Subarachnoid Hemorrhage: An Update for Internists

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Subarachnoid Hemorrhage: What Every Internist Should Know

Subarachnoid Hemorrhage (SAH) is a neurological emergency that affects 30,000 Americans each year. Internists frequently do the initial evaluation of these patients when they present with headache, syncope or new neurological deficit. The incidence is perhaps surprisingly higher than several other "common" neurological diagnoses. (See Table 1) Prompt recognition, appropriate evaluation and referral for neurosurgical evaluation and care are critical, as the initial management has great impact on outcomes. Neurosurgeons, neuroradiologists, critical care physicians, cardiologists and general internists often manage these patients together, and a level of common understanding is desirable and necessary.

SAH is characterized by extravasation of blood into the cerebrospinal fluid (CSF) containing spaces around the central nervous system (CNS) and is the cause of 2-5 percent of all strokes and 5 percent of stroke deaths. Rupture of an intracranial aneurysm (ICA) is the cause in 80 percent of non-traumatic SAH, and the prognosis is grave with an average case fatality rate of 51 percent. Among the remaining causes of non-traumatic SAH is isolated perimesencephalic subarachnoid hemorrhage. It is associated with a good prognosis and rarely causes neurological complications. Approximately 10 percent of patients suffer sudden death from the acute and catastrophic increase in intracranial pressure and an additional 10-20 percent arrives in the Emergency Department in coma.

TABLE 1. INCIDENCE OF SELECTED MAJOR NEUROLOGIC DISORDERS IN THE UNITED STATES*

DISORDER	Annual Incidence (per 10,000 Persons)
Cerebral infarction	12.0
Aneurysmal subarachnoid hemorrhage	1.0
Bacterial meningitis	0.9
Multiple sclerosis	0.6
Intracranial glioma	0.5
Guillain-Barré syndrome	0.2
Amyotrophic lateral sclerosis	0.2

*Data are from population studies in Rochester (Olmstead County), Minnesota
Schievink WI. N Engl J Med. 1997;Jan 2:(1)28-40.

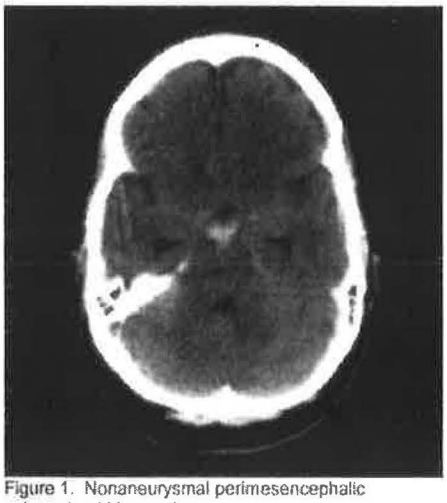


Figure 1. Nonaneurysmal perimesencephalic subarachnoid hemorrhage.
Wijdicks EF. *Mayo Clin Proc.* 2005;80(40):550-9

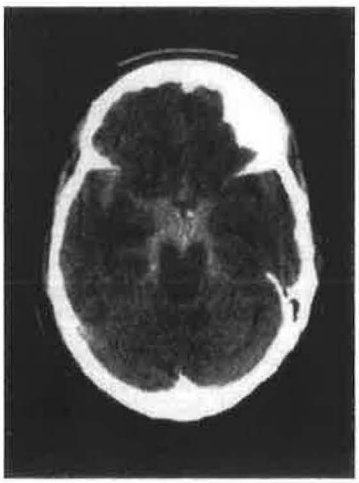


Figure 2. Aneurysmal Subarachnoid hemorrhage
Schievink WI. N Engl J Med. 1997;Jan 2:(1)28-40.

Morbidity and mortality from SAH result from a broad spectrum of complications. Approximately 25-30 percent of deaths and disabilities following SAH can be attributed to the initial hemorrhage. Up to 30 percent will suffer a delayed ischemic neurologic deficit due to cerebral vasospasm. Hydrocephalus occurs acutely in about one fifth of patients, half of whom will require permanent ventriculoperitoneal (VP) shunt placement. Almost half of survivors suffer long-term cognitive impairment, many of whom never return to work.

This review will focus predominantly on SAH from intracranial aneurysm rupture and highlight the aspects most pertinent to internists who participate in their care.

Demographics

The incidence of SAH has remained stable over the last 30 years with an aggregate worldwide incidence of 10.5 cases per 100,000 populations. It affects women 1.6 times more commonly than men, blacks 2.1 times more often than whites and has a peak incidence around age 55. The major risk factors include cigarette smoking, hypertension, cocaine use and heavy alcohol use. Patients with first degree relatives who suffered SAH are at higher risk. To date, no single gene has been identified as responsible for ICA formation. The genetics of the disorder appear to be complex, involving multiple loci and interactions of multiple genes. In total the risk is three to seven times higher in first degree relatives of patients with SAH than the general population. Japan and Finland have higher incidences of SAH with estimates at between 14 and 19 per 100,000 persons. Another high risk group includes patients with heritable diseases associated with the presence of ICA such as Ehlers-Danlos type IV, Autosomal Dominant Polycystic Kidney Disease, pseudoxanthoma elasticum and glucocorticoid remediable aldosteronism (note that Marfan Syndrome is not among these). In these diseases and in familial ICA, rupture occurs earlier, in smaller aneurysms, and causes more morbidity and mortality.

Intracranial Aneurysms

The prevalence of saccular intracranial aneurysms in autopsy series is between 1 and 5 percent, but many are very small (less than 4mm in size). The prevalence of incidental intracranial aneurysms among adults undergoing angiography is closer to 0.5-1 percent. The number of affected Americans then is 2-10 million with multiple aneurysms occurring in twenty to thirty percent of those affected.

