Early Changes in Rabbit Cerebral Artery Reactivity After Subarachnoid Hemorrhage

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Background and Purpose: Subarachnoid hemorrhage frequently leads to long-term cerebral artery narrowing called vasospasm. Very early changes in cerebral arteries have not been studied extensively and may be critical for the later pathological developments. We therefore determined what changes in the reactivity of cerebral arteries could be observed after 10 minutes' or 24 hours' contact with subarachnoid blood.

Methods: Ten minutes or 24 hours after the injection of blood or physiological solution (sham hemorrhage) into the cisterna magna of anesthetized rabbits or no injection (control rabbits), segments of the middle cerebral, basilar, and vertebral arteries were removed for conventional in vitro tension measurements. Concentration–response curves to four endogenous constrictors likely to be released after hemorrhage were obtained, and the maximum relaxation to acetylcholine was determined.

Results: There were no significant differences between the sham hemorrhage and control groups. Compared with control rabbits, treated animals showed increased reactivity to uridine triphosphate in the basilar and vertebral arteries at 10 minutes but not at 24 hours, whereas reactivity was increased in the middle cerebral artery only at 24 hours. Reactivity to serotonin was greatly increased in all arteries at both latencies (up to 2.7 times). Reactivity to noradrenaline was unchanged in the basilar and vertebral arteries at 10 minutes; reactivity in both the basilar and middle cerebral arteries was increased at 24 hours, which is compatible with denervation supersensitivity. There were only minor changes in the reactivity to histamine, and only at 10 minutes. Relaxation to acetylcholine was increased for the middle cerebral artery at 10 minutes but otherwise was not significantly changed.

Conclusions: Reactivity to uridine triphosphate, serotonin, and noradrenaline greatly increases by 10 minutes to 24 hours after subarachnoid hemorrhage, and this increase is not owing to the mechanical effects of intracranial hypertension, nor is it related to impaired endothelium-dependent relaxation. It is suggested that these and other spasmogens cause excessive muscular calcium loading with a very rapid onset after subarachnoid hemorrhage. (Stroke 1992;23:1154–1162)

KEY WORDS • norepinephrine • rabbits • serotonin • subarachnoid hemorrhage

Cerebral vasospasm is one of the most dangerous sequelae that may appear after a subarachnoid hemorrhage (SAH) secondary to the rupture of an intracranial aneurysm.1 The mechanism by which subarachnoid blood leads to delayed, long-term narrowing of the vessels of the brain is very poorly understood. Current hypotheses suggest that at the time of this chronic vasospasm (angiographically in humans beginning at ≥4 days after SAH, maximal at about 7 days) structural changes such as fibrosis, smooth muscle proliferation, and necrosis have occurred in the vessels, increasing their rigidity and decreasing their diameter.2,3 Apparently, this process requires several days to develop and is initially triggered by the various consequences of contact of the cerebral arteries with blood and possibly by the effects of the increase in intracranial pressure (ICP). In animal models it has been established that an early phase of short-lived cerebral vasospasm exists,4–7 which may well be associated with the initial causes of damage leading to chronic artery narrowing. Among the numerous substances suspected to be involved in early vasoconstriction, one can cite blood elements and by-products released by degradation, catecholamines and serotonin (5-HT), and prostaglandins.2,3

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Considering, therefore, that late chronic vasospasm may well be derived in relation to the action of vasoconstrictors released from and by the blood clot at an early stage, our aim in the present work was to determine whether functional changes in the arteries could be detected after very brief contact with subarachnoid blood. Although several studies have reported the effects on cerebral artery reactivity of experimental SAH,8–11 no group has examined the possibility that modifications may occur within minutes, despite the fact that basilar artery (BA) narrowing and a blood flow decrease have been demonstrated at 10 minutes after an exposure to blood.5,12

Using a model of SAH developed in rabbits, we determined whether a brief (10-minute) exposure to
blood in the subarachnoid space produces significant changes in the responsiveness of cerebral arteries to 5-HT, noradrenaline (NA), histamine (HA) (a strong constrictor in rabbits), and uridine triphosphate (UTP) (which can be released from platelets). The functional state of the endothelium was examined by testing the ability of the arteries to dilate to acetylcholine (ACh). These results were compared with those obtained after 24 hours' exposure to blood under the same conditions to detect any evolution in the state of vessel reactivity.

