Perfusion pressure breakthrough threshold of cerebral autoregulation in the chronically ischemic brain: an experimental study in cats

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✓ A study was designed to investigate hyperperfusion syndrome after the restoration of normal cerebral blood flow in a chronically cerebral ischemic state resulting from high-flow arteriovenous malformations or severe carotid stenosis. A fistula between the left distal common carotid artery and the jugular vein was created and the left vertebral artery was simultaneously occluded in 44 cats to produce a chronic cerebral ischemic state. For control experiments, 10 cats underwent occlusion of the left common carotid and vertebral arteries. Six weeks later, pial arterial behavior, disruption of the blood-brain barrier (BBB), and cerebral histological changes were investigated using three experimental methods. In the first, in which a fistula was occluded under normal conditions, pial arteries contracted to some 80% of the resting state; however, no BBB disruption or histological changes were observed. In the second experiment, in which a 20-minute occlusion of the left middle cerebral artery was performed in the cats with a patent fistula, a 30% to 40% dilated state of the pial arteries continued after recirculation, and BBB disruption-induced cerebral edema and infarction were observed. These findings were more prominent in the cats that underwent occlusion of the fistula. On the other hand, in the control group, the pial arteries returned to resting size within 40 minutes, and no BBB disruption or histological changes were observed. In the third experiment, in which moderate hypertension was induced for 1 hour, the pial arteries dilated much more remarkably. BBB disruption and cerebral edema were revealed to be more extensive in the cases of fistula occlusion than within those with a patent fistula. In the control group, however, the pial arteries contracted 10% during hypertension, while BBB disruption and histological changes were not evident. The results indicate that the perfusion pressure breakthrough threshold in the chronically ischemic brain may not be reduced by the restoration of normal blood flow, but may be decreased by the addition of new ischemic insults or hypertension.

Key Words • perfusion pressure • hyperperfusion • carotid endarterectomy • arteriovenous malformation • cat

A fter endarterectomy in cases with high-grade carotid artery stenosis, an increase in cerebral blood flow (CBF) to well above normal values may occur, causing hyperperfusion in a cerebral hemisphere that had adjusted to low perfusion and had been functioning normally.3 Sundt, et al.,29 reported postoperative blood flow rates two to three times greater than preoperatively, in some cases as high as 85.5 ml/100 gm/min, suggesting paralysis of autoregulatory mechanisms. In such cases, seizures, migraine-like headache, and intracerebral hemorrhage may develop. The term "normal perfusion pressure breakthrough" coined by Spetzler, et al.,26 to describe the malignant edema or hemorrhage that sometimes occurs in the hemisphere on the side of a high-flow arteriovenous malformation (AVM) following resection, may also apply in cases of hyperperfusion after correction of high-grade carotid artery stenosis. However, the factors most often associated with postendarterectomy cerebral hemorrhage include recent cerebral infarction6,8,31,34 and severe postoperative hypertension.4,5,18 Moreover, the hemorrhage after resection of high-flow AVM's may be secondary to insecure hemostasis with a high-pressure afterload,4,11 or simply due to bleeding from the unresected AVM.13 The present study was undertaken to identify the factor most responsible for cerebral edema or hemorrhage after correction of chronic cerebral low perfusion due to high-grade carotid artery stenosis or secondary to blood steal through high-flow AVM's.
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Materials and Methods

Laboratory Preparation

The experiment involved 54 adult cats of either sex (each weighing 2.5 to 4 kg). All were anesthetized using halothane inhalation, immobilized with 60 μg/kg of pancuronium, intubated, and ventilated with a 3:1 mixture of N₂O:O₂. The experiment was performed in two stages.

Initial Procedure. First, we divided the left common carotid artery (CCA) and the adjacent internal or external jugular vein for microsurgical anastomosis between the rostral carotid and caudal jugular vessel ends; the remaining vessel stumps were ligated and the left vertebral artery was exposed and occluded with a bipolar coagulator to obtain a low cerebral perfusion state in 44 cats. An extracranial “steal” from the cerebral circulation and a state of cerebral hyperperfusion were thus established. Control studies were performed in 10 cats following left carotid artery ligation without anastomosis and left vertebral artery occlusion. The surgical wound was closed after blood flow was recorded through the shunt using an electromagnetic flowmeter.* The survival time was 6 weeks.

