Response of Cerebral Arteries to Sympathetic Stimulation During Acute Hypertension

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SUMMARY Our goal was to determine whether sympathetic stimulation during acute hypertension constricts large cerebral arteries and attenuates increases in cerebral microvascular pressure. We measured cerebral blood flow with microspheres and pressure in small pial arteries with a servonull device in anesthetized cats. During moderate hypertension, sympathetic stimulation had little effect on resistance of large or small cerebral vessels. During severe hypertension, sympathetic stimulation prevented passive decreases in resistance of large cerebral arteries and allowed pronounced constriction of small vessels. During hypertension, there was a large increase in pressure in small pial arteries. Although sympathetic stimulation prevented decreases in resistance of large arteries during severe hypertension, it did not attenuate increases in pressure in pial arteries approximately 200 μm in diameter and only modestly attenuated increases in pressure in pial arteries approximately 100 μm in diameter. These findings indicate that sympathetic stimulation has important effects on resistance of both large and small cerebral vessels during severe hypertension. Thus, although stimulation produces dilatation of small cerebral vessels during normotension, sympathetic stimulation allowed constriction of small vessels during severe hypertension. These results also indicate that sympathetic stimulation does not prevent increases in pressure in small pial arteries. Thus, protection of the blood-brain barrier by stimulation of sympathetic nerves during hypertension is not the result of attenuation of increases in pial artery pressure. (Hypertension 8: 911-917, 1986)

KEY WORDS • cerebral circulation • microvascular pressure • autoregulation

LARGE arteries, as well as arterioles, are major determinants of cerebral vascular resistance. Under normal conditions, large arteries account for 25 to 50% of cerebral vascular resistance. Changes in resistance of large cerebral arteries contribute importantly to the cerebral vascular responses to alterations in arterial pressure and blood gases.

We have suggested that sympathetic stimulation increases resistance of large cerebral arteries under normal conditions, but that cerebral blood flow is unchanged because the resistance of small cerebral vessels decreases. In contrast to the limited role of sympathetic nerves under normal conditions, sympathetic stimulation has important effects on cerebral vessels during acute hypertension. Sympathetic stimulation attenuates passive dilatation of cerebral vessels, attenuates increases in cerebral blood flow, and protects against disruption of the blood-brain barrier during acute hypertension. We speculated that sympathetic stimulation might increase the resistance of large cerebral arteries during acute hypertension, as it does during normotension. Neural constriction of large arteries might attenuate increases in cerebral microvascular pressure during acute hypertension and thereby protect small cerebral vessels.

In this study, we examined the response of large and small cerebral vessels to acute hypertension, in the presence and absence of sympathetic stimulation. Our goals were to determine whether 1) sympathetic stimulation increases resistance of large cerebral arteries during acute hypertension, as it does during normotension, 2) constriction of large arteries by sympathetic stimulation attenuates increases in cerebral microvascular pressure, and 3) sympathetic stimulation, which does not increase the resistance of small cerebral vessels during normotension, allows small vessels to constrict during acute hypertension and thereby affects cerebral blood flow.
Materials and Methods

We studied 34 cats that weighed 2.7 ± 0.2 kg. The cats were anesthetized initially with sodium methohexitol (30 mg/kg i.p.), and chloralose was given intravenously as needed. The cats were paralyzed with decamethonium bromide (0.5 mg/kg), intubated, and ventilated mechanically with room air and supplemental oxygen. The procedures were in accordance with institutional guidelines. Body temperature was maintained between 37 and 38°C with a heating pad. Arterial carbon dioxide tension was 33 ± 3 mm Hg, pH was 7.33 ± 0.03, and arterial oxygen tension was 159 ± 35 mm Hg.

A catheter was inserted into a femoral artery and advanced to the thoracic aorta for measurement of systemic arterial pressure and to obtain blood. Catheters also were inserted into both axillary arteries to obtain reference blood samples of microspheres and into the femoral and axillary veins for injection of fluids and drugs. All cats underwent a thoracotomy, and a catheter then was inserted into the left atrium for injection of microspheres. A ligature was placed loosely around the descending aorta, below the tip of the arterial catheter, and tightened intermittently to raise arterial pressure above the ligature.

