Impairment of Cerebellar Blood Flow Autoregulation During Cerebral Ischemia in Spontaneously Hypertensive Rats

Osamu Shiokawa, MD, Seizo Sadoshima, MD, Kenichiro Fujii, MD, Hiroshi Yao, MD, and Masatoshi Fujishima, MD

Participation of the autonomic nervous system in cerebellar autoregulation during supratentorial cerebral ischemia induced by bilateral carotid ligation was studied using 23 spontaneously hypertensive rats. Cerebral and cerebellar blood flows measured by a hydrogen clearance method were evaluated under stepwise hemorrhagic hypotension before and 30 minutes after ligation and after a 30-minute recirculation period following 1 hour of ligation. \( \alpha \)-Adrenergic blockade with phenoxybenzamine, \( \beta \)-adrenergic blockade with propranolol, and muscarinic cholinergic blockade with atropine were selectively administered before ligation for inhibition of sympathetic and parasympathetic tone. Cerebral blood flow autoregulation was severely impaired during and after cerebral ischemia in each treatment group. During cerebral ischemia, cerebellar blood flow autoregulation was also significantly impaired in both the propranolol and atropine groups although it was better preserved in the phenoxybenzamine group. After recirculation, cerebellar blood flow autoregulation recovered almost to the normal range in the phenoxybenzamine and atropine groups but remained impaired in the propranolol group. Our results suggest that impaired cerebellar blood flow autoregulation in supratentorial cerebral ischemia is partly modulated by the \( \alpha \)-adrenoceptor system, which is activated by hypertensive stimuli and cerebral ischemia, leading to vasoconstriction in the cerebellum. (Stroke 1988;19:615-622)

Our previous study demonstrated that in experimental ischemia induced in the cerebrum, autoregulation is impaired not only in the cerebrum but also in the nonischemic cerebellum.\(^1\) The precise mechanism of decreased flow in the cerebellum is under dispute. Neuronal factors seem to be involved since many recent reports indicate the importance of either innervation to or function of neuropeptides in cerebral blood vessels.

Sympathetic nerves are known to constrict cerebral blood vessels in response to changes in perfusion pressure.\(^2,^3\) It is pertinent to note that cerebral ischemia activates the noradrenergic system of the brain, with large amounts of catecholamines being released in the ischemic site\(^5\) as well as from nonischemic nerve terminals,\(^6\) which in turn affect vasoreactivity to various stimuli such as autoregulation and CO\(_2\) response.

To examine whether sympathetic nerves or catecholamines relate to the impairment of autoregulation in remote areas of the brain, we tested autoregulation in the cerebellum during cerebral ischemia in spontaneously hypertensive rats treated with \( \alpha \)-adrenergic or muscarinic cholinergic blockade.

Materials and Methods

Preparation of Rats

Female spontaneously hypertensive rats (SHR) aged 6–7 months were anesthetized with 100 mg/kg body wt i.p. amobarbital. The right femoral artery and vein were cannulated for continuous recording of mean arterial blood pressure (MAP) and for infusion of the autonomic blocking agents, respectively. The left femoral artery was cannulated for sampling of arterial blood and for exsanguination in the stepwise reduction of arterial blood pressure.

To induce cerebral ischemia both common carotid arteries were separated carefully from the vagosympathetic trunks and surrounding connective tissue and loosely encircled with sutures. The arteries were then occluded by gently pulling the sutures tight to produce bilateral carotid ligation (BCL). After tracheotomy the rats were paralyzed with 0.45 mg/100 g body wt \( d \)-tubocurarine and artificially ventilated with a Harvard respirator (South Natick, Massachusetts) using room air. The hydrogen clearance technique was used to measure blood flow in the cerebral and cerebellar cortices. The rat’s head was fixed in a head holder, and two burr holes were made in the right skull. One was 2 mm lateral to the bregma, and the other was 3 mm posterior and lateral to the confluence of the sinuses. Teflon-coated platinum electrodes 200 \( \mu \)m in diameter were placed in the cerebral and cerebellar cortices 2 mm in depth from the surface of the brain, using a stereotaxic apparatus. An Ag-AgCl reference electrode was inserted under the skin. Rectal temperature was maintained at approximately 37°C by a heat lamp.
Arterial pH, PaCO₂, and PaO₂ were determined with an IL model 113 meter (Instrumentation Laboratories, Inc.).

