Cerebral arterial responses to induced hypertension following subarachnoid hemorrhage in the monkey

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Regional cerebral blood flow (rCBF), angiographic cerebral arterial caliber, and cerebrospinal fluid (CSF) pressure were measured in rhesus monkeys to determine the effect of experimentally induced subarachnoid hemorrhage (SAH) on cerebral arterial responses to graded increases in blood pressure. These measurements were also performed in a control group of monkeys subjected to a mock SAH by injection of artificial CSF into the cerebral space.

Before subarachnoid injection of blood or artificial CSF, graded increases in mean arterial blood pressure (MABP) to a level 40% to 50% above baseline values had no effect on rCBF. The major cerebral arteries constricted and CSF pressure remained unchanged. Similar responses were observed after injection of artificial CSF. When MABP was increased in animals that had been subjected to subarachnoid injection of blood, rCBF increased and was associated with dilatation of the major cerebral arteries and moderate increases in CSF pressure. These results demonstrate that cerebral arterial responses to increases in blood pressure may be abnormal in the presence of subarachnoid blood. The manner in which abnormal cerebral arterial reactivity, changes in blood pressure, and vasospasm combine to determine the level of cerebral perfusion following SAH is postulated.

KEY WORDS • subarachnoid hemorrhage • cerebral arterial reactivity • hypertension • rhesus monkey

Cerebral vasospasm and increased intracranial pressure (ICP) are frequently observed in patients with subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm. However, the conditions under which these factors contribute to the development of post-SAH cerebral ischemia have not been elucidated.

Angiographically demonstrated spasm of the major cerebral arteries appears to be more frequent and severe in SAH patients with poor neurological status. Such observations, usually derived from retrospective analyses of patient data, form the basis for the widely held view that vasospasm produces cerebral ischemia. It is well known, however, that patients can have marked vasospasm without concurrent neurological deficit or significant reduction in cerebral blood flow (CBF). Thus, the ischemic potential of cerebral vasospasm appears to depend on other factors. In particular, the ability of cerebral arteries distal to the constricted area to react in a compensatory fashion by dilatation may be important. This ability presumably depends on the status of cerebral arterial reactivity (commonly termed "autoregulation") to changes in local
and systemic cerebral perfusion pressure. Normally, autoregulatory constriction or dilatation of the cerebral arteries maintains CBF at normal levels over a wide range of arterial or intracranial pressures. When autoregulation is impaired, CBF tends to vary passively with changes in ICP or blood pressure.

These considerations indicate that the nature of cerebral arterial responses to changes in systemic or local perfusion pressure may have considerable importance in determining post-SAH cerebral perfusion. The results of previous laboratory investigations, although variable, indicate that SAH causes impairment of CBF autoregulation. The present study was undertaken to further investigate the effect of experimentally induced SAH on CBF autoregulation and arterial caliber responses to increases in blood pressure.

**Materials and Methods**

**Animal Preparation**

The experiments were performed on 17 female rhesus (Macaca mulatta) monkeys weighing 2.2 to 4.3 kg. Sedation for the surgery was achieved with intravenous sodium pentothal (25 to 30 mg/kg). The animals were intubated and ventilated with a 2:1 nitrous oxide-oxygen mixture. Paralysis was induced with intravenous tubocurarine and maintained with additional supplements as required.

Body temperature was continuously monitored by an esophageal thermometer, and maintained at 36° to 38° C by a small heating pad under the animal. Standard lead electrocardiography was performed in all animals. A femoral vein and artery were catheterized to administer drugs and measure arterial pressure. Arterial pCO₂ and pO₂ were measured during each determination of CBF. Hematocrit determinations, used for CBF calculation, were carried out frequently in the course of each experiment. In some animals, cerebrospinal fluid (CSF) pressure was continuously monitored from a needle positioned in the lumbar subarachnoid space. The pressure transducers were calibrated against a mercury manometer before each experiment.

