Autoregulation of Cerebral Blood Flow

ELECTROMAGNETIC FLOW MEASUREMENTS DURING ACUTE HYPERTENSION IN THE MONKEY

By Kouzo Yoshida, M.D., John S. Meyer, M.D., Ko Sakamoto, M.D., and Jyoji Handa, M.D.

ABSTRACT

Changes in blood flow through the internal carotid, vertebral and external carotid arteries were measured by electromagnetic flowmeters during and after acute hypertension induced by closing a clamp around the thoracic aorta in anesthetized monkeys.

The internal carotid and vertebral arterial system showed both rapid and delayed autoregulatory responses to rapid increases in blood pressure; the rapid (primary) responses occurred within seconds, the progressive (delayed) within 3 to 4 minutes. In contrast, the flow response within the external carotid system appeared to be passive. Cervical sympathetic innervation and myogenic reflexes (Bayliss reflex) both appear to play a part in the rapidly occurring (primary) regulation of cerebral blood flow. The mechanism responsible for delayed and progressive (secondary) autoregulation in the cerebral vasculature appeared to be metabolic, since it was predominantly influenced by changes in blood $\text{PCO}_2$. Changes in intracranial pressure did not seem to be involved in autoregulation.

ADDITIONAL KEY WORDS
vertebral blood flow
carotid blood flow
intracranial pressure

In a previous study, autoregulation of internal carotid artery flow was demonstrated when the blood pressure was reduced by fractional withdrawal of venous blood (1). Cerebral arterial blood flow showed little or no decrease until a critical blood pressure was reached, then a sharp drop in cerebral blood flow accompanied any further fall in blood pressure.

Some data from studies in man suggest that there is autoregulation of cerebral blood flow during hypertension. In essential hypertension (2), toxemia of pregnancy with hypertension, and during drug-induced hypertension, cerebral blood flow was within normal limits. These data and the whole question of autoregulation of cerebral blood flow are summarized in Lassen's excellent review and are often quoted to support the concept that autoregulation also exists in man, although effects of age and the level of carbon dioxide tension in arterial blood were not considered (3). We are unaware of quantitative studies of autoregulation of cerebral blood flow during non-pharmacologically induced hypertension, although there are the qualitative observations that pial vessels constrict during elevation of the blood pressure (5-7).

The present study was designed to measure blood flow through the major cerebral arteries in the necks of monkeys, by means of electromagnetic flowmeters before and after induction of acute hypertension without the use of drugs. From quantitative data on pressure, flow, and resistance, the existence of autoregulation within the cerebral arterial system was determined and its mechanisms were investigated.

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AUTOREGULATION OF CEREBRAL BLOOD FLOW

Methods

Twenty-two monkeys (6 Macacus rhesus and 16 Anubis baboons) weighing 3 to 4 kg were used. Results obtained from the two species were not significantly different. Each animal was anesthetized with pentobarbital sodium (initially 35 to 40 mg/kg, intravenously), with supplements given as needed. Atrpine sulfate (0.4 mg intramuscularly) was also given to each monkey.

Polyethylene catheters were threaded into the subclavian artery via the brachial artery, and into the abdominal aorta via the femoral artery. These were connected to Statham pressure transducers (Statham Instruments, Puerto Rico). A Crutchfield adjustable clamp (V. Mueller Co., Chicago) was placed around the descending thoracic aorta and blood pressure was recorded both cranially and caudally to it. When the clamp was closed, the blood pressure rose rapidly in the cranial vessels and approached zero in the vessels caudal to the clamp (7).

Tracheostomy was performed and an endotracheal cannula inserted. After intravenous injection of 20 mg of gallamine triethiodide, constant artificial respiration was maintained with a Harvard variable speed mechanical respirator (Model 606, Harvard Apparatus Co., Inc., Dover, Mass.). Endotracheal end-tidal CO₂ concentration of the expired air was monitored by means of a Beckman infra-red gas analyzer (Spinco Model LB-1, Beckman Instruments, Inc., Palo Alto, Calif.), and was maintained between 3% and 4% in the steady state.

