Hemodynamics of subarachnoid hemorrhage arrest

PATRICK W. MCCORMICK, M.D., JOHN MCCORMICK, B.S., JOSEPH M. ZABRAMSKI, M.D.,
AND ROBERT F. SPETZLER, M.D.

Division of Neurological Surgery, Barrow Neurological Institute, Phoenix, Arizona

Subarachnoid hemorrhage (SAH) causes a spectrum of clinical syndromes from mild discomfort to rapid brain death. The reason for these heterogeneous consequences is poorly understood. A canine autologous shunt model of SAH was used to study this problem. The duration and volume of hemorrhage into the suprasellar cistern at each animal’s mean arterial blood pressure were measured at variable hemorrhage flow rates. At high rates of bleeding in seven dogs (18.7 ± 2.2 ml/min, mean ± standard deviation), hemorrhage duration was significantly less (191 ± 116 seconds, p < 0.03) and hemorrhage volume was significantly greater (15.1 ± 7.0 ml, p < 0.05) than at low flow rates. At low flow rates of bleeding in nine dogs (4.4 ± 2.2 ml/min), hemorrhage duration was 394 ± 202 seconds and volume was 10.9 ± 6.5 ml. Cerebral perfusion pressure (CPP) decreased at all hemorrhage rates but never to 0 mm Hg (perfusion arrest). No correlation between a decrease in CPP and SAH volume or duration was identified. The initial flow rate of SAH had a positive linear correlation with the volume of hemorrhage (23 dogs, r = 0.64, p < 0.01). The data suggest that initial SAH flow rate, and not CPP, has a primary influence on hemorrhage arrest. This finding may influence the clinical rationale for acute management of SAH-induced brain injury.

KEY WORDS • subarachnoid hemorrhage • hemostasis • brain injury • perfusion arrest • dog

Hemorrhage into the subarachnoid space is a self-limited event that results in a spectrum of clinical presentations from mild meningeal irritation to brain death. The underlying event, vessel rupture, is uniform despite the heterogeneous clinical consequences. The reason for this is poorly understood. Primary issues are what mechanism arrests the hemorrhage and how it is linked to brain injury.

Chance observations in patients who have suffered a hemorrhage while awaiting aneurysm repair have been reported. The apparent mechanism of hemorrhage arrest was rapid reduction of cerebral perfusion pressure (CPP) to zero as intracranial pressure (ICP) rose. When ICP rises as high as the mean arterial blood pressure (MAP), there is so-called “perfusion arrest” of the cerebral circulation. However, hemorrhages monitored in humans are second or third hemorrhages and may be fundamentally different from initial subarachnoid hemorrhage (SAH).

Most laboratory data on SAH models indicate that hemorrhage does not lead to a CPP of 0 mm Hg (71-13,15,19) Dorsch, et al., measured CPP and cerebral blood flow (CBF) in their primate SAH model and concluded that hemorrhage arrest could not be explained by perfusion arrest alone. Steiner, et al., noted that hemorrhage did not stop when CPP was lowest but rather when CPP was returning to baseline. Clinical experience demonstrates that SAH patients often do not lose consciousness, and this is not compatible with an episode of cerebral perfusion arrest. Indeed, in their awake model of SAH in cats, Hayakawa and Waltz saw no immediate neurological change or loss of consciousness. In an effort to better define the mechanism of SAH arrest, we performed a series of experiments addressing this issue using an autologous shunt model of SAH in dogs.

Materials and Methods

This study was conducted in accordance with all published guidelines of the United States Department of Health and Human Services and the National Institutes of Health. The protocols were approved by the Animal Welfare Committee of the Barrow Neurological Institute. This facility is approved by the American Association of Accreditation of Laboratory Animal Care.

