The Sympathetic Nervous System and the Regulation of Cerebral Blood Flow in Man

BY ERIK SKINHOJ, M.D.

Abstract:
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Pharmacological blockade of the α adrenergic system by 20 mg phentolamine I.V. was shown not to influence CBF in 14 patients with an intact cerebral autoregulation. If the autoregulation—tested with angiotensin—was impaired for some reason, CBF was found to follow proportionally the blood pressure changes provoked by the blockade. The physiological sympathetic stimulation provoked by distention of the bladder did not alter the CBF (seven patients). The CO₂ reactivity was unaffected by the sympathetic α blockade (six patients).

It appears from these studies that the sympathetic system does not play any substantial role in regulation of CBF in man, and thus it would seem useless to try to influence the cerebral circulation for therapeutic purposes by systemic application of drugs, which directly or indirectly work via the sympathetic system.

Additional Key Words sympathetic stimulation sympathetic blockade CO₂ reactivity cerebral circulation ¹³³Xe intracarotid injection method CBF autoregulation

In a recent issue of this Journal Rosenblum¹ gave an extensive and critical review of the literature concerning neurogenic control of cerebral circulation. He came to the conclusion that anatomically a sympathetic innervation as far distal as minor arterioles is now beyond doubt, and he found increasing evidence of some kind of sympathetic control of the diameter of the intracerebral vessels. However, the data obtained by different investigators are conflicting and often difficult to interpret because of the numerous pitfalls in this research field, i.e., contamination with blood flow in the external carotid system, steady state problems, insufficient control with changes in blood gases (especially CO₂), changes in cerebral metabolism provoked by the experimental situation, impaired autoregulation due to the experimental procedure, inhomogeneous blood flow changes in different parts of the brain, etc. Furthermore, the review leaves the impression that there might be differences between species. If so, conclusions concerning therapeutic approaches from such basic investigations must be based upon human studies, of which only a few are available.

The present study deals with the possible influence of sympathetic blockade and stimulation on rCBF in man and with the possible sympathetic influence on the CO₂ reactivity of CBF.

Methods
The intracarotid ¹³³Xenon clearance method has been described previously in this Journal.²,³ It has the advantage that CBF can be measured quantitatively from different areas of the brain—in these series 35 areas—simultaneously without contamination from the external carotid system and without disturbing the mechanism of autoregulation. During the measurements the blood pressure in the carotid artery was monitored. The patients were awake and not premedicated. Of the 32 patients in the study, six had an abolished or grossly impaired autoregulation when tested with
TABLE 1

The Effect of \( \alpha \)-Adrenergic Blockade on Cerebral Blood Flow in Patients With an Intact Autoregulation

<table>
<thead>
<tr>
<th>CBF (ml/100 gm/min)</th>
<th>BP (mm Hg)</th>
<th>CBF (ml/100 gm/min*)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Corrected for remaining activity and possible changes in Pa CO\(_2\).*

The figures given in tables 1 through 3 are average CBF\(_{10}\) values from the 35 recordings in each examination; in table 4, CBF\(_{\text{initial}}\) values are preferred due to steady state problems in Pa CO\(_2\) during inhalation of 7% CO\(_2\).

Results

In none of the 14 patients tested did the phentolamine show any significant change in CBF, and the average values of CBF before and after the blockade are close to a statistical identity. At the same time the blood pressure decreased approximately 16% (table 1).

In the five patients with lost autoregulation the result of the \( \alpha \) blockade showed a 24% decrease in blood pressure and a reduction in cerebral blood flow of 21%. (Flow values: 0.05 > \( p \) > 0.02; blood pressure values: 0.02 > \( p \) > 0.01) (table 2).

Distention of the bladder is a very strong sympathetic stimulation. In this series it raised the blood pressure approximately 35%. The concomitant small increase in cerebral blood flow does not reach statistical significance (table 3).

