Effects of Hemorrhagic Hypotension on the Cerebral Circulation

I. Cerebral Blood Flow and Pial Arteriolar Caliber

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SUMMARY The relationship between local cerebral blood flow (measured by the hydrogen clearance technique) and stepwise reductions in mean arterial pressure was studied in 8 anesthetized cats. The relationship between pial arteriolar caliber and hypotension was studied in a further 5 cats. Hypotension was induced by graded hemorrhage. Autoregulation maintained a fairly constant cerebral blood flow over the arterial pressure range 60-120 mm Hg. At mean arterial pressures below 60 mm Hg, cerebral blood flow fell with decreasing arterial pressure. Pial arteriolar and arterial caliber increased as mean arterial pressure was decreased. In the smaller arterioles (<50 \( \mu \)m in diameter at a mean arterial pressure of 100 mm Hg), dilatation was maximal (average of 39%) in the arterial pressure range 30-39 mm Hg. The maximal dilatation was less (<56%) in the larger arterioles and small arteries (>50 \( \mu \)m in reference diameter), but occurred in the same arterial pressure range (30-39 mm Hg). Thus, the lower limit of cerebrovascular autoregulation (~65 mm Hg) occurred at a significantly higher pressure than that at which the pial vessels were maximally dilated (~35 mm Hg). Therefore, it would appear that the lower limit of autoregulation should not be equated with maximal pial vasodilatation, as it has tended to be in the past, but with the arterial pressure at which the cerebral dilatation responses can no longer compensate sufficiently for the decreasing perfusion pressure.

THE RELATIONSHIP between perfusion pressure and the cerebral circulation is of paramount importance in situations as diverse as hemorrhagic shock, deliberate hypotension during surgery, and raised intracranial pressure. This relationship is governed primarily by the phenomenon of autoregulation of cerebral blood flow, which may be defined as the intrinsic tendency of the brain to maintain a relatively constant blood flow in response to moderate variations in perfusion pressure (for review, see Lassen\(^1\)).

The present communication relates changes in local cerebral blood flow and in pial arteriolar caliber to changes in mean arterial pressure induced by graded hemorrhagic hypotension. Such mechanisms and relationships have not previously been described systematically. In the accompanying communications, the vascular mechanisms will be related to changes in electrocortical function,\(^2\) and to the development of neuropathological changes in the cerebral parenchyma.\(^3\)

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Methods

General Description

The experiments were carried out in 13 cats, of either sex, weighing between 2.0 and 4.5 kg. The cats were anesthetized initially by the intravenous injection of the rapidly metabolized steroid anesthetic, Saffan (alphaxalone, 6.75 mg/kg and alphadalone acetate, 2.25 mg/kg) (Glaxo Laboratories Ltd.). Following intubation of the trachea, a cannula was placed in the inferior vena cava and 2 cannulae were placed in the abdominal aorta, all being inserted via the femoral vessels. The cats were connected to an intermittent positive-pressure ventilator which delivered 100% O₂ in open circuit. The respirator was adjusted so that the cats remained normocapnic (Pco₂ ≈ 32 mm Hg) throughout the experiment. End-tidal Pco₂ was monitored continuously, and arterial Pco₂, Po₂ and pH were measured frequently. Anesthesia was maintained by the intravenous injection of α-chloralose (6 ml/kg of a 1% solution).

Mean arterial pressure was measured continuously via one of the aortic catheters. An intravenous infusion of Hartmann's solution (0.1 ml/min) was administered throughout to counteract fluid losses. In a few cats, gallamine (3 mg/kg, i.v.) was administered in order to control ventilation. By the use of a heating blanket, body temperature was maintained at 37-38°C.

Measurement of Local Cerebral Blood Flow

Cerebral blood flow was calculated from the tissue desaturation of inhaled hydrogen gas by the technique developed by Pasztor et al. The hydrogen-selective electrodes were made of platinum wire (200 μm in diameter) and were insulated with epoxy resin. The tips of the electrodes were left bare (~1.5 mm in length) and were platinized using platinum chloride. The electrodes (up to 6 per cat) were inserted into the cortex of the parietal lobes through small burr holes and then sealed in place with dental acrylic cement. The currents from the platinum electrodes were amplified and displayed by an electronic system similar to that described by Pasztor et al.

