Effects of Alpha Adrenergic Blockade on Autoregulation and Chemical Vasomotor Control of CBF in Stroke

BY JOHN STIRLING MEYER, M.D., KUNIO SHIMAZU, M.D., SHIGEMICHI OKAMOTO, M.D., ATSUO KOTO, M.D., TADAO OHUCHI, M.D., ATSUO SARI, M.D., AND ARTHUR DALE ERICSSON, M.D.

Abstract:

Autoregulation and chemical vasomotor control of cerebral blood flow (CBF) were quantitatively tested in 19 patients with various types and sites of cerebral ischemia and infarction. The effect of alpha adrenergic blockade of cerebral vessels by phenoxybenzamine (PBZ) also was evaluated in more than half of the patients. No correlation was found between the degree of cerebral dysautoregulation and impairment of chemical vasomotor control of CBF. Patients with brainstem ischemia and infarction showed normal vasomotor reactivity of CBF to changes in PaCO2 despite the impairment of cerebral autoregulation during both induced hypotension and hypertension.

Following intracarotid injection of 10 mg PBZ, the degree of cerebral dysautoregulation lessened during induced hypotension but increased during induced hypertension. Chemical vasomotor control of CBF in response to changes in PaCO2 was not significantly altered by the PBZ injection. Changes in autoregulation index (a quantitative measure of cerebral autoregulation) after the infusion were compared with changes in chemical regulation index (a quantitative measure of cerebral vasomotor reactivity). Induced hypotension and hypercapnia yielded a proportional correlation between these two indexes, while induced hypotension and hypocapnia revealed a significant inverse correlation.

This study demonstrates that cerebral autoregulation is influenced by the autonomic innervation of cerebral vessels. Alpha adrenergic blockade improves impaired autoregulation when cerebral perfusion pressure (CPP) is lowered but worsens it when CPP is raised, indicating that PBZ impairs the ability of cerebral vessels to constrict during induced hypertension and improves their ability to dilate during induced hypotension. This study also supports the view that chemical vasomotor control is regulated not directly by autonomic innervations of cerebral vessels but by a local controlling mechanism.

Additional Key Words

quantitative analysis
dual control mechanism of CBF

Introduction

The regulatory responses of the cerebral vasculature are disordered by a number of cerebral pathological processes that alter the integrity of the cerebral vessels. In particular, acute cerebral ischemia may severely impair or abolish the capacity of cerebral vessels to respond to changes in cerebral perfusion pressure (CPP) and/or arterial carbon dioxide tension (PaCO2).

The first systematic observations of the intrinsic regulation of cerebral blood vessels during changes in systemic blood pressure were made by Fog, who observed the pial vessels through a cranial window and found that a rise in systemic blood pressure was followed by cerebral vasoconstriction while a fall in blood pressure was followed by vasodilatation.

Autoregulation of cerebral blood flow (CBF) may be defined in the broader sense as the intrinsic capacity of the brain to control its blood flow according to its needs. More correctly, however, the
term is used in a restricted sense to indicate the intrinsic tendency of the brain to maintain a constant blood flow despite changes in CPP. Loss of autoregulation results in CBF which changes passively with CPP. The exact nature of the autoregulatory mechanism is unknown but hypotheses attributing it to neurogenic control have generally been considered less plausible than those attributing it to metabolic or myogenic control.\(^2\) Even those investigators who argued that myogenic or metabolic control was responsible were not able to prove that neurogenic control played no part; on the contrary, considerable data have now accumulated concerning the neurogenic control of cerebral circulation and its importance in autoregulation.\(^7\)\(^-\)\(^13\)

There is universal agreement that changes in \(P_{aCO_2}\) produce striking alterations in cerebral blood flow and vascular resistance. However, the importance of neurogenic influences on this mechanism is unknown or supported by conflicting data so that opposing hypotheses have resulted.\(^14\)\(^-\)\(^20\)

Some investigators have assumed that cerebral autoregulation and cerebral vasomotor reactivity to \(P_{aCO_2}\) changes depend partly or totally on the same mechanism,\(^2\)\(^,\)\(^6\)\(^,\)\(^12\) despite the fact that dissociated cerebral vasomotor responses to changes in CPP and \(P_{aCO_2}\) have been encountered frequently in cerebral ischemia. These consist of preserved capacity to respond to \(P_{aCO_2}\) changes (normal chemical regulation) and abolished response to CPP changes (loss of autoregulation), or vice versa.\(^3\)\(^,\)\(^6\)\(^,\)\(^21\)

Seldom have combined, comparative investigations been made of the effects of changes in CPP and \(P_{aCO_2}\) on cerebral vasomotor capacitance. And, as far as we are aware, there has been no study in which the quantitative autoregulatory response to both hypotension and hypertension and the quantitative chemical regulatory response to induced hypocapnia and hypercapnia has been made in a series of subjects with different types of cerebrovascular disease; nor have such studies been performed before and after the use of adrenergic blocking agents in order to assess any neurogenic influences on these responses.