Both cervical sympathetic trunks were exposed and separated from the vagus using a dissecting microscope. In one group of cats, both sympathetic trunks were cut caudal to the superior cervical sympathetic ganglion. In the other group of cats, the sympathetic trunk was prepared for stimulation. The sympathetic trunk caudal to the ganglion was placed across bipolar platinum electrodes and surrounded with dental acrylic (Reposil light, L. D. Caulk, Milford, DE, USA) to maintain contact. The nerve trunk was cut caudal to the electrodes. Heparin (500 U/kg) was given intravenously.

Measurement of Pial Artery Pressure and Cerebral Blood Flow

We previously described the methods used to measure pial artery pressure and cerebral blood flow. Pial artery pressure and diameter were measured in an open skull preparation. A left parietal craniotomy was made with rongeurs. The craniotomy was extended to the midline to expose the dorsal sagittal sinus, and a 24-gauge Intracath was inserted into the sinus to measure cerebral venous pressure. A wax dam was made around the craniotomy, the dura was resected, and the dural opening was superfused with artificial cerebrospinal fluid.

Pial artery pressure was measured using a micropipette with a sharpened, beveled tip 3 to 5 μm in diameter. The micropipette was filled with 1.5 M NaCl solution and connected to a servonull pressure measuring device (Model 4A; Instruments for Medicine and Physiology, San Diego, CA, USA). We used a micromanipulator to insert the micropipette into the lumen of a pial artery. Pressure was measured in pial arteries approximately 200 μm in diameter in one group of cats and in arteries approximately 100 μm in diameter in another group.

Insertion of the pipette into pial arteries had no detectable effect on most vessels. The diameter of the vessel occasionally changed after insertion of the pipette, but the changes were always transient. Hemorrhage at the puncture site occurred only when the pipette tip was removed from the vessel. No animals were excluded from the study because of spasm or hemorrhage produced by the pipette.

Pial artery diameter was measured with an electronic micrometer (Model 142A; ITP, Sunnyvale, CA, USA), a television camera mounted on a Leitz compound microscope, and a video monitor. Radioactive microspheres with a mean diameter of 15 μm were used to measure cerebral blood flow four times in each experiment. Spheres were injected into the left atrium in 20 seconds. Reference blood samples were taken from both axillary arteries at 1.03 ml/min for 10 seconds before until 1 minute after injection of spheres. At the end of each experiment, the cat was killed with an intravenous injection of KCl and the brain was removed. Tissue and blood samples were weighed and counted in a gamma counter, and nuclide separation was accomplished with standard methods.

Cerebral blood flow was calculated from the following equation: flow = (counts/gram of brain × 100 × withdrawal rate of reference blood samples)/counts in the reference blood samples.

Experimental Groups and Protocol

Two studies were performed. In the first study, we measured pressure in pial arteries approximately 200 μm in diameter in two groups of cats: one group after bilateral superior cervical sympathetic denervation and the other group during bilateral sympathetic stimulation. In the second study, we also examined responses in one group after sympathetic denervation and in one group during sympathetic stimulation, but pressure was measured in smaller pial arteries (approximately 100 μm in diameter) to determine whether effects of sympathetic nerves on pressure were greater in smaller arteries.

In the first study, pial artery pressure was measured continuously and cerebral blood flow was measured four times in each experiment: during a control period, moderate hypertension, a second control period, and severe hypertension. Moderate hypertension was induced with infusion of norepinephrine, 2 to 4 μg/min i.v., and severe hypertension was induced with norepinephrine, 200 μg/min i.v., and occlusion of the descending thoracic aorta. Blood flow was measured approximately 1 minute after the hypertensive plateau was reached.

In the group with sympathetic stimulation, the sympathetic trunk was stimulated at 15 V, 0.3 msec, and 15 Hz. Bilateral stimulation was begun approximately 15 seconds before each episode of hypertension, and stimulation was continued until withdrawal of each reference arterial blood sample was completed. Sym-
Sympathetic stimulation produced maximal dilation of the pupils bilaterally.

In the second study, in which pressure was measured in pial arteries approximately 100 μm in diameter, cerebral blood flow was measured four times in each experiment: during a control period, intravenous infusion of norepinephrine and hypovolemia to prevent hypertension (see below), a second control period, and severe hypertension induced with norepinephrine, 20 μg/min i.v., and aortic occlusion.

