Spontaneous tone of cerebral parenchymal arterioles: a role in cerebral hyperemic phenomena

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An isolated cerebral arteriole preparation was used to test the hypothesis that a temporary reduction in transmural pressure causes a subsequent vasodilation mediated by mechanisms intrinsic to the vessel wall. Thirty-five cerebral vessels of 44.7 ± 1.4 μm (± standard error of the mean) mean diameter were cannulated in vitro and pressurized at a transmural pressure of 60 mm Hg; after an equilibration period the vessels developed spontaneous tone. When transmural pressure was decreased to 0 mm Hg for a period of 4 minutes then returned to 60 mm Hg, vessels dilated to 155.1% ± 6.8% of control diameter before gradually redeveloping spontaneous tone in 5.5 ± 0.7 minutes. Varying the duration of the period during which transmural pressure was at 0 mm Hg had no significant effect on the degree of vasodilation. Conversely, varying the level of decreased transmural pressure between 0 and 20 mm Hg significantly affected both the magnitude of vasodilation and the time course of spontaneous tone recovery. These findings indicate that a temporary period of decreased transmural pressure may result in a loss of spontaneous tone in the resistance vessels of the cerebral microcirculation. Mechanisms intrinsic to the vessel wall may play a significant role in the early stage of post-reperfusion hyperemia. Such mechanisms could also be implicated in other hyperemic phenomena affecting the cerebral circulation, such as the rapid increase in intracranial pressure after subarachnoid hemorrhage, the development of the normal perfusion pressure breakthrough phenomenon, and the initiation of intracranial pressure plateau waves.

KEY WORDS • cerebral circulation • cerebral hyperemia • cerebral ischemia • vasomotor tone • transmural pressure • spontaneous tone
permit the direct observation of the reactivity of viable cerebral parenchymal arterioles under conditions of known transmural pressure. The effects of both duration and degree of decreased transmural pressure on spontaneous arteriolar tone were examined.

**Materials and Methods**

**Isolation and Cannulation of Vessels**

Animal experimentation was conducted in conformity with the American Physiological Society's "Guiding Principles in the Care and Use of Animals." Methods for the isolation and cannulation techniques have been described in detail previously. Briefly, penetrating cerebral arterioles, 30 to 70 μm in diameter, were surgically isolated from the first (M₁) portion of the middle cerebral artery in the brains of pentobarbital-anesthetized Sprague-Dawley rats, each weighing 300 to 400 gm. The vessel segments were transferred to a temperature solution from room temperature to between 37° and 38°C. Over an equilibration period of approximately 45 minutes, during which time the bath solution of pH 7.30 was changed three or four times, spontaneous tone developed with a maximum passive diameter. Responsiveness of the vessels was then assessed by changing the extraluminal pH from 7.30 to 6.80 and from 7.30 to 7.60. Vessels with only weak responses to pH change (< 15% dilation or constriction) were discarded at this stage.

**Perfusion and Bath Solutions**

The physiological salt solutions used in this preparation were modified Ringer's solutions with compositions as follows (in mM): NaCl 144, KCl 3.0, CaCl₂ 2.5, MgSO₄ 1.5, glucose 5, pyruvate 2.0, ethylenediaminetetra-acetic acid 0.02, 3-[N-morpholino]propanesulfonic acid (MOPS) 2.0, and NaH₂PO₄ 1.21; bovine serum albumin was added at 0.9 to 1 gm/100 ml. The intraluminal solution was maintained at pH 7.30 throughout the experiments. The extraluminal solution contained no albumin and was also maintained at pH 7.30, except when pH responses were assessed.

**Duration of Decreased Transmural Pressure**

Control vessel diameter was defined as the diameter to which the vessels spontaneously contracted during the equilibration period in a bath solution of pH 7.30. Once vessels developed spontaneous tone, vessel diameters remained relatively stable for several hours. The organ bath solution was changed every 4 to 5 minutes throughout the experiments.

In the initial experiments, the effects of duration of decreased transmural pressure on vessel diameter were examined. From a control pressure of 60 mm Hg, transmural pressure was decreased to 0 mm Hg for varying time periods (0.5, 2, 4, and 8 minutes), then returned to 60 mm Hg. Changes in vessel diameter were monitored continuously both during and after these procedures.