For measuring intracranial pressure, a balloon introduced into the subdural space in the temporoparietal region was connected to a Statham pressure transducer by a catheter.

A midcervical incision was made. The sternomastoid and omohyoid muscles were cut, and both carotid arteries were exposed. To eliminate the effect of carotid sinus reflexes during acute hypertension, both carotid sinuses were denervated. The completeness of denervation was demonstrated by the failure of systemic blood pressure to increase when the common carotid artery was occluded on either side. In animals in which vertebral flow was measured, the manubrium sterni and the medial one-third of the clavicle were removed and the vertebral artery was exposed. The vagus nerve and the cervical sympathetic chains were carefully preserved during these surgical procedures.

Blood flow was measured with two electromagnetic flowmeters simultaneously. A Microflo flowmeter (Model M-4001, Medicon Division of Statham Instruments, Inc., Los Angeles, Calif.) with 1- or 2-mm lumen-diameter probes was used for measuring vertebral artery flow. A Metroflo flowmeter (Series 6000, Avionics Research Products Corp., Los Angeles, Calif.) with a 2-mm lumen-diameter probe was used for measuring internal or external carotid artery flow. Because of technical difficulties in applying probes directly on either the internal or external carotid artery, the meter was placed on the common carotid artery; when the external carotid artery was clamped the meter recorded internal carotid flow and when the internal carotid was clamped it measured external carotid flow (8). Methods for calibration of flow rate in vitro and determination of zero reference in vivo have been described (8).

Acute hypertension within the cerebral vessels was induced by rapidly closing the Crutchfield clamp around the thoracic aorta. To expose the aorta, an incision was made along the medial border of the left scapula and a thoracotomy performed between the fourth and fifth ribs. The Crutchfield clamp was placed loosely around the most proximal part of the descending thoracic aorta with the handle for tightening the clamp protruding from the closed wound.

Surgical procedures were performed so that blood loss was minimal. At frequent intervals, the hematocrits of venous blood samples was measured by a micro method. Since anemia changes cerebral vascular resistance, records made when the hematocrit values fell below 40% were discarded.

Integrated rates of flow, blood pressure, end-tidal CO₂ concentrations and cerebrospinal fluid pressures were recorded continuously on a Grass Model 5 ink-writing polygraph (Grass Instrument Co., Quincy, Mass.). After recording the steady state, any effects of acute hypertension were observed for 3 min. Records were also taken for at least 5 min after release of the clamp.

Zero references for the flowmeters were checked before induction of hypertension and after its termination. Only records giving constant readings for both zero references were used for statistical studies.

To analyze the data statistically, values for subclavian blood pressure and of internal carotid, external carotid and vertebral flow were obtained from the records at intervals of 1 min during and after hypertension. The steady-state value was obtained at a point 30 sec before the onset of hypertension. Regional peripheral vascular resistance was calculated by dividing mean arterial blood pressure by the flow.

Results

Sudden, sustained increase of the intraluminal pressure of the cerebral arterial system was successfully produced by closing the
clamp around the thoracic aorta. In some cases, bradycardia occurred when the clamp was applied; if a significant change in heart rate occurred, the record was discarded. The value for mean subclavian arterial blood pressure increased from 105.5 to 160.8 mm Hg immediately and remained fairly constant during the period of clamping with mean values of 157.5, 160.0 and 160.8 mm Hg at 1, 2 and 3 min respectively. When the clamp was released, mean arterial blood pressure decreased rapidly to a mean value of 52.5 mm Hg and then gradually returned to the steady state within 5 min.

**CHANGES IN INTERNAL CAROTID AND VERTEBRAL FLOW DURING AND AFTER ACUTE CEREBRAL VASCULAR HYPERTENSION**

Twelve successful flow measurements were made in the internal carotid and 10 in the vertebral arteries. The data are summarized in Table 1 and Figure 1.

