Cerebral Hemodynamics in Shy-Drager Syndrome

Variability of Cerebral Blood Flow Dysautoregulation and the Compensatory Role of Chemical Control in Dysautoregulation

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SUMMARY Cerebrovascular autoregulation and CO₂ reactivity were measured repeatedly in 3 patients with the multiple system atrophy type of autonomic insufficiency (Shy-Drager syndrome) by means of the ¹³³Xe injection method. The degree of cerebral blood flow (CBF) dysautoregulation showed day-to-day variations in 2 of the 3 patients. The CO₂ reactivity was normal or supernormal in the supine position in patients with impaired autoregulation. In the head-up position the response to CO₂ was slightly suppressed in 2 of the patients, suggesting that chemical control may have tended to compensate for CBF dysautoregulation. It is concluded that the mechanism of chemical control of the cerebrovasculature is different from that which controls autoregulation and may have partially compensated for CBF dysautoregulation.

IT HAS BEEN well documented that cerebral circulation is regulated by both chemical control and autoregulatory mechanisms. The mode and sites of action of these regulatory mechanisms are, however, still a matter of debate.

In a previous report,¹ we demonstrated a loss of autoregulation of cerebral circulation in patients with Shy-Drager syndrome and in some patients with orthostatic hypotension² in which the autonomic nervous system was known to be involved. It was therefore presumed that the autonomic nervous system plays an important role in the mechanism of autoregulation in man.³ ⁴ Some investigators⁵ ⁶ have reported normal autoregulation in patients with Shy-Drager syndrome. The reasons for this discrepancy remain undetermined.

From animal studies, we found evidence which suggested that the intracellular pH of smooth muscle fibers of the cerebral arterioles might be a pathway responsible for chemical control of the cerebral circulation,⁷⁻⁸ and that the mechanism producing cerebrovascular autoregulation may be different from that of chemical control.⁹ However, this has not yet been demonstrated in the human cerebral circulation.

The purpose of this report is to establish reasons for the discrepancy among various reports concerning autoregulation in patients with Shy-Drager syndrome; to determine whether or not the mechanism of autoregulation is different from that of chemical control of the human cerebral circulation; and, also, to clarify the variability in dysautoregulation among patients with Shy-Drager syndrome.

Materials and Methods

Three patients with Shy-Drager syndrome of the multiple system atrophy type were studied. Clinical characteristics are shown in table 1.

Cerebral blood flow was measured by the ¹³³Xe arterial injection method. Clearance curves were obtained using a large external counter placed over the fronto-parieto-temporal area on the injected side. The cylindrical lead collimator used in this study was 88 mm long and 80 mm in diameter. Clearance curves were analyzed and calculated by stochastic analysis. The value obtained was considered to be representative of the mean hemispheric cerebral blood flow (CBF). CBF was usually measured in the right cerebral hemisphere.

The carotid arterial pressure was monitored from a strain gauge inserted into the internal carotid artery. The effective mean arterial pressure (effective MABP) was calculated from the carotid diastolic pressure plus one-third of the pulse pressure. Arterial Po₂, Pco₂ and pH were also determined during each procedure.

Cerebrovascular autoregulation was estimated by the effect of head-up tilting on CBF. When the arterial carbon dioxide tension showed a significant change in the head-up tilted position, the data were excluded from the series. The CBF measurements and estimation of autoregulation were repeated several times in each patient. The time intervals between the first and final measurements were 1 yr and 10 months for patients 1 and 3, and 3 yrs for patient 2.

Autonomic functional tests and their results are shown in table 2. The results were compared with the severity of dysautoregulation in each case.

Results

1) Day-to-day Variation of CBF Dysautoregulation

Figure 1 shows the effect of head-up tilting and reduction in cerebral perfusion pressure on CBF in patient 1. The CBF measurements and estimation of autoregulation were repeated 6 times during the follow-up period of 1 yr and 10 months. CBF was always decreased along with a reduction in perfusion pressure. The degree of CBF reduction was generally similar with each measurement except for the 3rd measurement, indicating that CBF autoregulation was impaired to the same extent in this patient.