Experimental Protocol

Autoregulation of cerebral (CBF) and cerebellar blood flow (CeBF) were determined after administration of each autonomic blocker before cerebral ischemia and then after 30 minutes of ischemia and again after 30 minutes of recirculation following 1 hour of ischemia (Figure 1). Stepwise reduction of MAP was induced by exsanguination from the femoral artery. Each level of MAP was maintained for 5-10 minutes during blood flow measurement. Immediately after each flow study, blood that had been withdrawn was rein infused into the femoral artery. Blood gases and acid-base parameters were determined before drug infusion and after each flow study. Heart rate was recorded before and after the administration of drugs.

At the end of the experiment, the rats were killed by an intravenous infusion of saturated KCl, and the rats’ brains were macroscopically examined. When either improper placement of the electrode or macroscopic damage of the tissue was found, the data were excluded.

Experimental Groups

Blood flow autoregulation was determined in three groups: eight SHR treated with phenoxybenzamine (PBZ), nine SHR treated with propranolol (PPL), and six SHR treated with atropine (AP). PBZ (1.5 mg/kg, α-adrenergic blocker) was intravenously infused for 5 minutes 1 hour before the flow study. PPL (2.0 mg/kg, β-adrenergic blocker) was administered intravenously 15 minutes before the flow study, with 1.0 mg/kg supplements administered just before BCL and recirculation. AP (1.0 mg/kg, antimuscarinic cholinergic drug) was administered intravenously 15 minutes before the flow study. Doses of each drug were chosen in accordance with data of other investigators.3,7-9

Statistics

Resting CBF and CeBF before and after administration of drugs were compared using Student’s t test. Significance of the differences between blood flow before and during stepwise hypotension was assessed using the paired t test. Acid-base parameters and blood gases between groups were evaluated by analysis of variance. Both resting MAP and heart rate before and after drug administration were also analyzed using the paired t test.

Results

Figure 2 summarizes our previous data of CBF and CeBF autoregulation examined in SHR without drug administration.1 Both CBF and CeBF autoregulation were impaired during supratentorial cerebral ischemia, with CeBF in particular decreasing to 58% (p < 0.001) of baseline CeBF during 30% reduction of MAP. After recirculation, CBF autoregulation remained impaired, while CeBF autoregulation recovered almost completely.
Phenoxybenzamine-Treated Group

PBZ reduced MAP from 177 to 135 mm Hg \((p < 0.005;\ Table 1)\), and increased the mean \pm SEM\ heart rate from 337 ± 8 to 370 ± 9 beats/min \((p < 0.01)\). Resting CBF and CeBF were slightly decreased, by 5% and 4%, respectively, after PBZ infusion \((p > 0.05;\ Figure 3)\). Blood gases and pH did not change during the study.

Before cerebral ischemia. When MAP was reduced from 135 to 115 mm Hg (85% of that before exsanguination) and then to 95 mm Hg (70%), neither CBF nor CeBF changed, indicating preserved autoregulation. The average total amount of blood withdrawn for hypotension was 1.7 ml/rat.

During cerebral ischemia. MAP was decreased to 124 mm Hg 30 minutes after BCL. At that time, CBF was reduced to 5.1 ml/100 g/min (9.3% of that before BCL, \(p < 0.005)\), but CeBF was preserved at 51.0 ml/100 g/min. During stepwise hypotension, CBF was reduced to 16% \((p < 0.01)\) of baseline CBF. On the other hand, CeBF was decreased by only 13% \((p < 0.05)\), indicating that autoregulation in the cerebellum was working well during supratentorial ischemia. Withdrawn blood averaged 1.0 ml/rat.