Large artery resistance was calculated from the following equation: large artery resistance = (aortic pressure — pial artery pressure)/cerebral blood flow. In the second study (in which pressure was measured in pial arteries approximately 100 μm in diameter), small vessel resistance was calculated from the following equation: small vessel resistance = (pial artery pressure — dorsal sagittal sinus pressure)/cerebral blood flow. Because we found that dorsal sagittal sinus pressure was very low and changed minimally during the interventions (2 ± 1 mm Hg during control and 3 ± 1 mm Hg during hypertension), in the first study (in which pressure was measured in pial arteries approximately 200 μm in diameter), dorsal sagittal sinus pressure was not used in the calculations of small vessel resistance. Thus, small vessel resistance was calculated as pial artery pressure/cerebral blood flow.

We have attempted in more than 20 cats to perform a third study, in which pressure was measured in pial venules with a micropipette during acute hypertension. The study has not been feasible, however, because the micropipette has lacerated the vein during movement of the brain during hypertension or the micropipette has come out of the vein, with bleeding from the site.

Because large doses of norepinephrine were used to raise arterial pressure, it was necessary to determine whether the resistance of large and small cerebral vessels is independent of the effect of norepinephrine on arterial pressure. To answer this question, we infused norepinephrine, 20 to 200 μg/min i.v., and withdrew blood, so that mean systemic arterial pressure did not increase (66 ± 3 mm Hg during control and norepinephrine infusion). Pial artery pressure and cerebral blood flow were measured in six cats. Norepinephrine infusion did not alter pial artery pressure (32 ± 2 and 36 ± 4 mm Hg during control and norepinephrine infusion, respectively) or cerebral blood flow (27 ± 4 and 26 ± 3 ml/min per 100 g during control and norepinephrine infusion). Norepinephrine infusion did not alter large artery resistance (1.6 ± 0.3 and 1.4 ± 0.3 mm Hg per ml/min per 100 g during control and norepinephrine infusion) or small vessel resistance (1.4 ± 0.3 and 1.6 ± 0.3 mm Hg per ml/min per 100 g during control and norepinephrine infusion).

Statistics

Statistical analysis was performed by comparing a control value with an intervention using the paired t-test and by comparing responses to acute hypertension in groups after denervation and during stimulation with the unpaired t-test.

Results

Under control conditions, resistance of large arteries (>200 μm in diameter) accounted for almost half of the total cerebral vascular resistance (Table 1). This observation supports previous findings.1,2,4,5 Moderate hypertension (raising aortic pressure approximately 60 mm Hg) after sympathetic denervation produced an increase in total cerebral vascular resistance (see Table 1). The autoregulatory response to moderate hypertension tended to increase large artery resistance, and small vessel resistance increased significantly. During

<table>
<thead>
<tr>
<th>Variable</th>
<th>Denervation (n = 8)</th>
<th>Sympathetic stimulation (n = 8)</th>
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<tr>
<td>SAP (mm Hg)</td>
<td>PAP (mm Hg)</td>
<td>CBF (ml/min × 100 g)</td>
</tr>
<tr>
<td>Control 1</td>
<td>78 ± 5</td>
<td>39 ± 4</td>
</tr>
<tr>
<td>Moderate hypertension</td>
<td>133 ± 4</td>
<td>78 ± 6*</td>
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<tr>
<td>Control 2</td>
<td>74 ± 5</td>
<td>36 ± 3</td>
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<tr>
<td>Severe hypertension</td>
<td>216 ± 8</td>
<td>128 ± 11*</td>
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<tr>
<td>Control 1</td>
<td>76 ± 3</td>
<td>36 ± 4</td>
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<tr>
<td>Moderate hypertension</td>
<td>137 ± 8</td>
<td>74 ± 8*</td>
</tr>
<tr>
<td>Control 2</td>
<td>76 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>210 ± 4</td>
<td>129 ± 11*</td>
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Values are means ± SE. Pial artery diameter was 207 ± 23 μm in the denervated group and 194 ± 16 μm in the sympathetic stimulation group under control conditions.