Intracranial aneurysms are more common than aneurysms arising from the extracranial arteries of similar size. One possible reason for this observation is that the intracranial arteries have an attenuated tunica media and lack external elastic lamina. On microscopic examination, typical saccular aneurysms have very thin tunica media or none, and the internal elastic lamina is either absent or severely fragmented. On macroscopic examination, ruptured ICAs have irregular appearance and the point of rupture is generally at the dome of the aneurysm.

Table 2. Location of aneurysms

Anterior Circulation 85%	Posterior Circulation 15%
Posterior Communicating Artery 25%	Basilar Artery 10 %
Middle Cerebral Artery 20%	Vertebral Artery
Anterior Cerebral Artery 30%	Posterior cerebral artery, PICA, AICA
Ophthalmic ICA, ICA bifurcation, Anterior Communicating Artery	

Aneurysms are named for the nearest branch of the parent artery to which the sac has a hemodynamic relationship. Anterior circulation aneurysms comprise about 85 percent of aneurysms and posterior or vertebrobasilar system aneurysm make up 15 percent. The anatomic location of the aneurysm has significance with respect to rates of rupture.

Screening for ICA

Screening is currently recommended for only select groups of patients at high risk based on family or personal history, and for whom treatment is likely to prevent death or disability. Asymptomatic patients in families with two or more affected members should be screened with magnetic resonance angiography (MRA). Currently, screening in patients with ADPKD is controversial, but can be individualized based on the presentation of affected family members.

Natural History

The risk of rupture in ICA depends on the size and location of the aneurysm. The most important study of the natural history of ICAs is the International Study of Unruptured Intracranial Aneurysms (ISUIA). The first publication of the ISUIA investigators was a retrospective analysis of 1937 aneurysms divided into those without history of SAH (group 1) and those with history of previous SAH (group 2). The cumulative risk of rupture per year in group one was 0.05% for aneurysm less than 10mm and approximately 1% for aneurysms greater than or equal to 10mm. The most important finding was that, after 7.5 years of follow-up, the rate of rupture for aneurysms less that 10mm was 11 times higher in patients with a history of prior SAH (0.5% per year) than for those without. Rupture rates for aneurysms larger than 10mm was 0.65% per year for patients with a history of SAH, although, large and posterior circulation aneurysms were notably infrequent in that group. This study, however, was controversial. Because it included intracavernous carotid aneurysms (outside the subarachnoid space, very low risk of rupture) and infraclinoid ophthalmic aneurysms (often protected by dura and bone), the results were felt to under-represent the risk of ICA rupture.

In 2003 the ISUIA investigators published a prospective study of 4060 patients with ICAs in the US, Europe and Canada. The natural history group included 1692 that did not have aneurysm repair and were followed to assess their risk of SAH. Patients were divided into two groups based on personal history of SAH (group 1 – no history of SAH, group 2 – prior SAH). Rates of rupture were lowest in the cavernous carotid, intermediate in the anterior circulation, and highest in the posterior circulation. Cumulative 5 year rates (based on mean follow-up of 4.1 years) are as follows:

Table 3. Rates of aneurysm rupture.

	<7mm		7-12mm	13-24mm	>25mm
	Group 1	Group 2			
Cavernous carotid artery (n=210)	0	0	0	3.00%	6.40%
AC/MC/IC (n=1037)	0	1.50%	2.60%	14.50%	40%
Post-P comm (n=445)	2.50%	3.40%	14.50%	18.40%	50%

AC= anterior communicating or anterior cerebral artery. IC=internal carotid artery (not cavernous carotid artery). MC= middle cerebral artery. Post-P comm=vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery

ISUIA Lancet 2003; 362: 103-110

Interestingly, prior history of SAH was associated with increased rate of rupture only with aneurysms less than **7mm** in size. Patients without prior history of SAH and lesion greater than 7mm in size had higher rates of aneurysm rupture than was suggested by the retrospective study. The risk was greatest for aneurysms 7-9mm in diameter. The five year mortality in the observational group was 12.7%.

Management of Unruptured ICA

The ISUIA 2003 paper also reported outcomes for patients undergoing surgical or endovascular repair of their aneurysm. Risk of surgery increased with advancing age, aneurysm size greater than 12mm and posterior circulation aneurysm. Risk of endovascular repair increased with size and posterior location of aneurysm but not with age. The authors note that in many clinical scenarios, the likelihood of poor outcome from surgery was greater than or equal to the risk of rupture at 5 years, and therefore the clinical approach should be individualized for each patient. There are examples of those patients who clearly benefit, such as a person less than 50 years of age with a posterior communicating artery aneurysm between 7-24mm in size.

The Stroke Council of the AHA issued a scientific statement to offer guidelines for the management of patients with unruptured ICA in 2000. Subsequent study of the natural history of unruptured ICAs has determined the risk of rupture is higher at a size of 7mm. The main concepts of these guidelines are still relevant to much of the clinical decision making, although smaller aneurysms would be considered for treatment on the basis of information from the ISUIA.

1. Treatment of small incidental intracavernous ICA aneurysms is not indicated. Management of symptomatic aneurysms in this location should be approached with consideration of patient age, severity and progression of symptoms, life expectancy and available treatment options.

2. Symptomatic intradural aneurysms of all sizes should be considered for treatment with relative urgency if acutely symptomatic. Symptomatic large or giant aneurysms should be evaluated by neurovascular surgeons in centers with expertise, and with careful analysis of patient specific characteristics.

3. Coexisting or remaining aneurysm of all sizes in patient with SAH from another aneurysm have higher risk for future hemorrhage than do similar aneurysms in patients without history of SAH. Accordingly, these aneurysms require consideration of treatment. Aneurysms of the basilar apex carry relatively high risk of rupture. Treatment decisions must consider patient characteristics and risk of repair. If a decision is made to observe the aneurysm, then periodic reexamination with CTA/MRA or selective contrast angiography should be performed, with consideration of technical factors that affect reliability of measurements obtained.