After recirculation. One hour after BCL, the occluded carotid arteries were reopened by releasing the sutures. Thirty minutes later, CBF and CeBF were 62.3 and 54.5 ml/100 g/min, respectively. During 70% hypotension (from 112 to 79 mm Hg) CBF was reduced to 72% \((p < 0.05)\) of baseline CBF, while CeBF was unchanged (91%). The total amount of blood withdrawn averaged 1.2 ml/rat.

Propranolol-Treated Group

Fifteen minutes after administration of PPL, MAP was very slightly increased, from 178 to 181 mm Hg \((p > 0.05;\ Table 1)\), and heart rate decreased from 341 ± 8 to 276 ± 6 beats/min \((p < 0.01)\). Neither resting CBF nor CeBF changed significantly before or after PPL administration (Figure 4). Blood gases and acid-base parameters were not altered during the experiment.

Before cerebral ischemia. When MAP was reduced 70% (from 181 to 127 mm Hg), CBF remained constant. In contrast, CeBF decreased to 84% \((p < 0.001)\) of baseline CeBF at 127 mm Hg. Withdrawn blood averaged 3.4 ml/rat.

During cerebral ischemia. MAP increased to 193 mm Hg 30 minutes after BCL. CBF was reduced to 4.3 ml/100 g/min (11% of that before BCL, \(p < 0.005)\), and CeBF decreased slightly to 45.6 ml/100 g/min. During hypotension, CBF decreased to 19% \((p < 0.01)\) of baseline CBF. CeBF was also reduced, to 64% \((p < 0.001)\) of baseline CeBF. Withdrawn blood averaged 2.0 ml/rat.

After recirculation. Thirty minutes after recirculation, MAP was 170 mm Hg, and CBF and CeBF recovered fully to 65.6 and 56.5 ml/100 g/min, respectively. During hypotension, both CBF and CeBF were reduced to 63% \((p < 0.001)\) and 76% \((p < 0.05)\) of their respective baseline values, indicating lingering autoregulatory dysfunction after supratentorial ischemia. The total amount of blood withdrawn averaged 2.1 ml/rat.

Atropine-Treated Group

After intravenous infusion of AP, the pupils of the rats were fully dilated, although MAP and heart rate were unchanged. Blood gases and acid-base parameters remained constant (Table 1). Neither resting CBF nor CeBF were altered by AP administration (Figure 5).

Before cerebral ischemia. When MAP was reduced 70% (from 173 to 121 mm Hg), neither CBF nor CeBF...
Table 1. Acid-Base Parameters, MAP, CBF, and CeBF in Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>At rest, before drug</th>
<th>Before ischemia</th>
<th>During ischemia</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>−15%</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>177 ± 5</td>
<td>135 ± 7</td>
<td>115 ± 6</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>50.5 ± 6.5</td>
<td>47.8 ± 6.5</td>
<td>46.1 ± 7.2</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>96 ± 2</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>CeBF (ml/100 g/min)</td>
<td>55.2 ± 3.3</td>
<td>52.9 ± 4.4</td>
<td>51.8 ± 5.1</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>98 ± 3</td>
<td>91 ± 4</td>
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</table>

Propranolol

<table>
<thead>
<tr>
<th>At rest, before drug</th>
<th>Before ischemia</th>
<th>During ischemia</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>−15%</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>178 ± 6</td>
<td>181 ± 7</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>49.3 ± 4.8</td>
<td>46.0 ± 3.5</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>99 ± 2</td>
</tr>
<tr>
<td>CeBF (ml/100 g/min)</td>
<td>58.3 ± 3.8</td>
<td>54.3 ± 4.3</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>96 ± 2</td>
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</table>

Atropine

<table>
<thead>
<tr>
<th>At rest, before drug</th>
<th>Before ischemia</th>
<th>During ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>−15%</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>172 ± 5</td>
<td>173 ± 5</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>51.4 ± 5.8</td>
<td>53.2 ± 5.2</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>CeBF (ml/100 g/min)</td>
<td>49.7 ± 2.6</td>
<td>51.4 ± 3.0</td>
</tr>
<tr>
<td>(% of before)</td>
<td>100</td>
<td>97 ± 1</td>
</tr>
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</table>

MAP, mean arterial blood pressure; CBF, cerebral blood flow; CeBF, cerebellar blood flow. Before, before induction of hemorrhagic hypotension. Values are mean ± SEM.