SAP = systemic arterial pressure; PAP = pial artery pressure; CBF = cerebral blood flow; TCVR = total cerebral vascular resistance; LAR = large artery resistance; SVR = small vessel resistance. Units for resistance are mm Hg per ml/min per 100 g.

*p < 0.05, compared with preceding control value. Statistical comparisons between denervated group and sympathetic stimulation are indicated in Figures 1 and 2.
severe hypertension (raising aortic pressure more than 110 mm Hg) after sympathetic denervation, the autoregulatory capacity of cerebral vessels was exceeded. Total cerebral vascular resistance decreased or failed to increase, and there was a marked increase in cerebral blood flow (Tables 1 and 2, Figures 1 and 2). Resistance of large cerebral arteries decreased, and resistance of small cerebral vessels failed to increase. There was a large increase in the pressure in small cerebral arteries.

During moderate hypertension, sympathetic stimulation had only modest effects on cerebral vessels: increases in large and small vessel resistance during moderate hypertension were minimally greater during sympathetic stimulation than after denervation (see Table 1). Thus, the autoregulatory constrictor response of large and small cerebral vessels during moderate hypertension was not significantly augmented by sympathetic stimulation. In contrast, sympathetic stimulation had major effects on cerebral vessels during severe hypertension. The increase in cerebral blood flow in response to severe hypertension was attenuated significantly by sympathetic stimulation (see Tables 1 and 2, Figure 1). Stimulation of sympathetic nerves during severe hypertension prevented passive decreases in resistance of large arteries (see Tables 1 and 2, Figure 2). Sympathetic stimulation also allowed the resistance of small cerebral vessels to increase during severe hypertension (see Tables 1 and 2, Figure 2).

Although sympathetic stimulation had important effects on both large and small cerebral vessels during severe hypertension, stimulation did not attenuate increases in pressure in pial arteries approximately 200 μm in diameter (see Table 1, Figure 1) and only modestly attenuated increases in pressure in pial arteries approximately 100 μm in diameter (see Table 2).

Discussion

This study provides new insight into the effects of sympathetic stimulation on segmental resistance of cerebral vessels during acute hypertension. The major new findings are 1) sympathetic stimulation prevents decreases in the resistance of large cerebral arteries during severe hypertension; 2) sympathetic stimulation, which does not constrict small cerebral vessels during normotension, allows pronounced constriction of small vessels during severe hypertension; and 3) sympathetic stimulation, which reduces pressure in moderate-sized cerebral arteries (=200 μm in diameter) during normotension, does not attenuate increases in pressure in these vessels during acute hypertension. Thus, protection of the blood-brain barrier by sympathetic nerves during acute hypertension is not the result of attenuation of increases in pial artery pressure. This finding suggests that sympathetic stimulation may protect the blood-brain barrier largely at a more distal site in small vessels.

We infused large doses of norepinephrine to raise arterial pressure. With this approach we assume that norepinephrine has a minimal direct effect on the resistance of large and small cerebral vessels that is independent of its effect on arterial pressure. Several findings suggest that infusion of norepinephrine is an appropriate stimulus for the study of effects of hypertension on cerebral vessels. First, circulating catecholamines do not pass the blood-brain barrier readily. Second, intravenously administered norepinephrine has no direct effect on pial artery diameter when hypertension is prevented. Third, disruption of the barrier by acute hypertension may expose cerebral vessels to circulating norepinephrine, but the venules are the primary site of disruption of the barrier. Cerebral venules do not have a continuous layer of smooth muscle and thus, even when the barrier is disrupted, presumably would not be affected significantly by norepinephrine. Fourth, and most important in relation to this study, norepinephrine has little or no direct effect on the resistance of large or small cerebral vessels (as observed in this study).