The CO\(_2\) response after inhalation of 7% CO\(_2\) was tested in six patients before and after blockade. The CO\(_2\) reactivity was calculated as

\[
\frac{\Delta \log \text{CBF}}{\Delta \text{Pa CO}_2}
\]

TABLE 2

The Effect of \( \alpha \)-Adrenergic Blockade by 20 mg Phentolamine I.V. on Cerebral Blood Flow in Patients With an Impaired Autoregulation

<table>
<thead>
<tr>
<th>CBF (ml/100 gm/min)</th>
<th>BP (mm Hg)</th>
<th>CBF (ml/100 gm/min*)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Corrected for remaining activity and possible changes in Pa CO\(_2\).*
TABLE 3

The Effect of Sympathetic Stimulation by Bladder Distention on Cerebral Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>CBF (ml/100 gm/min)</th>
<th>BP (mm Hg)</th>
<th>After distention of the bladder</th>
<th>CBF (ml/100 gm/min)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Int.</td>
<td>P (mm Hg)</td>
<td></td>
<td>Aft.</td>
<td>r dbtamHon</td>
</tr>
<tr>
<td>Average</td>
<td>20.9</td>
<td>120</td>
<td>23.3</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>34.8</td>
<td>100</td>
<td>35.3</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>24.8</td>
<td>90</td>
<td>27.3</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>22.4</td>
<td>110</td>
<td>26.4</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>75.7</td>
<td>92</td>
<td>81.7</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>33.8</td>
<td>96</td>
<td>32.3</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>26.0</td>
<td>112</td>
<td>28.0</td>
<td>169</td>
<td>169</td>
</tr>
<tr>
<td>Average</td>
<td>34.1</td>
<td>103</td>
<td>36.3</td>
<td>139</td>
<td>139</td>
</tr>
</tbody>
</table>

and then expressed as percent change in CBF per 1 mm Hg change in P_{\text{aCO}_2} according to Olesen et al. The slight decrease in CO_{2} re-
activity after the blockade will be discussed.

Discussion

The fact that \( \alpha \) blockade was not found to influence CBF in man is not surprising. It is in accordance with the majority of findings including our own, which show that none of the sympatholytic substances tested in man have any significant effect on CBF when given intravenously or intra-arterially. It is also in accordance with the fact that chronic sympa-
thectomy in animals does not change CBF, and with our own observations of a patient with a severe orthostatic hypotension which was possibly a first state of a Shy-Drager syndrome. In spite of no remaining sympa-
thetic activity, the cerebral blood flow, its autoregulation, and reactivity upon CO_{2} were found to be normal.

In the present study the decrease of 17% in blood pressure after \( \alpha \) blockade did not change CBF at all. The interpretation of this fact as an isolated phenomenon could be one of three: (1) sympathetic blockade has no effect upon either CBF or its autoregulation, (2) sympa-
thetic blockade affects the cerebral resistance vessels in exactly the same way as it affects blood pressure-determining vessels elsewhere in the body, thus keeping cerebral blood flow constant, and (3) a possible dilatation of the bigger afferent vessels might be compensated by an autoregulation unaffected by the block-
ade. To evaluate the possibilities, the studies also were carried out in patients with abolished autoregulation. In such patients CBF was found to follow the blood pressure, indicating that the \( \alpha \) blockade did not have any significant hemodynamic influence upon the larger affer-
cent vessels to the brain. This result also would appear to rule out the second possibility. Our conclusion is that the cerebral resistance vessels, taken as a whole, have no sympathetic tonus. This, too, is in accordance with most animal experiments (see Rosenblum's review).

On the other hand, sympathetic stimulation is claimed to cause a reduction in flow in experiments with animals. In man sympa-
thismimetic drugs applied via the blood stream do not influence CBF. This might be due to the blood-brain barrier, which is known to be very resistant to these drugs. Evidence on this was found recently by Wahl et al., who demonstrated that cerebral arterioles as a matter of fact are sensitive to perivascularly applied sympathetic transmitter substances when large doses were applied. But the effect was negligible compared with the effect of even minute changes in perivascular pH.

Only a single study concerning CBF in man during a more physiological sympathetic stimulation is known to us. Olesen examined focal flow changes in the contralateral motor cortex during ischemic work by the hand. This stimulus evoked a marked general sympathetic stimulation. In a few cases he noticed a global increase in cerebral blood flow beyond the focal increase in the motor cortex, but never a decrease.