The present study was designed to explore any functional effect on chemical regulation and autoregulation of a long-acting alpha adrenergic blocking agent (phenoxybenzamine).

**Case Material and Methods**

Cerebral autoregulation and chemical regulation were studied in 19 patients with various anatomical locations of cerebral ischemia and infarction classified according to clinical, angiographical, EEG, CSF and brain scan findings. Age, sex, clinical diagnosis, clinical severity, and the interval of time between the ischemic episode and the time of the study are shown in table 1. There were 15 males and four females ranging in age from 42 to 77 years with a mean age of 58 years. Nine patients had cerebral hemispheric infarction, eight patients had brainstem ischemia or infarction, and two patients had transient ischemic attacks related to both carotid and vertebrobasilar systems.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>Duration after onset</th>
<th>Clinical course</th>
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<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>R-cerebral infarction</td>
<td>6 days</td>
<td>2</td>
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<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>R-cerebral infarction</td>
<td>9 days</td>
<td>3</td>
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<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>L-cerebral infarction</td>
<td>15 days</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>R-cerebral infarction</td>
<td>16 days</td>
<td>3</td>
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<td>5</td>
<td>54</td>
<td>F</td>
<td>L-cerebral infarction</td>
<td>17 days</td>
<td>3</td>
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<tr>
<td>6</td>
<td>52</td>
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<td>7</td>
<td>42</td>
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<td>3</td>
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<td>8</td>
<td>69</td>
<td>F</td>
<td>Bilateral cerebral infarction</td>
<td>18 days</td>
<td>4</td>
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<tr>
<td>9</td>
<td>48</td>
<td>M</td>
<td>L-cerebral infarction</td>
<td>19 days</td>
<td>3</td>
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<tr>
<td>10</td>
<td>63</td>
<td>M</td>
<td>Vertebrobasilar insufficiency</td>
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<td>1</td>
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<tr>
<td>11</td>
<td>66</td>
<td>M</td>
<td>Brainstem infarction</td>
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<td>2</td>
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<tr>
<td>12</td>
<td>77</td>
<td>M</td>
<td>Brainstem infarction</td>
<td>12 days</td>
<td>2</td>
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<tr>
<td>13</td>
<td>54</td>
<td>M</td>
<td>Vertebrobasilar insufficiency</td>
<td>15 days</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>63</td>
<td>M</td>
<td>Brainstem infarction</td>
<td>15 days</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>F</td>
<td>Transient ischemic attack</td>
<td>16 days</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>62</td>
<td>M</td>
<td>Transient ischemic attack</td>
<td>(carotid and vertebrobasilar systems)</td>
<td>16 days</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>M</td>
<td>Vertebrobasilar insufficiency</td>
<td>3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>50</td>
<td>F</td>
<td>Vertebrobasilar insufficiency</td>
<td>22 days</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>M</td>
<td>Brainstem infarction</td>
<td>31 days</td>
<td>2</td>
</tr>
</tbody>
</table>

M = male, F = female, R = right, L = left.
The clinical course and severity of the attack were arbitrarily classified into four grades. There were six patients in Grade 1 (transient ischemic attacks), five patients in Grade 2 (reversible ischemic neurological deficits), seven patients in Grade 3 (presumed cerebral infarction with moderate residual disabilities), and one patient in Grade 4 (presumed cerebral infarction with severe neurological deficits). The interval of time between the cerebral ischemic episode and test measurements ranged from 1 to 31 days with a mean of 15 days.

Prior to the study all patients were examined by a cardiologist in consultation in order to gain assurance that the cardiac status was satisfactory to withstand the measurements. Informed consent was obtained in writing for the procedure.

References giving detailed descriptions of the clinical evaluation and methods for monitoring CBF and metabolism used in this study are cited. In brief, each patient initially was given 50 mg of meperidine hydrochloride intramuscularly. Under fluoroscopic control, catheters were placed via the antecubital veins into each cerebral transverse sinus and the superior vena cava. Other catheters were placed at the origin of the left vertebral artery, in the right brachial artery and in the femoral vein. One percent procaine hydrochloride was applied to all puncture sites.