When acute cerebral vascular hypertension was induced, both internal carotid and vertebral flow increased significantly ($P < 0.005$), reaching maximal values immediately after the onset of hypertension. The average increase of flow was 45.6% for the internal carotid and 39.5% for the vertebral arteries, whereas the average increase of blood pressure was 55.8% for the internal carotid and 67.6% for vertebral flow measurements. The rise in flow was proportionately smaller than the increase in blood pressure. As might be expected, the computed values for vascular resistances showed significant increases in both internal carotid and vertebral arteries ($P < 0.005$).

After the initial increase, blood flow in both vessels began to decrease progressively despite the fact that hypertension was sustained. Internal carotid flow after 2 and 3 min and vertebral flow after 2 min of sustained hy-
# TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Internal carotid artery</th>
<th>Vertebral artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(12 measurements; 6 monkeys)</td>
<td>(10 measurements; 4 monkeys)</td>
</tr>
<tr>
<td><strong>MABP</strong> (mm Hg)</td>
<td>Mean ± SD</td>
<td>% of resting</td>
</tr>
<tr>
<td>0 min</td>
<td>103.4 ± 20.8</td>
<td>25.0 ± 6.8</td>
</tr>
<tr>
<td>1 min</td>
<td>158.4 ± 15.4</td>
<td>155.8</td>
</tr>
<tr>
<td>2 min</td>
<td>162.3 ± 8.2†</td>
<td>153.2</td>
</tr>
<tr>
<td>3 min</td>
<td>162.1 ± 6.9†</td>
<td>156.8</td>
</tr>
</tbody>
</table>

**During hypertension**

|                          | Mean ± SD | % of resting | Mean ± SD | % of resting | Mean ± SD | % of resting | Mean ± SD | % of resting |
| 0 min                    | 55.8 ± 10.3† | 54.0 | 13.9 ± 4.5† | 55.6 | 4.70 ± 2.03 | 102.4§ | 53.0 ± 7.6† | 56.6 | 8.1 ± 1.7† | 68.1 | 6.86 ± 1.80¶ | 81.5§ |
| 1 min                    | 71.0 ± 18.0† | 68.7 | 19.9 ± 4.0† | 79.6 | 3.81 ± 1.50† | 83.0 | 62.8 ± 15.8† | 67.0 | 10.8 ± 2.9 | 90.8 | 6.31 ± 2.41† | 74.9 |
| 2 min                    | 85.6 ± 21.6† | 82.8 | 23.8 ± 4.9 | 93.2 | 3.83 ± 1.50† | 83.4 | 74.5 ± 20.0† | 79.5 | 11.8 ± 3.7 | 99.2 | 6.95 ± 2.69† | 82.5 |
| 3 min                    | 91.6 ± 22.7† | 88.6 | 25.0 ± 6.1 | 100.0 | 3.90 ± 1.508 | 85.0 | 82.9 ± 21.0† | 88.5 | 12.7 ± 3.9 | 108.7 | 7.05 ± 2.38† | 83.7 |
| 4 min                    | 98.4 ± 25.9 | 95.2 | 26.1 ± 6.9 | 104.4 | 4.02 ± 1.588 | 87.6 | 97.8 ± 20.4 | 104.4 | 13.8 ± 4.7 | 116.0 | 7.63 ± 2.54 | 90.6 |

**Resistance (PRU)**

|                          | Mean ± SD | % of resting | Mean ± SD | % of resting | Mean ± SD | % of resting | Mean ± SD | % of resting |
| 0 min                    | 4.59 ± 1.91 | 4.59 ± 1.91 | 5.11 ± 1.77† | 5.11 ± 1.77† | 5.15 ± 1.70† | 5.15 ± 1.70† | 5.69 ± 2.06† | 5.69 ± 2.06† | 5.75 ± 1.85§ | 5.75 ± 1.85§ |
| 1 min                    | 5.75 ± 1.85§ | 5.75 ± 1.85§ | 6.81 ± 2.41† | 6.81 ± 2.41† | 6.95 ± 2.69† | 6.95 ± 2.69† | 7.05 ± 2.38† | 7.05 ± 2.38† | 7.63 ± 2.54 | 7.63 ± 2.54 |

**Hypertension**

*PRU = peripheral resistance unit measured as mm Hg/(ml/min).