Model of Subarachnoid Hemorrhage

Healthy adult dogs (each weighing 20 to 25 kg) were initially anesthetized intramuscularly with 225 mg ke-
Hemodynamics of subarachnoid hemorrhage arrest

tamine and 50 mg xylazine. Anesthesia was maintained by intravenous pentobarbital infusion. The barbiturate infusion was titrated to eliminate noxious withdrawal reflexes. Compressed spectral analysis monitoring was used to ensure that anesthesia provided minimal suppression of electroencephalographic (EEG) activity. The animals were intubated and ventilated mechanically. Respiratory parameters were adjusted to maintain pCO₂, between 35 and 40 torr and pO₂, between 120 and 250 torr. An arterial line was placed in both femoral arteries, and samples were drawn for laboratory profiles, including complete blood count, platelet count, prothrombin time, partial thromboplastin time, and electrolyte levels.

The animals were positioned in a stereotactic headframe. A scalp flap was turned to expose the temporal muscle, which was elevated and reflected anteriorly. A drill was used to make a 1.0-cm craniotomy over the lesser sphenoid wing. With the aid of an operating microscope, the dura was opened and gentle dissection was carried out along the sphenoid wing to identify the suprasellar cistern.

The cistern was catheterized in a standard fashion. A single sharp puncture of the arachnoid was made, and a dual-lumen catheter, primed with saline, was passed through the hole. The diameter of the catheter occluded the arachnoid defect. The dura was sutured, and the suture line was covered with an autologous dural graft glued in place to ensure a watertight seal. The bone plate was replaced, and a cranioplasty was performed to securely reconstruct the skull. Passive return of cerebrospinal fluid (CSF) assured patency of the catheter.

One port of the suprasellar catheter was attached by a low-volume fluid-filled pressure-monitoring line to a transducer and the other to the femoral-cisternal shunt line. With the guidance of stereotactic coordinates, the lateral ventricle was cannulated and similarly monitored. The cisterna magna was also cannulated for pressure recordings. All pressures were referenced to the level of the heart and recorded on a multichannel strip recorder.

The femoral-cisternal shunt was adapted from that described by Steiner, et al. Our modification consisted of adding a pressurized reservoir that allowed only unidirectional flow. The reservoir pressure was monitored by a transducer, and the pressure in the air bladder could be adjusted to maintain the desired delivery pressure throughout the experiment. Delivery rate and volume were recorded using an interposed calibrated drip chamber adapted from that described by Blasberg, et al. In all experiments reported, SAH was delivered at the animal’s physiological MABP.

Experimental Protocol

Twenty-three animals were separated into three experimental groups. The resistance to flow was varied among the groups by using suprasellar catheters of three different diameters. In the first group (nine dogs) a No. 22 catheter (0.7 mm in diameter) was used, in the second group (seven dogs) a No. 19 catheter (1.5 mm in diameter), and in the third group (seven dogs) a No. 16 catheter (1.7 mm in diameter). After baseline data collection, the arterial line was used to prime the shunt reservoir with 60 ml of blood. This blood was maintained at the animal’s MABP. Hemorrhage was initiated by opening the shunt to the cisternal catheter and allowed to continue until it stopped spontaneously. The ICP data were collected for 30 minutes after the hemorrhage had ceased. Once ICP returned to within 20 mm Hg of baseline pressure and no rehemorrhage had occurred, the reservoir was emptied though the shunt to demonstrate that the blood had not clotted in the reservoir or tubing.

The SAH was characterized by continuous recording of the ICP, the SAH driving pressure (MABP − ICP), the SAH flow rate, and the SAH volume. Resistance to CSF outflow (Rₛ) was measured before and 30 minutes after SAH using the bolus technique. The animals were sacrificed by a lethal overdose of barbiturate (recommeded method) and the brains were removed and inspected.

Data Analysis

All parametric data are given as means ± standard deviation. Statistical analysis was performed using an analysis of variance and statistical significance was accepted for p less than 0.05.

Results

Compartmental ICP Recordings

In each experimental group the pressure rose in all measured compartments after SAH, but not uniformly. The pressure increase was most rapid in the suprasellar cistern, and a persistent gradient of 3.5 mm Hg between this cistern and the lateral ventricle was demonstrable in all but two animals. Temporal changes in ventricular pressure during the initial 30 seconds of SAH were similar but significantly slower than in the suprasellar cistern (p < 0.05) (Fig. 1). Five minutes after SAH, the pressures in all three compartments were not significantly different, but a trend toward higher pressure in the suprasellar cistern was identified.