By means of a peristaltic pump, blood was drawn at a constant rate from the right brachial artery and transverse sinus. Arterial and cerebral venous blood samples were propelled through cuvettes containing electrodes and sensors to measure oxygen tension (P \text{O}_2), carbon dioxide tension (P \text{CO}_2), pH, and oxygen saturation (S \text{O}_2). The blood was returned to the circulatory system by means of an indwelling catheter in the femoral vein. Each parameter was recorded on a polygraph.

To measure hemispheric blood flow (HBF), an 8 to 10 ml bolus of hydrogen-saturated saline was injected into the carotid artery. HBF was calculated from the clearance curve for hydrogen obtained from the transverse sinus.

Arterial and cerebral venous difference in oxygen content (A-V)O_2 was calculated from measurements of S \text{O}_2, P \text{O}_2, P \text{CO}_2, \text{pH}, and oxygen capacity. After measuring HBF, any changes in cerebral blood flow (CBF) induced by body tilting, by 5% to 7% CO_2 in air inhalation and by active hyperventilation were calculated from the (A-V)O_2 differences, since the cerebral metabolic rate for oxygen has been shown to be constant during these procedures. In patients with unilateral cerebral infarction, the HBF measurements were carried out on the same side as the hemispheric lesion.

Arterial blood pressure was monitored by the use of a strain gauge connected to the arterial catheter whose tip was placed at the origin of the left vertebral artery. The degree of tilting was measured with a goniometer. The strain gauge sensor was taped to the tilt table at the level of the external ear in order to record the effective arterial blood pressure (effective BP) at the brain when the patient's position was altered. Intracranial venous pressure (ICVP) also was monitored at the level of the external ear by the strain gauge connected to the venous catheter whose tip lay in the transverse sinus.

Intracranial pressure (ICP) was monitored by directing a catheter in a cephalad direction into the subarachnoid space after lumbar puncture with its sensor placed at the level of the cisterna magna. Central venous pressure (CVP) was recorded with the baseline adjusted at the level of the heart. Effective mean arterial blood pressure (effective MABP) was calculated by adding one-third of the pulse pressure to the diastolic pressure. Mean CVP (MICVP), mean ICP (MICP) and mean CVP (MCVP) were computed as the minimum recorded pressures plus one-third of the pulse pressures. Cerebral perfusion pressure (CPP) across the brain was calculated as effective MABP minus MICVP.

Quantitative analysis of the impairment of cerebral autoregulation and chemical vasomotor reactivity was based on the following formulae which we term the autoregulation index (A.I.) and the chemical regulation index (C.I.).

\[
\text{A.I.} = \frac{\Delta \text{CBF}}{\Delta \text{CPP}}, \quad \text{C.I.} = \frac{\Delta \text{CBF}}{\Delta P_{\text{A-CO}_2}},
\]

where \(\Delta \text{CBF}\) equals the change of cerebral blood flow (ml/100 gm brain/min) when CPP was changed from the steady state horizontal position to head-up or head-down tilted position (\(\Delta \text{CPP}\) expressed in mm Hg), or when arterial carbon dioxide tension (\(P_{\text{A-CO}_2}\)) was changed from the steady state level to hypercapnic or hypocapnic levels (\(\Delta P_{\text{A-CO}_2}\) expressed in mm Hg).

It is well known that when cerebral autoregulation is intact, the caliber of cerebral vessels is adjusted to maintain CBF constant during changes in perfusion pressure of as much as 180 to 200 mm Hg. Thus, when autoregulation is intact, A.I. should be zero or close to zero, and any deviation of A.I. from zero in a plus or minus direction will be in direct proportion to the degree of dysautoregulation. C.I. is reportedly greater than unity under normal conditions. Any deviation below unity indicates impaired \(\text{CO}_2\) reactivity or impaired chemical regulation.

The \(t\)-test was used to compare differences in the means, and the results were checked for significance at the 5% level. Cochran’s approximation was used for those analyses in which the populations under study had different standard deviations.

