blood flow through the femoral was approximately equal to one half the total blood flow through both carotids and equal to considerably more than the blood flow through both vertebrals.

Tying the external carotids in 3 animals did not qualitatively change the cerebral
vasopressor response on occlusion of the carotids. Quantitatively, however, the response was slightly decreased. Because the internal carotids in dogs are extremely small arteries in comparison with the external carotids, it is reasoned that the brain probably receives a considerable proportion of its blood supply through anastomoses from the external carotids as well as through the internal carotids.

At the conclusion of one of the experiments in which the animal had had its entire neck sectioned and in which the carotid arteries as well as the vertebral arteries had been ligated, the entire spinal column was rapidly sectioned between vertebrae C 2 and 3. Although both vertebrals had been ligated at their origin immediately above the first rib, the animal bled to death through these vertebrals in approximately two minutes, thus showing that there was still a marked anastomotic supply between the cephalad end of the vertebrals and blood vessels of the thoracic region. This could easily have occurred because the neck had been sectioned in the region of C 2 and 3 rather than at the point at which the vertebrals had been tied. The collateral blood supply to the brain appears to be exceptionally well developed. This makes it difficult to state the precise degree of cerebral ischemia which occurs after carotid and vertebral ligation.

I. The effect of cerebral ischemia on respiration varied with the duration and degree of ischemia. In approximately two thirds of the animals having the carotids, the vertebrals and accessory blood vessels occluded, respiration ceased between 45 seconds and 8 minutes after occlusion. In the other one third of the animals the respiration continued indefinitely at a slow rate. The degree of hypertension produced by cerebral ischemia was greatest in those few animals which were on the verge of total respiratory arrest but did not actually stop breathing. Likewise, the pressure response in these animals was sustained over a longer period of time than in the others. This indicates that there is a particular point in cerebral ischemia at which high levels of blood pressure can be maintained, whereas greater ischemia than this will cause a fall in blood pressure due to functional inactivation of those cells which cause the vasopressor response. During all periods of respiratory arrest, artificial respiration was instituted to prevent systemic anoxia.

J. Prolonged cerebral ischemia in those animals which experienced complete respiratory arrest caused, within a period of 8 to 14 minutes, a complete medullary paralysis. The blood pressure levels by this time had fallen to approximately 70 mm. Hg and clamping or releasing the arteries to the brain caused no further blood pressure responses. The animal was thereafter essentially a spinal animal and of no further use for these acute experiments.

K. The pulse rate in total cerebral ischemia invariably decreased after approximately 45 seconds of arterial occlusion. Before the vagi were cut, this decrease was often as much as 30 per cent. It was still present, however, even after the vagi were cut, though usually around 5 per cent in these instances rather than up to 30 per cent. Before the vagi were cut there also was often a rapid rise in blood pressure for the first 30 seconds, a small fall in blood pressure for the next 30 seconds, and then a secondary rise to higher levels at 1½ minutes. After cutting the vagi this blood pressure dip was still noted to a slight degree in several of the animals, and it was associated with mild slowing of the pulse rate.
DISCUSSION

Long before the description of the carotid sinus reflex, the pressor response elicited by cerebral ischemia had become well known and was extensively reviewed by Winkin (7). Most of these experiments became invalidated with the discovery of the carotid sinuses, because clamping of the common carotids, which was almost always the experimental technic, caused both the cerebral ischemic response and the carotid sinus reflex response. McDowall, however, in a series of experiments designed to study the chemical control of the vasomotor center, demonstrated that a striking elevation of blood pressure could still be obtained by occluding the blood supply to the brain peripheral to the carotid sinuses and that the response persisted after the carotid sinuses had been denervated (4). It has been the purpose of the present set of experiments to evaluate this cerebral ischemic pressor response in relation to the better known peripheral pressoreceptor reflexes.

Comparison of the results of cerebral ischemia produced by arterial occlusion with those of ischemia produced by increased cerebrospinal fluid pressure in Cushing's experiments (1) is striking. There is the same slow rise in blood pressure in both procedures as well as the vagal slowing of pulse rate in the early stages. Likewise, there is the same blood pressure dip which often occurs simultaneously with the pulse slowing. The changes which take place after cutting the vagi are also the same, that is, the blood pressure rise is much more rapid, and the vagal slowing and early blood pressure dip are almost completely abolished. Cushing's original conclusion, that increased cerebrospinal fluid pressure causes the blood pressure response by producing cerebral ischemia rather than by some other mechanism, agrees quite accurately with observations in the present experiment.

Location of the centers responsible for the pressor response in the cerebral vault might be in the actual cerebral nuclei or possibly in the arterial system of the brain. It is well known that stimulation of certain areas of the hypothalamus, the mesencephalon, the pons and the medulla will cause either a rise or fall in blood pressure depending on the point of stimulation (8). It is therefore reasonable to assume that the location of the vasopressor centers concerned in the present observations could be in one of these areas. The fact that respiratory depression and rise in blood pressure correlate very closely indicates that the medulla is the area possibly concerned.