In the first state of the endothelium was examined by testing the constrictor in rabbits), and uridine triphosphate (UTP) was injected under identical conditions. In the first series, the arteries were washed three times, and an interval of 30 minutes elapsed between tests. A single maximal concentration of $10^{-4}$ M ACh was used to produce vasodilatation in the precontracted preparations. The relaxation was expressed as percent of the tonic contraction induced by $10^{-4}$ M HA.

Mean values from control, sham SAH, and SAH vessels were compared by using analysis of variance followed by Scheffe's tests for multiple comparisons, and in specific cases SAH group versus control group differences were compared by using the $t$ test; $p<0.05$ was taken to indicate significant differences.

**Materials and Methods**

Sixty Fauve de Bourgogne rabbits weighing between 2.5 and 3 kg were used. We studied an SAH group, a sham SAH group, and a control group. All rabbits were anesthetized with 17 mg/kg acepromazine and 20 mg/kg sodium pentobarbital administered intravenously. In the SAH group the femoral artery was catheterized to allow blood to be withdrawn, and the equivalent of a hemorrhage was induced by the slow (2–3 minutes) injection of 1 ml fresh autologous arterial blood into the cisterna magna via a permanent percutaneous catheter.

In the sham SAH group, instead of blood, physiological solution (the same as used for incubating the arteries) was injected under identical conditions. In the first series, after the cisternal injection the animals of the SAH and sham SAH groups were tilted in a head-down position for approximately 5 minutes and decapitated 10 minutes after the end of the injection. Rabbio tics of the control group had no injection and were decapitated as soon as anesthesia was induced.

In the second series, animals of the control, SAH, and sham SAH groups were treated as above except that the rabbits of the sham SAH and SAH groups were not killed at 10 minutes but were returned to their cage for 24 hours, anesthetized again as before, and decapitated immediately. Three other rabbits were killed 10 minutes after the injection of a solution of Evans blue instead of blood.

After decapitation the brain was removed and placed in a physiological solution, as previously described. Three millimeter segments of the vertebral artery (VA) (10-minute series only), BA, and middle cerebral artery (MCA) were removed under a surgical microscope. The artery segments were then placed in 5-ml organ baths containing a solution of the following millimolar composition: 126 NaCl, 5 KCl, 1.2 NaH2PO4, 1.3 MgCl2, 20 NaHCO3, 2.5 CaCl2, and 5.5 glucose and were gassed with 4% CO2/20% O2/76% N2 with a pH of 7.3–7.4.

The segments, mounted on L-shaped holders, were allowed to equilibrate at least 1 hour at 37°C before the isometric tension measurements were begun. During the equilibration period, the vessels were frequently stretched until a stable resting tension of approximately 500 mg (BA) or 300 mg (VA and MCA) was obtained. The agonists were then administered in the following order: UTP, NA, HA, 5-HT, and ACh; this order was maintained in all experiments. Tests with HA did not precede those with NA because of the reported enhancing effects of the former on adrenergic constriction.

Similarly, tests with 5-HT were separated from those with NA to avoid any interaction of either agonist with receptors of the other type. At the end of each test the preparations were washed three times, and an interval of 30 minutes elapsed between tests. A single maximal concentration of $10^{-4}$ M ACh was used to produce vasodilatation in the precontracted preparations. The relaxation was expressed as percent of the tonic contraction induced by $10^{-4}$ M HA.

**Results**

After removal of the brain from the cranium, it was observed that the blood injected into the cisterna magna had flowed around the brain stem to form a clot along the BA and the rostral portion of the VA, as well as flowing along the circle of Willis and the proximal part of the MCA. The trials with Evans blue confirmed this distribution; all the vessels tested were stained.

In studying the reactivity of the arteries to constrictor agents, we found virtually identical results in the 10-minute series for the BA and VA (see below). We therefore examined only the MCA and BA, in the 24-hour series. We were thus able to increase the number of MCA segments tested, this vessel being more delicate to prepare and showing, for some agents, less pronounced differences between groups.