**Level of Decreased Transmural Pressure**

In subsequent experiments, transmural pressure was lowered to 0, 5, 10, or 20 mm Hg for a duration of 4 minutes, then returned to 60 mm Hg. Changes in vessel diameter were again monitored continuously during and after these procedures.

**Statistical Analysis**

Basic reactivity parameters, such as control vessel diameter and response to pH 6.8 and pH 7.6 were compared by one-way analysis of variance (ANOVA) in order to determine whether vessel characteristics expressed as these parameters were homogeneously distributed in each vessel group. Group mean diameters for each time point during the recovery of spontaneous tone, expressed as a percent of initial vessel diameter, were compared by ANOVA with repeated measures and subsequently by Bonferroni t-tests. The time taken to return to the initial diameter range (100% ± 5% of the initial diameter) was compared by ANOVA and subsequently by Student-Newman-Keuls multiple-range tests. Values are expressed as the mean ± standard error of the mean. Null hypotheses were rejected at a probability of 0.05 or less.

**Results**

The mean control vessel diameter was 44.7 ± 1.4 μm for 35 vessels. Vessels dilated to 120.7% ± 0.8% of control diameter when the extraluminal solution pH was lowered to 6.8 and constricted to 77.2% ± 0.8% of

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<th>Table 1: Basic parameters of each vessel group*</th>
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<td><strong>Experimental Protocol</strong></td>
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<td><strong>TMP (mm Hg)</strong></td>
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* Values are means ± standard errors of the means for five vessels in each group. TMP = transmural pressure; ANOVA = analysis of variance (p value in parentheses); NS = difference not significant.
† Response is expressed as percentage of control diameter.
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Fig. 1. Representative recording of the vessel diameter and transmural pressure (TMP) in isolated cerebral parenchymal arterioles. The TMP was lowered to 0 mm Hg for 4 minutes before being returned to 60 mm Hg. The vessel diameter was reduced to 93% when the TMP was lowered to 0 mm Hg and remained relatively stable while TMP was at 0 mm Hg. Immediately after TMP was returned to 60 mm Hg, the vessel diameter increased to 164% and gradually returned to its initial diameter range (100% ± 5%) in 5 minutes.

control diameter when the pH was raised to 7.6. These basic vessel parameters were not significantly different across each of seven experimental groups (p values ranged from 0.144 to 0.256 in ANOVA, Table 1).

Duration of Decreased Transmural Pressure

When transmural pressure was lowered to 0 mm Hg from 60 mm Hg, vessel diameters were reduced to approximately 90% of control and remained below the initial diameter throughout the period that transmural pressure was at 0 mm Hg (Figs. 1 and 2, and Table 2). Vessels maintained at a transmural pressure of 0 mm Hg for 4 and 8 minutes had a tendency to dilate; however, the degree of dilation was not statistically significant. Immediately after transmural pressure was returned to 60 mm Hg, vessels dilated to 159.9% ± 6.1%, 146.9% ± 4.4%, 155.1% ± 6.8%, and 163.8% ± 10.2% for groups of vessels (five in each group) maintained at 0 mm Hg transmural pressure for 0.5, 2, 4, and 8 minutes, respectively (Table 2). The duration of 0 mm Hg transmural pressure had no significant effect on the magnitude of vasodilation (p = 0.5639). Over the 5 to 6 minutes after transmural pressure was returned to 60 mm Hg, vessels gradually returned to their initial diameter. Time for return to the initial diameter range (100% ± 5% of initial diameter) was not significantly different for any of the groups (Table 3). The recovery time courses of vessel diameter were not significantly affected by the time during which transmural pressure was at 0 mm Hg transmural pressure when

<table>
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<th>Time of</th>
<th>Duration of TMP = 0 mm Hg</th>
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<tr>
<td>Measurement</td>
<td>0.5 Min</td>
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<td>90.5 ± 1.7</td>
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<td>late</td>
<td>90.7 ± 1.7</td>
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<td>0 min</td>
<td>159.9 ± 6.1</td>
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<td>1 min</td>
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<td>2 min</td>
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<td>3 min</td>
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<td>4 min</td>
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<td>5 min</td>
<td>103.1 ± 1.6</td>
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<td>6 min</td>
<td>102.5 ± 1.5</td>
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<tr>
<td>7 min</td>
<td>98.3 ± 1.8</td>
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* Vessel diameters are expressed as percentage of initial diameter. Values are means ± standard errors of the means for five vessels in each group.