**Results**

**CEREBRAL AUTOREGULATION AND CHEMICAL VASOMOTOR CONTROL IN STROKE**

Excluded from the quantitative analysis of cerebral autoregulation were measurements in which CPP decreased below the known autoregulatory range (CPP below 60 mm Hg) and those in which \(P_{\text{A-CO}_2}\) was appreciably altered. Discarded as a potential interference in pure evaluation of chemical vasomotor control were measurements in which conspicuous changes in arterial blood pressure resulted during induced hypercapnia or hypocapnia since most patients had impaired cerebral autoregulation.
Also discarded were cases where \( \text{Paco}_2 \) increased over 60 mm Hg during 5% to 7% \( \text{CO}_2 \) inhalation or decreased below 20 mm Hg during active hyperventilation, since even in normal conditions cerebral vasomotor reactivity is thought to decrease in the range over 60 mm Hg or below 20 mm Hg of \( \text{Paco}_2 \).26-28

Measurements of arterial and cerebral venous gases and \( \text{pH} \) did not show hypoxemia, hypercapnia or hyperacidemia in any of the patients studied here.

Examples of continuous recordings of cerebral venous and arterial hemodynamics and of pressure measurements made in this test of autoregulation and chemical vasomotor control of CBF are given in the left half of figures 1, 2, 3, and 4. The quantitative analysis of autoregulation and chemical regulation is listed in table 2 and illustrated in figure 5. The degree of impairment of autoregulation (A.I.) during induced hypotension and hypertension in the steady state appears in the left half of table 2. We rigorously evaluated the validity of the body-tilt procedure as a test of cerebral autoregulation in a previous study and found that if \( \text{Paco}_2 \) is sustained near a constant level this is a simple and instructive method.22 Since this criterion was met in our study, we were able to make more accurate and quantitative evaluations than had been possible in the past.

The results of the test of autoregulation in the steady state showed that all patients except one had a fall in CBF during induced hypotension (A.I. = 0.286 ± 0.211), while during induced hypertension three of 16 patients displayed a decreased CBF in spite of a rise in CPP (A.I. = 0.157 ± 0.328). The degree of dysautoregulation was the same or less for patients with cerebral hemispheric infarction than for patients with brainstem ischemia and transient ischemic attacks affecting both carotid and vertebrobasilar systems but with no

![FIGURE 1](image)

To show continuous recording of head-up tilting (induced hypotension) made in Case No. 8: Change of the patient’s position was carefully and slowly performed in order to avoid apprehension and abrupt change in arterial perfusion pressure (effective BP). Before phenoxybenzamine (PBZ) infusion, cerebral venous oxygen tension (CVP\(_{O_2}\)) and oxygen saturation (CVS\(_{O_2}\)) remarkably decreased in proportion to change in effective BP during head-up position, indicating impairment of cerebral autoregulation.

Following the intracarotid infusion of 10 mg PBZ, decreases in CVP\(_{O_2}\) and CVS\(_{O_2}\) were much less than before the infusion for the same degree of head-up tilting. Arterial blood gases and \( \text{pH} \) showed no change before, during, and after the tilting procedure.
EFFECTS OF ALPHA ADRENERGIC BLOCKADE

before PBZ

after PBZ

L-CVPO₂

L-CVPO₂

CVSO₂

CVPO₂

CVP₂

CVP₂

Pao₂

Pao₂

59.2% 35.7

Pao₂

51.8mm Hg 31.6

91.3% 90.7

91.3% 90.7

PaCO₂

PaCO₂

apH

apH

7.386 7.307

7.386 7.307

Resp.

Resp.

CVP

CVP

ICVP

ICVP

ICP

ICP

BP (Effective)

BP (Effective)

200mm Sali

300mm Sali

300mm Sali

300mm Sali

200mm Hg

200mm Hg

1 Min.

1 Min.

FIGURE 2

To show continuous recording of head-down tilting (induced hypertension) made in Case No. 9: Before PBZ infusion, cerebral venous gases and pH showed virtually no change during head-down position, indicating normal autoregulation of CBF. After the infusion, however, CVPO₂ and CVSO₂ increased precipitously, indicating loss of cerebral autoregulation.

established damage to the tissue in the cerebral hemisphere. Cases with a high degree of dysautoregulation during induced hypotension also showed marked dysautoregulation during induced hypertension.

The results of the test for chemical vasomotor control in the steady state appear in the right half of table 2 as the ratio of CBF change per unit change in Paco₂ (= C.I.). These results indicate that, in general, vasomotor capacity to respond to altered Paco₂ during both induced hypercapnia and hypocapnia was well preserved. All patients with brainstem lesions and transient ischemic attacks had well-preserved regulatory response to changes in Paco₂, whereas a few patients with acute hemispheric infarction and severe neurological deficit showed a diminished response. Another noteworthy finding is that the cerebral vessels did not necessarily respond equally to induced hypercapnia and hypocapnia; the vasomotor reactivity was in some cases more sensitive during hypocapnia than hypercapnia and in other cases the reverse.

