Cerebrovascular reactivity in patients with ruptured intracranial aneurysms

BO VOLDBY, M.D., ERNA M. ENEVOLDSEN, M.D., AND FINN T. JENSEN, M.Sc.

University Departments of Neurosurgery and Nuclear Medicine, Aarhus Kommunehospital, Aarhus, Denmark

The cerebral vasomotor reactivity to arterial hypotension and hypocapnia was studied in 34 patients between the 3rd and 13th day after rupture of an intracranial saccular aneurysm. Using the intra-arterial xenon-133 injection method, regional cerebral blood flow (rCBF) and cerebral metabolic rate of oxygen (CMRO2) were measured. The intraventricular pressure and cerebrospinal fluid (CSF) lactate and pH levels were determined. The degree of vasospasm was measured on angiograms taken immediately following the rCBF study. The patients were graded clinically according to the system of Hunt and Hess.

Cerebral autoregulation was intact in patients in good clinical condition, but was impaired in patients in poor clinical condition. There was a close correlation between the degree of vasospasm and the degree of autoregulatory impairment, which varied from focal disturbances to global impairment. Intracranial hypertension and CSF lactic acidosis were commonly found in association with vasoparalysis. Cerebrovascular response to hyperventilation was generally preserved, although often reduced. During hyperventilation, the cerebral perfusion pressure became elevated, and increases in CMRO2 were often found, even in patients with severe diffuse spasm and cerebral ischemia. The clinical significance of the results in relation to the treatment of delayed cerebral ischemia and to the use of intraoperative induced hypotension is discussed.

KEY WORDS • subarachnoid hemorrhage • cerebral aneurysm • vasospasm • autoregulation • CO2 reactivity

During the first 2 weeks after a subarachnoid hemorrhage (SAH) from an intracranial saccular aneurysm, several events may make heavy demands on the capability of the cerebral vasculature to react adequately. Cerebral arterial spasm and recurrent hemorrhage occurring within the same period, surgical repair of the ruptured aneurysm is usually performed. In patients in a poor clinical state, attempts have been directed at treating delayed cerebral ischemia with induced arterial hypertension and vasodilating agents. A better knowledge of the reactivity and autoregulatory capacity of the damaged cerebral circulation would be of clinical importance under such circumstances.

Experimental studies have shown that, during the initial bleed, cerebral autoregulation is operating. Both autoregulation and CO2 response are impaired in the acute stage of SAH. Some authors found both variables still impaired about 1 week later, while others demonstrated that animals in neurological Grades I and II (classification of Hunt and Hess) had better recovery of autoregulation and CO2 reactivity than those in Grades III and IV. A few human studies have suggested a correlation between defective cerebrovascular reactivity and cerebral vasospasm and raised intracranial pressure.

We have previously reported that regional cerebral blood flow (rCBF) and cerebral metabolic rate of oxygen (CMRO2) are decreased following SAH, and that this decrease correlates with the degree of angiographic vasospasm. In the present study, we have investigated the cerebral autoregulation and the CO2 reactivity in patients with recent SAH, with special reference to cerebral vasospasm.

Clinical Material and Methods

Patient Population

A detailed description of material and methodology has been given in a companion paper and will only be summarized here. The series comprised 38 patients (22 women and 16 men) with SAH from a ruptured saccular intracranial aneurysm. They ranged in age between 27 and 65 years (mean 49 years). All patients were admitted during the acute phase, and the diagnosis...
was confirmed by lumbar puncture or computerized tomography (CT) scanning, followed by cerebral angiography. Patients with intracerebral hematomas and cerebral arteriosclerosis were excluded from this series. The clinical state of the patients was graded according to the system of Hunt and Hess. 10 Surgical repair of the aneurysm was performed in 25 patients (65%) within 3 weeks of the initial SAH. Follow-up examination, including CT scanning, was carried out in all 21 surviving patients 1 to 2 years later. Fourteen recovered and seven remained disabled. Seventeen patients (45%) died, and autopsy was performed in all but two.