The Rₛ of the femoral-cisternal shunt affected the time course and magnitude of ICP changes measured intraventricularly. The No. 22 catheter group generated less ICP elevation and took longer to do so. The maximum ICP, measured intraventricularly, was 48 ± 27 mm Hg for the No. 22 catheter group and 96 ± 31 mm Hg for the No. 16 and 19 catheter groups combined. The time to maximum ICP was 90 ± 61 seconds for the No. 22 catheter group and 52 ± 20 seconds for the other two groups combined. Both differences were statistically significant (p < 0.05). No significant difference in maximum ICP or time to maximum ICP was noted between the No. 16 and 19 catheter groups.

The ICP elevation caused by SAH gradually subsided in each measured compartment after hemorrhage. The time course of these changes in the No. 16 catheter group is shown in Fig. 1.
P. W. McCormick, et al.

Resistance to CSF Outflow

The resistance to CSF outflow ($R_o$) significantly increased after SAH in each experimental group. With a baseline $R_o$ of $48 \pm 23$ mm Hg/ml/min, the No. 22 catheter group increased to an $R_o$ of $87 \pm 59$ mm Hg/ml/min ($p < 0.03$), the No. 19 catheter group to $156 \pm 98$ mm Hg/ml/min ($p < 0.01$), and the No. 16 catheter group to $273 \pm 152$ mm Hg/ml/min ($p < 0.01$). The difference in the final $R_o$ between each experimental group was statistically significant ($p < 0.05$), indicating a dose-dependent response of $R_o$ to the volume of whole blood deposited.

Duration and Volume of SAH

The No. 22 catheter group hemorrhaged for $394 \pm 202$ seconds and the No. 16 catheter group for $191 \pm 116$ seconds ($p < 0.03$). No significant difference between the No. 16 and 19 catheter groups was noted. The volume of hemorrhage was $10.9 \pm 6.5$ ml for the No. 22 catheter group and $15.1 \pm 7.0$ ml for the No. 16 catheter group ($p < 0.05$). No significant difference between the No. 19 catheter group and the other two groups was found.

CPP and Extent of Hemorrhage

The CPP, measured based on intraventricular pressure, did not drop to zero in any of the animals. For the No. 22 catheter group, the minimum CPP was $67 \pm 29$ mm Hg, which was significantly higher than in the other two groups ($p < 0.01$). The minimum CPP’s for the No. 16 and 19 catheter groups were $31 \pm 15$ mm Hg and $24 \pm 6$ mm Hg, respectively, and were not significantly different.

The CPP nadir marked the point at which the rate of hemorrhage through the shunt began to slow. However, the point of hemorrhage arrest occurred when CPP was returning to baseline (Fig. 2). No correlation was noted between the minimum CPP experienced by an animal and the volume or duration of hemorrhage.

Initial SAH Rate and Extent of Hemorrhage

The initial hemorrhage rate was significantly different ($p < 0.05$) for each of the three groups because of variation in the $R_o$ of the cisternal catheter. The initial flow was $4.4 \pm 2.2$ ml/min in the No. 22 catheter group, $14.6 \pm 2.7$ ml/min in the No. 19 catheter group, and $18.7 \pm 2.2$ ml/min in the No. 16 catheter group.

This initial volumetric flow rate of SAH had a significant positive linear correlation with the volume of blood deposited in the subarachnoid space (23 dogs, $r = 0.64, p < 0.01$) (Fig. 3). A significant negative linear correlation between the minimum CPP and initial volumetric flow rate of hemorrhage was also noted (23 dogs, $r = -0.83, p < 0.01$) (Fig. 4).

