Peripheral Vasomotor Effects of Adrenaline and Noradrenaline Acting upon the Isolated Perfused Central Nervous System

By Robert D. Taylor, M.D., and Irvine H. Page, M.D.

The problem of the participation of the nervous system in the control of blood pressure has received scant attention. Our purpose was to learn more of the nervous mechanisms which participate in its control. By means of a special technic which allows the brain to be perfused with blood from another animal and yet be connected with the body only by the nervous system, it was shown that pressor substances perfused through the brain cause a fall in pressure in the body. On the contrary, substances which are depressor in the donor’s body cause a rise in pressure in the recipient’s body when they act on the brain. We conclude that the brain contains hitherto unrecognized chemoreceptors independent of the carotid sinuses. Baroreceptors were not found in the blood vessels. This cerebral buffer mechanism must have important functions in determining the response to vasoactive substances, especially in hypertension and shock.

The contributions of the central nervous system to the maintenance of arterial blood pressure are poorly understood. Least well known are the remote peripheral effects, mediated by nerves as the result of action of vasoactive substances on vasomotor centers. For instance, adrenaline has been said to be depressor, pressor, and inactive when circulated through the brain. Oliver and Shafer in 1895 first considered it to have a central action and suggested that simulation of the vasodepressor center by adrenaline might account for the fall of blood pressure observed following its intravenous injection. Experimental support for this was furnished by Hartman, Kilborn and Fraser and Gayet, Gayet and Guillaumie. They reported vasodilatation in perfused limbs of dogs which were connected to the animal only by nerves when adrenaline was injected intravenously into the body. Cyon and Tournade used similar preparations but concluded that peripheral vasoconstriction rather than vasodilatation was induced by adrenaline which circulated through the central nervous system.

Pilcher and Sollman perfused spleens which were separated from the bodies of the dog except for nervous connection. They found no change of splenic volume following administration of adrenaline to the body and concluded that the drug had no effects mediated through the nervous system. Anrep and Starling perfused the brain by cannulating the basilar artery, noting peripheral dilatation when adrenaline was injected into the perfusing blood. Simultaneously, there occurred a rise of the blood pressure in the circle of Willis. They believed the hypertension resulted from vasoconstriction of the extracranial vessels which directed blood intracranially into the nonresponsive vessels of the brain. The peripheral vasodilatation they observed was then attributed to increased perfusion of the vasomotor centers rather than to the action of adrenaline as such.

Heymans and associates perfused the isolated carotid sinus of an otherwise intact dog and also prepared animals so that the heads could be perfused by donor blood which did not reach the body of the recipient animal. In the latter experiments the only nervous connections which remained were the vagus nerves. Injection of adrenaline into the donor circulation caused bradycardia and fall of blood pressure in the body of the recipient animal. Since similar peripheral effects were brought about by sudden elevation of the perfusion pressure these workers attributed them to the
rise of blood pressure adrenaline induced in the donor animals. The demonstration of such depressor reflexes led to the assumption that no central effects of adrenaline existed, although this was not shown by direct experimentation.

Subsequent to these studies, Tournade and Malmejac and Gayet, Gayet, and Quivy repeated their experiments with isolated perfused limbs but with the carotid sinus and the aortic depressor nerves destroyed. Vasodilatation was noted, although to a lesser degree than in their previous experiments.

These variant observations and conclusions probably are attributable to the fact that a satisfactory method had not been devised for direct perfusion of the head such that nervous connections are intact but that donor-head circulation and that of the body are entirely separate. The many attempts to develop such a method prior to 1932 disregarded the large intraspinal venous sinuses which extend the length of the spinal column just anterior to the cord, and permit free mixture of the blood of the body and donor-head circulation. Lewis attempted to obliterate these sinuses by injecting them with liquid paraffin but made no provision to prevent interchange of blood through the intercostal arteries, so that his method was also unsatisfactory.

Nowak and Samaan reviewed the history of efforts toperfuse the isolated nervous system and described a method which accomplished this in 1934. It depended upon: (1) exposing the cord by laminectomy at C-2, (2) opening the dura and retracting the cord to ligate the anterior spinal artery, and (3) obliterating the intraspinal venous sinuses with a U-shaped metal clamp placed below the cord. With this preparation they observed sharp reduction of peripheral blood pressure in response to centrally acting adrenaline when the carotid sinuses and aortic depressor nerves were intact. When the buffer nerves had been sectioned, adrenaline injected into the circulation of the recipient dog’s head still caused vasodilatation in the body, although it was sometimes slight and inconstant. They concluded, as did Heymans, that the depressor effects of adrenaline injected into the cerebral circula-

tion were primarily due to reflex responses of the carotid sinus mechanism to adrenaline hypertension of the donor dog. They believed that the depression noted after destruction of the buffer nerves occurred only because adrenaline hypertension of the donor animal perfused the vasopressor centers better and thus reduced peripheral vasmotor tone. In support of this concept, they perfused the dog’s head with a pump and mechanically elevated the perfusion pressure which caused a fall of blood pressure in the body of the animal. However, they depended upon sectioning the nerve of Hering as it arises from the bifurcation of the carotid artery to inactivate the carotid sinuses and did not test the preparation for carotid sinus activity before pump perfusion.