*†‡p<0.001, p<0.01, p<0.05 different from before.

Table continued...

Discussion

The results were as follows: 1) neither PBZ, PPL, nor AP changed resting CBF or CeBF, nor did they influence CBF or CeBF autoregulation before cerebral ischemia; 2) CBF autoregulation during cerebral ischemia and after recirculation was severely impaired in all groups; 3) CeBF autoregulation during cerebral ischemia was significantly impaired in both PPL- and AP-treated groups, whereas it was better preserved in hypotension to 112 mm Hg, CBF was reduced to 52% (p<0.001) of baseline CBF. Contrarily, CeBF autoregulation returned to almost normal, 86% of baseline values. Withdrawn blood amounted to 1.6 ml/rat.

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TABLE 1. (continued)

<table>
<thead>
<tr>
<th>Drug Application</th>
<th>After drug</th>
<th>During recirculation</th>
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<tbody>
<tr>
<td>Before</td>
<td>-15%</td>
<td>-30%</td>
</tr>
<tr>
<td>112 ± 10</td>
<td>95 ± 9</td>
<td>79 ± 7</td>
</tr>
<tr>
<td>62.3 ± 13.9</td>
<td>50.6 ± 13.3</td>
<td>44.6 ± 12.1†</td>
</tr>
<tr>
<td>100</td>
<td>81 ± 8</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>54.5 ± 4.1</td>
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<tr>
<td>100</td>
<td>99 ± 3</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>170 ± 7</td>
<td>145 ± 6</td>
<td>119 ± 6</td>
</tr>
<tr>
<td>65.6 ± 8.9</td>
<td>55.7 ± 10.8;†</td>
<td>41.5 ± 8.1*</td>
</tr>
<tr>
<td>100</td>
<td>85 ± 6</td>
<td>63 ± 6</td>
</tr>
<tr>
<td>56.5 ± 5.1</td>
<td>50.3 ± 4.7</td>
<td>43.2 ± 4.7;‡</td>
</tr>
<tr>
<td>100</td>
<td>89 ± 5</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>159 ± 9</td>
<td>135 ± 8</td>
<td>112 ± 7</td>
</tr>
<tr>
<td>86.6 ± 8.7</td>
<td>65.7 ± 7.6;‡</td>
<td>44.8 ± 6.2*</td>
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<tr>
<td>100</td>
<td>76 ± 6</td>
<td>52 ± 6</td>
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<td>58.8 ± 5.2</td>
<td>55.1 ± 1.4</td>
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<tr>
<td>100</td>
<td>94 ± 6</td>
<td>86 ± 6</td>
</tr>
</tbody>
</table>

the PBZ-treated group; and 4) CeBF autoregulation recovered well after recirculation in the PBZ- and AP-treated groups but remained impaired in the PPL-treated group. It was especially interesting to note that CeBF dysautoregulation during cerebral ischemia, observed in our previous work (Figure 2),1 was not manifest in the PBZ-treated group.