Measurement of Regional Cerebral Blood Flow

The rCBF study was performed between Days 3 and 13 (mean Day 7) after SAH, and only if an indication for angiography was present on clinical grounds. Informed consent was obtained from the patient or one of his relatives. The xenon-133 ($^{133}$Xe) intra-arterial injection method was used.9 The clearance of $^{133}$Xe from the relevant hemisphere was recorded by 16 external NaJ detectors. The rCBF was calculated using the initial-slope index method.4 22 A total of four rCBF measurements was performed in each patient: an initial resting study, an autoregulation study, a control resting study, and finally a hyperventilation study. Comparing the functional tests with the preceding resting value, a change in rCBF of more than 20% was considered abnormal, and regions were described as abnormal only if changes were present in two or more adjacent channels.

Cerebral autoregulation was tested in a total of 25 patients (11 were in Grade II, 11 in Grade III, and three in Grade IV) by reducing the mean arterial blood pressure (MABP) 10% to 20% for approximately 5 minutes. This was considered to carry minimal risk to the ruptured aneurysm. In the first 16 patients trimethaphan (Arfonad) was infused intravenously, but in the last nine patients we used sodium nitroprusside (Nipride), the short-lasting action of which is more easily controlled. From the outset it was decided not to perform this test in patients with resting rCBF values below the threshold of ischemia (20 ml/100 gm/min); however, the result of hypotension on rCBF in Case 21 (see Fig. 3) made us raise this limit to 25 ml/100 gm/min. Three Grade IV patients were thus excluded (Cases 18, 27, and 54). In six other patients this test was abandoned due to technical (Cases 1, 11, 16, and 29) or medical (Cases 22 and 59) problems.

Cerebrovascular reactivity to hypocapnia was tested by spontaneous hyperventilation for 3 to 5 minutes. In two patients who were on a respirator (Cases 18 and 54) this was done artificially. A hyperventilation test was performed in a total of 29 patients (13 in Grade II, 10 in Grade III, and six in Grade IV). In four patients (Cases 19, 21, 36, and 37) PaCO$_2$ did not decrease due to inability to cooperate. In another patient (Case 9), the study was interrupted as she became stuporous following the infusion of trimethaphan. She gradually regained consciousness in an hour. This was the only complication during the entire study. Due to an extremely low resting rCBF and poor clinical condition, no functional tests were performed in four patients (Cases 45, 48, 53, and 57).

Through heparinized polyethylene catheters placed in the internal carotid artery and internal jugular vein, blood samples were withdrawn immediately before each rCBF run for the determination of pO$_2$, pCO$_2$, O$_2$ saturation, and pH. The CMRO$_2$ was calculated from the arteriovenous difference of oxygen (AVDO$_2$) and the average hemispheric flow (CMRO$_2$ = AVDO$_2$ x mean rCBF/100).

Pressure Measurements

Continuous measurement of the intraventricular pressure (IVP)17 and MABP was carried out during the study, and the cerebral perfusion pressure (CPP) was calculated (CPP = MABP − IVP). Following termination of the rCBF study, 2 ml of CSF was withdrawn from the ventricular catheter for measurement of CSF lactate and pH.32

Angiography

After the last rCBF run, angiography was performed through the carotid catheter. The degree of cerebral arterial spasm was measured on the angiograms:31 a reduction of the arterial caliber of more than 50% was defined as severe vasospasm, while slight vasospasm represented a reduction of 25% to 50%. Severe spasm in one major artery only was called focal.

Results

Cerebral Autoregulation

For this study, patients were separated into three groups: those without vasospasm, those with slight vasospasm, and those with severe vasospasm. Differences in the reductions obtained in MABP of the three patient groups were insignificant (analysis of variance, $p > 0.05$). Changes in PaCO$_2$ during hypotension were small, varying between −2 and +2 mm Hg in the majority of patients. In Cases 8, 37, and 51, however, changes of −4, +3, and −5 mm Hg, respectively, were measured, probably accounting for some of the small rCBF changes observed in these patients. Corrections for changes in PaCO$_2$ have not been performed in the rCBF values in Tables 1, 2, and 3.