Secondary Procedure. The animals were then placed in the supine position and a double-lumen catheter was inserted through the left femoral artery. The tip of the catheter was first placed in the ascending thoracic aorta for performing angiography, measuring blood pressure, and sampling blood gases, and then placed in the descending thoracic aorta immediately distal to the left subclavian artery for induction of hypertension by balloon inflation. Metabolic acidosis was prevented with the intravenous infusion of a sodium bicarbonate solution as required, and a 37°C body temperature was maintained with a heating pad. Brain temperature was monitored at the suboccipital muscle with a body temperature sensor.† Arterial oxygen tension was maintained at approximately 100 mm Hg, arterial bicarbonate tension at approximately 30 mm Hg, and blood pH at approximately 7.4. Electrocardiogram tracings were also recorded continuously. The region of carotid artery-jugular vein anastomosis was exposed. After angiographic confirmation of blood steal from the cerebral circulation, the blood flow through the efferent carotid-jugular shunt was measured with an electromagnetic flowmeter. The cats with a carotid-jugular fistula and a left vertebral artery occlusion were turned to the sphinx position and the head was fixed in a stereotactic headholder. After a longitudinal skin incision and removal of the temporal muscle, a cranial window was made in the left parietal region over the ectosylvian gyrus using a hand-driven trephine. The cranial window was made according the method of Auer.1 A polyvinyl chloride catheter was inserted into the subdural space for continuous measurement of intracranial pressure (ICP).

Experimental Protocols

Protocol 1: Occlusion of the Left Carotid-Jugular Fistula Only. Using alternating randomization in seven cats with a left carotid-jugular fistula and a left vertebral artery occlusion, we observed pial arterial diameter changes continuously through the cranial window for 5 hours after occlusion of the fistula. Blood-brain barrier (BBB) disruption and any histological changes of the brain were estimated.

Protocol 2: Middle Cerebral Artery Occlusion Loading. Fourteen cats with a left carotid-jugular fistula and a left vertebral artery occlusion, together with the five animals with left CCA and vertebral artery occlusion only, underwent 20-minute occlusion of the left middle cerebral artery (MCA). The left MCA trunk was exposed in all cats according to the method of O'Brien and Waltz7 for temporary occlusion of the MCA and was occluded with a microsurgical clip.12 On occlusion of the MCA, a cessation of pial arterial pulsation and a marked slowing of pial venous blood flow were confirmed through the window. In cases where these signs were not observed, even after reclipping of the MCA, the animal was excluded from the study because of inadequate ischemic insult in the region of the MCA. In seven of the animals with a patent fistula, occlusion of the carotid-jugular fistula was performed before the MCA occlusion.

Protocol 3: Hypertension Loading. In 16 cats with a left carotid-jugular fistula and a left vertebral artery occlusion, 1-hour elevation of blood pressure was performed with an inflated balloon catheter. In eight cats, blood pressure elevation was started soon after occlusion of the fistula. Five cats with left CCA and vertebral artery ligation also underwent a 1-hour elevation of blood pressure by means of the same maneuver. The survival time for these animals was 5 hours after deflation of the balloon.

Microvascular Observations

For continuous recording and observation of pial arterial calibers, an intravitral microscope and video recorder were used. The images of the pial arteries observed through the cranial window were stored on video tape and analyzed later using a microcomputer imaging analyzer.‡

In all cats, changes in the pial arterial diameter were observed continuously through the cranial window from the start of the experiment until 5 hours after release from loading. During the whole period, continuous ICP recording and frequent analysis of blood gases were performed; every 2nd hour, blood sodium

* Electromagnetic flowmeter manufactured by Nihon Kohden, Tokyo, Japan.
† Temperature sensor, Model TW511G, manufactured by Nihon Kohden, Tokyo, Japan.
‡ Imaging analyzer manufactured by Imaging Research, Inc. Ontario, Canada.

J. Neurosurg. / Volume 76 / March, 1992
and potassium levels and hematocrit were checked. Fluid balance was performed by checking the serum osmopressure and monitoring water intake and urine outflow.