**MABP for the internal carotid and vertebral arteries are not equal because (1) flow in the two arteries was not always measured simultaneously and (2) there were more measurements of internal carotid, than of vertebral, artery flow.

†P < 0.005.

‡P < 0.05.

§P < 0.01.

¶P < 0.025.
Hypertension were significantly lower than values obtained immediately after the onset of hypertension ($P < 0.05$ after 2 min, $< 0.005$ after 3 min for internal carotid flow and $< 0.05$ after 3 min for vertebral flow). Internal carotid and vertebral vascular resistance continued to show gradual increases during sustained hypertension. The increase in internal carotid vascular resistance was significant at 2 min ($P < 0.01$) and 3 min ($P < 0.005$) compared to the value immediately after the onset of hypertension.

With the sudden decrease in blood pressure when the clamp was released, both internal carotid and vertebral flow decreased significantly ($P < 0.005$). As the blood pressure gradually returned to the steady state, flow in both vessels increased slowly. Since recovery was faster for blood flow than for blood pressure, vascular resistances remained significantly lower than steady-state values.

During acute hypertension the percentage increase of blood flow was smaller for the vertebral than for the internal carotid artery, even though the blood pressure was raised to higher levels during the vertebral measurements. The percentage increase in the vascular resistance during hypertension was greater for the vertebral than for the internal carotid vascular bed. After hypertension was terminated, recovery of blood flow to steady-state values was more rapid for the vertebral than for the internal carotid artery. Vascular resistance tended to persist at lower levels for the vertebral than for the internal carotid system after normotension was restored. The difference was statistically significant immediately after release of the clamp ($P < 0.05$).

Figure 2 illustrates a typical experiment showing these differences.

**CHANGES OF INTRACRANIAL PRESSURE DURING AND FOLLOWING ACUTE HYPERTENSION**

Intracranial pressure increased simultaneously with the rise in blood pressure, the average maximal increase being 50.3 mm H$_2$O. When hypertension was terminated, intracranial pressure decreased promptly, reaching an average minimum value of 14.2 mm H$_2$O below the steady-state reading. Thereafter, it slowly returned to the steady state within 3 min.

If intracranial pressure can be equated with the tissue pressure within the brain substance, then it could be considered that the changes in tissue pressure might explain the autoregulation peculiar to cerebral vessels. However, the average maximal rise of intracranial pressure of only 50.3 mm H$_2$O alone cannot account for the increase of either internal carotid or vertebral vascular resistance. Furthermore, changes in intracranial pressure were passively dependent on changes in internal carotid or vertebral flow and did not correlate with changes in vascular resistance. This relationship is illustrated in Figure 6B. Changes in intracranial pressure, therefore, did not appear to determine cerebral autoregulation.

**EFFECT OF CHANGES IN PaCO$_2$ ON INTERNAL CAROTID AND VERTEBRAL FLOW**

End-tidal CO$_2$ concentration tended to decrease progressively during sustained hypertension, reaching minimal values within 3 min. After hypertension was discontinued, it increased promptly to reach maximal values within a few seconds, then gradually returned to the steady state within 2 to 3 min. Basal, minimal and maximal values averaged 3.34, 2.85 and 3.75, respectively. Since changes in end-tidal CO$_2$ are equal to alveolar and arterial Pco$_2$, progressive reduction of the latter may be one factor influencing cerebral vascular resistance in this type of experimental hypertension.