A cranial twist-drill hole was made approximately 1.0 cm dorsal to the nasion. Hemostasis was achieved with bone wax and the defect was sealed until the time of subarachnoid injection. With the aid of an operating microscope, the external carotid artery was isolated and doubly ligated immediately distal to the origin of the external maxillary artery. The external maxillary artery was then carefully dissected from surrounding tissues, distally ligated, and catheterized with a No. 21 polyethylene catheter, so that the tip was positioned in the internal carotid artery.

**Cerebral Blood Flow Measurements**

Regional cerebral blood flow (rCBF) was measured by the intraarterial technique. An automatic injector device was used to inject 2.5 to 3.5 mCi of xenon-133 (¹³³Xe) into the internal carotid artery. The design, operating characteristics, and in vivo testing of this injector system are described in detail elsewhere.

Regional clearance of ¹³³Xe was measured with a collimated assembly of six scintillation detectors (NaI-thallium activated). Four of the detectors recorded the radioactivity from the supratentorial regions (frontal, parietal, occipital, and temporal), while the other two detectors were positioned over the orbito-maxillary and cerebellar regions.

Cerebral blood flow values were calculated using the height/area and initial-slope-index methods. Although all flow values were corrected to a PaCO₂ of 40 mm Hg, care was taken to maintain PaCO₂ values near 40 mm Hg, particularly during the posthemorrhage period. In the four supratentorial regions CBF values were always found to change in a similar manner. Therefore, the mean flow values derived by averaging these four regions were used in the statistical analysis.

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*Tele-Thermometer manufactured by the Yellow Springs Instrument Co., Yellow Springs, Ohio.
†Dynograph (Type R) recorder manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California.
‡IL pH/gas analyzer manufactured by Instrumentation Laboratory, Inc., 113 Hartwell Avenue, Lexington, Massachusetts.
§Statham P23db pressure transducers manufactured by Statham Instruments, 2230 Statham Boulevard, Oxnard, California.
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Cerebral Arterial Caliber

The technique used for obtaining caliber measurements of the major cerebral arteries from angiograms has previously been described. Briefly, four arteries were measured: intradural internal carotid (ICA), middle cerebral, proximal pericallosal, and distal pericallosal arteries. Of the two to three films obtained from each angiographical sitting, the one showing the arterial phase most distinctly was selected for measurement. Comparison of arterial calibers in 30 pairs of films revealed no difference between measurements obtained from the first or second film, taken approximately 3 minutes apart.

Subarachnoid Injection

Immediately before subarachnoid injection, a circumferentially bevelled No. 19 spinal needle was carefully inserted (under fluoroscopy) into the chiasmatic cistern via the frontal twist-drill hole. Adequate placement of the needle was confirmed with return of CSF. The needle was then secured to the skull by a screw device.

Subarachnoid hemorrhage was induced by manual injection of 4 ml of fresh autogenous blood over a period of approximately 25 seconds. In a control group of animals, a mock SAH (MSAH) was induced by the same procedure, using artificial CSF at pH 7.35 and temperature 37°C.

Experimental Design

Regional CBF autoregulatory responses to increases in mean arterial blood pressure (MABP) were determined in 17 monkeys during the prehemorrhage period. Increases in MABP were made in steps of 10 to 15 mm Hg by slow intravenous infusion of Aramine (metaraminol bitartrate), and a CBF measurement was done at each blood pressure level. A minimum of 5 minutes was allowed for stabilization of the cerebrovascular response to an increase in MABP before a flow measurement was carried out. Following completion of prehemorrhage testing of rCBF autoregulation, angiography was performed at normotension and, within 10 to 15 minutes, during induced hypertension.

The monkeys were allowed to recover from the anesthetic for 2 to 3 hours, at which time a neurological examination was performed. A five-division neurological grading system was used for evaluation of the animals (Grade I = normal, Grade V = moribund). They were then injected with a lethal dose of sodium pentobarbital, and the brains were removed for gross pathological examination.