4. Incidental small (<10mm) aneurysms carry a generally low risk of rupture in patients without history of SAH, and observation is generally advocated in favor of treatment. Young patients deserve special consideration as do those with more unstable aneurysm anatomy such as the presence of a daughter sac, or in patients with family history of SAH. Follow up imaging may demonstrate a change in size or configuration that can lead to consideration of intervention.

5. Asymptomatic aneurysms of 10mm or greater in size warrant strong consideration of treatment after evaluation of operative risk based on patient age, comorbidities and relative risk of the treatment options available.

Bederson JB. Circulation. 2000;102(18):2300-8.

Diagnosis of Subarachnoid Hemorrhage

Most ICAs remain asymptomatic until they rupture. The typical presentation encompasses a spectrum from sudden death to an unusual and severe headache with acute onset often called a "thunderclap headache". These headaches are frequently accompanied by stiff neck, nausea or vomiting and sometimes loss of consciousness. Up to one third of patients with SAH have a history of an unusual headache in the days to weeks preceding hospitalization. This

phenomenon is known as a "warning leak" or "sentinel bleed". These headaches develop in seconds, gain maximal intensity in minutes and then last for hours to days. In some cases the intensity of the headache is moderate to mild, and it may resolve spontaneously or be relieved by over the counter analgesics, but the abrupt onset and unique characteristics should raise suspicion. In two prospective studies of patients with an initial presentation of "the worst headache" of their lives and normal neurological exam the incidence of SAH was 12 percent.

Misdiagnosis in patients with SAH has been estimated at between 12 and 50 percent in various studies. Patterns of diagnostic error include failure to appreciate the spectrum of clinical presentations, failure to understand the limitations of CT and failure to perform and correctly interpret the results of lumbar puncture. Patients with normal physical exam, smaller hemorrhages and characteristics of patients with lower health literacy are more likely to be misdiagnosed. Common diagnoses given to these patients include migraine, tension or cluster headache, sinusitis, neck strain, sciatica and meningitis. When the diagnosis is missed in this subset of patients with good condition initially, morbidity and mortality are significantly higher.

The physical examination may show retinal hemorrhages (including Terson syndrome), nuchal rigidity, restlessness, diminished LOC and cranial nerve palsies, aphasia and focal motor findings. Note that aneurysmal third nerve palsy dilates the pupil, whereas microvascular infarction frequently does not. None the less, patients with partial lesions that spare the pupil should still be evaluated for aneurysm.

TABLE 4. Physical Findings in Patients with Subarachnoid Hemorrhage

FINDING	LIKELY LOCATION OF ANEURYSM
Nuchal rigidity	Any
Diminished level of consciousness	Any (could result from possible complications of aneurysmal rupture; hydrocephalus, hematoma or ischemia).
Papilledema	Any
Retinal and subhyaloid hemorrhage	Any
Third-nerve palsy	Posterior communicating artery
Sixth-nerve palsy	Posterior fossa*
Bilateral weakness in legs or abulia	Anterior communicating artery
Nystagmus or ataxia	Posterior fossa
Aphasia, hemiparesis, or left-sided visual neglect	Middle cerebral artery

*Sixth-nerve palsy may also be associated with nonspecific changes related to increased intracranial pressure. Edlow JA NEJM 2000; 342:29-36

Non-contrasted head CT should be the first diagnostic test, but the technique is important. Three mm cuts through the base of the brain in the plane of the small palate are recommended as they have better sensitivity for detecting small collections of blood while minimizing artifact from adjacent bone. The sensitivity of CT decreases over time from the onset of symptoms with 98-100 percent recognized within twelve hours and 93 percent recognized in the first 24 hours. By seven days after the event, the sensitivity drops to 50 percent. It is important to consider the skill and experience of the radiologist interpreting scans when extrapolating this data. Correct interpretation of head CT in SAH requires careful examination of the posterior horns, sylvian fissure and sulci where the appearance of subarachnoid blood can be subtle. Intracerebral extension is present in 20-40 percent and subdural blood in 2-5 percent respectively. MRI is inferior to CT for the detection of acute SAH and is more expensive and less readily available

Lumbar puncture should be performed in every patient whose presentation suggests SAH and whose CT scan is negative, equivocal, or technically difficult. Traumatic taps occur in up to 20 percent of lumbar punctures and must be distinguished from true SAH. Misinterpretation of CSF red cell counts is a contributor to missed diagnosis of SAH. The utility of comparing the number of red cells between tubes 1 and 4 is debated. Some authors recommend clarification of bloody CSF interpretation by repeat LP one interspace higher than the initial attempt. Immediate

centrifugation of the sample can help differentiate the xanthochromia seen with the presence of hemoglobin degradation products in the CSF from traumatic tap. It takes two hours for xanthochromia to occur after SAH, thus it is recommended that LP be deferred for at least six hours. Xanthochromia can last for up to two weeks. The specimen should be examined in bright light against a white background. Clinical circumstances that obfuscate the detection of xanthochromia include marked hyperbilirubinemia, elevated CSF protein concentrations (greater than 150 mg/dL), greater than 100K RBC in the specimen and contamination with betadine. Visual inspection of the CSF can be unreliable in the presence of hemolyzed clot or bilirubin. Spectrophotometry has been shown to be more sensitive and in Europe, is used more routinely.

Once a diagnosis of SAH is suspected or confirmed, 4 vessel angiography or CT angiography should be obtained promptly to identify and characterize the source of the hemorrhage. Three dimensional rotational angiography allows volumetric data acquisition during the angiogram. Its primary advantage over two dimensional angiography is the delineation of the complex relationships between the aneurysmal neck and adjacent arteries. CT angiography is gaining popularity due to its noninvasive nature and sensitivity and specificity that approaches that of cerebral angiography. It also offers information about the relationship of the aneurysm to the skull base. Of note, the contrast dye load for CT angiography and conventional angiography are comparable and generally in the range of 100cc. The risks of standard cerebral angiography are 0.1% mortality and 0.5% permanent neurological injury. These unfortunate outcomes are more common in the elderly, those with atherosclerotic disease and Ehlers-Danlos type IV.