Graphical comparisons of cases in which both autoregulation and chemical vasomotor control were tested appear in figure 6. There was no significant correlation between the degree of impairment of autoregulation (A.I.) and chemical vasomotor control (C.I.) in any of the four paired comparisons. The three patients with a flow decrease during increased CPP (a paradoxical response) showed preserved cerebral vasomotor capacity during CO₂ inhalation, which speaks against the speculation proposed by others that this type of paradoxical flow decrease is induced by the “intracerebral steal effect” and supports the view that these paradoxical effects are dependent on changes in CSF pressure or the so-called “intracerebral squeeze” effect.

Each graph in figure 6 suggests that autoregulation and chemical vasomotor control of CBF are regulated by independent control mechanisms: if both were regulated by the same mechanism, A.I. and C.I. would have been inversely correlated (since A.I. usually increases positively from zero if autoregulation is impaired while C.I. decreases to zero when chemical vasomotor capacity is disturbed).
EFFECT OF ALPHA ADRENERGIC BLOCKADE BY PHENOXYBENZAMINE ON CEREBRAL AUTOREGULATION AND CHEMICAL VASOMOTOR CONTROL

After intracarotid infusion of 10 mg phenoxybenzamine hydrochloride, the procedures were repeated in more than half of the patients. Measurements of CBF by the hydrogen bolus method and of arterial hemodynamics showed no change from the values prior to the infusion, while intracranial and extracranial venous pressures displayed increases which reflect an increase in cerebral blood volume due to vasodilatation.

The effect of phenoxybenzamine (PBZ) on cerebral autoregulation is illustrated in the right side of figures 1 and 2 and summarized in figure 7. After the PBZ injection, the degree of dysautoregulation (A.I.) during induced hypotension decreased significantly compared to the steady-state value, while it increased significantly during induced hypertension. These results strongly suggest that cerebral autoregulation is influenced by alpha adrenergic innervation of the autonomic nervous system.

Comparison of changes in the value of A.I. from the steady state (E-C) during induced hypotension and hypertension showed an inverse correlation: the greater the decrease of A.I. during induced hypotension, the greater the increase of A.I. during induced hypertension.

The effect of PBZ on chemical vasomotor control (C.I.) is shown in figure 8 and illustrated in the right half of figures 3 and 4. After PBZ infusion the cerebral vasomotor capacitance did not change significantly during either induced hypercapnia or hypocapnia. Comparison of the degree of changes in C.I. values from the steady state showed a significant inverse correlation between induced hypercapnia and hypocapnia (right panel of fig. 8). That is, the more the vasodilator capacity to Pao2 increase was diminished, the more enhanced was the vasoconstrictor capacitance to Paco2 decrease.

Changes in the values of A.I. and C.I. from the steady state after the PBZ injection were compared together (fig. 9). Induced hypotension and hypercapnia showed a proportional correlation which was close to the significant level (upper left panel). There was a significant inverse correlation between
EFFECTS OF ALPHA ADRENERGIC BLOCKADE

FIGURE 4
To show recording of active hyperventilation (induced hypocapnia) made in the same case as figure 3: Before and after PBZ infusion, CVP and CVS decreased during hyperventilation. Cerebral vasomotor reactivities (C.I.) were 1.13 before and 1.32 after the infusion, indicating normal responses to induced hypocapnia.

FIGURE 5
Cerebral autoregulation and chemical vasomotor control: Quantitative analysis of the impairment of cerebral autoregulation (A.I.) in an individual case is shown on the left panel and that of chemical vasomotor reactivity (C.I.) on the right panel.
TABLE 2

Effect of Phenoxybenzamine on Cerebral Autoregulation and Chemical Vasomotor Reactivity

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th>Hypertension</th>
<th>Autoregulation Index (A.I.)</th>
<th>Chemical regulation Index (C.I.)</th>
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<tr>
<td></td>
<td>Steady state</td>
<td>After PBZ</td>
<td>Steady state</td>
<td>After PBZ</td>
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<td>0.105</td>
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<td>0.209</td>
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<td>0.071</td>
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<td>0.302</td>
<td>0.452</td>
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<td>0.617</td>
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<td>17</td>
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<td>0.286</td>
<td>0.220</td>
<td>0.157</td>
<td>0.315</td>
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A.I. = \( \frac{\Delta \text{CBF}}{\text{CPP}} \) ml/100 gm brain/min

C.I. = \( \frac{\Delta \text{CBF}}{\Delta P_{\text{CO}_2}} \) ml/100 gm brain/min

PBZ = phenoxybenzamine hydrochloride.