Results

A total of 151 rCBF measurements were made in the 17 monkeys. Of these, 89 were prehemorrhage, 57 post-SAH, and 25 post-MSAH. The PaCO2 values (mean ± SD) during the flow measurements were 40.3 ± 2.9 mm Hg (pre-SAH), 37.9 ± 5.9 mm Hg (post-SAH), 40.7 ± 3.8 mm Hg (pre-MSAH), and 38.0 ± 4.0 mm Hg (post-MSAH). Baseline MABP for the 17 animals was 111 ± 6 mm Hg.

Cerebrospinal Fluid Pressure

Lumbar CSF pressure was measured in six animals subjected to SAH and in three animals subjected to MSAH. During the prehemorrhage period, CSF pressure was 7.9 ± 3.7 mm Hg for the SAH group and 8.7 ± 1.9 mm Hg for the MSAH group. No effect of increased MABP on CSF pressure was noted during prehemorrhage testing of rCBF autoregulation.

Cerebrospinal fluid pressure increased rapidly during subarachnoid injection of blood or artificial CSF, the peak pressure occurring 20 to 30 seconds after beginning injection. When CSF pressure approached MABP levels, the MABP increased and in some animals was associated with transient (2 to 3 minutes) bradycardia and electrocardiographic changes. Sinus arrhythmias, premature ventricular contractions, increased T-wave amplitude, and S-T elevations were noted. The maximum CSF pressure occurring with subarachnoid injection of 4 ml of artificial CSF or blood was 138 ± 9 mm Hg and 141 ± 58 mm Hg, respectively. The CSF pressure never exceeded MABP.
FIG. 1. Post-subarachnoid hemorrhage (post-SAH) relationship between cerebrospinal fluid pressure (CSFP) and mean arterial blood pressure (MaBP). The equation for the regression line shown is: CSF pressure = 0.73 + 0.13 MaBP.

The MABP returned to normotensive levels within 3 to 5 minutes after injection. Similarly, CSF pressure returned to the prehemorrhage level in the MSAH group. In contrast, CSF pressure was 18.4 ± 5.1 mm Hg in the post-SAH group (p < 0.01, unpaired t-test). This elevation in CSF pressure appeared to be partly due to moderate increases which occurred when MABP was elevated to test autoregulation; therefore, linear regression analysis of the post-SAH relationship between CSF pressure and MABP was done (Fig. 1). The slope of the regression line was significantly different from zero (p < 0.01, covariance analysis), thus confirming that CSF pressure increased with increases in MABP.

Cerebral Blood Flow Autoregulation

In general, the maximum induced increase in MABP for testing autoregulations was 40 to 50 mm Hg. The regional effects of a 25% MABP increase on CBF are shown for one animal in Table 1. When tested before SAH, flow remained relatively constant in all regions. After SAH, flow was markedly increased in all regions by a similar increase in MABP, thus demonstrating globally impaired autoregulation.

The results of linear regression analysis of the pre- and posthemorrhage group data are shown in Fig. 2. Values for CBF representing the mean of the four supratentorial regions measured were used for this analysis, and comparisons of the regression lines were performed using covariance analysis. The regression line slope of the prehemorrhage data is positive but not significantly different from zero (p > 0.05). This regression line was subsequently used as an index of normal CBF autoregulation and compared to the results obtained from regression analysis of the posthemorrhage data.

No significant difference was found between the slope of the post-MSAH regression line and the slope of the prehemorrhage

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TABLE 1

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<thead>
<tr>
<th>MABP (mm Hg)</th>
<th>rCBF (ml/100 gm/min)</th>
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<tr>
<td></td>
<td>Frontal</td>
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<tr>
<td>pre-SAH</td>
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<td>121</td>
<td>33</td>
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<td>151</td>
<td>35</td>
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<tr>
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<td>120</td>
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<td>150</td>
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![Graph showing linear regression lines](image)

**Fig. 2.** Linear regression lines showing the relationship between cerebral blood flow (CBF) (mean hemispheric blood flow, initial-slope-index method) and mean arterial pressure (MaBP). The regression equations are: Pre-hem·CBF = 36.8 + 0.05 MABP; SAH·CBF = 11.1 + 0.23 MABP; MSAH·CBF = 32.9 + 0.06 MABP.