In patients without vasospasm (Table 1), autoregulation was normal in all but one (Case 36), in whom a significant global decrease was seen. This patient also had the highest CSF lactate of the group. In addition, this patient had arterial hypertension (MABP 127 mm Hg), which may partly explain the decrease in rCBF as due to a shift of the lower limit of autoregulation.27

Arterial hypertension was demonstrated in one further patient (Case 22) in whom an autoregulation test was not performed as she was treated with three different antihypertensive drugs.
In contradistinction to this, autoregulation was impaired in most patients with slight vasospasm (Table 2). Paradoxical responses with focally increased flow were found in two patients, one of whom developed an infarction in the middle cerebral arterial territory. Focal decreases were found in three patients, but in none of them were infarctions found subsequently on CT scanning. One patient with a high IVP and pronounced CSF lactic acidosis had a global impairment of autoregulation. At follow-up examination, this patient had bilateral frontal infarctions and was incapacitated. Even though the MABP reduction in this patient was inadvertently large (from 130 to 87 mm Hg), MABP did not fall below the normal lower limit of autoregulation.

Autoregulation was defective in all patients with se-

**TABLE 2**

*Cerebrovascular reactivity following SAH*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Clinical Grade†</th>
<th>IVP (mm Hg)</th>
<th>CSF Lactate (mmol/liter)</th>
<th>ΔMABP (%)</th>
<th>Mean rCBF$ (ml/100 gm/min)</th>
<th>Regional Findings</th>
<th>ΔPaCO$_2$ (mm Hg)</th>
<th>Mean rCBF$ (ml/100 gm/min)</th>
<th>Regional Findings</th>
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<td>44/44 normal</td>
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<td>4</td>
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</table>

* Abbreviations: IVP = intraventricular pressure; CSF = cerebrospinal fluid; MABP = mean arterial blood pressure; rCBF = regional cerebral blood flow; SD = standard deviation.
† Clinical grade according to Hunt and Hess.‡ Resting/hypotenotive studies.
§ Resting/hyperventilation studies.
REST FLOW:
Mean rCBF 40
AVDO2 4.39
CMRO2 1.76
MABP 100
IVP 7
PaCO2 32

HYPOTENSION:
Mean rCBF 45
AVDO2 4.82
CMRO2 2.17
MABP 92
IVP 4
PaCO2 32

FIG. 1. Case 10. This 46-year-old woman had a right middle cerebral artery (MCA) aneurysm. Angiography on Day 1 showed no vasospasm. A resting study on Day 4 was normal, but during hypotension paradoxical flow increases were seen (shaded regions). Angiography now revealed slight diffuse vasospasm. During operation on Day 10 the brain was edematous and the vessels were spastic. The patient died 2 days later from intracranial hypertension. Autopsy showed large infarction of the right MCA territory. Abbreviations are defined in Fig. 1.

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REST FLOW:
Mean rCBF 41
AVDO2 4.90
CMRO2 2.01
MABP 157
IVP 22
PaCO2 36

HYPOTENSION:
Mean rCBF 40
AVDO2 2.57
CMRO2 1.41
MABP 141
IVP 22
PaCO2 35

FIG. 2. Case 46. This 46-year-old man had a left middle cerebral artery (MCA) aneurysm. Angiography on Day 2 showed no vasospasm. A resting study on Day 7 showed regions of both relatively high and low perfusion. During hypotension, focal flow decreases were seen (shaded regions). Angiography now revealed severe spasm of the left MCA, and aphasia subsequently developed. An operation was performed on Day 26 without incident. Two years postoperatively the patient was incapacitated by aphasia and intellectual impairment. Infarction was seen in left temporal region on computed tomography scanning. Abbreviations are defined in Fig. 1.

vere vasospasm who were tested (Table 3). In cases with severe focal spasm, regional decreases of rCBF were found in the territory of the spastic arteries corresponding to infarctions demonstrated on follow-up CT scans (Fig. 2). In all three cases of severe diffuse spasm tested, autoregulation was globally impaired (Fig. 3). High IVP and CSF lactic acidosis were prominent features in this group, but it is noteworthy that normal lactate values were also found (Cases 15 and 19).

The effect of induced arterial hypotension on cerebral metabolism was studied in 19 patients (Fig. 4). Generally, small reductions in rCBF were counteracted by small increases in AVDO2, ensuring a constant CMRO2. This tendency was influenced by impairment of autoregulation in only one patient with severe diffuse vasospasm (Case 19), in whom AVDO2 decreased from 2.63 to 0.87 ml%.