During studies of the central effects of vasoactive drugs, we have developed a method for perfusion of the isolated nervous system which effectively separates the circulation of the body and head yet does not require release of cerebrospinal fluid or manipulation of the cord as in the method of Nowak and Samaan.

**Methods**

Two mongrel dogs were used in each of 127 experiments. The animals weighed from 6 to 15 kilograms. The donor dog was usually slightly larger than the recipient. Pentobarbital, 35 mg. per Kg., was given intravenously for anesthesia. A femoral artery of each dog was connected to a mercury manometer which recorded blood pressure changes on the smoked drums of two kymographs. Heparin was used as an anticoagulant both in the tubing leading to the manometers and for perfusion of the head of the recipient dog.

During preparation of recipient dogs, an infusion of 200 cc. of whole dog’s blood was given. The dissection was carried out with an electrocautery unit and blunt dissection. With the dog on its back, a collar of skin 4 to 5 cm. in breadth was removed over the third to fifth cervical vertebrae. Both jugular veins, carotid arteries, and vagus nerves were isolated for a length of 8 cm. to 10 cm. and wrapped with moist gauze, both to prevent drying and to retract them from the field of operation. A segment of trachea was resected and the proximal end cannulated with a rubber cannula 40 cm. in length for connection to a respirator, if necessary.

Using the coagulating current, the cautery knife was used to cut the esophagus and neck muscles in a collar-like shape so that the fourth and fifth cervical vertebrae were exposed. Coagulation and contraction of the muscles controlled hemorrhage. The vertebral
bodies were denuded of muscle by blunt dissection. With the dog on its belly a laminectomy at C-4 and C-5 was then performed. The articular facets were removed by ronguer to expose the vertebral arteries and veins. This usually caused brisk bleeding which could be controlled with muscle pledges, coagulation, and finger pressure. The bone dissection was carried out so that the laminae and facets were removed flush with the vertebral body; otherwise a bridge of bone prevented complete occlusion of the anterior spinal veins by the wire snare which was applied.

By means of a flat, grooved, curved guide, which adapted to the contour of the spinal canal, a strand of No. 8 piano wire was passed beneath the cord. The wire was held in place with hemostats to prevent trauma to the cord while the two ends of the wire were threaded into a tonsil snare. This snare was used to tighten the wire firmly about the intervertebral disk, thus obliterating all vascular connections except those within the dura (figs. 1 and 2). Of these, the anterior spinal artery is the only one of appreciable size and it becomes imperceptible below C-3 since it is dissipated as large branches to the first three cervical nerve roots which were destroyed during the dissection of the neck muscles. Every effort was made to control bleeding points so that heparinized blood to be perfused through the dog’s head would not escape during the course of the experiment.

The donor dog was heparinized by giving 4 mg. of heparin intravenously per kilogram of body weight. The anastomosis between the two dogs was limited to one carotid artery and one jugular vein of each dog. This was accomplished by appropriate sized plastic tubing previously filled with saline solution. When the circuit was functioning a clamp was placed on the remaining jugular vein and carotid artery of the recipient dog. The use of one vessel simplified the procedure and was quite adequate as evidenced by the continuation of respiration and the persistence of both corneal reflexes of recipient dogs after perfusion was started. Also cerebral anemia caused by clamping the perfusing artery caused sharp rise of the recipient dog’s blood pressure much as complete and sudden cerebral anemia does in an intact animal. The carotid sinuses were inactivated unless otherwise indicated.

Injections were made into the arterial circulation through a three-way stopcock spliced into the circuit by a glass T tube. Whenever an intra-arterial injection is referred to in this paper it means this circuit. Adrenaline in doses of 0.01 mg., except as indicated elsewhere in the text, and noradrenaline, 0.01 mg., were used as standard in these experiments.

The completeness of the isolation was established by the failure of Evans Blue, given to the donor dog, to appear in the body of the recipient dog. Further, postmortem dissection showed no vascular com-

munication between the head and body of the recipient animal.