For UTP, in the 10-minute series essentially similar upward shifts in the concentration–response curves in the SAH group compared with the sham SAH and control groups were observed for the BA and VA (Figure 1b and 1c). No significant differences were noted for the MCA (Figure 1a). In the 24-hour series, in contrast, the MCA of the SAH group reacted more strongly than that of the sham SAH group; in the case of the BA the differences between groups were no longer significant.

Concerning 5-HT, in the 10-minute series no significant differences were found for the BA and MCA of the SAH group compared with the sham SAH and control groups (Figure 2b and 2c). A similar, though less pronounced, trend was observed for the MCA of the SAH group (Figure 2a), significant differences occurring only at the lower concentrations. In the 24-hour series the general trends were similar, but the BA of the SAH group reacted relatively less (Figure 2e) than in the 10-minute series ($p<0.001$ for differences at $10^{-3}$ M, $t$ test).

For NA, in contrast, in the 10-minute series, despite a general upward shift, the reactivities of the VA and BA in the SAH group (Figure 3b and 3c) were not significantly different from those in the other groups. In the case of the MCA (Figure 3a), there was little difference between groups. In the 24-hour series, the situation had changed dramatically; both the BA and MCA of the SAH group were substantially more reactive than the corresponding arteries of the sham SAH and control groups (Figure 3d and 3e).

Regarding HA, in the 10-minute series no significant differences were observed between groups for the VA and BA (Figure 4b and 4c). In contrast, the MCA of the
SAH group contracted less at high concentrations than the MCA of the control group (Figure 4a). In the 24-hour series, no significant differences were found between groups for either the BA or MCA.

The effects of $10^{-4}$ M ACh administered at the end of the experiment are shown in Figure 5. In the 10-minute series, there were similar tendencies in all arteries (decreased responses in the sham SAH group, increased responses in the SAH group), the differences between groups being significant for the MCA. In contrast, in the 24-hour series there were no significant differences between groups and no tendency toward increased responses in the SAH group.

**Discussion**

These results relate to relatively early events following SAH and demonstrate that significant changes occur in the properties of cerebral arteries even after only minutes of contact with extravascular blood. Before discussing these changes in detail, it is necessary to consider the model and the different groups studied.

Although it is now clear that primate models of SAH best reproduce the human situation following aneurysmal rupture,1,16 many useful subprimate models that give satisfactory results angiographically have been developed. Injections of blood into the cisterns now appear to provide a suitable model for studying at least the morphological and physiological properties of the affected blood vessels.5-9,11,17,18 Considerable quantitative differences between the models seem present inasmuch as the volume of blood injected and the rate of injection vary considerably with respect to brain size (probably a more critical parameter than body weight). Thus the increase in ICP incurred is surely an extremely variable factor, although only infrequently monitored. Some authors have apparently sought to limit ICP changes by first withdrawing cerebrospinal fluid (CSF), but this approach neglects the fact that SAH in humans is usually accompanied by headache thought to be symp-
tomato of intracranial hypertension. The first question we asked, therefore, was what are the consequences on reactivity of the cerebral arteries of a moderate SAH induced by the intracisternal injection of blood, regardless of ICP? The important comparison here is between the SAH and control groups. The second question is how much of the differences observed can be attributed to "mechanical" effects, i.e., the local pressure changes around the arteries during and for a short period after the injection? The sham SAH group versus control group comparison should elucidate some elements of the response. It should perhaps be borne in mind that the transmission of pressure changes to the BA and VA may be quantitatively different from that to the MCA.

One frequent aspect of the results is the differentiation of the properties of the MCA compared with the BA and VA. This differentiation raises a question as to the uniformity of the effects of injection of blood or mock CSF on the vertebrobasilar trunk compared with the MCA. Although blood and Evans blue were both clearly disseminated around the latter arteries, it remains possible that the rapidity of onset of either the blood vessel contact and/or the immediate local mechanical effects could differ; if so, one would expect greater differentiation in the 10-minute series. With the exception of the constrictions to UTP, for which at 24 hours there is essentially an inversion of the BA/MCA differences noted at 10 minutes (Figure 1), this seems to hold true; the marked difference in the behaviors of the BA and MCA observed at 10 minutes seems to be largely attenuated at 24 hours (compare in Figures 2-5). An alternative explanation would be that different cerebral arteries react differently to the stimuli given; despite known differences in reactivity to neurotransmitters, it seems to us that some more fundamental difference must be envisaged to explain the present divergence.