CO2 Reactivity
As seen from Tables 1, 2, and 3, there were no significant differences in mean PaCO2 reduction among the three groups of patients (p > 0.05). A PaCO2 reduction of between 6% and 1.00%/mm Hg of PaCO2 reduction (2.55% ± 0.8%). Reductions below 2.00% were seen in only one patient with slight vasospasm (Case 59), in two patients with severe focal spasm (Cases 32 and 56, Fig. 5), and in all four patients with severe diffuse spasm. Regional disturbances during hyperventilation were only found in one patient (Case 15). Impairment of CO2 reactivity was always associated with an increased IVP and/or increased CSF lactate.

Hyperventilation had a beneficial effect on IVP, which was reduced from 1 to 31 mm Hg (8 ± 6 mm Hg, Fig. 6). As MABP in the majority of patients decreased concomitantly with IVP but to a lesser degree, and in a few patients even increased, the net result was an increase in CPP of between 2 and 22 mm Hg (7 ± 5 mm Hg). A fall in CPP of more than 10 mm Hg was seen in a few patients (Cases 11, 22, and 44) due to a marked fall in MABP. In patients with impaired autoregulation, an induced MABP fall may result in a decrease in rCBF, and an impaired CO2 response would, under such circumstances, be overlooked or underestimated. In two patients (Cases 6 and 46) this possibility of "a false CO2 reactivity" cannot be excluded.

The effect of hyperventilation on cerebral metabolism is shown in Fig. 7. The decrease in rCBF was associated with an increase in AVDO2 in two-thirds of the patients. In 12 of these, the increase in AVDO2.
Cerebrovascular reactivity following SAH

REST FLOW:
Mean rCBF 21
AVDO$_2$ 5.33
CMRO$_2$ 1.12
MABP 95
IVP 15
PaCO$_2$ 29

HYPOTENSION:
Mean rCBF 15
AVDO$_2$ 6.23
CMRO$_2$ 0.93
MABP 83
IVP 14
PaCO$_2$ 28

FIG. 3. Case 21. This 38-year-old man had a right internal carotid artery aneurysm. Angiography on Day 1 showed no vasospasm. The patient was stuporous (Grade IV) and was subjected to controlled ventilation. A resting study on Day 8 showed that the regional cerebral blood flow (rCBF) was severely reduced and autoregulation globally impaired during short-lasting hypotension. Angiography now revealed severe diffuse vasospasm. Despite hyperventilation and drainage of cerebrospinal fluid, the patient died 2 days later from intracranial hypertension. Abbreviations are defined in Fig. 1.

FIG. 4. Effects of arterial hypotension on regional cerebral blood flow (rCBF), arteriovenous difference of oxygen (AVDO$_2$), and cerebral metabolic rate of oxygen (CMRO$_2$) in 19 patients with recent rupture of an intracranial saccular aneurysm.

TABLE 3
Cerebral autoregulation and CO$_2$ reactivity in 11 patients with severe cerebral vasospasm*

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<tr>
<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Clinical Grade†</th>
<th>IVP (mm Hg)</th>
<th>CSF Lactate (mmol/liter)</th>
<th>ΔMABP (%)</th>
<th>Mean rCBF$\ddagger$ (ml/100 gm/min)</th>
<th>Regional Findings</th>
<th>ΔPaCO$_2$ (mm Hg)</th>
<th>Mean rCBF$\dagger$ (ml/100 gm/min)</th>
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<td>7.4 ± 3.3</td>
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* Abbreviations: IVP = intraventricular pressure; CSF = cerebrospinal fluid; MABP = mean arterial blood pressure; rCBF = regional cerebral blood flow; SD = standard deviation.
† Clinical grade according to Hunt and Hess.10
‡ Resting/hypotensive studies.
§ Resting/hyperventilation studies.

REST FLOW:
Mean rCBF 43
AVDO2 2.81
CMRO2 1.21
MABP 176
IVP 75
PaCO2 41

HYPERVENTILATION:
Mean rCBF 38
AVDO2 2.75
CMRO2 1.05
MABP 163
IVP 59
PaCO2 34

Fig. 5. Case 56. This 46-year-old woman had a right middle cerebral artery (MCA) aneurysm. At admission on Day 1 she was somnolent (Grade III). A resting study on Day 4 showed slightly decreased flow with severely increased intraventricular pressure (IVP). Response to hyperventilation was globally impaired. Angiography revealed slight diffuse spasm with severe focal spasm of the right MCA. Due to clinical deterioration to Grade IV, this patient did not undergo surgery. Two years after subarachnoid hemorrhage she was incapacitated by aphasia and left hemiplegia. Computerized tomography showed right frontotemporal infarction. Abbreviations are defined in Fig. 1.