After inserting the electrodes, a polarizing voltage was applied and the electrodes were allowed to stabilize for at least one hour before any determinations of blood flow were attempted. To determine local cerebral blood flow the cats were ventilated with approximately 10% H₂ in O₂ for 10 min, that is, until the concentration of H₂ in brain tissue had reached a plateau. The inhalation of H₂ was discontinued and the desaturation curves of the tissue H₂ clearance followed until a clearly defined monoexponential tail was obtained. This desaturation usually took 10 min, the initial component (~40 sec) being discarded to avoid the artifacts that result from arterial recirculation. Eight cats were used in this part of the investigation and a total of 28 functional cortical electrodes were inserted.

Three parameters were calculated from the desaturation curves of the inhaled hydrogen. In the great majority of instances, the clearances were biexponential and so allowed the resolution of a fast and a slow component (understood conventionally to represent blood flow through gray and subcortical white matter respectively). An initial slope index (ISI) was assessed over the first 2 min of the desaturation curve so as to obtain a measurement of mean blood flow. The reliability and usefulness of this initial slope index in the measurement of wide variations in flow, by comparison to the stochastic analysis of 133Xenon clearance, has been demonstrated. The reliability and usefulness of this initial slope index in the measurement of wide variations in flow, by comparison to the stochastic analysis of 133Xenon clearance, has been demonstrated.

Measurement of Pial Vessel Caliber

The cats were placed in a head-holder, and the scalp was incised along the midline and reflected back so as to form a bath for the mineral oil applied later. A 2.0 X 1.0 cm craniotomy was performed, using a saline-cooled dental drill, over one parietal cortex. The dura was incised and reflected, and the cut dural margins sealed with bi-polar diathermy. The exposed cortex was bathed with paraffin oil to a depth of approximately 20 mm; by adjusting either the flow rate or the temperature of the oil, the surface temperature of the brain was maintained close to 37.5°C as measured by a thermistor thermometer.

The caliber of 25 pial arterioles and small arteries was measured in 5 cats by the television image-splitting technique, as modified by Wahl and his colleagues. The cortical vessels were observed through a triocular stereomicroscope (Bausch & Lomb) at magnifications of × 40 or, most commonly, × 70 in the microscope (the eventual magnification of the television system was considerably greater). For the measurement of vascular caliber, the image was passed through one of the oculars to an image-splitting eyepiece (Vickers) and thence to a highly light-sensitive television camera (Grundig, FA 70). The split image was viewed on a standard laboratory video monitor (Shibaden). The shearing screw of the image-splitting eyepiece — which controls the degree of image-splitting, or tangential shear — was connected to a direct writing pen recorder. The degree of shear that was required to appose tangentially the 2 images of any particular vessel was directly proportional to the vessel caliber. Prior to each experiment the system was calibrated against filaments of known, uniform caliber, thus allowing the absolute caliber of the pial vessels to be calculated. The cortical surface was illuminated from suitable cold light sources (Schott).

A number of pial arterioles and arteries were selected randomly at the beginning of the experiment. At a mean arterial pressure of 100 mm Hg (which was chosen as the reference pressure in this study), the resting diameter of the vessels was from 23 to 221 μm.

Induction of Hemorrhagic Hypotension

Following 2 or 3 base line measurements of local cerebral blood flow and pial vessel caliber at nor-
motension (a mean arterial pressure of about 100 mm Hg), mean arterial pressure was decreased by bleeding the cats (via the second aortic catheter) into a heparinized reservoir, maintained at 37°C. This reservoir was connected to a sphygmomanometer so that the cats' mean arterial pressures could be maintained at any desired level. Mean arterial pressure was reduced in decrements of approximately 10 mm Hg on each occasion and was held at the desired level for around 10 min prior to, and 10 min during, the measurement of cortical blood flow or pial vessel caliber. The total period of hemorrhage-induced hypotension ranged between 2 and 3 h.

**Results**

**Cerebral Blood Flow**

The absolute values for base line cerebral blood flow are presented in the table. Although the electrodes were inserted into cortical tissue, the vast majority (24 out of the 25 satisfactory electrodes) displayed a biexponential clearance at normal arterial pressures. The resolution of the hydrogen clearance curve into 2 components was assumed to reflect gray matter (fast component) and subcortical (slow component) blood flow. The single autoregulating electrode that recorded a monoexponential clearance was similar in character to the slow component of the biexponential clearances. Three electrodes (11% of the total) were considered to be unsatisfactory because of a failure to demonstrate any autoregulatory plateau even over very moderate changes in perfusion pressure. This pressure-passiveness probably reflected local tissue damage secondary to the insertion of the electrodes.