It is important to notice that, despite minor tendencies in some cases, there was never any significant difference
between the control and sham SAH groups, indicating that the changes in reactivity observed are attributable essentially to the specific influence of the injected blood. Urquilla\textsuperscript{21} proposed that UTP, a relatively specific strong constrictor of cerebral arteries, could be involved in the vasospasm subsequent to SAH. Indeed, platelets contain UTP and other nucleotides,\textsuperscript{22} and uridine diphosphate is an equally strong constrictor.\textsuperscript{23,24} However, there appears to have been little attempt to study the possible involvement of UTP, except for the experiments of Shirasawa et al.\textsuperscript{23} in which UTP diluted in CSF was injected into the cisterna magna. An angiographically demonstrable vasoconstriction (33%) of the BA was observed for at least 60 minutes, showing that even without modification of the arterial sensitivity a spastic type of action may well be exerted by UTP in vivo. Our results indicate that, after 10 minutes' or 24 hours' contact with blood, depending on the vessel considered, even relatively low perivascular concentrations of UTP (10\textsuperscript{-5} to 3.10\textsuperscript{-5} M) can have substantially exaggerated contractile effects. From the roughly parallel shifts of the concentration-response curves, it appears as if the sensitivity of the pyrimidine receptors\textsuperscript{24} had been increased.

The early effects (10-minute series) of 5-HT parallel those of UTP in that a substantially increased contraction was observed in the BA and VA of the SAH group compared with either the control group or the sham SAH group. However, 5-HT–induced contractions also increased rapidly in the MCA of the SAH group. The potentiation of both MCA and BA contractions to 5-HT persisted at 24 hours. There have been few studies on the very early phases of blood-induced changes in reactivity, most reports involving vessels removed 3–7 days after the first injection of blood, which probably corresponds in humans to the phase of greatest risk for vasospasm\textsuperscript{1} but does not necessarily reflect the early
FIGURE 4. Concentration–response curves to histamine of middle cerebral artery (MCA), basilar artery (BA), and vertebral artery (VA) removed from rabbits killed 10 minutes (top) or 24 hours (bottom) after injection of blood (SAH group, * - - -) or physiological solution (sham group, □, - - -) or from control animals ( - - -). x axis, logarithm of molar concentration; y axis, response of group expressed as percent of maximum response of control group. Absolute values (mean±SD) of these maxima were (a) 1.64±1.55 g, (b) 4.38±1.33 g, (c) 2.01±0.78 g, (d) 2.23±0.57 g, and (e) 5.86±0.99 g. ▲, different (p<0.05) from control group; ●, different (p<0.05) from sham group. n=6–17 for SAH, n=6–14 for sham, and n=10–19 for control arteries.

posthemorrhagic phase of pathophysiological alterations. Perhaps the most pertinent comparison to be made is with the investigation of Tsuji and Cook.\(^{25}\) In their study the BA was first removed from the animal and maintained under perfusion in vitro before blood was administered to the adventitial surface. One hour after blood administration the responses to two doses of 5-HT had increased, and these responses increased further at 4 hours, but not at 8 hours. This increased reactivity appears to be in contradiction to the results of Young et al,\(^8\) who described an early phase of decreased reactivity and sensitivity of rabbit BA to 5-HT at 1 and 6 hours after SAH, with a subsequent potentiation attaining a maximum at 36 hours (there was no group at 24 hours). One difference compared with our study is that the blood was injected (quantity and injection rate not given) into the cisterna chiasmatica, not the cisterna magna, in which case the BA was possibly in contact with less blood (depending on the volume injected). Nonetheless, the general conclusion of these authors, that there may be a continuum of change in the vascular reactivity to 5-HT, is certainly compatible with our results (including those on other agonists).