RESULTS

Effects of Adrenaline and Noradrenaline. Repeated injections of adrenaline and noradrena-

line into the arterial circulation of the recipient dog’s head caused an immediate and sharp fall of arterial pressure of the isolated body in each of the 127 experiments (fig. 3). The degree of fall varied widely from animal to animal (10 to 100 mm. Hg). In general, it depended upon the height of the control pressure in the recipient’s body and the duration of the ex-
periment. Table 1 shows responses which occurred in 12 representative experiments. These were chosen to illustrate the greater fall of blood pressure which usually occurred when the recipient’s body pressure was elevated. When the blood pressure was above 130 mm. Hg, adrenaline or noradrenaline usually caused the pressure to fall 50 to 100 mm. Hg. On the other hand, when the control pressure was difficult, or required large amounts of fluid during the period of dissection to maintain normal blood pressure, had relatively poorer responses than did more rugged animals.

The degree of depression of the blood pressure was roughly in proportion to the amount of pressor agent administered. For instance, 0.01 mg. of adrenaline given intra-arterially into the recipient’s head reduced the body pressure 18 mm. Hg from a control level of 160 and caused a 10 mm. rise of donor dog’s pressure, while 0.02 mg. of adrenaline reduced the recipient’s body pressure 40 mm. Hg and caused a rise of donor’s pressure of 20 mm. Hg.

Injections into the tubing leading to the head were much more effective than those given intravenously into the circulation of the donor dog. Further, the degree of depressor response of the recipient’s body bore no relationship to the elevation of blood pressure these drugs produced in the donor. The re-

![Figure 3](image-url)
sponse of the recipient following intra-arterial injections into the cerebral circulation began before any drug reached the donor, and often there was enough dilution, at least of the small doses, to prevent change in the donor dog’s pressure. Also, when the donor dog’s blood pressure was elevated to similar levels by renin injections, the recipient dog’s pressure showed slight, if any, change. Representative results are shown in table 2. Comparison is made of the effects of similar amounts of adrenaline and noradrenaline injected alternately into the recipient’s head and intravenously into the donor body. The results show that the depressor response of the recipient’s body is independent, to a large degree, of the pressor response of the donor.

In 6 experiments the effects of adrenaline and noradrenaline upon the peripheral circulation were tested by injecting the drugs into the cerebrospinal fluid. In 3 normal dogs, burr holes were made into the skull so that the tip of a needle could be passed into the lateral ventricle. Neither adrenaline nor noradrenaline had measurable effects upon the blood pressure when given in doses as high as 0.1 mg. In 3 experiments the drugs placed in the cisterna magna caused no rise of systemic pressure.

Effects of Change of Perfusion Pressure and Injection of Saline into the Carotid Sinus of the Recipient Dog. These were tested by injecting saline solution in amounts of from 1 to 25 cc., by varying the blood pressure of the donor dog, by bleeding until hypotension occurred, and by intra-arterial transfusions given under pressure to the donor dog. When the carotid sinuses of the recipient dog were denervated or coca
cized none of these procedures affected the blood pressure in the body of the recipient animal. If the carotid sinuses were intact, the intra-arterial injection into the recipient’s cerebral circulation of 1 cc. of normal saline usually had no effect and rarely caused a fall of the recipient’s blood pressure. If 10 to 25 cc. of normal saline were rapidly injected into the carotid artery perfusing the head, peripheral pressure of the recipient dog usually fell 10 to 25 mm. Hg, while if a similar volume containing 0.01 mg. of adrenaline were injected the fall amounted to 40 to 50 mm. Hg (table 3).

In 4 experiments the arterial blood pressure within the carotid sinus of the recipient dog was varied widely by alternately bleeding the donor until hypotension (30 to 50 mm. Hg) occurred and retransfusing the blood into the donor dog’s femoral artery under pressure, so that hypertensive levels were maintained (250

<table>
<thead>
<tr>
<th>Control Blood</th>
<th>Response to Intravenous</th>
<th>Response to Intra-arterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>Injections to Donor</td>
<td>Injections to Perfused Head</td>
</tr>
<tr>
<td></td>
<td>mm. Hg</td>
<td>mm. Hg</td>
</tr>
<tr>
<td>Donor</td>
<td>120</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>146</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 2.—Depressor Effects of Adrenaline and Noradrenaline When Similar Doses Were Given Intravenously to Donor and Intra-arterially to Perfused Head.