The absolute values at normotension (mean arterial pressure = 115 mm Hg) for the initial slope index (55 ± 31 ml/100 g min, mean), for the fast component (125 ± 47 ml/100 g min, mean), and for the slow component (19 ± 5 ml/100 g min, mean) are very similar to those obtained in earlier studies in cats, and in monkeys that have used the hydrogen clearance technique. These values also compare favorably to those obtained in conscious cats with dissimilar methods, such as with the freely diffusible tracers (trifluoro [133I] iodomethane and iodo [14C] antipyrine autoradiography). Following the induction of hypotension, local cerebral blood flow remained remarkably constant until the mean arterial pressure was decreased to 60-69 mm Hg (fig. 1). At this level, the lower limit of autoregulation, blood flow was 90 ± 3% (mean ± SEM) of base line values, this being a significant decrease (p < 0.05). For ease of analysis, the value of cerebral blood flow at the mean arterial pressure closest to 100 mm Hg was expressed as 100% in each electrode. Changes in blood flow recorded from each electrode were then calculated as a percentage of the appropriate reference value. The blood flow results were combined in 10 mm Hg arterial pressure bins (for instance, 50-59 and 60-69 mm Hg), and Student's t-test was used for statistical comparisons. At mean arterial pressures below the lower limit of autoregulation, cerebral blood flow decreased with decreasing perfusion pressure.

The scatter of the individual observations is demonstrated in fig. 2. Zero blood flow was observed in 12 electrodes at arterial pressures ranging from 18 to 59 mm Hg. A 50% decrease in cerebral blood flow

![Figure 1](http://stroke.ahajournals.org/)  
*Figure 1. The relationship between cortical blood flow (CBF) and mean arterial pressure (MABP) in 8 cats subjected to hemorrhagic hypotension. CBF was calculated from the initial slope of the hydrogen clearance curves and the values are presented as a percentage of the value in the arterial pressure range 100-109 mm Hg in each animal. Each point represents mean ± SEM of the blood flow value in a 10 mm Hg arterial pressure range, and the curve was fitted by hand.*
which would normally be considered a critical reduction — was observed at mean arterial pressures that ranged from 24 to 65 mm Hg. At mean arterial pressures of 35 mm Hg, the average value for local cerebral blood flow was 28 ml/100g min (51% of base line); at mean arterial pressures of 25 mm Hg, the average value for local cerebral blood flow was approximately 9.5 ml/100g min (14% of base line). These 2 levels of arterial pressure (35 and 25 mm Hg) were used in a later study in which the evolution of ischemic cell changes was examined.

The calculated fast and slow components of the hydrogen clearance curves are presented in figs. 3 and 4 respectively. There were no significant differences between the shape of the autoregulatory curves in the 2 components. As with the autoregulatory curve calculated from the initial slope index, both fast and slow flows displayed little change with decreasing arterial pressure until values of ~65 mm Hg. Thereafter, blood flow decreased with decreasing perfusion pressure.

Pial Arteriolar Caliber

The caliber of pial arterioles and arteries increased as arterial pressure was decreased. As the absolute diameter of the vessels in this study ranged from 23 to 221 μm at a reference pressure of 100 mm Hg, they were separated into 2 groups (<50 μm and >50 μm in reference diameter) to facilitate analysis. The changes in the 12 smaller arterioles (<50 μm in reference diameter) are presented in fig. 5. The smaller arterioles increased progressively in size and reached their maximum caliber (+93 ± 7%, mean ± SEM) in

**Figure 2.** Scatter diagram, based on the data presented in Fig. 1.

![Figure 2](image)

**Figure 3.** The relationship between the fast component of cortical blood flow (CBF) and mean arterial pressure (MAP) in 8 cats subjected to hemorrhagic hypotension. (See Fig. 1.)

![Figure 3](image)

**Figure 4.** The relationship between the slow component of cortical blood flow (CBF) and mean arterial pressure (MAP) in 8 cats subjected to hemorrhagic hypotension. (See Fig. 1.)

![Figure 4](image)
Arteriolar Calibre (percent change)

-100 - 0 0 10 20 30 40 50 60 70 80 90 100

M A P (m m H g)

Figure 6. The relationship between pial arteriolar caliber and mean arterial blood pressure (MAP) in 5 cats subjected to hemorrhagic hypotension. At mean arterial pressures in the range 100–109 mm Hg, the base line diameters of the 13 vessels studied were all greater than 50 μm. (See Fig. 1).

Figure 5. The relationship between pial arteriolar and small arterial calibers and mean arterial pressure (MAP) in 5 cats subjected to hemorrhagic hypotension. At mean arterial pressures in the range 100–109 mm Hg, the base line diameters of the 12 vessels studied were all greater than 50 μm. (See Fig. 1).