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Thus, CBF autoregulatory responses were still normal following subarachnoid injection of artificial CSF. In contrast, subarachnoid injection of blood resulted in impairment of autoregulation as evidenced by the significant (p < 0.01) increase in the slope of the regression line for this group.

### Arterial Caliber

The same methods of analysis employed for the CBF data were applied to assess the relationship between cerebral caliber and MABP. Only data obtained from measurements of the intradural ICA were used. Since the intradural ICA was the artery most consistently well visualized on lateral angiograms, measurements at this site provided the most accurate assessment of cerebral arterial caliber responses to changes in MABP. Satisfactory angiograms were obtained at different MABP levels in 13 animals during the prehemorrhage period, in eight animals following SAH, and in four animals following MSAH.

Figure 3 shows that, when tested during the prehemorrhage period, the intradural ICA constricted in response to increases in MABP. This response was unchanged following MSAH. The regression lines for both cases have a negative slope and are not significantly different. However, the response of the intradural ICA to an increase in MABP in the post-SAH animals was an increase in caliber, as shown by the positive slope of the post-SAH regression line, which was significantly different (p < 0.05) from the slope of the prehemorrhage line.

### Neurological Assessment

Of the 12 animals with SAH, four were classed as Grade II, four as Grade III, three as Grade IV, and one as Grade V. There was no clear relationship between neurological grade and degree of CBF autoregulation impairment following SAH. Mean regression line slope values for Grade II, III, and IV animals were 0.33, 0.35, and 0.30, respectively. The animal classed as Grade V had a post-SAH regression line slope of 0.13.

Two animals with MSAH were classed as Grade I, two as Grade II, and one, Grade V. There was no apparent cause found at post-mortem examination for the poor status of the Grade V animal. In general, the animals with MSAH fared better than those with SAH; however, some of the SAH animals were still improving at the time of sacrifice.

The 12 SAH animals in this study had pure SAH with blood extending throughout the basal cisterns and over most of the cortical surfaces. Two animals that had large subdural components of the hemorrhage were excluded from the study. No blood was found in
FIG. 3. Linear regression lines showing the relationship between vessel caliber (VC) of the intradural internal carotid artery and mean arterial blood pressure (MaBP). The regression equations are: Pre-hem-VC = 1.361 - 0.0018 MABP; SAH-VC = 0.679 + 0.0013 MABP; MSAH-VC = 1.381 - 0.0018 MABP.

the subarachnoid space of the animals injected with artificial CSF.

Discussion

The animals used in the present study demonstrated efficient prehemorrhage autoregulatory responses that maintained cerebral perfusion relatively constant in the presence of moderate increases in blood pressure. Furthermore, these increases in MABP produced vasoconstriction of the large cerebral arteries and were without effect on CSF pressure. Therefore, the cerebral arterial responses obtained before subarachnoid injection of blood or artificial CSF were unimpaired by the experimental preparation.

Subarachnoid hemorrhage was induced over a short period of time and resulted in CSF pressure increases similar to those reported in patients experiencing an SAH. After subarachnoid injection of blood, CSF pressure remained elevated at normotension, and when MABP was subsequently increased to test CBF autoregulation, concurrent further increase in CSF pressure occurred. There is experimental evidence to indicate that, when total "vasomotor paralysis" has developed, a completely passive relationship exists between ICP and MABP, and large increases in ICP result from moderate increases in MABP. The factors responsible for the increase in ICP appear to be acute cerebral edema and passive dilatation of cerebral vessels. In the present study, measurements of cerebral arterial caliber demonstrated that arterial dilatation occurred in response to increases in MABP after SAH, indicating that increased vascular volume was at least partly responsible for the elevation in ICP.