If the initial arteriogram is negative for ICA, follow up arteriography should be obtained in one to two weeks after the hemorrhage. In cases where no aneurysm is identified, MRI can be useful in detecting vascular malformations of the brain or spinal cord. MR Angiography is essentially without risk, but is used most commonly as a screening tool, and for detecting aneurysms with intraluminal thrombus that may be missed by conventional arteriography. MRA does not have utility in surgical planning in most circumstances.

The major factors that correlate with outcome are the patient's level of consciousness on admission, their age, and the amount of blood shown by the admission head CT. A variety of grading scales has been used to assess prognosis after SAH and are based on the patient's level of consciousness at presentation. In 1968 Hunt and Hess proposed the first such scale which is based on presenting neurological exam.

Table 5. Hunt-Hess Scale

Grade	Criteria
I	Asymptomatic, or minimal headache, nuchal rigidity
II	Moderate to severe headache, no neurologic deficit x cranial nerve palsy
III	Drowsiness, confusion, mild focal deficit
IV	Stupor, moderate to severe hemiparesis, early decerebrate posturing
V	Deep coma, decerebrate posturing, moribund

Hunt WE, Hess RM. J Neurosurg. 1968;28(1): 14-20.

Fisher described the extent of hemorrhage based on the CT appearance at initial presentation

Table 6. Fisher Scale.

Grade	
Fisher 1	normal CT
Fisher 2	Less than 1mm thickness of blood
Fisher 3	More than 1mm thickness of blood
Fisher 4	Any amount of subarachnoid blood with IVH and/or ICH

Fisher CM. Neurosurgery. 1980;6(1): 1-9.

Thick subarachnoid clot and bilateral ventricular hemorrhage are both predictive of poor outcome and can be reliably graded on head CT.

The World Federation of Neurosurgeons revised the clinical grading scale in 1998 to incorporate the less subjective Glasgow Coma Scale.

TABLE 7. Grading System Proposed by the World Federation of Neurosurgical Societies (WFSN) for the Classification of Subarachnoid Hemorrhage

WFNS Grade	Glasgow Coma Scale Score	Motor deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Report of World Federation of Neurological Surgeons. *J Neurosurg.* 1988;68(6):985-6.

The overall score on the Glasgow Coma Scale is the sum of points for eye opening (4 points), best motor response (6 points), and best verbal response (5 points).

General Management

After a ruptured aneurysm is diagnosed the aneurysm is secured as quickly as possible, typically within 48-72 hours of the hemorrhage. Immediate patient care priorities surround stabilizing the patient and minimizing the risk of rerupture. The risk of re-rupture in the first 24 hours is 4 percent with associated mortality of 27-43 percent. The risk of rebleeding then decreases to 1.5 percent per day and falls off over two to three weeks following the acute hemorrhage. Both elevations and sudden fluctuations in blood pressure can cause recurrent hemorrhage.

Close monitoring in a neurological intensive care unit is required to detect neurological deterioration due to aneurysmal rebleeding, acute hydrocephalus, early cerebral vasospasm, or medical complications. Protection of the airway when indicated, initiation of drugs to prevent vasospasm, anti-epileptic therapy if seizures have occurred and adequate intravenous fluids with isotonic fluids are the initial measures. Hypertension is commonly observed in patients with SAH, and should be treated to target systolic BP less than 180 or to MAP between 100 and 120 in patients with unsecured aneurysms. The use of short acting IV medications such as labetalol, nicardipine or hydralazine is generally preferred so that quick adjustments can be made as necessary.

Prevention of venous thromboembolic phenomena is achieved with sequential compression devices on the lower extremities. Hyperthermia and fever are associated with poor outcomes and should be treated with acetaminophen and cooling devices.

If acute hydrocephalus is felt to be the cause of obtundation, or if the ventricles are enlarging on serial CT scans, external ventricular drainage may be performed prior to surgery. A prompt clinical response is often seen, but if none occurs in the first 24 to 36 hours, the clinical state is more likely due to the effects of the hemorrhage itself.

Neurosurgical Management

Microsurgical clipping is the mainstay of surgical therapy for ruptured intracranial aneurysms. Aside from securing the aneurysm, operative strategies include evacuation important intracranial hematoma and subarachnoid clot to reduce the risk of hydrocephalus post operatively. Ideally, all patients should have the aneurysm secured, but the mortality is high if the patient is stuporous or comatose (Hunt Hess grade 4 or 5). Surgery may be delayed in higher grade patients whose prognosis is grave. In a large meta-analysis of complications of surgical clipping of ICAs that included 2460 patients, the overall mortality was 2.6% and permanent morbidity 10.6%. Surgical

risk for repair of unruptured intracranial aneurysm is lowest in small anterior circulation aneurysms (0.8% mortality, 1.9% morbidity) and highest in large posterior circulation aneurysms (9.5% mortality, 37.9% morbidity). There is lower morbidity and mortality in high volume hospitals (20 or more cases per year) versus low volume hospitals (fewer than 4 cases per year). There is a slow downward trend in surgical morbidity and mortality in some series likely attributable to the option of endovascular treatment of ICAs in some of the higher risk patients with larger posterior circulation aneurysms and the elderly.