N.E. = not examined.

AUTOREGULATION AND CHEMICAL VASOMOTOR CONTROL COMPARED

Comparison of impairments between autoregulation and chemical vasomotor control: In each figure an ordinate indicates the degree of an impairment of autoregulation (A.I.) and an abscissa means the vasomotor reactivity to \( P_{\text{CO}_2} \) changes (C.I.). In none of the four figures is there a significant inverse correlation.

FIGURE 6
EFFECTS OF ALPHA ADRENERGIC BLOCKADE

EFFECT OF α-ADRENERGIC BLOCKADE ON AUTOREGULATION

Changes in the degree of dysautoregulation during induced hypotension and changes in chemical regulation during induced hypocapnia (upper right panel). These data indicate that following the administration of PBZ, the greater the improvement in the cerebral vasomotor response during induced hypotension (A.I. [E-C] increasing negatively), the greater the loss of cerebral vasomotor response during induced hypercapnia (C.I. [E-C] increasing negatively) and the greater the increase in vasoconstrictor capacitance during induced hypocapnia (C.I. [E-C] increasing positively).

EFFECT OF α-ADRENERGIC BLOCKADE ON CHEMICAL VASOMOTOR CONTROL

Effect of PBZ on chemical vasomotor control: During both induced hypercapnia and hypocapnia, C.I., as an average, showed no significant change after the infusion. Changes in C.I. values from the steady state (E-C) showed a significant inverse correlation between hypercapnia and hypocapnia.

**FIGURE 7**

Effect of PBZ on autoregulation: After the infusion, A.I. decreased significantly during induced hypotension, but it increased significantly during induced hypertension. Comparison of changes in A.I. values after PBZ infusion (E-C) during induced hypotension and hypertension showed an inverse correlation.

**FIGURE 8**

Effect of PBZ on chemical vasomotor control: During both induced hypercapnia and hypocapnia, C.I., as an average, showed no significant change after the infusion. Changes in C.I. values from the steady state (E-C) showed a significant inverse correlation between hypercapnia and hypocapnia.
**Discussion**

This study was designed to clarify the nature of mechanisms responsible for autoregulation and chemical vasomotor control of CBF.

Several hypotheses have been postulated to date regarding the underlying mechanisms controlling cerebral vasomotor capacitance to changes in carbon dioxide tension. These include (1) the neurogenic hypothesis of a remote control mechanism; (2) metabolic and myogenic hypotheses of a locally regulated mechanism, either (a) within the intracellular space of smooth muscle of cerebral vessels, or (b) within the extracellular space of smooth muscle of cerebral vessels or within the cerebrospinal fluid; and (3) the hypothesis of a combined remote and local mechanism.

In 1961 we proposed that the final factor responsible for chemical vasomotor control of CBF is a change in intracellular hydrogen ion concentrations in smooth muscle fibers of cerebral arterioles (hypothesis 2a). A number of investigations suggest that cerebral vascular response to carbon dioxide is mediated by alteration of the pH of the interstitial or cerebrospinal fluid (hypothesis 2b). Evidence against this later view and therefore favorable to hypothesis 2a is found in a series of recent experimental and clinical studies.

Another moot point is whether carbon dioxide itself or one or both of the reaction products (hydrogen ion and bicarbonate ion) changes the diameter of cerebral vessels in the intracellular and/or extracellular spaces. No matter what the location may be, it is well established that under normal circumstances changes in hydrogen ion concentration play an important role in varying the local vascular resistance of cerebral vessels, although changes in concentrations of potassium, sodium and calcium also have been adduced to be involved in cerebrovascular regulation.

Let us now discuss possible mechanisms for cerebral autoregulation. For more than a decade this has been considered to be mainly metabolic and/or myogenic. Recent clinical observations have shown loss of autoregulation with preserved chemical vasomotor control of CBF in patients with Shy-Drager syndrome in which the central structures of the autonomic nervous system are known to be impaired. This appeared to indicate that cerebral autoregulation and chemical regulation have independent control mechanisms, the former being influenced by the autonomic nervous system (neurogenic mechanism) whereas the latter was more or less independent of neurogenic influences.