**Blood-Brain Barrier and Histological Studies**

At the end of the recording period, Evans blue dye was injected intravenously at a dose of 1.5 ml/kg of a filtered 2% solution in 0.9% sodium chloride. Thirty minutes later, transaortic perfusion fixation was performed under pressure control, first with Ringer’s solution and then with 10% formaldehyde. The brain was carefully removed from the remaining skull, avoiding pressure to the cerebral cortex. The brain was cut coronally at the tips of the temporal lobes, optic chiasm, and mammillary bodies to evaluate pathological changes. The coronal cross section at the optic chiasm usually lay through the center of the cranial window. To estimate the extent of Evans blue dye leakage, a photograph of the cut surface was taken, a histological preparation was made, and hematoxylin and eosin (H & E) and Klüver-Barrera myelin staining were performed to observe the extent of parenchymal damage. The degree of Evans blue dye leakage and histological changes in the brain were estimated from the ratio of the sum of the pathological areas to the sum of the total hemispheric areas in the three slices of brain. The pathological areas and hemispheric spaces were calculated using a microcomputer imaging device. The Evans blue dye leakage area and the ratio of it to the hemispheric area were calculated from the photographs. The areas with decreased staining were judged to have brain edema, and the areas with nuclear pyknosis, which were drawn on the coverglass of the preparation directly by the examiner (who was unaware of the animal’s history), were classified as cerebral infarction.

**Statistical Analysis**

Changes in pial artery diameter, blood pressure, and ICP, and brain pathological changes were analyzed statistically using the Mann-Whitney U-test.
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Results

Of the 44 cats undergoing fistula formation, two died before the experiment was concluded and another five had occlusion of the fistula, which was revealed by angiography, for an overall patency rate of 88.1%. The remaining 37 animals with a patent fistula demonstrated no evident neurological deficits, but chemosis of the affected side was seen in 10 cats. The cats with a patent fistula had a 10% to 25% increase in blood flow through the constituent vessels of the fistula as compared to the initial average flow which was measured by the electromagnetic flowmeter. Mean arterial blood pressure (MABP) and ICP were stable and within normal limits except for the cats with induced hypertension. The data for the experimental and control cats are summarized in Table 1.

Protocol 1

Systemic Parameters. Seven cats with a patent fistula were subjected to occlusion of the fistula. The MABP and ICP were stable during the observation periods. Physiological values of PaO₂ and PaCO₂ were maintained during the experiment. These parameters did not change significantly during the experimental period.

Microvascular Observation. Soon after occlusion of the fistula, the pial arteries contracted to some 80% of the resting-state caliber. They maintained this diameter until the end of the observation period.

Blood-Brain Barrier Disruption and Pathological Changes. In none of these cases did fistula occlusion lead to Evans blue staining of the brain. Meticulous observation failed to detect any area of evident cerebral edema or cerebral infarction in the histological preparations.

Protocol 2

Systemic Parameters. In all cats subjected to 20-minute MCA occlusion loading, the MABP, ICP, and hematocrit values were stable and within physiological parameters. No statistically significant difference occurred during the observation period. The PaO₂, PaCO₂, and blood pH were controlled to remain within physiological parameters during the experiment.

Microvascular Observation. In all cats, the pial arteries dilated by up to 75% soon after clipping of the MCA (Fig. 1). Although the pial arteries in the control cats returned promptly to the resting-state caliber after recirculation of the MCA, the arteries in the cats with a patent fistula never returned to resting-state size even after the removal of the clip, and maintained a 30% to 40% dilatation. There was some tendency toward more prominent dilatation of the pial arteries in the cats that underwent occlusion of the fistula than for the cats undergoing no such occlusion, but the difference was not statistically significant (Fig. 2).
Blood-Brain Barrier Disruption and Pathological Changes. All cats with a patent fistula demonstrated areas of Evans blue staining, cerebral edema, and infarction, although no such findings were revealed in the control cats. The area of Evans blue staining (26.1% ± 8.7% of the hemisphere, mean ± standard error of the mean) and cerebral edema (31.5% ± 11.0% of the hemisphere) were larger in the cases with occlusion of the fistula than in those with no occlusion (Evans blue staining 16.6% ± 5.5%; cerebral edema 22.8% ± 8.5% of the hemisphere). The difference was statistically significant (Fig. 3). The cerebral infarctions were observed mainly in the subcortical area, although they were also seen in the cortex and were almost the same size in both groups (12.6% ± 6.6% vs. 11.5% ± 4.9% of the hemisphere). These pathological areas were localized in the territory of the clipped MCA in all cats.

Protocol 3

Systemic Parameters. Sixteen cats with a patent fistula and five control group cats underwent induction of hypertension by means of inflation of an intra-aortic balloon that was maintained for 1 hour. The average pressure elevation was about 70% of the resting value (Table 1). In eight of the cats with a patent fistula, occlusion of the fistula was performed just before elevation of the arterial blood pressure.