In 1991 Guglielmi and colleagues introduced the detachable coil for treating intracranial aneurysms endovascularly. The GDC coil received FDA approval in 1995, and techniques for using the coils have been dynamically evolving ever since. The coils were originally composed of inert metals that, when deployed into the aneurysm, induced thrombosis by interrupting normal flow. New coated, biologically active coils promote clot formation and enhance cell proliferation and adhesion but carry the potential risk of stenosis of the parent artery. Even newer hydrocoils are made of platinum and a hydrogel that expands up to nine fold to fill the aneurysm cavity. Other advances include deployment of these coils assisted by balloon occlusion or concomitant stent placement, making more aneurysms suitable for coiling versus microsurgical clipping.

The obvious advantage offered by endovascular coiling is avoiding craniotomy. The drawbacks of endovascular treatment are the potential for reopening of the aneurysm over time due to impaction of the coils, increased need for retreatment and slightly increased risk of rebleeding. Follow up after coiling requires repeated angiographic evaluation. Currently, the risk of morbidity for endovascular treatment of unruptured aneurysms is 5-10% with essentially zero mortality.

In 2002 the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group published the first prospective randomized trial in 2143 patients with ruptured ICA comparing outcomes after endovascular coiling versus surgical clipping. The data monitoring committee stopped recruitment early on the basis of an interim analysis. In the endovascular group 23.7% of patients either required assistance with daily living or were dead at one year of follow up compared with 30.6% in the surgical group. The relative and absolute risk reductions were 22.6% and 6.9% respectively. Risk of rehemorrhage from the ruptured aneurysm after 1 year was 2/1276 patients treated with coils and 0/1081 patients treated surgically. The ISAT results suggest that if both treatments are suitable for a ruptured aneurysm, endovascular coil treatment is significantly more likely to result in survival free of disability at 1 year after SAH. The long term durability of coiling is still under investigation.

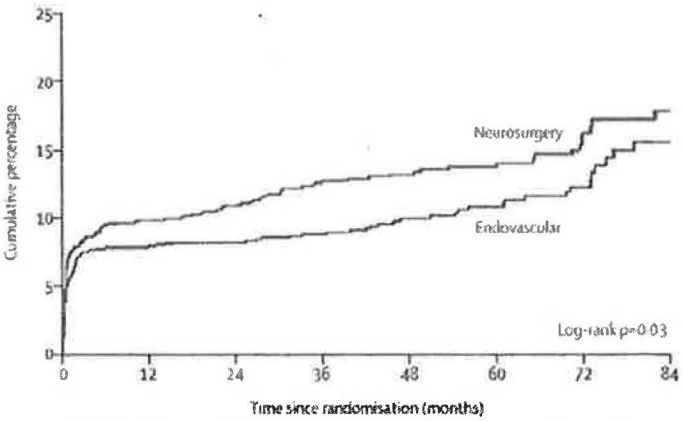


Fig 3. Kaplan Meier curve of cumulative mortality for 7 years from ISAT

Molyneux AJ et al. Lancet. 2005;366(9488):809-1 7.

In 2005 the ISAT follow up report on survival, dependency, seizures, rebleeding and aneurysm occlusion was published in the Lancet. At one year 23.5% of the patients allocated to endovascular treatment were dead or dependent compared with 30.9% of the surgically treated group with absolute risk reduction of 7.4%. The cumulative mortality curve to 7 years showed slightly more deaths in the neurosurgical group, but late aneurysm rebleeding was uncommon in both groups once again confirming that the early benefit of coiling is unlikely to be overcome by late rebleeding from endovascular repair. The relative risk of seizures is significantly lower with coiling than with neurosurgery (RR 0.52, CI 0.37-0.74).

Recent publication of a report from the Cerebral Aneurysm Rerupture After Treatment (CARAT) Investigators provides information on up to 9 years of follow up after either endovascular or surgical treatment after SAH. The study looked at 1010 patients (711 surgically clipped and 299 treated with coil embolization) and found that rerupture of aneurysms treated by either coil or surgical clipping is rare after the first year. Although late retreatment is more common after coil embolization, the complication rates are low. Late events related to rebleeding or retreatments are unlikely to overwhelm differences between procedures at 1 year follow up observed in the ISAT trial.

Several nonrandomized studies looked at the rates of symptomatic vasospasm and delayed ischemic neurologic deficits in operated and coiled patients and could not demonstrate a significant difference. Some small recent studies point out a trend towards better outcome scores at early follow up and a decrease in duration of hospital stays for patients treated with endovascular interventions. A comparison in The Netherlands published this year studied the cost of treating unruptured aneurysms with clipping versus coiling and showed a total cost $8,865 EUR for clipping and $10,370 EUR for coiling ($11,100 US versus $13,000 US). Costs of clipping were mainly determined by ICU care and length of stay (10.5 vs 3.4 days), whereas the main cost of coiling is the coils ($5600 EUR).

In 2005, Qureshi et al published an analysis of morbidity and mortality rates in patients hospitalized for ruptured and unruptured intracranial aneurysms. The analysis was intended to investigate the impact of endovascular interventions. Using the National Hospital Discharge Survey data, three time periods were studied: 1986-1990, 1991-1995, and 1996-2001. The mortality rates for hospitalization with SAH remained stable around 26 percent, but the mortality for unruptured aneurysm treatment showed a significant downward trend from around 6 percent to 1.4%. In contrast, a study of all outcomes in population based studies from 1960-1992 found the case fatality rates varied between 67 percent and 32 percent, with an average decrease of 0.5-0.9 percent per year.

There are no published or generally accepted guidelines to choose between surgical and endovascular treatment of unruptured ICA. The following factors influence the selection of treatment modalities:

1. Location of the aneurysm
2. Relationship of the aneurysm with its parent vessel and other branches
3. Aneurysm dome-to-neck ratio (aneurysm neck size less than 4mm or dome/neck ratio of 2 are favorable for coiling)
4. Surgical and endovascular accessibility
5. The presence of local mass effect attributable to the aneurysm (may favor surgery).
6. Age and general medical condition of the patient
7. Patient's preference.