Distention of the urinary bladder gives a very strong sympathetic stimulation as seen by the sharp increase in pulse rate, blood pressure...
and dilatation of the pupils. In the present series blood pressure rose from an average of 103 mm Hg to 139 mm Hg. In spite of this no significant change in cerebral blood flow was seen.

This means that in man neither sympathetic blockade nor general sympathetic stimulation influences cerebral blood flow if the cerebral autoregulation is intact. The possibility that the sympathetic system might play a role under special conditions still remains—for example, protection of the brain against a dangerously high blood flow during hypercapnia with the risk of edema due to an abnormally high perfusion-pressure in the capillary system. In some previous studies, Høedt-Rasmussen and this author have examined the effect upon CBF after blockade of the ganglion stellatum on both sides during hypercapnia and heavy exercise. The series was never completed due to potential pulmonary and cardiac risks to the patients, but in the three cases studied we saw no effect on CBF by the stellatum blockade even under these physiologically stressing circumstances.

In the present study we tried to approach the problem in a different way by examining the possible effect of changes in the Pco₂ reactivity after phentolamine blockade. In animal experiments Harper et al. have found that stimulation of the cervical sympathetic system reduces the response of CBF to CO₂. James et al. found that sympathetic stimulation had a decreasing effect upon CBF during hypercapnia but not during hypocapnia. On the other hand Meyer et al. found the same response during hypercapnia and hypocapnia. Frazer et al. found an adrenergic blockade of hypocapnic cerebral arterial constriction in the monkey.

In the present series we found a slight tendency to a decrease in CO₂ reactivity after a sympathetic blockade. The most likely explanation of this phenomenon is that the autoregulation is impaired at the high Paco₂ values, and at the same time the rise in blood pressure following CO₂ inhalation is decreased or even inverted after phentolamine. It should be stressed that in no case did sympathetic blockade increase the CO₂ response, which would have been expected if the sympathetic system served a protective role against CO₂-provoked dilatation of the cerebral resistance vessels.
SYMPATHETIC NERVOUS SYSTEM

The conclusion of these experiments is that in man neither blocking nor stimulation of the sympathetic system has any acute influence upon CBF, its autoregulation or the reactivity to CO₂. Chronic medication with the possibility of a slow penetration of the applied drug through the blood-liquor barrier might give different results, but no convincing evidence pointing to this is available. Another limitation of our rather absolute conclusion is, of course, that these studies do not include patients with pathological arterial spasms in connection with subarachnoid hemorrhage, head and neck injuries, etc. With these possible reservations our conclusion leaves an unsolved paradox. The brain has anatomically a sympathetic innervation, but it does not seem to play any physiological role. Harper et al.¹⁸ have suggested that the sympathetic nerve fibers in the cerebral vessels have a more phylogenetical than a functional significance.

Whatever the final explanation, the practical consequence of our up-to-date pathophysiological knowledge must be that the present enormous investments of resources, both physical and financial, in an attempt to influence the cerebral blood flow therapeutically by means of drugs which act directly or indirectly via the sympathetic system still have no rational basis.

Addendum

After the delivery of this manuscript, some studies were published claiming that α-adrenergic drugs block the normal hypocapnic cerebral vasoconstriction (Lancet 2: 457-460, 461-463 [Sept 2] 1972). The studies cited used the 133Xenon inhalation method by which contamination of isotope from the external carotid system is inevitable. This is a fact which seems crucial, especially in situations where blood flow changes independently in the brain and in extracerebral tissues. As the CO₂ reactivity in our present study was tested only by induced hypocapnia, we extended the series with estimation of rCBF during hyperventilation after blockade of the α-adrenergic system. This is a fact which seems crucial. We found the hypocapnic cerebral vasoconstriction was preserved to a completely normal degree within the brain itself. Only in the supraorbital regions, where contamination from the internal carotid artery via the ophthalmic artery to external carotid areas could be demonstrated by injection of T-1824, was the hypocapnic response abolished. At the same time, these findings confirm the observations referred to above, and indicate that they are due to the error of contamination by the inhalation method.

References

3. Olesen J, Paulson OB, Lassen NA: Regional cerebral blood flow in man determined by the initial slope of the clearance of intra-arterially injected 133Xe. Stroke 2: 519-540, 1972


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