<table>
<thead>
<tr>
<th>Control Blood Pressure</th>
<th>Blood Pressure Fall after 25 cc. NaCl</th>
<th>Blood Pressure Fall after 25 cc. NaCl plus 0.01 mg. Adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
</tr>
<tr>
<td>144</td>
<td>-10</td>
<td>-34</td>
</tr>
<tr>
<td>98</td>
<td>-10</td>
<td>-42</td>
</tr>
<tr>
<td>130</td>
<td>-12</td>
<td>-66</td>
</tr>
<tr>
<td>130</td>
<td>-8</td>
<td>-70</td>
</tr>
<tr>
<td>180</td>
<td>-22</td>
<td>-74</td>
</tr>
</tbody>
</table>

Table 3.—Effects of Injecting 25 cc. of Saline and 25 cc. of Saline with 0.01 mg. of Adrenaline into Carotid Sinus of Recipient Dog.

to 300 mm. Hg). These variations of perfusion pressure in the donor dog caused no significant change of arterial pressure in the body of the recipient dog.

Effects of Excision of Carotid Bodies. Heymans\(^8\) has shown that the carotid bodies act as chemoreceptors which reflexly influence respiratory and vasomotor centers in response to chemical agents circulating through them. To determine whether or not the carotid bodies were the site of action of adrenaline or noradrenaline which might have caused the de-
pressor effect we have observed, they were surgically removed by exposing the carotid bifurcation and excising them from 6 recipient animals 24 to 48 hours before the experiment. The depressor effects of centrally acting adrenaline or noradrenaline remained.

**Effects of Section of Buffer Nerves and Excision of the Carotid Sinuses.** After control responses to intra-arterial injections of adrenaline and noradrenaline were determined in 12 experiments, the carotid sinuses, aortic depressor nerves, and vagus nerves were successively inactivated, repeating the tests at each step. Of denervation in each case was demonstrated by the absence of blood pressure change, either when the carotid arteries were clamped separately, or following distention of them by intra-arterial injection of saline solution. Both vagus nerves were then sectioned. In most experiments this procedure caused a sharp elevation of blood pressure (fig. 3) due probably to the unopposed action of the sympathetic nervous system. These animals showed peripheral vasodepressor reactions in response to centrally injected adrenaline and noradrenaline. In some cases there was a greater response after the

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drug</th>
<th>Experiment No. 1</th>
<th>Experiment No. 2</th>
<th>Experiment No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial B.P.</td>
<td>Depressor Response</td>
<td>Initial B.P.</td>
</tr>
<tr>
<td>Control</td>
<td>Adrenaline</td>
<td>114</td>
<td>-16</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>92</td>
<td>-14</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td></td>
<td>132</td>
<td>-16</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>-22</td>
<td>120</td>
</tr>
<tr>
<td>Left vagosympathetic trunk cut</td>
<td>Adrenaline</td>
<td>94</td>
<td>-24</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>110</td>
<td>-22</td>
<td>164</td>
</tr>
<tr>
<td>Rt. aortic depressor nerve cut</td>
<td>Adrenaline</td>
<td>114</td>
<td>-34</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>110</td>
<td>-22</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td></td>
<td>122</td>
<td>-12</td>
<td>170</td>
</tr>
<tr>
<td>Right vagotomy</td>
<td>Adrenaline</td>
<td>122</td>
<td>-12</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>124</td>
<td>-12</td>
<td>168</td>
</tr>
<tr>
<td>lt. carotid sinus cocainized</td>
<td>Adrenaline</td>
<td>134</td>
<td>-22</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>126</td>
<td>-16</td>
<td>166</td>
</tr>
<tr>
<td>Rr. carotid sinus cocainized</td>
<td>Adrenaline</td>
<td>122</td>
<td>-22</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline</td>
<td>130</td>
<td>-50</td>
<td>184</td>
</tr>
</tbody>
</table>

Initially, the left vagus nerve was cut, then the right aortic depressor nerve was isolated from the vagus and sectioned, followed by sectioning the remaining vagus nerve. The carotid sinuses were then exposed and inactivated by applying cocaine (10 per cent) solution. Three experiments are recorded in table 4. The central action of adrenaline and noradrenaline was not only present after the buffer nerves were inactivated but in some cases was enhanced.

In 10 experiments the carotid sinuses were denervated by cutting the nerves of Hering and stripping the sinuses of adventitia, or by complete excision of the sinuses four to five days before the experiment. The completeness vagus and aortic depressor nerves were sectioned (fig. 3).