The arterial pressure range 30–39 mm Hg. Vessel caliber then decreased rapidly and markedly as the pressure was lowered below the level at which maximum dilatation was observed. On a number of occasions complete collapse of the small arteriolar vessels was noted, especially at mean arterial pressures below 20 mm Hg. Although not the subject of detailed analysis, total collapse of some or all of the pial veins was noted at pressures greater than those at which pial arteriolar or arterial collapse occurred. The complete closure of vessels tended to be a generalized, rather than focal, cortical phenomenon.

Alterations in the caliber of the 13 pial vessels >50 μm in reference diameter are shown in fig. 6. The maximum dilatation attained by the larger arterioles and small cortical arteries (56 ± 9%, mean ± SEM) was less than that of the smaller arterioles (p < 0.01), but the maximum dilatation occurred in the same range of arterial pressure (30–39 mm Hg).

When the maximum dilatation of each of the 25 pial vessels studied was compared to their reference caliber at a mean arterial pressure of 100 mm Hg, then an exponential relationship was noted (fig. 7). The data

Maximal Dilatation (percent base line)

-150 -100 -50 0 50 100 150

Resting Calibre (μm)

Figure 7. The dependency of the pial arteriolar response to induced hypotension on the resting vascular diameter. The data are based on 25 arterioles and small arteries from 5 cats. The correlation coefficient (r = 0.82) has a probability value <0.001 for the exponential regression.
fitted an exponential regression of the following general form:

\[ y = A - B \log x, \]

where \( y \) = maximal percent increase in caliber/100, \( x \) = reference vessel caliber in \( \mu m \), \( A = 2.497 \) and \( B = 0.428 \). The correlation coefficient of the regression (\( r = 0.8165 \)) had a probability value of <0.001.

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\begin{align*}
\text{Discussion} \\
\text{Many of the methodological factors have been considered already in the results section. However, a few others should be discussed here. The fact that the vast majority of cortical electrodes displayed biexponential clearances implies that the hydrogen electrodes were responsive to tissue perfusion over a fairly large volume of tissue: the slow clearing component of the washout was, in all probability, due to changes in hydrogen concentration in the subcortical white matter. With regard to the measurement of pial vessel caliber, one point merits discussion. In the course of measuring the caliber of pial arterioles during extreme hypotension, and especially at the point at which these vessels collapsed completely, it became apparent that the image-splitting technique was measuring the internal caliber of the pial arterioles under the conditions of illumination present in this study, i.e. we were really measuring the diameter of the red blood cell column within the arterioles. Thus, should the diameter of the red blood cell column deviate from the internal diameter then there will be a systematic error in the calculation of pial vessel caliber. We calculate that this deviation caused us to underestimate the true internal vessel diameter by approximately 5%,}^{12}
\end{align*}
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Cerebral Blood Flow

The lower limit of autoregulation of cerebral blood flow (arterial pressure, 60–69 mm Hg) identified in the present study correlates well with other published studies: in dogs, using \(^{85}Krypton clearance,^{13}\) or angiographic circulation time;\(^{14}\) and in primates, using \(^{133}Xenon clearance,^{15,16}\) or hydrogen,\(^{17}\) or \(H_2^{18}O^{18}\). Zero blood flow was observed frequently at extreme levels of hypotension, a finding that is in contrast to that of Symon et al.\(^{17}\) who noted zero blood flow in white matter only, at comparable levels of hemorrhagic hypotension. One possible reason for this discrepancy is that many of our electrodes were placed in the general region of the arterial boundary zone between the common pericallosal and middle cerebral arteries of the cat.\(^{9}\) Based on many neuropathological studies,\(^{19,20}\) it has been postulated that the arterial boundary zones are the sites of selective hypoperfusion in severe hypotension, and there is limited direct evidence which might support this postulate.\(^{21}\) Accordingly, it is quite possible that the high frequency of zero blood flow observations in the present study could be ascribed to the placement of electrodes in the arterial boundary zones. However, our electrodes were inserted in the crests of gyri, whereas boundary zone infarcts are found mainly in the depths of sul-