In patient 2 (fig. 2), despite orthostatic hypotension...
TABLE 1 Clinical Symptoms in the 3 Patients with Shy-Drager Syndrome

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47</td>
<td>55</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Onset</td>
<td>Impotence</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>++</td>
<td>+~++</td>
</tr>
<tr>
<td>Other autonomic dysfunction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fasciculation</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

at the time of the first and second measurements, CBF autoregulation was not impaired. CBF autoregulation was adequately maintained in spite of orthostatic hypotension in the initial stage of the disease. This patient was observed for approximately 3 years, and, as shown in figure 2, a decline of CBF with orthostatic hypotension gradually became evident in the course of the disease (3rd and 4th CBF measurements). However, the 5th and 6th CBF measurements showed a return to normal. On the basis of these results, it is clear that the severity of orthostatic hypotension does not necessarily parallel the degree of dysautoregulation.

The third patient was followed for 1 yr and 10 months. A decline of CBF with orthostatic hypotension was noted during the observation period (fig. 3).

2) Relationship between Autonomic Functioning Tests and Dysautoregulation Severity

Table 2 shows the results of various autonomic functioning tests in patients 1-3. There was impairment of autonomic nervous function in all 3, but no conclusive relationship between these test results and dysautoregulation was detected. No single pharmacological test of the autonomic nervous system was sufficient to predict the severity of cerebral dysautoregulation. The autonomic functioning tests were repeated several times in each patient. The results were almost the same apart from the degree of orthostatic hypotension.

3) Effect of CO2 Inhalation in Shy-Drager Syndrome

The CO2 reactivity in each patient with Shy-Drager syndrome was examined after inhalation of 5-7% CO2. Figure 4 shows the effect of CO2 inhalation on CBF in the supine and erect positions in patient 1. The cerebrovascular reactivity to CO2 was examined twice, one year apart. The first results indicated that CO2 inhalation increased the CBF despite a reduction in the perfusion pressure in the supine position. The CO2 reactivity index \( \Delta \text{CBF/} \Delta \text{Paco}_2 \) was calculated as 1.6 ml/100 g/min/mm Hg. This suggests that CO2 reactivity is well maintained in patients with Shy-

![Figure 1. Effect of head-up tilting on CBF in patient 1.](http://www.ahajournals.org/doi/figure/10.1161/01.STR.24.5.955)

Drager syndrome despite a reduction in blood pressure. The reduction in systemic blood pressure with CO₂ inhalation in this patient is probably due to vasodilatation of denervated peripheral vessels. CO₂ inhalation in the erect position also increased the CBF but to a lesser extent than when supine despite a slight increase in perfusion pressure. The CO₂ reactivity index was 0.9 ml/100 g/min/mm Hg. The elevation in PaCO₂ was almost the same in both the supine and erect positions (49.8 and 49.5 mm Hg, respectively). Twelve months later, the CO₂ inhalation tests were repeated, but the results were essentially similar as shown in figure 4.

In the second patient CO₂ inhalation increased the CBF to almost the same extent in both the supine and head-up tilt positions (fig. 5). The measurements were repeated twice, and the results were similar each time. In the second patient CBF autoregulation was well maintained when the CO₂ inhalation tests were carried out. Similar CO₂ reactivity was observed in both the supine and erect positions.

In the third patient, CO₂ inhalation increased the CBF in the supine position (steady state), but in the head-up position the increase in CBF was less than in the supine position (fig. 6). The lower CO₂ reactivity in the erect position may be due to a reduction in perfusion pressure during CO₂ inhalation.
Discussion

The interrelationships between the autonomic nervous system and the mechanism of cerebrovascular regulation are not yet established. Some investigators conclude that cerebrovascular autonomic innervation is without physiological importance, but it is well known that the cerebrovascular bed possesses a relatively rich autonomic supply which must have biological significance.