A typical experiment to show the effect of CO$_2$ inhalation is illustrated in Figure 3. With the sudden rise in blood pressure, both internal carotid and vertebral flow rapidly increased to reach maximal values. Thereafter they tended to decrease in association with the gradual decrease of end-tidal CO$_2$. One minute after the onset of hypertension, approximately 5% CO$_2$ in air was inhaled. This produced a rapid rise in end-tidal CO$_2$ concentrations to above steady-state levels. Vertebral and carotid flow started to increase within the first minute and reached their maximal values within another half minute. Nevertheless, these maximum values did not reach...
The values recorded immediately after the onset of hypertension. Inhalation of 5% CO₂ interrupted the progressive increase of vascular resistance; however, vascular resistance still remained significantly elevated. Hence changes in CO₂ content of the blood is not the only factor controlling the cerebral vascular resistance.

**EFFECT OF CERVICAL SYMPATHECTOMY ON INTERNAL CAROTID AND VERTEBRAL FLOW**

Effects of cervical sympathectomy were studied in 5 monkeys. Under aseptic precautions, both the superior cervical and stellate ganglia were completely removed on one side. The effect of sympathectomy was confirmed by ipsilateral signs of miosis and ptosis. In previous studies, it was shown that the effect of CO₂ inhalation on external carotid flow was significantly altered by sympathectomy (1) when this was used as a test. In the present series of experiments, sympathectomy was performed in the same manner. In addition, it has been shown in this laboratory (unpublished work) that stimulation of the superior cervical sympathetic ganglion of monkeys resulted in a 28.7% decrease of internal carotid flow and a 17.6% decrease in vertebral flow; stimulation of the stellate ganglion resulted in a 22.4% decrease in internal carotid and a 13.8% reduction in vertebral flow. After cervical sympathectomy, as described in the present communication, stimulation of the stellate ganglion no longer produced this reduction of cerebral blood flow. Furthermore, stimulation of the petrosal nerve produced no change in carotid blood flow.
so that there is no evidence that the so-called cerebral vasodilator fibers of the seventh cranial nerve play any part in cerebral autoregulation.

After allowing 7 days for degeneration of nerves, the ipsilateral internal carotid and vertebral arteries were exposed and flow measurements were made during acute hypertension.

Results are summarized in Table 2. Sympathectomy changed the response of internal carotid and vertebral flow during acute hypertension. Immediately after the onset of hypotension...

TABLE 2
Summary of Measurements of Blood Flow in Internal Carotid and Vertebral Arteries during Acute Hypertension in Five Monkeys after Cervical Sympathectomy*

<table>
<thead>
<tr>
<th></th>
<th>Internal carotid artery</th>
<th>Vertebral artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MABP (mm Hg)</td>
<td>Flow (ml/min)</td>
</tr>
<tr>
<td>Resting values</td>
<td>122.6</td>
<td>13.3</td>
</tr>
<tr>
<td>0 min</td>
<td>180.0</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>(146.8%)</td>
<td>(171.4%)</td>
</tr>
<tr>
<td>1 min</td>
<td>168.4</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>(137.4%)</td>
<td>(144.4%)</td>
</tr>
<tr>
<td>2 min</td>
<td>169.4</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>(138.2%)</td>
<td>(134.6%)</td>
</tr>
<tr>
<td>3 min</td>
<td>168.8</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>(137.7%)</td>
<td>(131.6%)</td>
</tr>
</tbody>
</table>

*Percentage changes from resting values are shown in parentheses.

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pertension, internal carotid vascular resistance showed no initial increase in 4 of 5 monkeys, nor did vertebral vascular resistance in 3 of 5 monkeys. For the average of 5 monkeys, initial increases of internal carotid and vertebral flow were slightly greater in proportion to the increases of blood pressure, hence vascular resistances of both arteries were decreased. Changes in flow and vascular resistance after the initial changes were not significantly different from those in the group without sympathectomy. Both flows tended to decrease progressively, with accompanying increases in vascular resistances. A typical experiment is illustrated in Figure 4.

CHANGES IN EXTERNAL CAROTID FLOW DURING AND AFTER ACUTE HYPERTENSION

Statistical summaries of the data for 10 measurements of external carotid flow and computed vascular resistances are shown in Table 3 and Figure 5. A sudden rise in blood pressure was accompanied by a significant increase in external carotid flow ($P < 0.005$). In contrast with the results in internal carotid or vertebral arterial system, external carotid vascular resistance showed a significant decrease ($P < 0.01$). Thereafter, external carotid flow remained elevated, with reduced vascular resistance during sustained hypertension.