The decision should be made by a team of experts in neurovascular surgery, interventional neuroradiology and stroke neurology.

COMPLICATIONS

Cerebral Vasospasm

Cerebral arterial vasospasm following SAH is a complex problem whose pathophysiology is not completely understood. In general SAH is associated with global reduction and/or dysregulation in cerebral blood flow (CBF) and cerebral oxygen metabolism, which worsens with the severity of hemorrhage. Arterial narrowing, predominantly in the large intradural arteries of the circle of Willis, is demonstrable on angiography usually between 4 and 14 days after the hemorrhage.

Although the phenomenon is seen radiologically in 60 percent of patients, in only half of those does it cause neurologic symptoms (delayed ischemic neurologic deficits, or DINDs). Whether a patient with angiographic vasospasm develops symptoms depends on the length and severity of the arterial narrowing and other factors that influence cerebral blood flow such as BP, ICP, CO, viscosity and brain metabolic demand as influenced by temperature, seizures and drugs. Symptoms and signs probably do not develop unless there is a greater than fifty percent narrowing of the arteries.

Cerebral vasospasm is unique among vasospastic processes in that there are acute histopathological changes in the arterial walls including thickening of the wall, loss of capacitance, and derangement of autoregulation. Later, as the spasm reverses, there may be some fibrosis and proliferation of the myointimal cells and extracellular matrix in the tunica intima. It can occur in any setting where there is blood or clot in the subarachnoid space such as trauma, hemorrhage from AVMs and after surgery in the basal cisterns as well as after SAH. The search for the "spasmogen" occupies a good deal of the neurosurgical literature about SAH.

The most powerful predictors of vasospasm are the volume, density and prolonged presence of subarachnoid blood around extradural arteries. Data extracted from the studies of the drug tirilizad in the early 1990s suggest that patients at highest risk are those with worse neurological grade, thicker clot on admission head CT, larger aneurysm size, intraventricular hemorrhage. The etiology is felt to be related to the exposure of the adventitial side of the artery to clot and its breakdown products in part because it takes 3 days for erythrocytes to degrade in the subarachnoid space corresponding well with the onset of clinical vasospasm. Oxyhemoglobin has been shown in animal models to produce vasospasm directly. Oxyhemoglobin also stimulates secretion of endothelin and generates activated oxygen species that play a role in lipid peroxidation and smooth muscle spasm. It can also decrease production of vasodilating substances such as nitric oxide. Vasospasm is felt to be predominantly a hemodynamic problem with speculation as to the role of thromboembolic phenomena.

The onset of symptomatic vasospasm can be sudden or insidious. The usual clinical scenario is progressive confusion, delirium and decline in consciousness with or without focal neurological deficit. Careful and frequent neurological assessment is a critical tool for detecting vasospasm. The differential diagnosis of DIND after SAH is broad and patients often manifest more than one cause simultaneously. Investigation of changes in neurological status in SAH patients during the 'vasospastic period' involves detailed neurological and general examination to determine the cause. CT of the head is done first to exclude rebleeding, surgical complications, hypodense areas which would indicate infarction, and hydrocephalus. Concomitant investigation for metabolic disturbance, infection, and seizure activity is recommended. The incidence of non-convulsive status epilepticus is quoted at between 8 and 20 percent in comatose SAH patients. Ultimately a specific test to look for vasospasm such as Transcranial Doppler (TCD), CT angiography and or perfusion scanning, or arteriography is often required to definitively answer the question about the contribution of vasospasm.

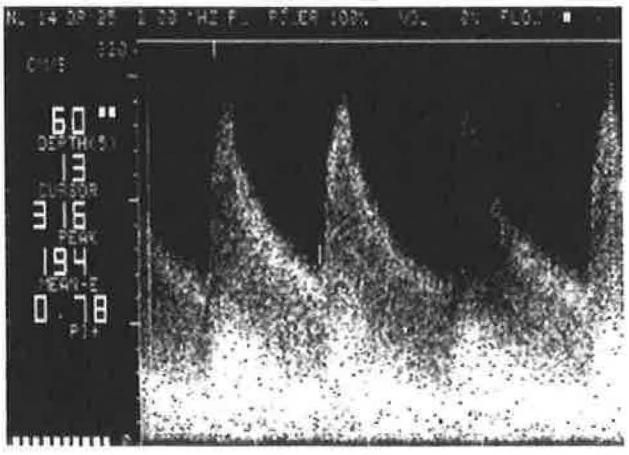


Figure 4. Transcranial Doppler Ultrasound of Middle Cerebral Artery

The only ancillary diagnostic tool available at the bedside is Transcranial Doppler ultrasound. This technique examines the MCA (most accessible) and requires both adequate anatomic windows through the skull and a skilled operator. An increase in velocity of blood flow indicates

that vasospasm is present. Velocity of less that 100cm/sec by TCD is considered normal. Velocity of 120-150cm.sec, is very specific for the presence of vasospasm (greater than 90%), though not especially sensitive (50-60%). The likelihood of severe arteriographic vasospasm is high with velocities greater than 200cm/sec. Sensitivity can be improved by looking at the trend of flow velocities over time. Increases of more than 50cm/s over 24 hours are worrisome for onset of clinical vasospasm.

CT angiography is improving as a tool for the diagnosis of vasospasm, particularly in proximal arteries, but is less useful than conventional angiography for evaluation of distal vessels and for differentiating mild and moderate spasm. MRA is not very useful because it takes a long time to acquire the images and high incidence of motion artifact. CT angiography has the obvious advantage of being noninvasive, and the dye load for CT versus conventional angiography is comparable at approximately 100-130cc. Other advances in measurement and monitoring of cerebral blood flow include Xenon CT, perfusion CT, diffusion and perfusion weighed MRI, continuous EEG monitoring, jugular bulb oximetry, and microdialysis in the distribution of the affected artery with measurement of lactate/glucose and lactate/pyruvate ratios.