**Effects of Mechanical Elevation of Perfusion Pressure with a Pump.** Our data suggest that the mechanical effects of perfusion pressure in the isolated head have little effect upon the peripheral blood pressure of the recipient dogs. However, Nowak and Smaan used a pump to mimic the pressure change adrenaline caused in the circulation of the isolated head after the buffer nerves were supposedly inactivated. Rise in perfusion pressure resulted in fall in arterial pressure in the recipient's body. They believed these changes occurred because of decrease of peripheral vasomotor tone resulting from better perfusion of the vasopressor centers. To explore
this apparent discrepancy 6 experiments were performed in which the isolated head was alternately perfused with a rubber tube pump and the arterial circulation of a donor dog. The carotid sinuses were intact in 3 of these

Fig. 4. Simultaneous record of blood pressure in recipient's cerebral circulation (upper tracing); in recipient's body (lower tracing). 1. Elevation of cerebral perfusion pressure by means of a pump. No significant change in arterial pressure of the recipient's body. 2. Change from pump perfusion to perfusion by a donor dog. 3. Adrenaline (0.01 mg.) given into circulation perfusing the recipient's head. A fall in blood pressure occurs in the recipient's body.

dogs and inactivated in the other 3. The vagus nerves of all 6 were cut. The pump delivered blood from the right carotid artery of the donor dog and when not functioning the donor's left carotid perfused the recipient's head. Pressure changes within the head were measured by manometer recording the retrograde arterial pressure as present in the cephalic end of the clamped carotid artery of the recipient dog.

When the head was perfused by pump, the rate of flow was adjusted so that the level of this retrograde pressure was the same as when the heart of the donor dog provided the perfusing force. The flow was then increased so that the changes of arterial pressure within the head mimicked, as nearly as possible, those produced by intra-arterial injections of adrenaline and noradrenaline (fig. 4). Afterward, the pressure was elevated as high as the pump would permit (84 to 188 mm. Hg).

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>B.P. Changes in Head Measured in Opposite Carotid Artery</th>
<th>Net Change</th>
<th>Fall of Peripheral Blood Pressure in Recipient Dog</th>
<th>Net Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline 0.01 mg.</td>
<td>mm. Hg</td>
<td>+18</td>
<td>108 to 74</td>
<td>-34</td>
</tr>
<tr>
<td>Noradrenaline 0.01 mg.</td>
<td>mm. Hg</td>
<td>+14</td>
<td>104 to 74</td>
<td>-30</td>
</tr>
<tr>
<td>Pump</td>
<td>mm. Hg</td>
<td>+60</td>
<td>118 to 104</td>
<td>-14</td>
</tr>
<tr>
<td>Adrenaline 0.01 mg.</td>
<td>mm. Hg</td>
<td>+12</td>
<td>184 to 132</td>
<td>-52</td>
</tr>
<tr>
<td>Pump</td>
<td>mm. Hg</td>
<td>+58</td>
<td>176 to 160</td>
<td>-16</td>
</tr>
</tbody>
</table>

In those animals in which the carotid sinuses were denervated, mechanical elevation of the perfusion pressure had no influence upon the recipient dog's peripheral blood pressure, while adrenaline and noradrenaline elicited prompt vasodepressor effects. Further, in those animals having functioning carotid sinuses, the depressor responses following adrenaline or noradrenaline were constantly greater, in proportion to the degree of intracranial hypertension they induced, than the fall in pressure which followed equal or greater degrees of mechanically induced hypertension (table 5).

Effects of Blockade of Autonomic Ganglia and Partial Section of the Spinal Cord. Injection of tetraethylammonium chloride (TEAC) (15 mg. per Kg. of body weight) into the body of the recipient animal completely abolished the
The depressor effects of adrenaline and noradrenaline circulating through the animal’s head. The blood pressure of the body fell as a result of tetraethylammonium chloride, much as it does in an intact animal (fig. 5). However, it is important to note that tetraethylammonium chloride did not reduce the blood pressure to as low levels as were previously attained by the central action of adrenaline in the same animal. Further, vasomotor tone of central origin was eliminated by permitting the head of the animal to die by discontinuing perfusion. If the body was kept alive by artificial respiration, blood pressure in the body was 20 to 30 mm. Hg greater than the levels which previously had been noted after injection of adrenaline or noradrenaline.

The spinal cords of 6 animals were progressively, transversely cut with a razor blade while the depressor effects of adrenaline injected into the recipient’s cerebral circulation were being observed. The response was not changed until the final sixth of the cord was cut. Histologic study of these cords demonstrated that the fibers which presumably effect the vasodilatation were located in the most peripheral portions of the anterolateral columns. This area has been shown by Wang and Ranson to be the pathway of the sympathetic nervous system.

**Effects of Surgical Sympathectomy.** Seven animals were subjected to four-stage sympathectomy during which paravertebral ganglia and sympathetic chains were removed bilaterally from the stellate to the fourth lumbar ganglia. After six to eight weeks’ recovery, these dogs were used as recipients in perfusion experiments. During the preparation the carotid sinuses were denervated and the vagus nerves were sectioned. None of these animals exhibited a fall in blood pressure regardless of the amount of adrenaline injected into the arterial circulation of the isolated head. Dosages as high as 0.1 mg. of adrenaline were without peripheral effect.