Both the metabolic and myogenic theories of autoregulation assume that autoregulation involves an active vasomotor response of the cerebral vessels.
and that the arterioles are the primary site for this response; superficially this assumption favorably explains local impairment of autoregulation after local cerebral injury. On the other hand, the neurogenic theory assumes that loss of autoregulation will be diffuse since the autonomic nervous system, centrally located in the brainstem, radiates its vasomotor innervation throughout the entire hemisphere.

Let us examine this point in greater detail. Consider the well-established situation in which only in one region have cerebral vessels lost their normal dilating or constricting reactivity to changes in cerebral perfusion pressure (CPP) as a result of local injury. Although regional cerebral dysautoregulation in this situation is easily explained by a metabolic or myogenic mechanism as mentioned above, nevertheless neurogenic mechanisms also may play a part. Autonomic nerves have been shown to innervate the cerebral vessels down to 20 to 40 μ in diameter,4-6 thus local damage to the vessel wall also will cause regional damage to the peripheral autonomic innervation so that local loss of autoregulation could result. In addition, cerebral dysautoregulation found in the so-called "healthy hemisphere" as well as in the hemisphere subjected to a unilateral hemispheric lesion6,35 is best, perhaps only, explained by a neurogenic mechanism, since the metabolic or myogenic hypothesis cannot be applied to a healthy hemisphere where the cerebral vessels and metabolism are not severely disordered.

In a companion study22 published in this Journal it was observed that patients with brainstem ischemia or infarction showed a significantly higher cerebral dysautoregulation than those with hemispheric infarction; furthermore, subcortical hemispheric infarction caused a greater loss of autoregulation than did infarction of the cerebral cortex. Such findings indicate that brainstem lesions affect not only CBF and metabolism8 but also global cerebral autoregulation, offering further support to the hypothesis that neurogenic vasomotor control plays a part in cerebral autoregulation.

The present study was undertaken in order to compare the mechanisms underlying autoregulation and chemical vasomotor control of CBF in the same patients. In this population of patients with cerebral ischemia and infarction, loss of autoregulation was marked while chemical regulation was relatively well preserved. In particular, patients with vertebrobasilar insufficiency had marked dysautoregulation comparable to patients with extensive cerebral infarction, while none of these patients showed marked impairment of chemical regulation. Such observations are consonant with those of Skinhøj et al.,8,16 who reported that in cases with brainstem lesions, the response of cerebral hemispheric vessels to changes in P_{a_CO_2} was not abolished despite a marked reduction in cerebral hemispheric blood flow.

Dissociation between autoregulated and chemically regulated cerebral vasomotor responses has been reported previously in patients with cerebral ischemia and brain tumors, in which tissue acidosis or anoxia was usually evident.5,5,21 However, it also has been reported in the postictal period resulting from experimental seizures in artificially respirated animals without either cerebral hypoxia or cerebral acidosis.27 The present study shows that there was no correlation between the degree of cerebral dysautoregulation and the degree of impairment of chemical vasomotor control (fig. 6). Thus, previous data combined with the present findings speak against the hypotheses that both autoregulation and chemical regulation are dependent on neurogenic mechanisms3,4 or that both are regulated by metabolic mechanisms5,3 or that neither is influenced by a neurogenic mechanism.9,36 If regional extravascular pH and autonomic innervation of the brain are, as some authors suggest,2,5,6 the main factors controlling cerebrovascular response to both changes in CPP and P_{a_CO_2}, then autoregulation also should be normal when the chemical regulatory response to carbon dioxide is not impaired.

In an attempt to explain such a dissociation of chemical and autoregulation on the basis of the metabolic hypothesis as the regulating mechanism in both autoregulation and chemical vasomotor control, Paulson et al.6,37 demonstrated that improvement of cerebral dysautoregulation can be induced by hypocapnia which they believed reduced brain tissue acidosis. However, effects of autonomic innervation and neurotransmitters on the cerebral vessels are reportedly inhibited by tissue acidosis of the brain;7,38 furthermore, hyperventilation reduces increased intracranial pressure and vascular compression so that their findings do not exclude the importance of neurogenic influences in cerebral autoregulation.

In order to further examine the hypothesis that autoregulation is influenced by the autonomic nervous system (neurogenic mechanism) while chemical vasomotor response is primarily controlled by local changes in intracellular pH of the cerebral vessels, we extended our study to include measurements following the infusion of 10 mg of phenoxybenzamine (PBZ) into the carotid artery since the vasoconstricting action of alpha adrenergic receptors and the vasodilating action of beta adrenergic receptors upon the cerebral vessels have been substantiated.16 The blockade of alpha adrenergic receptors by PBZ leads to a relative beta adrenergic and parasympathetic dominance, the net
effect being predominantly a preservation of its vasodilating action.