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\begin{align*}
\text{Pial Arteriolar Caliber} \\
\text{The classical studies of Fog}^{22,23}\text{ demonstrated that the pial resistance vessels dilate and constrict in response to a decrease and increase in arterial pressure respectively. Our current investigation extends previous investigations}^{22-24}\text{ in 2 areas: by establishing that smaller arterioles are more reactive than larger arterioles and small arteries and that pial vessels continue to dilate below the lower limit of autoregulation.} \\
\text{In most peripheral tissues it is known that the primary vascular resistance is located in the precapillary sphincters and arterioles (for review, see Folkow and Neil}\text{25), and the cerebral circulation would appear to be no exception to this rule.}\text{26 There is a marked increase in the wall/lumen ratio of pial arterioles with an external diameter less than 60 \(\mu m\), when compared to larger arterioles and arteries.}\text{27 This observation would again implicate the smaller (parenchymal as well as pial) arterioles as being the principal resistance element within the cerebral circulation, particularly since vessels <50 \(\mu m\) in reference caliber showed the most marked responses to induced hemorrhagic hypotension; and it is these same pial arterioles that respond most markedly to angiotensin-induced hypertension}\text{28} \text{and to the perivascular application of a vasodilator agent, 5-hydroxytryptamine.}^{29,30} \\
\text{Another factor which might account, at least partially, for the lesser reactivity of the larger cerebral vessels to induced hemorrhagic hypotension, is the 'dual effects' hypothesis.}^{30}\text{This hypothesis, put simply, states that the larger cerebral vessels are more likely to be affected by neurogenic mechanisms, whereas the smaller vessels are more responsive to the metabolic demands of, and autoregulatory demands on, cerebral tissue. This postulate is supported by angiographic studies which have shown that there is a constriction, and not an autoregulatory dilatation, of the large cerebral arteries during hemorrhagic hypotension.}^{31}\text{In preliminary studies — not presented here — we have noted that the administration of the \(\alpha\)-adrenergic blocking agent, phenoxybenzamine (1.5 mg/kg, i.v.), will dilate cerebral vessels further when given at an}
\end{align*}
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716 STROKE VOL 10, No 6, NOVEMBER-DECEMBER 1979
arterial pressure of 40 mm Hg. Arterial pressure was maintained constant by transfusion following the administration of phenoxybenzamine which effected a most marked vasodilatation, albeit superimposed on the dilatation induced by the hemorrhagic hypotension. Thus, the sympathetic discharge which accompanies hemorrhagic hypotension would appear to limit the pial vascular response to low perfusion pressures, as postulated previously. However, a phenoxybenzamine-induced vasodilatation was observed in both large and small vessels. Although there is a greater number of adrenergic nerves around the larger cerebral vessels, which respond more markedly to the stimulation of the superior cervical trunk, it has been aptly pointed out that the functional effects of neurotransmitter release may be just as great in the smaller pial vessels which have simply less vascular smooth muscle to innervate.

Following submission of the present manuscript, a major study has appeared in which the responses of the pial vessels to hypotension — induced by a variety of maneuvers — were examined. One other apparent difference between that study and the present report is that Kontos et al. examined the vessels through a cranial window under which mock cerebrospinal fluid was perfused into the subdural space. The results of both studies are in close agreement, with the exception that Kontos and his associates were unable to note any dilatation of the smaller vessels to moderate hypotension; when pressure was reduced from resting levels to 90 mm Hg. We have since re-examined this point by inducing very moderate hypotension (via the partial inflation of a balloon catheter in the inferior vena cava) and, at the same time, measuring the responses of pial arterioles with a resting caliber <50 μm. Autoregulatory responses of the arterioles were invariably seen. Following the induction of hypotension (to mean arterial pressures never less than 90 mm Hg) the arterioles dilated, although an initial stage of constriction (or collapse) was seen sometimes. Our results are, therefore, in accord with those of Fog, who used a cranial window technique, and the reason for the discrepancy between Kontos and his co-workers and Fog and ourselves remains unresolved.

In the current investigation, the lower limit of autoregulation occurred at a significantly higher mean arterial pressure (~65 mm Hg) than the arterial pressure at which the pial vessels were maximally dilated (~35 mm Hg). Thus, the lower limit of autoregulation should not be equated with maximal dilatation of the cerebral vessels. One criticism of this statement might be that cerebral blood flow was measured in a closed-skull situation; and it is possible that changes in intracranial pressure in the former situation would affect overall cerebral perfusion pressure, so explaining the discrepancy between the lower limit of autoregulation and the maximal vascular dilatation. However, intracranial pressure falls from ~6 to 0 mm Hg during hemorrhagic hypotension in anesthetized cats (Farrar, unpublished observations). Furthermore, we have investigated pial arteriolar caliber and local cerebral blood flow simultaneously in 2 additional animals, and in both cats found that the lower limit of autoregulation was approximately 30 mm Hg greater than the pressure at which maximal pial vasodilatation occurred.

We would suggest that the lower limit of autoregulation is reached when the dilatation of the cerebral resistance vessels becomes inadequate (as opposed to maximal) to compensate for further decreases in arterial pressure.

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