The presence of arterial pressoreceptor areas, similar to the carotid sinuses, inside the cerebral vault is untenable for two reasons. First, the rise in blood pressure in cerebral ischemia is usually somewhat slower than the rapid carotid sinus response, and the ischemic response often is not maintained as is the carotid sinus response. Second, characteristics of the blood pressure response in cerebral ischemia are exactly the same as those which occur when the cerebrospinal fluid pressure is increased. In this latter instance the applied pressure is external to the blood vessels, and the blood pressure should fall rather than rise if pressoreceptor areas similar to the carotid sinuses should exist within the arterial tree of the brain.

Whether the pressor response is due to actual pressoreceptor nuclei or to chemo-receptor nuclei responding to metabolic effects of hypotension is impossible to state.
The long, slow rise in blood pressure seen in the responses of figure 2 would imply a chemoreceptor system. Also, McDowall's work (4) on the chemical control of the vasomotor center indicates that carbon dioxide concentration is an important factor. On the other hand, very rapid responses occurred in a few animals as illustrated in figure 1d. These responses are more characteristic of a pressoreceptor system but not necessarily so. It is difficult to imagine the mechanical construction of a nerve cell which can respond to pressure, though such is not an impossibility. Regardless of which type of system is responsible for the pressor response, the activity of the system is rapid enough to be of protective value in animals with a falling blood pressure.

It is probable that the pressor response in cerebral ischemia is mediated through the sympathetic nervous system. The very rapid and marked fall in blood pressure when the clamps are removed from the occluded arteries indicates that the response is neurogenic rather than humoral. The vagi, of course, had been cut in these experiments and therefore could not have been concerned. Also, it has been adequately demonstrated that the rise in blood pressure due to the similar condition of increased cerebrospinal fluid pressure is mediated through the sympathetics (1, 9). Further-

Fig. 1. Blood pressure responses during progressive stages of the experiment: a) Clamping of both common carotids with the animal otherwise intact; b) clamping of both common carotids with the vertebrals tied; c) clamping of both common carotids with the vertebrals tied and the carotid sinuses denervated; d) clamping of both common carotids with the vertebrals tied, the carotid sinuses denervated and the vagi cut. Note in b the dip in blood pressure at approximately 40 seconds; this occurred frequently when the brain was almost totally deprived of blood flow but was usually entirely abolished after the vagi were cut. Note, also, the compensatory subnormal pressures after the clamps were removed from the carotids. (Time intervals—5 sec.)
more, McDowall (4) demonstrated by several methods of cerebral asphyxia that the response is opposed by removal of portions of the sympathetics.

The present experiments indicate forcefully that the peripheral pressoreceptors are not the only major neurogenic pressoresponsive system. Indeed, it is even questionable whether the carotid and aortic sinuses are as powerful as the cerebral centers.
It is regrettable that many of the experiments to produce chronic hypertension by carotid sinus denervation have been carried out by actual ablation of the carotid bifurcation (10-12). This procedure could easily cause a low-grade deficiency in blood supply to the brain, and what the effects of this may be have not been determined. For this reason, and because the results of chronic experiments with sinus denervation have been extremely variable (10-14), the precise function of the carotid sinuses, the aortic arch and the mesenteric pressoreceptors (15, 16) is still quite clouded.

The relation of these experiments to essential hypertension in man is of interest. Certainly, no one has succeeded in implicating the carotid sinus mechanism as a causative factor. Yet, excessive neurogenic pressor responses in such patients have been demonstrated by postural and ice water tests (6). Also, it has been shown many times that spinal (17), caudal (18), and differential block (19) anesthesia, which effectively block the sympathetic nervous system, will cause a marked blood pressure fall in many hypertensive patients, whereas these procedures hardly affect the blood pressure of normal individuals. These observations indicate a cerebro origin of excess sympathetic activity in hypertensive patients. Because stimulation of an extremely small area of the medulla has been shown to cause extreme changes in blood pressure (8), there is no reason to doubt that local vasospasm or arteriosclerotic occlusion of a small blood vessel might be responsible for the hyperactive sympathetics. Indeed there might well be a vicious cycle with localized vasospasm initiating a neurogenic hypertension and this in turn reflexly increasing the vasospasm.

Recent war experiments concerning the effect of increased gravitational force on the body indicate that man’s ability to rapidly adjust the blood pressure under changing forces is more highly developed than that of lower animals (20). This is reasonable because of man’s erect posture, and it might also explain why essential hypertension is principally a disease of mankind.

Chronic hypertension has been produced in dogs by progressively occluding the arterial blood supply to the brain (21). To cause this state, it has been necessary to occlude even the anterior spinal artery, and it might be reasoned that such extreme ischemia could hardly exist under natural conditions. One must remember, however, that very minute areas of the brain may exert powerful pressor effects, and severe localized ischemia in these areas can easily occur.

**SUMMARY**

A marked rise in blood pressure occurs in response to acute cerebral ischemia. This response is still present after reflexes from the carotid sinuses have been abolished. Quantitative data indicate the cerebral pressoreceptor response to be as powerful as the carotid sinus response though of a slightly different character. Respiration is also depressed by acute cerebral ischemia, and the rise in blood pressure generally is greatest when the respiration is barely present. Prolonged cerebral ischemia produces complete medullary paralysis causing the blood pressure to fall to levels of a spinal animal. It is postulated that the centers responsible for the blood pressure response are located in the medulla. The blood pressure response due to cerebral ischemia is almost identical with that shown by Cushing to occur.
in increased cerebrospinal fluid pressure. The possible relationship of these observations to essential hypertension is discussed.

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REFERENCES