Other rabbit studies have tested the reactivity at 3 or 4 days after the injection of blood or the first of two injections. Svendgaard et al\(^6\) found that the maximum response of the BA to 5-HT increased by about threefold, whereas Nakagomi et al\(^26\) observed that 10\(^{-6}\) M 5-HT induced contractions of the BA that were increased by 21.5–36.6% at 4 days (nonsignificant, but partially reversible at 3 weeks). There were, however, no sham injections in these studies, so it is difficult to evaluate the possible contribution of the mechanical effects of cisternal injection on their preparations. Such effects were particularly large in the latter study\(^26\) since the authors found ICP increases of about 195 and 90 mm Hg at the first and second injections of blood, respectively. In a study on canine MCAs and BAs (with no sham injections), Pickard and Perry\(^10\) also observed increased reactivity to 5-HT at 3 days (nonsignificant) and 7 days (significant). Lobato et al\(^11\) observed in feline BAs a larger increase (>200%) in reactivity to 5-HT 3
responses of control vessels were for 10-minute series acetylcholine of middle cerebral artery (MCA), basilar artery (BA), and vertebral artery (VA) preconstricted with 10⁻⁴ M histamine. Arteries were removed from rabbits killed 10 minutes (top) or 24 hours (bottom) after injection of blood (SAH group) or physiological solution (sham group) or from control animals. Responses are expressed as mean ± SD percent of response of control arteries. Absolute values of responses of control vessels were for 10-minute series 48.8 ± 22.9% (MCA), 31.3 ± 18.6% (BA), and 21.8 ± 14.6% (VA); and for 24-hour series 38 ± 19% (MCA) and 33.3 ± 29.5% (BA). ▲, different (p < 0.05) from control group; ★, different (p < 0.05) from sham group.

days after SAH, and in certain but not all, primate studies 5-HT has been found to induce relatively increased artery responses 5-7 days after SAH. Overall, our data together with those of other workers indicate that reactivity to 5-HT increases rapidly and substantially within minutes or hours after the hemorrhagic event and that such increased reactivity persists to a greater or lesser degree for 5-7 days at least.

As shown by Figure 3, hyperreactivity to NA developed only after 24 hours. Similarly, observations on piglet pial arterioles showed no change in the constritor action of NA at 30 minutes after blood administration. Other workers have noted increased reactivity, to varying degrees, at 3 days after SAH²⁹-¹¹ and have attributed this to supersensitivity of the receptors resulting from denervation-like effects of the injected blood, although Duff et al³⁰ did not find increased reactivity to NA (or 5-HT) in the BA in vivo 7 days after sympathetic denervation. Lobato et al³¹ have shown in cats a loss of NA uptake and a reduced NA content in posterior communicating arteries 3 and 7 days after SAH, and Edvinsson et al³² showed in rabbits a loss of adrenergic fiber fluorescence in the BA at 3 days after SAH; similar results were obtained in monkey MCAs and rat BAs 2 and 7 days after SAH³³ and in cat BAs 4 and 7 days after SAH.⁴⁴ In parallel to such changes, Endo and Suzuki³⁵ observed within 30–60 minutes a loss of small dense-cored vesicles in perivascular nerve varicosities when cat BAs were treated in situ with blood incubated 5 days in CSF, but not if treated with fresh blood. This result suggests that the denervation-like effects of SAH may not begin immediately but may require a certain “incubation” time. Our results are compatible with a delayed onset of hyperreactivity (up to 24 hours), which could indeed result from denervation supersensitivity. The study of Jackowsky et al³⁶ also indicates that SAH induced a reduction of neuropeptide Y — localized in sympathetic fibers — beginning at 15 minutes and maximal at 24 hours.

The results for HA in the 10-minute series indicate a depressed contraction for the MCA of the SAH group compared with the control group. It appears that this was a transient phenomenon because there were no significant changes in the 24-hour series. Little work has been performed on HA during SAH, despite the fact that the mast cell population of human cerebral arteries has been shown to increase after SAH,³⁷ but our results suggest that the early vascular modifications following SAH do not include HA-induced constriction. Such constriction has been shown to be due to H₁ receptors in rabbit cerebral arteries,³⁸ whereas dilatory effects, dependent on the endothelium, are mediated by H₂ receptors.³⁹⁴⁰