After hypertension was terminated, external carotid flow remained slightly higher than the basal values, then gradually returned to the resting values. External carotid vascular resistance decreased further immediately after termination of hypertension, and returned to the steady state within a few minutes.

A typical experiment showing the considerable difference in response between the internal and external carotid arteries is illustrated in Figure 6A; note that changes characteristic of autoregulation occurred only in the internal carotid system.
TABLE 3

<table>
<thead>
<tr>
<th>Resting values</th>
<th>MABP (mm Hg)</th>
<th>Flow (ml/min)</th>
<th>Resistance (PRU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>110.6 ± 15.1</td>
<td>13.8 ± 5.3</td>
<td>9.81 ± 5.22</td>
<td></td>
</tr>
<tr>
<td><strong>During hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>162.0 ± 13.0*</td>
<td>32.7 ± 15.9*</td>
<td>6.09 ± 2.51†</td>
</tr>
<tr>
<td>1 min</td>
<td>157.5 ± 6.9*</td>
<td>30.9 ± 14.5*</td>
<td>6.11 ± 2.29†</td>
</tr>
<tr>
<td>2 min</td>
<td>160.8 ± 5.1*</td>
<td>31.1 ± 11.7*</td>
<td>5.86 ± 1.86§</td>
</tr>
<tr>
<td>3 min</td>
<td>161.7 ± 3.1*</td>
<td>29.7 ± 10.1*</td>
<td>5.97 ± 1.61§</td>
</tr>
<tr>
<td><strong>After hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>56.1 ± 8.9*</td>
<td>16.0 ± 6.3</td>
<td>4.59 ± 2.93*</td>
</tr>
<tr>
<td>1 min</td>
<td>71.8 ± 15.6*</td>
<td>16.3 ± 5.2</td>
<td>4.82 ± 1.91§</td>
</tr>
<tr>
<td>2 min</td>
<td>90.8 ± 18.6*</td>
<td>15.8 ± 4.8</td>
<td>6.21 ± 2.00</td>
</tr>
<tr>
<td>3 min</td>
<td>98.0 ± 23.7§</td>
<td>15.8 ± 4.8</td>
<td>6.60 ± 2.50</td>
</tr>
<tr>
<td>4-5 min</td>
<td>106.0 ± 25.1</td>
<td>14.7 ± 3.2</td>
<td>7.58 ± 2.33</td>
</tr>
</tbody>
</table>

*P < 0.005.
†P < 0.01.
§P < 0.005.

To eliminate the effect of the aortic depressor nerves during acute hypertension, both vagus nerves were cut in the neck (in addition to carotid sinus denervation), and flow measurements were repeated during acute hypertension (Figure 6B). External carotid flow now increased almost proportionally to the increase of mean arterial blood pressure, and vascular resistance did not show as much decrease as before vagotomy. After the termination of hypertension, the external carotid resistance now increased significantly and slowly returned to the steady state. Vagotomy also changed the response of internal carotid vascular resistance during acute hypertension. It remained increased for 30 sec even after hypertension was terminated.

Discussion

The cerebral circulation of the monkey is anatomically similar to that of man. The internal carotid artery has few extracerebral branches. These are the ophthalmic artery and small twigs supplying the dura mater, periosteum and bones. The vertebral artery supplies a few small branches to the cervical muscles. Under physiological circumstances, this extracerebral contribution represents a small proportion of the total internal carotid or vertebral flow (9). When acute hypertension is produced, the relation between intra-
craniocerebral and extracranial flow may be altered. However, since the vascular resistance of the extracranial vessels decreases during acute hypertension, it seems reasonable to assume that the increased vascular resistance of the total internal carotid or vertebral flow is entirely due to the increased intracerebral vascular resistance.