Discussion
Methodological Considerations
In the present study, we used the two-dimensional 133Xe intra-arterial injection method for measuring rCBF. The limitations of the method for a quantitative evaluation of ischemic brain tissue due to the look-through phenomenon and Compton scatter have been discussed previously.23 The necessity of puncture of the carotid artery limits the applicability of the method in clinical work. The recent development of noninvasive, three-dimensional methods seems promising for clinical use, in particular for high-risk patient categories such as aneurysm patients.19

Cerebral Autoregulation
By varying the degree of constriction of the cerebral arterioles, CBF is kept constant during changes in MABP within certain limits. A reduction in MABP of approximately 40% below the resting level is accompanied by a decrease in CBF. Beyond this so-called “lower limit of autoregulation” further vasodilatation is no longer possible. The exact mechanism of autoregulation is unknown, but myogenic, metabolic, and neurogenic factors have been proposed.36

surpassed the decrease in rCBF, resulting in an increase in CMRO2. This phenomenon was seen even in cases with severe ischemia (Cases 18 and 27). In six patients, rCBF decreased more than AVDO2 increased, resulting in a slight decrease in CMRO2. In six patients a paradoxical reaction to the fall in rCBF was found as AVDO2 decreased. In four of them (Cases 29, 54, 56, and 59) the CSF lactate level was increased, and in the remaining two (Cases 26 and 47) IVP was elevated.

Fig. 6. Effects of hyperventilation on mean arterial blood pressure (MABP), intraventricular pressure (IVP), and cerebral perfusion pressure (CPP) in 27 patients with recent rupture of an intracranial saccular aneurysm.

Fig. 7. Effects of hyperventilation on regional cerebral blood flow (rCBF), arteriovenous difference of oxygen (AVDO2), and cerebral metabolic rate of oxygen (CMRO2) in 24 patients with recent rupture of an intracranial saccular aneurysm.
Cerebrovascular reactivity following SAH

Impairment of cerebral autoregulation has frequently been observed in patients with stroke and traumatic brain injury. Heilbrun, et al., studied preoperatively the cerebral autoregulatory response to hypotension in five patients with SAH, and found both focal abnormalities and global impairment. However, no relationship to vasospasm was revealed, whereas hydrocephalus seemed to be of importance. Unfortunately, intracranial pressure was not measured.

In the present study, we found a clear correlation between the presence of cerebral vasospasm and impaired autoregulation. Furthermore, the degree and extension of vasospasm was related to the severity of autoregulatory impairment. An association between severe spasm and globally defective autoregulation is not surprising and is in accordance with similar findings in other states of cerebral ischemia. However, the frequent finding of focally impaired autoregulation in cases of slight spasm was unexpected. These patients had a normal or slightly reduced rCBF during resting-state studies without focal abnormalities. The demonstration of focal disturbances during hypotension suggests that the autoregulatory range in these good-risk patients was diminished by the slight vasospasm demonstrated at angiography.

According to the myogenic hypothesis of autoregulation, changes in transmural pressure will elicit a reflex change in the tone of arteriolar smooth muscle — the so-called "Bayliss effect". In cerebral arterial spasm, the tone of the resistance vessels, primarily the pial arterioles, is probably increased due to constriction of the vessel wall induced by an unknown factor circulating in the CSF after SAH. Consequently, the normal response of the vessel wall to changes in pressure gradients across it is diminished, and the normal response to arterial hypotension, which is a dilatation, is probably weakened or abolished depending on the degree of spasm. As the transmural pressure is identical with CPP, the increased IVP found in most patients with vasospasm may further tend to diminish the pressure gradient and, thereby, the normal reaction to a fall in MABP.

Increased values of CSF lactate were commonly found in association with impaired autoregulation. In patients with recent SAH, CSF lactic acidosis may reflect diffuse cerebral ischemia due to high IVP and vasospasm. Cerebral metabolic acidosis adversely influences cerebral vasomotor reactivity, leading to vasodilatation and ultimately to vasoparalysis which renders the vascular bed in the ischemic area pressure-dependent. The combination of slight arterial spasm and increased IVP will tend to reduce CPP. When CPP is further reduced during induced hypotension, the resultant ischemia apparently manifests itself as focal dysautoregulation. However, the occurrence of focal flow increases is difficult to explain. The presence of increased IVP and CSF lactic acidosis suggests focal cerebral edema and vasoparalysis. If the decrease in intracranial pressure is greater than the induced MABP decrease, the perfusion pressure and thus CBF may increase in such regions.