Therapy of Cerebral Vasospasm

The prevention of vasospasm involves early operation or intervention on the aneurysm, evacuation of important intracerebral hematomas and ventricular drainage, as well as maneuvers to optimize CBF and to reduce cerebral metabolic demand. The medical components include avoiding hypotension, fever, volume depletion, hyponatremia, hypomagnesemia, seizures, hypercapnia and hypoxia. Adjunct measures to lower ICP may include hyperventilation, mannitol, sedation and paralysis. Empiric steroids and prophylactic antiepileptic therapy are not recommended.

The main treatments for vasospasm are induced hypertension (hemodynamic augmentation) and dilation of spastic arteries with balloon angioplasty and selective intra-arterial infusions of papaverine or calcium channel blocking agents.

Hemodynamic therapy is called "Triple H" therapy and involves induced hypertension, hypervolemia and hemodilution. The idea behind induced hypertension is that by driving cerebral blood flow externally, one can minimize the damage done when autoregulation of cerebral blood vessels is lost. There is no clear guideline as to what the goal of therapy should be. Some experts recommend elevation of SBP to greater than 160, others suggest a goal of 20 mm Hg above the preoperative baseline. Early studies that attempted intracerebral vasodilatation with antihypertensive agents had negative consequences

The use of hypervolemia is based on the observation that volume depletion is a risk factor for vasospasm in patients with SAH, and that infusions of fluids and colloid are a necessary component of achieving elevated blood pressure. However, the risk of cardiac and pulmonary complications from iatrogenic volume overload is also significant. Therefore, a goal of maintaining or slightly augmenting effective arterial blood volume is likely the best strategy. Induced hypertension has a reasonable rationale as therapy given the loss of autoregulation in cerebral blood vessels seen in SAH and vasospasm and resultant compromise of CBF. Early studies that attempted intracerebral vasodilatation with antihypertensive agents had negative consequences. Reversal of neurological deficits can occur after blood pressure augmentation, but guidelines are not very helpful with regard to goal SBP or with respect to most effective pressor agents. Currently used pressor agents include phenylephrine, norepinephrine and dopamine. Some experts recommend elevation of SBP to greater than 160, others suggest a goal of 20 mm Hg above the preoperative baseline.

The third component of HHH therapy is hemodilution, and it is based on the theory that reduced blood viscosity improves cerebral blood flow. There is no evidence that hemodilution is effective.

Systematic reviews of triple H therapy as a prophylactic strategy showed a reduced risk of symptomatic vasospasm but not of DIND, and despite one study that suggested decreased mortality, there was insufficient evidence to recommend it. The studies are generally small, unrandomized, and limited by lack of standardization of parameters of the components of therapy (goal CVP, PCWP, CO). The complications of HHH therapy include rebleeding from unsecured aneurysms, hemorrhagic transformation of infarcts, myocardial ischemia and congestive heart failure, pulmonary edema, renal medullary washout and even hypertensive encephalopathy. De novo bleeding from an unruptured aneurysm is rare, and should not be considered a contraindication to hemodynamic therapy.

Endovascular treatment of vasospasm was first described in the early 1980s in a report of balloon catheter dilation for vasospasm in 33 SAH patients. Vasospasm did not recur in treated arteries, a finding that has been confirmed in other studies. Balloon angioplasty has not been studied in RCTs but it is reported that neurologic improvement occurs in 30-80 percent of patients. The drawback to the technique is serious complications, including vessel rupture (often fatal) and stroke from arterial occlusion which occur in 5 percent of patients. Therefore, this technique is reserved for patients with secured aneurysms who are deteriorating despite other treatments for vasospasm.

Superselective intra-arterial infusions of papaverine were first described in 1992. The vasodilatation is transient and less pronounced than with balloon angioplasty, and clinical improvement can also be transient, requiring repeat procedures. Complications include stroke, blindness, and increased ICP. This technique is used when medical therapy has failed and balloon angioplasty is not deemed possible. Currently, some centers use nicardipine, verapamil or nimodipine infusions based on their better safety profiles.

Neuroprotection is an area of intense interest. The risk of cerebral ischemic event related to SAH can occur at the time of the hemorrhage with acute rise in ICP, during the procedure undertaken to secure the aneurysm, or during the vasospasm period. Calcium channel antagonists including nimodipine and nicardipine are associated with reduced risk of poor outcomes. The results are most robust with nimodipine but an interesting finding is that its use did not affect the prevalence of angiographic vasospasm suggesting that the benefit is linked to its cytoprotective properties. Nimodipine is the standard drug administered to all patients with aneurysmal SAH. It is proven to increase the odds of a favorable outcome and reduce the odds of ischemic deficit, although the trend toward a mortality benefit was not statistically significant. In the US it is administered orally at a dose of 60mg every four hours. The incidence of hypotension at the dosages used in current practice is generally regarded as low but cannot be discounted. The use of higher dose intravenous Nimodipine or nicardipine, a related dihydropyridine calcium channel antagonist are limited by systemic hypotension.

Another area of development is endothelin antagonists. Evidence from experimental models of SAH and clinical studies of endothelin concentrations in humans with SAH suggest that alterations in the vasoconstricting endothelin system may contribute to vasospasm. Clazosentan, an A receptor specific endothelin antagonist has shown some promise in a small study of 32 patients with thick aneurysmal SAH. Angiographic vasospasm occurred in 88 percent of placebo patients but only 40 percent of the Clazosentan patients with p value of 0.008. The severity of vasospasm was reduced, and there was a trend toward reduction in the incidence of cerebral infarction in treated patients.

One limitation in the development of all potential vasodilators is the lack of selectivity for cerebral vessels. Systemic arterial vasodilatation results in limiting hypotension.