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TABLE 3
Time for return to initial diameter range*

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<tr>
<th>Vessel Group</th>
<th>Experimental Protocol</th>
<th>Time for Return to Initial Diameter</th>
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<tr>
<td></td>
<td>TMP (mm Hg)</td>
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<tr>
<td>G</td>
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* Values are means ± standard errors of the means for five vessels in each group. Initial diameter range is defined as 100% ± 5% of initial diameter. TMP = transmural pressure.
† Value is significantly different from that in Group D (p < 0.05).‡ Value is significantly different from those in Groups A, B, C, and D (p < 0.05).

compared for 0.5 and 8 minutes’ duration by ANOVA with repeated measures (p = 0.053); however, there appeared to be a tendency for shorter treatment periods to result in more rapid recovery.

Level of Decreased Transmural Pressure

When transmural pressure was lowered to 0, 5, 10, or 20 mm Hg for a duration of 4 minutes, vessel diameters were reduced to approximately 90% (Figs. 3 and 4, and Table 4). Over a period of 4 minutes of decreased transmural pressure, vessels dilated to 110.9% ± 2.1%, 118.3% ± 4.0%, or 111.8% ± 6.4% (five vessels in each group), when transmural pressure was lowered to 5, 10, or 20 mm Hg, respectively. Vessel diameters remained at about 90% of control with 0 mm Hg transmural pressure. Immediately after the transmural pressure was returned to 60 mm Hg, vessels dilated further with the magnitude of vasodilation being related to the level to which transmural pressure had been decreased: 155.1% ± 6.8% for 0 mm Hg transmural pressure, 153.2% ± 2.9% for 5 mm Hg transmural pressure, 141.3% ± 3.7% for 10 mm Hg transmural pressure, and 119.9% ± 5.8% for 20 mm Hg transmural pressure. The magnitude of vasodilation in the 20-mm Hg group was significantly less than that in both the 0-mm Hg and 5-mm Hg groups (Table 4). Vessel diameters then gradually returned to the initial diameter. The time for return to the initial diameter range was also related to the degree of decreased transmural pressure (Table 3). The time for return to the initial diameter was significantly shorter when transmural pressure had been lowered to 20 mm Hg (1.3 ± 0.3 minutes) than when it had been lowered to 0 mm Hg, irrespective of the duration of the decreased level. The recovery time courses of vessel diameters were significantly affected by the level of decreased transmural pressure when compared by ANOVA with repeated measures (p = 0.0005).

Discussion

In the present study, cerebral parenchymal arterioles were exposed to an experimental paradigm consisting of a period of temporary decrease in transmural pressure to 0–20 mm Hg followed by reestablishment of a control pressure of 60 mm Hg. These manipulations of transmural pressure resulted in an initial significant vasodilation followed by a gradual return to the initial vessel diameter. Both the magnitude of vasodilation and the time course for recovery of spontaneous vessel tone were related to the degree of decrement in transmural pressure, whereas the duration of decreased pressure was not correlated with the degree or time course of vasodilation between 0.5 and 8 minutes.

The concept of cerebral vasomotor paralysis in the setting of increased ICP was advanced by Langfitt, et al.,13 in 1965. They emphasized the role of increased cerebral blood volume due to vasomotor paralysis in the later stages of progression of intracranial hypertension. They concluded that vasomotor paralysis was due to severe local metabolic changes, but also indicated that destruction of nerve endings, abolition of some intrinsic vasoconstricting mechanism in the wall of the arterioles, or other pathological alterations in vessel function could constitute additional mechanisms in the development of vasomotor paralysis.13