The Shy-Drager syndrome is a disorder in which sympathetic and/or parasympathetic nervous system degeneration occurs. It thus provides a suitable model for investigating the influence of autonomic nervous function on the regulation of CBF. Several investigators, including ourselves, have examined CBF autoregulation in patients with Shy-Drager syndrome1 3 and found a loss of autoregulation. As a result, it was concluded that the autonomic nervous system plays a role in the mechanism of autoregulation in man. Caronna and Plum3 reported a loss of autoregulation in only 1 out of 4 patients, and Skinhøj et al.4 described normal autoregulation in a patient with idiopathic orthostatic hypotension. Caronna and Plum3 observed that CBF autoregulation was absent only in a patient who showed no mydriasis to 4% cocaine drops in either eye and concluded that the autoregulation was lost because of the patient's postganglionic autonomic denervation. However, in our third patient pupillary response to 4% cocaine was preserved on the right side, even though the CBF autoregulation for the right hemisphere was impaired. The discrepancies among various reports may be explained not only by differences in distribution of autonomic nervous system involvement in each patient but also by day-to-day variability in CBF dysautoregulation and autonomic dysfunction during the course of the illness.

Inhalation of 5-7% CO2 in air caused an increase in CBF in patients with Shy-Drager syndrome. This finding is in agreement with our previous work1 and with the studies of others.5-7 Blood pressure fell during CO2 inhalation in 2 out of 3 patients with Shy-Drager syndrome in the supine position. This is attributable to the direct vasodilatory action of carbon dioxide on the peripheral vessel wall, where neurogenic control is severely impaired by denervation. Reduction in blood pressure during CO2 inhalation made it difficult to compare the CO2 reactivity in Shy-Drager syndrome patients with that in control subjects. The CO2 reactivity index in the supine position in patient 1 was normal or slightly greater than the predicted change, despite a reduction in perfusion pressure. This suggests that the CO2 reactivity may be normal or supernormal in patients with Shy-Drager syndrome where autoregulation is impaired. The above results also confirm our previous assumption that the mechanism of autoregulation may be different from that of chemical control.6-9

CO2 reactivity in the erect position was less than that found in the supine position in patients 1 and 3. In patient 1, CO2 inhalation tests repeated after a 12-month interval gave similar results. The reason why the blood pressure increased during CO2 inhalation in the erect position in patient 1 is unknown. Despite the rise in blood pressure, the increase in CBF with CO2 inhalation in the head-up position was less than that in the supine position. This finding may be explained on the basis of our previous hypothesis10 that in patients with impaired autoregulation, accumulated CO2 and other acid metabolites produced by decreased CBF dilate cerebral vessels. Thus chemical control plays a compensatory role to some extent in the presence of impaired autoregulation.

Fully or slightly impaired autoregulation in hypercapnia has been observed by some investigators11-13 in animal experiments. It may, therefore, be that decreased CO2 reactivity in the head-up position is due to severe dysautoregulation in hypercapnia. There are no reports so far to support this conclusion in man. In the second patient in whom autoregulation was less
impaired, the CBF values obtained during CO₂ inhalation were almost the same in both the supine and erect positions despite a difference in perfusion pressure. If mild hypercapnia of this extent impaired the autoregulatory mechanism in man, the CBF value during CO₂ inhalation in the head-up position in patient 2 should have been far lower than the value obtained in the supine position.

Another possible explanation for decreased CO₂ reactivity in the erect position is that vessels which are already maximally or nearly maximally dilated by lower blood pressure are unable to dilate further in response to hypercapnia. However, as described, the mechanism of autoregulation appears to be different from that of chemical control and, based on our previous animal study, the site of action of these regulations is different. Thus, maximum dilatation of the cerebral vessels in the autoregulatory mechanism should not affect the CO₂ reactivity.

We therefore concluded that a compensatory role for chemical control in the presence of dysautoregulation may account for the results where the CO₂ reactivity is suppressed in the head-up tilted position in patient 1.

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References

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