Our results with a maximal concentration of ACh indicate that, as far as the endothelium-derived relaxing factor (EDRF) released by ACh is concerned, there was no functional deficit of the endothelium up to 24 hours after SAH. Surprisingly, the MCA of the SAH group showed an increased capacity to relax to 10⁻⁴ M ACh in the 10-minute series, suggesting that the brief contact of these vessels with blood induced either a greater release of EDRF from endothelial cells or increased reactivity of the smooth muscle to EDRF (either nitric oxide or a precursor). As already stressed, there might be some time lag between events in the MCA compared with the BA and VA; the MCA’s decreased or unchanged contractile responses after a 10-minute SAH might also result from a concurrent exacerbated endothelium-dependent relaxation since both HA and NA probably cause release of EDRF as well as constriction of cerebral arteries.¹⁵²⁹

Functional studies of endothelial activity do not appear to have been performed at so brief an interval after SAH, but reduced endothelium-dependent relaxation has been shown at 4 days after SAH in rabbits²⁶ and at 7 days after SAH in monkeys.⁴⁶ However, early morphological changes in the endothelium have been seen in some¹¹,¹₂ but not all¹³ experiments. Possibly the onset of endothelial damage depends on how aggressive an SAH is induced (amount of blood and rate of injection, ICP changes, site of injection) and the presence or absence of prolonged, extreme vasoconstriction such as occurs during the chronic (late) phase of vasospasm. Since in our experiments there does not appear to be an impairment of endothelium-dependent relaxation during the first 24 hours we believe that the suggestion that loss of such relaxation contributes to late vasospasm should be viewed with caution. Furthermore, according to Kim et al²¹ the endothelium of canine BAs removed during chronic vasospasm released as much EDRF as control arteries, suggesting that the
EDRF-releasing function of the endothelium may indeed be unaffected.

The present results show that at least three endogenous vasoconstrictors cause substantially increased contractions of large cerebral arteries within 24 hours after SAH, and for UTP and 5-HT this was true even in arteries removed only 10 minutes after the injection of blood. These agents are certainly present after SAH in greatly increased quantities in and around pial arteries because 5-HT has been documented in the CSF and degranulated platelets are present on and within cerebral arteries. An early vasoconstriction is suggested by decreases in cerebral blood flow (CBF), increased velocity of BA blood flow, and narrowing of the BA within 1-3 hours after SAH. We have observed a small but significant fall in regional CBF (grisea centralis) within 30 minutes after SAH but no significant change after sham injection of CSF. Other workers also noted relatively more transient effects or even no effects after sham injection of CSF. Other workers also noted relatively more transient effects or even no effects after sham injection of CSF.

There also appears to be a general consensus that 24 hours after SAH the BA still shows a (usually) significant degree of narrowing, although findings of BA blood flow velocity seem less conclusive in favor of significant vasoconstriction. This is still compatible with the enhanced reactivity to vasoconstrictors observed here, but at this stage blood flow and flow velocity measurements will integrate compensatory mechanisms such as anastomotic flow and release of dilator substances.

The consequences of the changed reactivity observed here at 10 minutes and 24 hours after SAH, combined with the effects of other spasmogens, may be a prolonged state of relative depolarization of the smooth muscle and excessive calcium loading (through intracellular and receptor-operated calcium channels). How critical this calcium overloading is for the development of later events remains to be investigated precisely. Calcium antagonist treatment given preventively has considerably reduced the degree of chronic arterial narrowing and has a detectable but reduced effect when given after SAH.

A recent study with an intracellular Ca²⁺ marker indicated that 1 hour after SAH 37% of smooth muscle cells were heavily loaded with calcium compared with 15% during a strong contraction induced by topical prostaglandin F₂α. In another study, cultured smooth muscle cells were subjected to human CSF taken from patients having had SAH; the cells showed significant transient (about 3 minutes) increases in intracellular calcium concentrations, the greatest effects being obtained with CSF drawn 2 days after the hemorrhage compared with that drawn at 6 or 11 days. Both intracellular calcium mobilization and extracellular calcium entry seemed to be involved. It seems likely, therefore, that multiple factors contribute to calcium loading in the early hours and days after SAH, resulting in an altered, pathological state of the smooth muscle associated with irreversible contraction.

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References
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