The use of the in vitro isolated vessel technique in this study allowed control of intra- and extraluminal fluid composition throughout the course of the experiments. Parenchymal effects such as those seen when transmural pressure is decreased in situ could not, therefore, have mediated the results observed. It is known that a variety of metabolic vasodilator products such as hydrogen ion through lactic acid formation, potassium ion from the intracellular pool, and adeno-
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![Graph showing changes in vessel diameter following decreased transmural pressure (TMP) to 0, 5, 10, or 20 mm Hg for a duration of 4 minutes in isolated cerebral parenchymal arterioles. Points represent mean diameters for five vessels in each group, expressed as a percent of initial diameter (standard error of the mean is not shown: see Table 3). On represurization to 60 mm Hg, vessels in all groups dilated significantly; however, both the magnitude of vasodilation and the recovery time courses of vessel diameters were significantly affected by the degree of decreased TMP (p = 0.0005 by ANOVA with repeated measures).](image)

**FIG. 4.** Changes in vessel diameter following decreased transmural pressure (TMP) to 0, 5, 10, or 20 mm Hg for a duration of 4 minutes in isolated cerebral parenchymal arterioles. Points represent mean diameters for five vessels in each group, expressed as a percent of initial diameter (standard error of the mean is not shown: see Table 3). On represurization to 60 mm Hg, vessels in all groups dilated significantly; however, both the magnitude of vasodilation and the recovery time courses of vessel diameters were significantly affected by the degree of decreased TMP (p = 0.0005 by ANOVA with repeated measures).

The accumulation of metabolic vasodilator products has been thought to constitute the primary mechanism whereby cerebral ischemia leads to postischemic hyperemia. The present study points to an additional mechanism for post-reperfusion hyperemia: a temporary loss of spontaneous tone in cerebral parenchymal arterioles occurs due to decreased transmural pressure during flow arrest, leading to a temporary vasomotor paralysis. The accumulation of metabolic vasodilators such as adenosine is clearly important in mediating this hyperemia. Myogenic mechanisms, however, probably contribute to the period of increased flow, especially immediately after restoration of the circulation. Later stages of postischemic hyperemia may be more directly related to metabolic vasodilator products since longer durations of ischemia result in more prolonged postischemic hyperemia.

Symon, et al., have suggested that post-reperfusion hyperemia could be mediated via normal autoregulatory processes which induce vasodilation and subsequently result in a transient overswing in perfusion following the restoration of normal perfusion pressure in a dilated vascular bed (Fig. 5). Our data indicate that autoregulation, while important, may not be the only mechanism for such an overswing. In the present study, autoregulatory increases in vessel diameter were noted during the period of time of transmural pressure decrement to 5, 10, or 20 mm Hg, while no increase was noted when transmural pressure was decreased to 0 mm Hg. These results suggest that the intrinsic passive viscoelastic properties of the vessel wall override vasodilator mechanisms at extremely low wall tensions. When transmural pressure was restored to control levels, however, a further vasodilation occurred — greater in magnitude than the autoregulatory vasodilation observed during the period of transmural pressure decrement. Thus, the diameter “overswing” appears to exceed in magnitude that which can be explained by autoregulation alone.

It is possible to estimate the contribution of intrinsic myogenic autoregulation in intraparenchymal arterioles by comparing our results with those reported in an in vivo rat system studied by Harper, et al. Data derived from in situ preparations such as that used by Harper, et al., represent the sum of metabolic and myogenic factors in autoregulation, whereas data from in vitro preparations such as ours indicate only the myogenic contribution. Harper's study, a microvascular pressure change from 60 to 20 mm Hg (corresponding to a change in mean arterial pressure from 140 to 50 mm Hg) in pial arterioles (designated 1A) with an average diameter of 48 μm induced a 45% increase in arteriolar diameters. In the present in vitro studies, a similar transmural pressure decrement of 60 to 20 mm Hg resulted in a 12% increase in vessel diameter. Since the blood flow correlates roughly with the fourth power of vessel diameter, the relative contribution of the myogenic mechanism in intraparenchymal cerebral arterioles can be calculated by the following equation: \[
\frac{[(1.12)^4 - 1]}{[(1.45)^4 - 1]} = 0.17
\] Therefore, the myogenic contribution can be estimated to be approximately 17% in the cerebral microcirculation when compared to other factors such as metabolic and neurogenic mechanisms.
Aneurysmal SAH results in an extreme increase in ICP. Nornes and Magnaes measured ICP during documented SAH. They found that ICP approached the range of the diastolic and even mean arterial blood pressures. This abrupt increase in ICP is thought to promote hemostasis by either circulatory arrest or a tamponade effect on the aneurysm. These authors speculated that this abrupt increase in ICP is due to acute vasodilation of distal cerebral arterioles with a resultant increase in cerebral blood volume. They inferred this mechanism from the rapid occurrence of the ICP change and the disproportionate rise in ICP as compared to the apparent volume of blood extravasated into the subarachnoid space. Pickard, et al., actually demonstrated an increase in cerebral blood flow measured by the intravenous xenon-133 technique in patients during intraoperative aneurysm rupture, and suggested that acute brain swelling following aneurysmal rupture is initially the result of brain engorgement. The present results demonstrate that a vasodilator mechanism intrinsic to the vessel wall exists in cerebral parenchymal arterioles after a temporary drop in transmural pressure such as would occur during aneurysmal bleeding. The time course of vasodilation in our experiments is compatible with that of ICP changes in patients during SAH as reported by Grote and Hassler, in which ICP showed extreme increases within 1 minute after SAH and then declined over several minutes.