CO₂ Reactivity

It is well established that a decrease in PaCO₂ (hypocapnia) causes a marked cerebral vasoconstriction. Thus, in the PaCO₂ range 25 to 60 mm Hg the relationship between CBF and PaCO₂ is exponential, with a flow change of approximately 4% (2% to 6%)/mm Hg. The site of action of CO₂ is probably regional, and the perivascular pH is considered the main factor in the regulation of rCBF.

In the present study, preserved although reduced CBF responses to hyperventilation were found in nearly all patients. In patients in good clinical condition without or with slight vasospasm, this reduction was about 25%. Global reduction of more than 50% was only seen in patients in poor clinical grade with severe vasospasm or increased CSF lactate levels and increased IVP. Preserved CO₂ response associated with defective autoregulation was often seen in patients with slight vasospasm — the so-called "dissociated vasomotor paralysis." As impaired autoregulation may be restored during hyperventilation, it has been proposed that this dissociation between autoregulation and CO₂ reactivity might be due to a slight tissue acidosis, while severe tissue acidosis would cause a complete vasoparalysis involving both modes of reactivity. Our findings of moderately increased CSF lactate concentrations in patients with dissociated vasoparalysis and severely increased CSF lactate levels in patients with total vasoparalysis seem to support this hypothesis.

The reactivity of spastic arteries to physiological stimuli may be abnormal. In the present study, however, paradoxical reactions (for instance "the inverse steal syndrome") were not observed. On the contrary, rCBF was reduced in all cases during hypocapnia, even in patients with diffuse severe vasospasm, indicating that the spastic arteries were capable of contracting further.

The concomitant increase in AVDO₂ often surpassed the rCBF reduction, resulting in an increase in CMRO₂. Even in patients with severe spasm and preexisting ischemia, the AVDO₂ increased 15% to 20%. As the CMRO₂ values are derived from the entire hemisphere, and not only from the cortical area situated beneath the detectors, one might suppose that brain tissue outside this detector field was less ischemic and therefore capable of increasing the extraction rate of O₂. In cases of diffuse spasm involving the whole brain, this explanation, however, could not be valid. Therefore, it seems reasonable to conclude that ischemic brain tissue with rCBF values of approximately 20 ml/100 gm/min is still capable of increasing O₂ extraction from the blood. As hyperventilation in the present study was only maintained for 3 to 5 minutes, the clinical significance of this observation is difficult to assess.
Conclusions

Our main results of investigations into the cerebral vasomotor reactivity in the early phase after SAH in patients with ruptured intracranial aneurysm may be summarized as follows:

1. Cerebral autoregulation was preserved in patients in good clinical condition but impaired in patients in poor clinical condition.

2. The most important factor for this impairment of autoregulation was cerebral vasospasm. There was a close correlation between the occurrence of spasm and the development of defective autoregulation, as well as a close correlation between the degree of vasospasm and the degree of autoregulatory impairment.

3. Other factors related to the impairment of autoregulation were intracranial hypertension and CSF lactic acidosis.

4. Cerebrovascular reactivity to hypocapnia was generally preserved in patients with SAH, although often reduced. Global impairment of CO₂ reactivity was associated with severe vasospasm and CSF lactic acidosis.

Despite numerous attempts at treating cerebral vasospasm with pharmacological agents, the only therapeutic measure currently considered of value in the management of delayed ischemic symptoms is volume expansion and induced hypertension. Our data support the rationale behind this regimen: that an increase in CPP will increase CBF in ischemic areas as autoregulation was preserved in patients with ruptured intracranial aneurysms. According to our results, this finding is probably explained by the presence of slight vasospasm. This category of patients in satisfactory preoperative clinical condition is also characterized by an elevated IVP and CSF lactate level. A simple and noninvasive method of estimating the autoregulatory capacity in such patients preoperatively would be useful.

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Address reprint requests to: Bo Voldby, M.D., University Neurosurgery Clinic, Rigshospitalet, DK-2100 Copenhagen, Denmark.