The degree of cerebral dysautoregulation lessened during induced hypotension and increased during induced hypertension, whereas chemical vasomotor control of CBF in response to $P_{a CO_2}$ changes in either direction was not significantly altered following the infusion of the alpha adrenergic blocking agent, strongly suggesting that autoregulation is controlled by alpha adrenergic innervation but chemical regulation is not.

If chemical vasomotor reactivity also were controlled by alpha adrenergic innervations, then cerebral vasomotor capacitance during induced hypercapnia would increase because of the predominant vasodilating function of the autonomic nervous system, and vasomotor reactivity during induced hypercapnia would decrease because of the inhibition of its vasoconstricting action by the drug. Our results, however, showed a tendency for decreased reactivity to hypercapnia and increased reactivity to hypocapnia after the PBZ infusion (fig. 8).

The present results of vasomotor reactivity to $P_{a CO_2}$ changes after the PBZ infusion are not compatible with the clinical observation by Corbett et al. of a significant depressed cerebral vasomotor capacitance during induced hypercapnia following intravenous infusion of another alpha adrenergic blocking agent (Thymoxamine). However, since the only other significant difference found between pre-infusion and post-infusion measurements in their study was a lesser decrease in the fast flow component of CBF, and since we observed a direct proportion between changes in CBF and increases in blood pressure following the block of cerebral alpha adrenergic innervations (see fig. 2), a significant increase in blood pressure seen in half of their cases might explain their findings. The increase in blood pressure in their patients would have inhibited the fall in CBF during induced hypercapnia.

Furthermore, the present data showed a significant inverse correlation between changes in cerebral vasomotor reactivity to induced hypotension and hypercapnia and a nearly significant proportional correlation between induced hypotension and hypercapnia after the PBZ infusion (fig. 9). A likely explanation follows. The patients with greater improvement of dysautoregulation during induced hypotension after the block of alpha adrenergic innervation were probably more sensitive to this blocking agent and therefore had a larger dilatation of vessels in response to a fall in CPP than did patients with a lower sensitivity. Indeed, the sympathetic nerves established a new basal vascular tone following alpha adrenergic blockade whereby in the more sensitive patients the vessels already dilated are unable to dilate further in response to an increase in $P_{a CO_2}$ but are more able to constrict in response to a fall in $P_{a CO_2}$ than are the vessels of patients who are relatively insensitive to the blocking agent. Consequently, the controlling mechanism of chemical regulation is probably located in the cerebral vessels themselves, and the degree of cerebral vascular response to $P_{a CO_2}$ changes is dependent upon the prior existing degree of dilatation or constriction of cerebral vessels.

This explanation of the mechanism underlying chemical vasomotor reactivity is in agreement with the findings of other investigations. Two separate studies have demonstrated that the cerebral vessels, which are assumed already dilated in cerebral ischemia, are not able to dilate further during $CO_2$ inhalation but constrict during hyperventilation. It also has been shown that the constricted vessels induced by sympathetic stimulation could respond less during induced hypocapnia.

In addition, the findings and theoretical discussions of other authors buttress our thesis that chemical vasomotor reactivity is controlled by local factors while autoregulation is controlled by a neurogenic mechanism. For instance, Harper et al. proposed that the intraparenchymal arteries are regulated locally by the products of cerebral metabolism, and the extraparenchymal arteries are to some degree under autonomic nervous control. Although they did not clarify how intraparenchymal and extraparenchymal vessels are differently affected by changes in CPP and $P_{a CO_2}$, others have added that in response to the same increase in $P_{a CO_2}$, the smaller vessels (13 to 40 $\mu m$ in diameter) increased in diameter much more significantly than the larger vessels, and that such small precapillary arteries were unresponsive to sympathetic nervous stimulations and chemical neurotransmitters.

In conclusion, we have hypothesized that a neurogenic mechanism via the autonomic nervous system is responsible for cerebral autoregulation while local factors control cerebral chemical regulation. Support for this thesis comes not only from our present data but also from prior related studies.

References
EFFECTS OF ALPHA ADRENERGIC BLOCKADE


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Effects of Alpha Adrenergic Blockade on Autoregulation and Chemical Vasomotor Control of CBF in Stroke
JOHN STIRLING MEYER, KUNIO SHIMAZU, SHIGEMICHI OKAMOTO, ATSUO KOTO, TADAO OHUCHI, ATSUO SARI and ARTHUR DALE ERICSSON

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