Discussion

The Femoral-Cisternal Shunt Model

There are three basic models of experimental SAH. The first is vessel disruption of avulsion via an implanted device. Although this model emulates changing MABP during SAH, it does not allow quantitative evaluation of the hemorrhage rate, volume, or time course. Furthermore, the extensive arachnoid dissection often needed to implant a device leaves the subarachnoid and subdural spaces in continuity. Subsequent hemorrhage will not be limited to the subarachnoid space, nor will the tamponading effects of the cisterns be present. The other two models are infusion models. One is a volume infusion model where a preselected volume of blood is delivered at an arbitrary pressure. The other is a pressure infusion model.
Hemodynamics of subarachnoid hemorrhage arrest

Fig. 2. Graph of the combined data from the No. 16 cisternal shunt group (seven dogs) demonstrating the time course of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) changes after subarachnoid hemorrhage. The point at which bleeding stopped is indicated near the abscissa. Note hemorrhage did not stop at the lowest CPP; rather, it stopped when CPP returned toward baseline values.

Fig. 3. Scattergram showing the volume of blood deposited in the subarachnoid space plotted against the initial volumetric flow of subarachnoid hemorrhage in 23 dogs. A significant positive linear correlation exists between these two variables ($r = 0.64$, $p < 0.01$).

Fig. 4. The minimum recorded cerebral perfusion pressure (minCPP) plotted against the initial volumetric flow of subarachnoid hemorrhage in 23 dogs. A significant negative linear correlation exists between these two variables ($r = -0.83$, $p < 0.01$).

where the infusion occurs at a selected pressure and volume varies accordingly. Our model is of the latter category.

The femoral-cisternal shunt described by Steiner, et al., is an effective way to deliver blood to a cistern at MABP. We have modified the shunt to allow hemorrhages above or below MABP as well. Great care was taken to ensure the delivery of blood at a pressure within 5.0 mm Hg of MABP throughout the hemorrhage. This accuracy was achieved by adjusting the pressurized reservoir that delivered the blood.

An important consideration is whether clotting occurred inside the shunt system and affected the hemorrhage time course and volume. Control studies in which the 60-ml reservoir was drained at 33% of MABP through a high-resistance catheter showed no evidence of clotting. In the present protocol, the fluidity of the blood was confirmed after hemorrhage had stopped by letting the reservoir empty through the shunt tubing. Finally, the fact that the longest hemorrhage duration occurred with the slowest flow condition (No. 22 catheter group) argues against premature clotting.

Compartmental ICP Changes With SAH

Although ruptured aneurysms are often found in a distended, clotted cistern and the anatomy of these barriers has been described thoroughly, their physiological significance has not been thoroughly studied. Temporal pressure changes in the suprasellar cistern, the lateral ventricle, and the cisterna magna are different, thereby indicating that the subarachnoid space behaves like a series of compartments separated by baffles. Cisternal anatomical integrity explains the nonuniform elastance of the subarachnoid space observed in feline models. By slowing blood dispersion, intact cisterns may promote clotting.

The overall change in the lateral ventricle pressure was triphasic (Fig. 1). Pressure rose rapidly with the initial hemorrhage (phase 1), leveled as hemorrhage slowed to a stop (phase 2), and fell toward baseline when hemorrhage was complete (phase 3). The etiology of the rise in ICP associated with SAH is controversial. Diffuse vasoparalysis increasing cerebral blood volume is unlikely, given that CO$_2$ reactivity and pressure autoregulation are preserved in animals with typical SAH-induced ICP changes. Direct observation of pial vessels has demonstrated widespread constriction of these vessels with SAH. Data from one primate model demonstrated an acute brain water increase with SAH, even when ICP rapidly returned to normal. The etiology of this edema did not appear to be ischemic.
Brain Injury With SAH

Autopsy data suggest that brain injury associated with SAH is due to diffuse ischemic damage. Several animal models have failed to demonstrate persistent ischemia below the critical level for infarction. Jakubowski, et al., were unable to demonstrate any relationship among ICP, CPP, or MABP associated with SAH and neurological outcome at 3 months in primates. Steiner, et al., noted EEG abnormalities at or below a CPP of 30 mm Hg, which reversed readily.