**Drug Application**

PBZ is a nonselective α-adrenoceptor blocker 250 times more potent in inactivating α1- than α2-adrenergic receptor binding sites.10 PBZ passes through the blood–brain barrier and binds competitively with α-receptors of blood vessels. Its maximal effect is obtained 1–2 hours after intravenous application, and the effect persists over 24 hours. In our present experiment, the amount of PBZ was believed to be sufficient for α-receptor blockade because of the lowered MAP and increased heart rate after the drug’s administration. Increased heart rate was caused by blockade of presynaptic α-receptors, which negatively regulate the release of noradrenaline.11

PPL is a nonselective β-adrenoceptor blocker that is lipophilic and thus easily passes through the blood–brain barrier. Since PPL rapidly dissociates from receptor binding sites and since its effect on cerebral hemodynamics and metabolism is transient,12 we administered initial and supplemental doses of PPL during the experiment. The total dose administered did not seem to induce nonspecific anesthetic effects but was sufficient to block β-adrenoceptors in the brain.13 Administration of PPL caused a significant reduction of the heart rate during induced hypotension as well as during the resting state in our present study, implying that this β-receptor blockade worked well.

AP passes quickly through the blood–brain barrier and binds to muscarinic cholinergic receptors.14 The effect of AP appears soon after intravenous administration and lasts for several hours. The effect of AP was documented by maximal dilatation of the pupils.

Effect of Autonomic Blocking Agents on Cerebellar Blood Flow Autoregulation

Phenoxybenzamine. We have previously reported that CeBF autoregulation during supratentorial cerebral ischemia was significantly impaired, namely, a 42% decline in CeBF during 30% reduction in MAP (Figure 2).1 In the PBZ-treated rats in our present study, CeBF reduction was obviously attenuated, from 42% to 13% during a 30% decrease in MAP, indicating that our previously observed CeBF dysautoregulation in supratentorial ischemia seemed to occur via α-adrenergic activation of noradrenergic fibers.

Many peripheral sympathetic and central catecholaminergic nerve fibers are histologically and histochemically evident in the cerebellum as well as in the cerebrum.15,16 Available evidence suggests that this intrinsic central noradrenergic system acts as a vasoconstrictor mediated by α-adrenergic receptors.17,18 Activation of noradrenergic fibers arising from the locus coeruleus inhibits the firing rate of neurons.19 Under normal conditions, although noradrenergic innervation has a minimal effect on CBF regulation, it plays an important role in preventing autoregulatory derangement during severe hypertension.2 In contrast, sympathetic nerves have little effect on the lower limit of autoregulation.20,21 However, denervation of sympathetic nerves was found to prevent CBF reduction in response to hemorrhagic hypotension.22 Likewise, Meyer et al23 have observed in patients with cerebral infarction that CBF reduction due to decreased perfusion pressure was suppressed by PBZ treatment. Our present results support these protective effects of PBZ on the lower limit of blood flow autoregulation. Brain ischemia leads to activation of catecholaminergic fibers in the ischemic focus and in the nonischemic area.8,24 In our animal model, an increase in activated sympa-
thetistic tone and increased catecholamine content in the brain were observed. Moreover, cerebral vessels of SHR have many α receptors, which induce vasoconstriction in some species, and a few β receptors, which cause vasodilation. Therefore, supratentorial ischemia may cause excessive firing of noradrenergic fibers all over the brain including the cerebellum, and a large amount of noradrenaline may be discharged from the sympathetic nerve and central noradrenergic fiber terminals, resulting in vasoconstriction of the cerebellum via α-adrenoceptors and in lowering of CeBF. If this is the case, noradrenaline-related vasoconstriction is attenuated by PBZ, and the reduction of CeBF is minimized during hypotension by dilating cerebellar vessels.

Propranolol. PPL had little effect on resting CBF and CeBF before brain ischemia, indicating that

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**Figure 4.** Cerebral (CBF) and cerebellar (CeBF) blood flow autoregulation in propranolol-treated spontaneously hypertensive rats. CBF autoregulation, normal before cerebral ischemia, was impaired during ischemia and remained impaired after recirculation. CeBF before cerebral ischemia decreased slightly during 30% hypotension. However, CeBF during cerebral ischemia decreased with lowered mean arterial blood pressure (MAP), indicating impairment of autoregulation. CeBF autoregulation remained impaired after recirculation.