Statistical analysis of the data obtained from these experiments indicated that there is an autoregulatory process within the cerebral arterial system which tends to maintain constant cerebral blood flow in the face of a sudden increase in blood pressure. Immediately after the onset of hypertension, vascular resistance of the internal carotid and vertebral arteries showed a rapid and significant increase, followed by a slow but progressive increase during the next 3 min of sustained hypertension. The initial increase in vascular resistance need not necessarily reflect vasomotor changes, since both the blood pressure and flow were altered at the same time, but the progressive increase in vascular resistance that followed while the blood pressure remained constant indicates that cerebral vasoconstriction occurred (10). These facts are in good agreement with direct observations by Forbes (6), Fog (5), and Meyer et al. (7), who described vasoconstriction of pial arterioles in response to a sudden rise in blood pressure.

In contrast, vascular resistance of the external carotid artery showed a significant decrease during the period of sustained hypertension. This was proved to be due mainly to the aortic depressor reflex, since the decrease in resistance was almost abolished by bilateral vagotomy. Nevertheless, the external carotid vascular resistance still showed a slight decrease in response to a rise in blood pressure even after vagotomy. Such a decrease in resistance, which indicates a proportionately greater increase in flow than in pressure as the pressure rises, appears to be a characteristic of a nonreactive or passive vascular bed as defined by Green (11).

Since acute cerebral hypertension was produced by tightening the clamp around the thoracic aorta, it might be considered that the resulting vasoconstriction was due to circulating vasoconstrictors such as angiotensin or epinephrine formed or released because of ischemia of the kidneys or adrenal glands. However, the effect of such vasoconstricting agents on cerebral vessels must be minimal because of complete occlusion of the aorta, slow venous return from the renal and adrenal region, and the rapidity of the cerebral response which began within a few seconds. The increase in intracranial pressure also failed to account for the autoregulatory process. Two possibilities remain as the factors responsible for autoregulation, myogenic constriction (12-16) and metabolic changes (such as in \( O_2 \) or \( CO_2 \)) acting on the vessel walls (17-19). Under usual circumstances the influence of \( PO_2 \) on cerebral vessels is relatively minor compared to that of \( PCO_2 \); therefore the latter is considered more important in autoregulation.

Endotracheal \( CO_2 \) concentration showed a progressive decrease during sustained hypertension because the animals were maintained on constant artificial respiration and there was a decrease of venous return from the parts of the body caudal to the clamp. The fact that the secondary progressive increase in vascular resistance was prevented by inhalation of 6.25% \( CO_2 \) supports the theory that a metabolic mechanism, especially changes in \( PCO_2 \), is involved in the secondary progressive autoregulation of cerebral arterial system during an increase in blood pressure.

It should be emphasized, however, that inhalation of \( CO_2 \) did not inhibit the initial (primary) increase in cerebral vascular resistance in response to acute hypertension. There appear to be at least two explanations for the initial (primary) increase in cerebral vascular resistance. The first is the Bayliss effect occurring as a myogenic reflex in the pial arterioles.

The second explanation considers the "closing mechanism" of major cerebral arteries (20). According to this hypothesis, the internal carotid and vertebral arteries can change their lumina in certain localized sections in response to changes in blood pressure,
thus maintaining a constant pressure in the circle of Willis. Results obtained from monkeys after cervical sympathectomy indicate that the cervical sympathetic ganglia play a part in causing initial increases of internal carotid or vertebral vascular resistance but do not affect their progressive increases in response to acute hypertension. This evidence supports Lassen's suggestion that the possibility cannot be excluded that perivascular nerves participate in regional control of cerebral blood flow in response to changes in perfusion pressure and regional changes in metabolism. In unpublished work, we have shown that stimulation of the superior cervical ganglion results in a decrease in internal carotid flow measured by electromagnetic flowmeters, which appears to be due not only to constriction of small cerebral vessels but also to constriction of the carotid artery in the neck. Therefore, it is possible that the sympathetic nervous system may also participate in a small way in autoregulation by governing a "closing mechanism" with the major cerebral arteries.

Acknowledgment

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