Our data demonstrate that the slow-hemorrhage (No. 22 catheter) group had a longer hemorrhage duration but a smaller volume of hemorrhage and less CPP reduction than the faster-hemorrhage (No. 16 and 19 catheter) groups. These faster-hemorrhage groups had shorter hemorrhage duration, but the hemorrhage volume and CPP reduction were significantly greater than in the slow-hemorrhage group.

Brain injury appears to be influenced by the volume of blood deposited in the subarachnoid space and its impact on ICP and CPP. The mechanism of injury may involve transient cerebral ischemia as well as brain distortion.

Arrest of SAH

Although an elevation of ICP with associated reduction in CPP definitely occurs in this and other models of SAH, their relationship to hemorrhage arrest is uncertain. Most experimental work with primates does not support absent perfusion pressure with arrest of CBF following SAH. Jakubowski, et al., found that the lowest CBF in primates was 17 ml/100 gm/min, recorded immediately after SAH. The average CBF immediately after SAH was 60% of baseline. Dorsch, et al., conducted a series of 29 SAH’s in primates and concluded that hemorrhage arrest could not be attributed to reduced CPP alone. Kuyama, et al., reported a vessel disruption model of SAH in the baboon in which the average reduction of CPP was 50%.

Data reported by Steiner, et al., from studies using a canine femoral-cisternal shunt did not demonstrate a drop in CPP to 0 mm Hg. Trojanowski noted a characteristic slowing of hemorrhage before it stopped in a feline SAH model. Both of these studies showed hemorrhage arrest after CPP was recovering from its nadir. As mentioned, clinical experience and results obtained in awake animal models of SAH are not compatible with a mechanism of perfusion arrest to stop SAH. Our data also demonstrate that hemorrhage arrest occurs well after CPP reaches its nadir (Fig. 2). In addition, no relationship between either the volume of blood deposited during SAH or duration of SAH and minimum CPP could be demonstrated. This finding is inconsistent with the concept that a reduction in CPP after SAH is primarily responsible for hemorrhage arrest.

An interesting correlation between the volumetric flow rate of hemorrhage and the volume of blood deposited emerged in this work. The greater the initial hemorrhage flow rate, the greater the volume of hemorrhage and the shorter the duration of hemorrhage. Effective blood clotting was essential for hemorrhage arrest in this and other SAH models and may be influenced by either the rate or the volume of SAH. One possible explanation for this is that a critical volume of blood must be deposited within the local CSF space to allow clot formation. Cerebrospinal fluid may retard clot formation and strength by direct or indirect effects on the coagulation cascade. Another interpretation is that a critical slowing of the hemorrhage rate is necessary and is achieved by reducing CPP to a level where effective clot disposition is possible. Both of these statements may be true and simultaneously influence the time course of SAH. A unifying concept is that the hemorrhage rate and volume influence SAH duration, suggesting that hemorrhage arrest may depend on the mechanics of CSF displacement from the local cistern by blood, which allows effective clot formation.

Clinical Implications

The important influence of initial hemorrhage rate on the dynamics of SAH can be explored using Poiseuille’s law. Mean arterial blood pressure and ICP determine the pressure gradient of the hemorrhage, the viscosity of blood is fixed, and variation in the thickness of the aneurysm wall is negligible. Consequently, the radius of the aneurysm breach is left as the major determinant of hemorrhage rate. This relationship supports current operative strategies for unclippable aneurysms. Reinforcing such aneurysms with muslin or other substances that induce a fibrotic response may prevent rupture. If rupture does occur, the fibrosis may limit the size of the aneurysm breach, the volume of hemorrhage, and the extent of damage.

References

Hemodynamics of subarachnoid hemorrhage arrest


Manuscript received November 19, 1991. Accepted in final form August 13, 1993.

Address reprint requests to: Robert F. Spetzler, M.D., c/o Editorial Office, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, Arizona 85013–4496.