Microvascular Observation. Pial arterial behavior was different in each group. The pial arteries of the cats with occlusion of the fistula were dilated passively by approximately 50% from resting-state caliber according to the blood pressure elevation, and continued to dilate by up to 60% at the end of the experiment, even after blood pressure returned to resting values. In the cats undergoing no occlusion of the fistula, the pial arteries also dilated by up to 30% 20 minutes after elevation of blood pressure, but they gradually returned to 10% dilatation from the resting-state caliber. In the control cats, the pial arteries contracted to 90% of the resting-state size in reaction to blood pressure elevation, then returned to the resting-state size after decrease of blood pressure to baseline values (Fig. 4).

Blood-Brain Barrier Disruption and Pathological Changes. All cats in which the fistula was occluded experienced disruption of the BBB, demonstrated by Evans blue staining (16.3% ± 4.2% of the brain). The five cats without occlusion of the fistula demonstrated disruption of the BBB (6.7% ± 5.1% of the brain). The difference was statistically significant. The uptake of Evans blue dye was petechial, ranging from the appearance of only a few cortical petechiae to widespread staining of the bilateral hemispheres. This staining was usually more remarkable in the hemisphere on the fistula side (Fig. 5). In contrast to the results of Protocol 2, in which the Evans blue dye uptake mainly involved the white matter, here the gray matter was also involved. All cats except those in the control group showed cerebral edema bilaterally. In the animals with occlusion of the fistula, however, the extent of edema (20.5% ± 6.5% of the brain) was significantly larger than in the animals without fistula occlusion (13.1% ± 7.2% of the brain). No cerebral infarction was observed in any animal (Fig. 6).
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Discussion

Literature Review

It has been suggested that, in chronically ischemic areas of the brain produced by severe stenosis of the carotid artery or by a steal phenomenon due to a large high-flow cerebral AVM, CBF may increase remarkably at normal perfusion pressure; cerebral edema or sometimes hemorrhage can occur after correction of such a stenosis1,2,5,27-29 or after surgical treatment of an AVM.7,10,14,16,26,33 This hyperemic phenomenon is considered to be secondary to impaired autoregulation (that is, maximum dilatation of the resistance vessels of the cerebral circulation) in an attempt to increase local CBF.14,25,27,28 This state may be especially vulnerable to edema and to the kinetic energy of blood flow.26,27

On theoretical grounds, it has been suggested that the abrupt correction due to carotid endarterectomy or occlusion of the arteriovenous shunt leads to a transfer of blood flow kinetic energy to potential energy in the form of increased pressure.18 In such cases, a restoration of arterial blood pressure even to normal levels in the cerebral circulation will bring about damage to the BBB. Although clinical evidence has been adduced from a series of case studies of AVM's7,14,15,19,26,33 and carotid endarterectomy,1,2,5,7,27-29 there is little experimental evidence to support this concept. Moreover, it has remained a suspicion that remarkable edema or uncontrollable bleeding at the time of surgery for AVM is attributable to normal pressure breakthrough, because the bleeding point may be tiny feeding vessels which are difficult to coagulate, and such a postoperative course cannot be observed in the skillfully resected AVM.35 It is also reported that the length of arterial feeders to the AVM has a more important relationship to hyperperfusion complication than the size of the arteriovenous shunt.10 On the basis of such a hypothesis we designed the present study.

The experimental model designed by Spetzler, et al.28 to confirm the existence of the "normal perfusion pressure breakthrough" contains a major deficiency: its failure to produce breakthrough edema or hemorrhage. We tried to confirm the breakthrough with the same model, but could never achieve the BBB disruption or cerebral edema after occlusion of the fistula even when blood pressure was increased (unpublished data).

Closure of Fistula Without Ischemia

In the present experiment, the left vertebral artery was occluded in addition to the fistula formation between the left distal CCA artery and jugular vein. In this model, we found about 20% pial arterial contraction after occlusion of the fistula under a normotensive state. This contraction is considered to be secondary to improvement of cerebral perfusion pressure after fistula occlusion. These pial arterial behaviors imply that the autoregulation system is functioning effectively to maintain the CBF against arterial steal, and perfusion pressure breakthrough and BBB disruption do not occur under a normotensive state or without the addition of ischemic insults.