**Figure 5.** Cerebral (CBF) and cerebellar (CeBF) blood flow autoregulation in atropine-treated spontaneously hypertensive rats. CBF autoregulation, normal before cerebral ischemia, was impaired during ischemia and remained impaired after recirculation. Although CeBF autoregulation was normal before cerebral ischemia, it was impaired during ischemia. After recirculation, CeBF autoregulation was almost normalized. MAP, mean arterial blood pressure.
baseline vascular tone is not mediated by β-adrenergic activity. Before ischemia, CBF and CeBF were reduced to 89% and 84% of resting values, respectively, as MAP fell by 30% (to 127 mm Hg). This MAP is higher than that of the lower limit of cerebral blood flow autoregulation of SHR (110–120 mm Hg), indicating that this reduction of CBF and CeBF during hemorrhagic hypotension is, in part, modulated by factors other than blood pressure. Reduced cardiac output and heart rate may be one factor. Suppression of cerebral vasodilation and increase in cerebral vascular resistance, which are direct responses to β-receptor antagonists, are suggested to be another factor. Reduction of cerebral metabolism by PPL may also be responsible for the blood flow reduction since β-receptors are evident in both neurons and in glial cells. During cerebral ischemia, CeBF during 30% hypotension (135 mm Hg) decreased to 64% of resting CeBF. This value was significantly lower than that before cerebral ischemia (84% of resting CeBF), indicating that the cerebellar dysautoregulation during cerebral ischemia in our previous work might not be protected by β-receptor blockade. After recirculation, CeBF autoregulation was still impaired. Derangement of the sympathetic nervous system and catecholaminergic system induced by cerebral ischemia may persist even after 30 minutes of recirculation. Suppressed cerebral vasodilation and brain metabolism by PPL might also be responsible for the prolonged CeBF reduction.

**Atropine.** AP is known to bind with muscarinic cholinergic receptors and to block the effect of acetylcholine (ACh). Anatomic and histochemical studies revealed that blood vessels in the cerebellum as well as in the cerebrum have cholinergic receptors and choline acetyltransferase activity. Although the specific role of cholinergic innervation on cerebral arteries has been discussed, previous studies show that ACh and stimulation of cholinergic nerves dilate cerebral vessels in many species. The site and mode of action of ACh has not been clarified, but it is suggested that ACh from nerves suppresses the release of norepinephrine from adrenergic nerves. Another report states that vasodilation by ACh is related to noninnervated receptors in endothelial layers since most blood vessels do not relax to ACh in the absence of the endothelial cell layer. Our present results showed that the resting blood flow and autoregulation before cerebral ischemia in both the cerebrum and the cerebellum were not affected by AP infusion. The effect of ACh on baseline tone of cerebral vessels is suggested to be small. During cerebral ischemia, CeBF autoregulation, however, was markedly impaired, which is the same result seen in the PPL-treated group, indicating that AP cannot protect CeBF from dysautoregulation during cerebral ischemia. Although several questions still remain about the action and role of cholinergic innervation on cerebral circulation, the CeBF dysautoregulation during cerebral ischemia shown in our previous study may not be the result of cholinergic nervous system dysfunction.

**Effect of Autonomic Blocking Agents on Cerebral Blood Flow Autoregulation**

It might be reasonable to assume that CBF dysautoregulation during BCL is due to vasoparalysis by ischemia. Moreover, CBF dysautoregulation is partly explained by reduced perfusion pressure in the cerebrum. The results imply that each autonomic blocking drug we used in this study has no protective effect on CBF regulation during severe ischemia.

In conclusion, our findings suggest that CeBF dysautoregulation during cerebral ischemia observed previously is, at least in part, produced by a vasocostrictive effect via α-adrenoceptors of the noradrenergic system although participation of other neural or humoral factors cannot be ruled out. The effect via β-adrenoceptors as well as muscarinic cholinergic fibers on CeBF regulation is obscure.

The clinical implications of our present results are that activation of the noradrenergic system in cerebrovascular events may deleteriously affect the lower limit of cerebral blood flow autoregulation and that maintenance of MAP at an appropriate level is very important during the acute phase of brain ischemia.

**References**

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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