To calculate the resistance of large and small cerebral vessels, we measured blood flow to the entire ipsilateral cerebral hemisphere and pressure in a single pial artery. Insertion of the micropipette does not appear to damage pial vessels or impair their responses. Nevertheless, this approach (using a global measurement of blood flow and a local measurement of pressure) may reduce the precision of our calculations of

<table>
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<tr>
<th>Variable</th>
<th>SAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>CBF (ml/min × 100 g)</th>
<th>TCVR</th>
<th>LAR</th>
<th>SVR</th>
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<tr>
<td>Denervation (n = 9)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>71 ± 3</td>
<td>32 ± 4</td>
<td>30 ± 4</td>
<td>2.8 ± 0.5</td>
<td>1.6 ± 0.3</td>
<td>1.2 ± 0.2</td>
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<td>Hypertension</td>
<td>188 ± 3</td>
<td>128 ± 7*</td>
<td>84 ± 14*</td>
<td>2.9 ± 0.5</td>
<td>0.8 ± 0.1*</td>
<td>2.0 ± 0.4</td>
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<tr>
<td>Denervation (n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>73 ± 3</td>
<td>29 ± 2</td>
<td>25 ± 4</td>
<td>3.4 ± 0.5</td>
<td>2.1 ± 0.3</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>194 ± 6</td>
<td>110 ± 5*</td>
<td>56 ± 8*</td>
<td>4.0 ± 0.6</td>
<td>1.8 ± 0.3</td>
<td>2.3 ± 0.3*</td>
</tr>
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</table>

Values are means ± SE. Pial artery diameter was 95 ± 5 μm in the denervated group and 90 ± 10 μm in the sympathetic stimulation group under control conditions.

Units for resistance are mm Hg per ml/min per 100 g. See Table 1 for key to abbreviations.

*p < 0.05, compared with control values.
Increased aortic pressure, pressure in pial arteries approximately 200 μm in diameter, and cerebral blood flow during severe hypertension. Values are means ± SE in denervated cats (black bars; n = 8) and during sympathetic stimulation (white bars; n = 8). Asterisk indicates significant difference (p<0.05) compared with values in denervated group.

Our calculation of small vessel resistance includes the resistance of arterioles, capillaries, venules, and large veins to the sagittal sinus. Because these segments may respond differently to interventions, our calculation of small vessel resistance may prevent detection of heterogeneous responses of the different segments. For example, direct observation of arterioles indicates that these vessels dilate during severe hypertension, but we found that small vessel resistance was unchanged or tended to increase during acute hypertension in denervated cats.

If acute hypertension produces dilatation of arterioles, and our value for small vessel resistance is unchanged, then resistance must increase in another segment that is included in our calculation of small vessel resistance. We speculate that resistance of veins may increase during acute hypertension in our preparation. We have found that acute hypertension in rats increases pressure in cerebral venules from 6 to 27 mm Hg and, in this study, that pressure in the sagittal sinus is only 2 mm Hg under control conditions and 3 mm Hg during acute hypertension. Thus, there may be a large drop in pressure (and increase in resistance) across the cerebral venous segment during acute hypertension, that is not present under control conditions. We speculate that, in our open skull preparation, there is collapse of veins between the venules and the sinuses under control conditions. During acute hypertension, increases in venular pressure may open collapsed veins, increase the length of these resistance vessels, and thereby increase small vessel resistance. An implication of this speculation is that we may have underestimated decreases in resistance of small vessels during acute hypertension.

The cerebral vascular segment that accounts for autoregulatory constriction may differ at various levels of aortic pressure. When mean aortic pressure is raised from approximately 75 to 100 mm Hg, small vessels (<200 μm in diameter) account for virtually all of the increase in cerebral vascular resistance. In contrast, when mean aortic pressure was raised from 80 to 130 mm Hg in this study, resistance of large arteries tended to increase and contribute to the increase in total cere-
bral vascular resistance. Kontos et al. have emphasized the contribution of large arteries to the cerebral vasoconstrictor response during somewhat greater levels of hypertension.

In this study, we found that both large and small vessels contribute to the failure of cerebral autoregulation during severe hypertension. Large artery resistance, which increased during moderate hypertension, decreased below control levels during severe hypertension, as the autoregulatory capacity of large arteries was exceeded and the vessels dilated passively. Resistance of small vessels, which increased during moderate hypertension, fell toward or even to control values during severe hypertension. Thus, neither vascular segment was able to maintain its autoregulatory constriction during severe hypertension.