Closure of Fistula With Ischemia

In our second experimental protocol, occlusion of the MCA was performed soon after occlusion of the fistula in seven animals. If the cessation of pial arterial pulsation and marked slowing of pial venous flow were not observed through the cranial window, the cats were excluded from this protocol, because these findings implied severe ischemia in the MCA territory.22,23 The animals with left CCA and vertebral artery occlusion demonstrated good recovery of pial arterial diameter following recirculation after 20 minutes of MCA occlusion, and never demonstrated BBB disruption, cerebral edema, or infarction. These pial arterial behaviors and pathological changes of the brain were the same as those shown in the 20-minute MCA occlusion experiment using cats without carotid and vertebral artery occlusion,23 indicating that cats with left carotid and

Figure 5. Photographs of cat brains from animals having undergone occlusion of the fistula soon before blood pressure elevation. These demonstrate typical petechial hemorrhage and staining by Evans blue dye which are prominent in the hemisphere on the side of the fistula (arrows, right). In the brain with bilateral staining (arrows, left), cerebral edema was remarkable.

Figure 6. Graph showing the areas of Evans blue dye staining (dots) and cerebral edema (diagonal lines) in bilateral hemispheres (Protocol 3). These areas were significantly larger in the cats with occlusion of the fistula (A) than in the cats that did not undergo fistula occlusion (B). Values shown are percentages of total hemispheric volume.
vertebral artery occlusion have a good CBF. If they do not also have a carotid-jugular fistula.

In the animals with a patent fistula, the pial arterial diameter did not return to resting-state size after the 20 minutes of occlusion. This means that a fistula may be the basis of abnormal pial arterial response following such a short period of MCA occlusion. Moreover, BBB disruption, cerebral edema, and cerebral infarction were demonstrated in the cats with a patent fistula after the 20-minute MCA occlusion. Blood-brain barrier disruption and cerebral edema were significantly more severe in the cats that underwent fistula occlusion. The brain with chronic hypoperfusion may be very vulnerable to additional ischemia. This may result in disruption of the BBB and the appearance of more severe cerebral edema due to the postocclusion increase of CBF, because of the loss of capacity for normal autoregulation caused by a long period of dilatation.

Fistula Closure With Hypertension. In our third experimental protocol, pial arteries in the animals with a patent fistula dilated more prominently than those in the control cats following hypertension, and a significantly more pronounced dilated state continued in the cats that underwent occlusion of the fistula. Blood-brain barrier disruption and cerebral edema also occurred reproducibly with moderate hypertension at a level below the threshold of hypertensive breakthrough identified by other authors. This disruption was more prominent in the hemisphere presumably deprived of blood by the fistula. This was also seen in five of the eight cats with a patent fistula, although the extent of disruption was significantly smaller than in the cats that underwent occlusion of the fistula. In the cats with a patent fistula, the pial arteries that seem to be resistant vessels of the cerebral circulation have already dilated to augment local blood flow in the resting state, and may dilate further with the development of moderate hypertension, because the threshold of hypertension breakthrough is reduced by the arteriovenous shunt. The results of this experimental protocol are consistent with those reported by Morgan et al., who created a carotid-jugular fistula in rats and observed BBB disruption after an 8-week interval by induced hypertension following fistula occlusion.

Microvascular Changes

We used the method of Auer to observe microvascular changes in this study. Pial arteries dilated remarkably soon after the development of ischemia or hypertension, and this dilatation was consistent with disruption of the BBB. In our experiment with cats, one of the histological preparations was always made at the coronal slice through the cranial window on the ectosylvian gyrus. These demonstrated a tendency for the cortical surface to be spared severe infarction. Although pial arteries dilated soon after occlusion of the MCA in our experiments, and their dilatation is in contrast to other reports, this difference of pial arterial behavior may be related to the area of observation (one of infarction or penumbra).

Histological Findings

The earliest ischemic cytological alterations, involving neurons, neuropile, and astrocyte, can be demonstrated convincingly 2 hours after the arterial occlusion in paraffin-embedded H & E-stained sections. As a matter of fact, it is quite difficult to estimate precisely the areas of BBB disruption, cerebral edema, and infarction at such an early stage (5 hours) after the ischemic or hypertensive insult. The area of BBB disruption can be calculated from the photographs of brain coronal slices and the area of cerebral edema from cerebral stained preparations exactly and objectively, because a microcomputer imaging analyzer can distinguish lesions from normal areas by measuring contrast differences in objects.

Conclusions

Our results in the surgical removal of high-flow AVM's indicate that both prolonged temporary clipping of feeding arteries at a point far from shunt and prevention of perioperative hypertension are significant factors for avoiding the breakthrough syndrome. In endarterectomy for severe carotid artery stenosis or high-flow bypass surgery using a vein or arterial graft for occlusive disease, a short occlusion time and prevention of perioperative hypertension are very important factors in avoiding the postoperative hypoperfusion syndrome.

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Manuscript received February 14, 1991.
Accepted in final form July 29, 1991.
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