**The Effects of Blocking Agents on the Vasodepressor Response of Centrally Acting Adrenaline and Noradrenaline.** Blocking agents were given in an attempt to define the nature of the vasodepressor response induced in the recipient dog’s body by centrally acting adrenaline or noradrenaline. Atropine sulfate (2.6 mg.) was given by vein to both the donor and recipient animals so that the depressor effect of intravenously injected Mecholyl (acetyl-β-methylcholine) (0.5 mg.) was abolished. This did not alter the depressor response of the recipient’s body to the injection of adrenaline or noradrenaline into the cerebral circulation.

Benzodiazoxide was given to the recipient’s body (as much as 5 mg. per Kg. of body weight). This was without effect upon the depressor response. However, this adrenolytic drug inhibits only the pressor effects of adrenaline and noradrenaline; hence this evidence does not exclude the possibility that the effector agent responsible for peripheral dilatation was an adrenaline-like substance with only vasodepressor qualities, such as Isuprel [1(3',A'-dihydroxyphenyl)-2-isopropylaminotanol].

Ergotamine tartrate at times will convert the depressor effects of Isuprel to pressor. In 4 experiments ergotamine tartrate was given to the recipient dog’s body in amounts as great as 5 mg. After ergotamine, intravenously injected Isuprel caused some initial pressor response; its action, however, continued to be predominantly depressor. Further, the depressor effects of centrally acting adrenaline and noradrenaline were unchanged.
Benadryl was given to the recipient dog until intravenous injection of 0.1 mg. of histamine phosphate caused no reduction of blood pressure. But it did not inhibit the depressor phenomenon under study.

Effects of Inhalation of Carbon Dioxide by Donor Dog. In 6 experiments the donor dogs were given mixtures of 5 to 70 per cent carbon dioxide and 30 to 95 per cent oxygen by respirator, after paralyzing doses of curare were given to prevent struggling and hyperpnea in response to the carbon dioxide. With concentrations 40, 50, 60 and 70 per cent, there was lowering of the donor dog’s blood pressure. The recipient dog showed no change even when the pH of the donor blood was as low as 6.5. The recipient animals exhibited hyperpnea in response to carbon dioxide brought by the blood of the donor animal and usually it was necessary to curarize them to prevent excessive respiratory combat.

In 5 experiments the recipient animals' bodies were given carbon dioxide and oxygen by respirator. Unless the concentration of carbon dioxide exceeded 40 per cent there was no change in blood pressure. With the higher concentrations the blood pressure was lowered by 40 to 50 mm. Hg from the control levels of 120 to 150.

Effects of Intravenous Injections of Adrenaline and Noradrenaline in the Decapitated Animal. In 4 experiments animals were decapitated and the body maintained alive by artificial respiration. Intravenous injections of adrenaline caused the usual rise and subsequent depressor phase commonly noted in intact animals. Noradrenaline was always pressor. After injection of tetraethylammonium chloride the pressor responses were augmented as in an intact animal. If the pressor effects of adrenaline or noradrenaline were inhibited by previous injection of Priscoline (3 to 5 mg. per Kg. of body weight) adrenaline was entirely vasodepressor while noradrenaline was almost without effect upon the blood pressure.

Peripheral Hemodynamic Changes Induced by Centrally Acting Adrenaline. Doctors J. W. Remington and W. F. Hamilton were kind enough to estimate the changes in cardiac output and peripheral resistance which occurred during the hypotensive state induced by centrally acting adrenaline. Calculation of these values was made from optical records of the carotid pulse wave. Records were made by Mr. F. Olmsted.

During adrenaline-induced hypotension there was little change in pulse rate, cardiac output was increased from 1.14 to 1.88 liters per minute and the ratio indicative of peripheral resistance reduced from 5.9 to 2.3 (table 6).

<table>
<thead>
<tr>
<th>TABLE 6.—Peripheral Hemodynamic Changes Induced by Centrally Acting Adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial B.P.</td>
</tr>
<tr>
<td>mm. Hg</td>
</tr>
<tr>
<td>Control         142/123</td>
</tr>
<tr>
<td>After Adrenaline  99/85</td>
</tr>
</tbody>
</table>

Discussion

These experiments demonstrate that adrenaline and noradrenaline acting solely on the central nervous system cause sudden sharp reduction of the peripheral blood pressure.