Pial artery pressure did not increase as much as aortic pressure during moderate or severe hypertension. The decrease in pressure from the aorta to pial arteries was determined by blood flow and by the ratio of resistance in large arteries upstream and small vessels downstream. During moderate hypertension, increases in pial artery pressure were attenuated in two ways: large artery resistance tended to increase, and blood flow increased modestly. Thus, elevation of pial artery pressure was blunted during moderate hypertension. During severe hypertension, pial artery pressure increased less than aortic pressure, even though large artery resistance decreased significantly. Thus, increases in pial artery pressure during severe hypertension were attenuated entirely by increases in blood flow and not by constriction of large arteries.

We observed previously that sympathetic stimulation increases the resistance of large cerebral arteries during normotension. Thus, it was not surprising to find in this study, that sympathetic stimulation also has important effects on large arteries during acute hypertension, as stimulation prevents passive decreases in large artery resistance during severe hypertension. We were unable to detect an effect of sympathetic stimulation on large arteries during moderate hypertension. The design of this study (comparison of different groups) was not as sensitive as the within-animal comparison that we made during normotension. We cannot exclude the possibility, therefore, that sympathetic stimulation has a modest effect on large cerebral arteries during moderate hypertension, but the design of the study prevented detection of the effect.

In a previous study, we found that sympathetic stimulation during normotension failed to increase the resistance of small cerebral arteries. This study indicates that small vessels are innervated sufficiently to respond vigorously to sympathetic stimulation under appropriate conditions.

We speculate that the intravascular pressure in small arteries is a critical determinant of their response to sympathetic stimulation. During normotension, sympathetic stimulation constricts large cerebral arteries and reduces pressure in small arteries, so the neural vasoconstrictor effect on small arteries is opposed by an autoregulatory vasodilator response to the reduction in intravascular pressure and blood flow. In contrast, during severe hypertension, the direct neural vasoconstrictor effect on small arteries is augmented by an autoregulatory response to a decrease in intravascular pressure and blood flow. Thus, an autoregulatory response to a decrease in microvascular pressure and flow during sympathetic stimulation may prevent constriction of small arteries during normotension, and an autoregulatory response to an increase in microvascular pressure and flow may contribute to constriction of small arteries during severe hypertension.

During moderate hypertension, sympathetic stimulation did not augment the increase in resistance of small vessels. This finding provides further support for the concept that sympathetic stimulation has little effect on cerebral vessels except when the autoregulatory capacity of the vessels is exceeded.

We began sympathetic stimulation before raising aortic pressure. Kontos and Wei demonstrated that sympathetic nerves attenuate increases in the diameter of pial arteries when stimulation is begun before raising pressure, but not when hypertension is established prior to stimulation. The authors speculated that, when acute hypertension is established first, production of free oxygen radicals might prevent the response to sympathetic stimulation. Oxygen radicals, which apparently are generated during acute hypertension, inactivate norepinephrine and thus may prevent responses to sympathetic stimulation. An alternative mechanism, as the authors suggested, may involve excessive stretch of vascular muscle during severe hypertension with inhibition of vasoconstrictor responses.

Sympathetic stimulation protects the blood-brain barrier during acute hypertension. It is not clear whether the primary site of disruption of the barrier is the arterioles, capillaries, or venules. If the primary site of disruption is the arterioles, one might expect that sympathetic stimulation would constrict primarily large arteries upstream and thereby protect arterioles against excessive increases in pressure. We found, however, that sympathetic stimulation effected only a modest attenuation of increases in arteriolar pressure. If, on the other hand, disruption of the barrier occurs primarily in capillaries or venules, sympathetic stimulation might constrict large and small vessels and thereby protect capillaries and venules downstream.

In a previous study, we found that sympathetic stimulation during normotension was unable to detect an effect of sympathetic stimulation on large cerebral arteries upstream and thereby protect capillaries and venules. We speculate that constriction of large arteries during sympathetic stimulation may attenuate increases in pressure in small arteries during acute hypertension and thereby protect the blood-brain barrier. We infer from the present findings that sympathetic nerves do not protect cerebral vessels by attenuation of increases in small artery pressure and that the protective effect must be directed at a more distal segment. Other studies are compatible with this concept. We have
suggested recently\(^{16}\) that the microvascular leak during severe hypertension occurs primarily in cerebral vessels, not in arterioles or capillaries. These findings lead us to speculate that sympathetic stimulation may protect against disruption of the blood-brain barrier at the venular level, not primarily at the arteriolar level.

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**References**

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