Cerebral hyperemia may also occur after the abrupt occlusion of arteries feeding AVM's, and sometimes leads to catastrophic edema and hemorrhage in brain adjacent to the AVM. This phenomenon has been termed “normal perfusion pressure breakthrough” by Spetzler, et al. In this disorder, vessels supplying the brain surrounding certain AVM's become dilated in an apparent attempt to divert blood from the malformation into the surrounding cerebral parenchyma. When the AVM is obliterated surgically, the blood flow previously shunted into the AVM is redistributed into these abnormally dilated vessels at normal perfusion pressures. It is speculated that the autoregulatory control (probably at the arteriolar level) cannot sufficiently increase the resistance to the new perfusion pressure to protect the capillary, leading to capillary breakthrough and resultant edema or hemorrhage. Loss of spontaneous tone in cerebral parenchymal arterioles appears to play a significant role in normal perfusion pressure breakthrough. The present study suggests that arterioles may dilate to a greater degree than would be expected purely by an autoregulatory vasodilation when perfusion pressure is reestablished to normal following resection of the AVM. This intrinsic myogenic mechanism in cerebral parenchymal arterioles may make a large contribution to normal perfusion-pressure breakthrough.

Rosner and Becker have conducted studies that point to the importance of a reduction of cerebral perfusion pressure (CPP) in the initiation of ICP plateau waves. Rosner and Coley extended this work to patients, and demonstrated that reduced CPP was the main cause of an increase in the severity and frequency of pressure-wave occurrence observed in patients whose head position was elevated. The plateau wave or A-wave is characterized by spontaneous and acute elevations in ICP rapidly rising above moderately elevated baseline levels (usually 15 to 25 mm Hg), reaching 50 to 100 mm Hg, and lasting from 2 to 30 minutes. Rosner and Becker suggested that plateau waves occur as a result of intact or mostly intact autoregulation responding to changes in CPP rather than “vasomotor paralysis” as described by Langfitt, et al. Our study suggests that temporary vasodilation due to spontaneous tone loss, or “vasomotor paralysis,” can occur following autoregulatory vasodilation when transmural pressure is lowered to 5 to 20 mm Hg then returned to 60 mm Hg. Therefore, a form of “vasomotor paralysis” together with autoregulatory vasodilation could con-
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tribute to the sudden temporary elevations of ICP seen in plateau waves. These findings are also consistent with the fact that the initial systemic arterial pressure decrement may not be apparent before pressure waves occur, since the relationship between perfusion pressure at the level of cerebral microcirculation and large-artery systemic arterial blood pressure may be extremely complicated in patients with elevated ICP.

In summary, our data suggest the existence of a myogenic mechanism intrinsic to the arteriolar wall which leads to a decrease in the ability of the microcirculation to maintain vasomotor tone after a temporary decrease in transmural pressure. This mechanism of temporary loss of spontaneous vessel tone may play a significant role in the early stages of post-reperfusion hyperemia and in other cerebral microcirculatory hyperemic phenomena such as cerebral engorgement immediately after SAH, normal perfusion pressure breakthrough in AVM surgery, and ICP plateau waves.

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