This vasodepressor effect occurs whether or not the carotid bodies, carotid sinuses, aortic depressor, or vagus nerves are present. When the carotid sinuses are functioning the degree of blood pressure fall which can be produced by distention of the carotid sinus by rapid injection of 25 cc. of normal saline into the carotid artery is not nearly as great as when 0.01 mg. of adrenaline in a similar volume of saline is so injected (12 to 20 as compared with 30 to 40 mm. Hg). Further, if the blood pressure in the isolated dog’s head with intact carotid sinuses is elevated equally, first with adrenaline and then with a pump, the fall in blood pressure of the recipient body which follows the mechanical elevation of perfusing pressure is about 40 per cent less than that produced by adrenaline.

If the carotid sinuses are denervated, changing the perfusion pressure by eliciting hypotension from bleeding of the donor dog, or elevating its pressure by intra-arterial transfusion of blood under pressure, does not change the blood pressure of the body of the recipient.
Further, altering the perfusing pressure by use of a pump so that the blood pressure curve of intracranial pressure, as recorded from the clamped carotid artery, resembles that produced by intra-arterial injection of adrenaline causes no change of pressure in the body of the recipient dog. These results differ from those of Nowak and Samaan who found a fall of blood pressure in the body of recipient dogs similarly studied. They depended, however, upon sectioning of the nerve of Hering as it arose from the carotid bifurcation to denervate the sinuses. Also they do not mention testing for carotid sinus activity before initiating their experiments. Since Code, Dingle and Moorhouse have demonstrated that nerve fibers can enter the nerve from the carotid sinus until it enters the jugular foramen, it seems possible the carotid sinuses of the dogs used by Nowak and Samaan were still functioning.

That the impulses which produce hypotension in the recipient as the result of perfusing pressor agents in the brain are mediated through the sympathetic nervous system is likely since (1) progressive transection of the cord showed the pathways involved to be in the peripheral aspect of the anterolateral columns, and (2) pharmacologic ganglionic blockade by tetraethylammonium chloride, surgical ganglionection and lumbo-dorsal sympathectomy abolished the response to centrally acting adrenaline and noradrenaline.

Since adrenaline and noradrenaline have no effect on peripheral arterial pressure when introduced into the fluid of the lateral ventricles or into the cisterna magna, it is reasonable to assume that impulses for peripheral vasodilatation arise from centers which are in some manner affected by the vasoconstrictor drugs in the blood circulating through them. These centers might be influenced by the rate of their perfusion as determined by local vasoconstriction or vasodilatation. Also, the drugs might have a direct action upon nerve cells. If the former explanation is correct, there must be adequate evidence that adrenaline constricts intra-cranial vessels, particularly those of the medulla. Support for this view is furnished by the work of Forbes and Wolff and Bouk-aert and Jordan. The former showed that injection of adrenaline into the carotid artery, application of it to the pia-arachnoid or stimulation of the cervical sympathetic nerves caused reduction of almost 10 per cent in the caliber of the pial vessels. Boucaert and Jordan isolated the intracranial from the extracranial circulation by ligation of all visible extracranial vessels, detached the head from the body and found elevation of intracranial arterial blood pressure after injection of adrenaline into the perfusing circuit.

Schmidt demonstrated the presence of vasoconstrictor innervation through the cervical sympathetics by means of a thermocouple in the hypothalamic and parietal areas of cats. Adrenaline and sympathetic stimulation caused no reduction of blood flow through the medulla which is the region believed to contain the vasoconstrictor centers. The only substance which significantly influenced the flow through this vascular bed was inspiration of carbon dioxide which produced easily measurable vasodilatation.

If the peripheral depressor response to adrenaline and noradrenaline was due to local vasoconstriction in the medulla, and the hypertension which follows circulation of Meeholyl and histamine through the brain resulted from local vasodilatation it would be expected that the potent vasodilator, carbon dioxide, would cause a rise of pressure in the body of the recipient dog. This was not the case. Hence, we ascribe the central action of drugs to action upon chemoreceptors, the location of which is not known.

The hypotension which follows the cerebral action of adrenaline is, then, the result of peripheral vasodilatation and decreased peripheral resistance. Since this effect is not abolished by atropine or Benadryl in the recipient animal’s body, it is unlikely that it occurs because of the release of acetylcholine or histamine at nerve endings. Although benzodioxane and ergotamine in amounts sufficient to reverse adrenaline or inhibit noradrenaline do not alter the response, this does not exclude the possibility that an adrenaline-like substance is released at the sympathetic nerve endings, since...
Isuprel continued to be vasodepressor when given to dogs that had received these blocking agents.