Increases in CSF pressure with elevation of MABP will tend to prevent an increase in CBF and may lead to an underestimation of the degree of autoregulatory impairment when MABP is used as an index of cerebral perfusion pressure. It is evident that this occurred to some degree in the present study. However, analysis of the post-SAH relationship between CBF and MABP still revealed significant impairment of CBF autoregulation.

It was considered possible that a subarachnoid injection causing a large transient increase in CSF pressure could of itself cause
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impaired cerebral autoregulatory responses. Therefore, a control group of animals was tested in which artificial CSF was injected into the subarachnoid space. Although these animals exhibited CSF pressure increases similar to those measured for the SAH group, the CBF, arterial caliber, and CSF pressure responses to increased MABP all remained normal. Thus, the changes in cerebral arterial reactivity observed with SAH were not related to an increase in CSF pressure but rather to the presence of blood in the subarachnoid space. Shannon, et al.,22 and Sugi, et al.,28 have reported increases in CSF lactate and pyruvate and decreases in CSF bicarbonate and pH within a few hours after injection of blood into the subarachnoid space in animals. Similar CSF acid-base and metabolic changes have been described in patients with SAH.4,20 Such increases in CSF acid metabolites occur following ischemia or hypoxia and are considered to be responsible for impairment of CBF autoregulation.15,26 However, experimental evidence indicates that similar increases in CSF acidity can originate from glucose metabolism of blood cells in CSF and presumably also lead to impaired autoregulation.3,22

The abnormal cerebrovascular responses observed following SAH in the present study are in agreement with recent clinical observations in patients with SAH. Hayashi, et al.,8 observed intracranial “pressure waves” that were related to periodic breathing of the Cheyne-Stokes type and variations in arterial pressure. The results of other investigations indicate that such repeated elevations in ICP may eventually lead to complete “vasomotor paralysis” and severe sustained intracranial hypertension. Indeed, the authors found that the more seriously ill patients demonstrated ICP levels in excess of 1000 mm H2O and total loss of normal cerebrovascular reactivity. Similarly, Sakurai, et al.,18 in testing CBF autoregulation and response to hypercapnia in patients with SAH, found a close relationship between degree of impaired reactivity and neurological condition.

The precise conditions under which cerebral vasospasm contributes to the development of cerebral ischemia have not been elucidated. Martins, et al.,13 have suggested that the interplay of many factors, including vasospasm, brain edema, and impaired autoregulation determines cerebral perfusion after SAH. Similarly, our results support the concept that the effect of vasospasm on CBF will depend in large measure on the status of autoregulation, ICP, and systemic blood pressure. However, the manner in which vasospasm and these factors are related in determining cerebral perfusion can only be postulated.

With normal reactivity and perfusion pressure, distal compensatory vasodilation can maintain normal CBF even in the presence of severe arterial constriction. Further dilatation to compensate for a fall in perfusion pressure, however, is impaired.21 Thus, a precarious state of “compensated vasospasm” may develop in SAH patients, and ischemia may be precipitated by systemic hypotension or increased ICP. On the other hand, the occurrence of severe vasospasm in a non-regulating vascular bed may produce ischemia directly due to lack of distal compensatory dilatation. Again, the ischemic potential of the vasospasm under these conditions is enhanced when associated with increased ICP or decreased MABP. It is evident that, even without vasospasm, the combination of severely impaired cerebrovascular reactivity and a fall in perfusion pressure can produce critically low levels of CBF.

These relationships indicate the importance of MABP and ICP in determining cerebral perfusion in patients with SAH and impaired autoregulation, whether or not significant vasospasm has developed. Moreover, they suggest that increases in blood pressure may improve cerebral perfusion, particularly in patients who develop hypotension and/or vasospasm. This concept is supported by recent studies in which induced hypertension produced recovery of neurological function and increased CBF in patients showing neurological deterioration after undergoing successful aneurysm surgery.8,10 It must be emphasized, however, that there is a potential danger to the brain from repeated or sustained increases in blood pressure if this results in severe concurrent increases in ICP. Therefore, careful monitoring and control of ICP, as well as MABP, is important in the management of these patients.

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