Another possible explanation of the hypotensive action of adrenaline or noradrenaline is central blockade of the vasomotor areas and consequent loss of vasomotor tone in the periphery. Against this is the fact that tetraethylammonium chloride, in doses known to cause autonomic ganglionic blockade and thus remove vasomotor tone of central origin, did not reduce the blood pressure of recipient dogs to as low a level as was previously observed following action of adrenaline and noradrenaline. Further, when the brain was permitted to die from anemia and central vasomotor tone was no longer a factor, the blood pressure did not fall to the levels elicited by adrenaline and noradrenaline. Thus since the hypotension is not merely a release of tone, we believe that adrenaline and noradrenaline, through central action, stimulate the sympathetic nervous system to produce active vasodilatation. The observation that vasodilatation may be induced by stimulation of the sympathetic nervous system is not new.24-27

The quantitative relationship of centrally induced peripheral vasodilatation to the peripheral vasoconstrictor effects of adrenaline and noradrenaline in the intact animal is not known. Central action is not the sole cause of the depressor phase of adrenaline action, since noradrenaline and adrenaline are both constantly vasodepressor when acting centrally, and yet, in intact animals, noradrenaline rarely induces a fall in blood pressure. Furthermore, we have shown that in the bodies of decapitated dogs, when the pressor action of adrenaline is inhibited by Priscoline, the vasodilator effect of adrenaline persists as in intact animals.

The demonstration that fall in blood pressure regularly follows the perfusion of the brain with pressor agents and rise follows depressor agents, and that the fall and rise are independent of the carotid sinus mechanism and the perfusing pressure, indicates that a chemoreceptor system exists within the brain. Although the location of the receptors is not known, the outflow is over the sympathetic nervous system.

The pressor action of a drug is thus modified by centrally induced peripheral vasodilatation and the vasodepressor effect of dilator drugs is buffered by centrally induced peripheral vasoconstriction. Abolishing the action of this central buffer mechanism by sympathectomy, spinal cord section at C-6, or tetraethylammonium chloride administration along with loss of the carotid sinus buffers, explains in part, we believe, the greatly augmented response to vasoactive drugs.28

Baroreceptors apparently do not occur within the blood vessels of the brain, because we were unable to change peripheral arterial pressure by elevating the pressure of the blood perfusing the dog’s brain with a pump. Pressures as high as those produced by injecting adrenaline into the donor animal produced no change while the adrenaline elicited a sharp fall in pressure. The baroreceptors responsive to changes in cerebrospinal fluid pressure we shall consider in a separate communication.

Alteration or loss of the ability of the cerebral buffer system to respond by peripheral dilatation to pressor substances manifestly might be a mechanism responsible for the development of essential hypertension.

**SUMMARY**

1. A method has been described for perfusion of a dog’s brain connected to its body only by the nervous system; by this method no blood leaks into the body.

2. In 127 experiments it was shown that adrenaline and noradrenaline injected into the perfusion circuit constantly reduced the blood pressure of the recipient’s body, roughly in proportion to the amount of pressor agent administered. The depressor response was largely independent of the pressor response of the donor. Neither drug causes this effect when injected into the cerebrospinal fluid.

3. Depressor substances such as histamine and acetylcholine when perfused through the brain caused a marked rise in the recipient’s blood pressure.

4. These effects could be produced inde-
pendently of the carotid sinus buffer mechanism. Mechanical elevation or lowering of the perfusion pressure within the brain failed to alter the arterial pressure of the recipient’s body, although pressures were attained comparable to those after injection of pressor and depressor substances.

5. Lumbodorsal sympathectomy, selective section of the spinal cord, and autonomic ganglionic blockade by tetraethylammonium chloride all abolished the central response to adrenaline and noradrenaline. Atropine, benzodioxane, ergotamine, and Benadryl given to the recipient’s body all failed to block the central depressor responses. Carbon dioxide lowered the arterial pressure in the curarized donor dog but did not affect the pressure of the recipient’s body. When the carbon dioxide was given to the recipient’s body, arterial pressure fell.

6. In decapitated animals adrenaline was both pressor and depressor and noradrenaline only pressor. Both were augmented by tetraethylammonium chloride, but after Priscoline adrenaline was depressor and noradrenaline almost inactive.

7. Estimation of cardiac output from pressure pulse tracings showed, after centrally induced adrenaline hypotension, an increase and reduction of peripheral resistance.

Conclusions

By means of a special technic for perfusing the brain of a dog joined to its body only by the nervous system, chemoreceptors have been found in the brain. These respond to adrenaline and noradrenaline by lowering arterial pressure sharply and to histamine and acetyl-β-methylcholine by raising it. Baroreceptors were not found within the vessels. This cerebral buffer system is probably of importance in determining the response to humoral vasoactive substances, hence in the mechanism of hypertension and shock.

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