The neuroprotective benefits of magnesium have been reported in experimental models of traumatic brain injury, cerebral ischemia and SAH. A recent pilot study of 60 patients with SAH using magnesium infusions at similar doses used to treat toxemia did not show statistically

significant reduction in delayed cerebral ischemia. Symptomatic vasospasm was reduced from 43% to 23% but did not reach statistical significance. Tirilazad is a 21-amino steroid developed to optimize the beneficial antioxidant properties with less glucocorticoid side effects. Four double blind RCTs in the 1990s suggested efficacy only in male subjects with poor Hunt-Hess grade SAH and the FDA did not approve its use in the US. Fasudil is used in Japan for SAH patients. It is a protein kinase inhibitor active at several kinases, but principally rho kinase which increases the sensitivity of the smooth muscle contractile apparatus to calcium. Inhibition of rho kinase is associated with smooth muscle relaxation. In a study of 256 patients in Japan, fasudil significantly reduced clinical vasospasm from 50 percent to 35 percent without significant improvement in outcome.

Other agents undergoing clinical trials at present include erythropoeitin and HMG Co-A reductase inhibitors. Statins improve endothelial function; have anti-inflammatory and cell-signaling effects, and upregulate eNOS expression all of which made them a reasonable candidate for therapy of SAH. There are two small studies that randomly allocated patients with SAH to receive a simvastatin or pravastatin versus placebo. Statin therapy was associated with significant reduction in TCD ultrasound evidence of vasospasm and in the pravastatin study with reduced duration of severe vasospasm, DINDs and reduced overall mortality. One retrospective study corroborated these promising results by looking at a retrospective cohort of 20 SAH patients on statins versus 40 control patients. Those patients on statins were found to have better functional outcomes and were less likely to develop delayed cerebral ischemia. One other retrospective observational study suggested that SAH patients admitted on statins had an increased risk of vasospasm, but they speculated that this might be due to abrupt discontinuation of the drug upon admission to the hospital. Erythropoeitin is neuroprotective following ischemic/hypoxic brain damage. In animal studies it can limit infarct size and inhibit neuronal apoptosis and subsequent inflammation. Due to its proven safety profile, ongoing research about its use in cerebrovascular disease is promising.

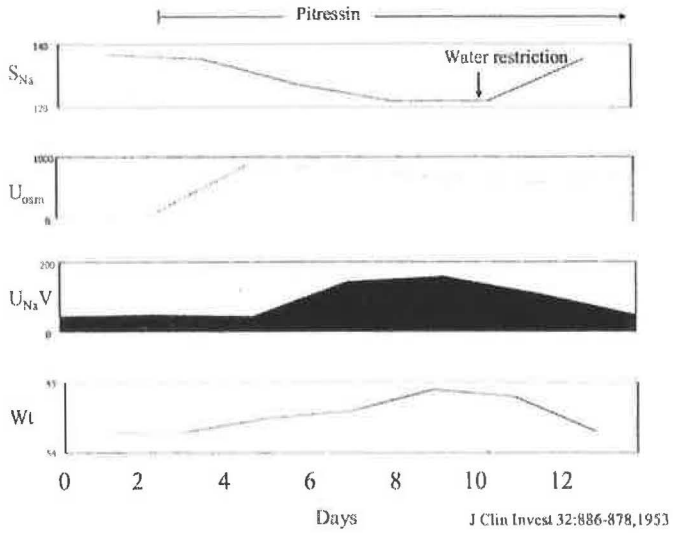
Although the conventional view of SAH management has focused on the pathophysiologic aspects of the initial hemorrhage and prevention of rebleeding, data suggests that the clot in both the intravascular and extravascular compartments is a key determinant of cerebral injury. The presence of thick clot in the subarachnoid space is consistently found to predict vasospasm after aSAH. Furthermore, the poor neuroanatomical correlation of radiologically defined vasospasm and cerebral infarction suggests that intravascular thrombosis is an important mechanism. Preliminary data indicate that placement of thrombolytic agents in the subarachnoid space may improve outcomes but adequately powered RCTs are needed to confirm these findings. Anti-platelet therapy and low molecular weight heparin do not have enough evidence yet to support their use.

Hyponatremia

Hyponatremia is the most common electrolyte disorder observed after SAH, affecting up to 30% of patients. The decline in serum sodium tends to occur between the second and tenth day after SAH, and overlaps with the timing of cerebral vasospasm. Severe hyponatremia (less than 120) is rare, and it is seldom the sole explanation for neurological deterioration in the clinical setting. The etiology is often SIADH, a syndrome characterized by hyponatremia in the setting of inappropriately concentrated urine, increase urine sodium concentration and evidence of normal or increased intravascular volume. Another putative mechanism is Cerebral Salt Wasting (CSW), a syndrome with many similar characteristics to SIADH, but with clinical evidence of contraction of the extracellular fluid volume. This form of hyponatremia is caused by excessive renal sodium excretion resulting from centrally mediated processes. The distinction between these disorders has clinical importance because of the divergent treatment required. SIADH is treated with fluid restriction, whereas CSW requires volume replacement.

Excessive antidiuretic hormone release is pathogenic in SIADH, and leads to renal water reabsorption and resultant extracellular fluid (ECF) volume expansion. This volume expansion is not generally accompanied physical findings of volume overload such as edema or distended neck veins because only one third of the retained water is distributed in the ECF space. Nonetheless, renal plasma flow and GFR are increased in response to the expansion in intravascular volume and result in decreased proximal sodium reabsorption. Urinary sodium excretion in this circumstance has been demonstrated in physiologic studies to equal sodium intake. Substances such as uric acid and urea nitrogen which are absorbed proximally with sodium also tend to be reduced in SIADH.

Figure 5. Effect of exogenous Pitressin on normal subjects

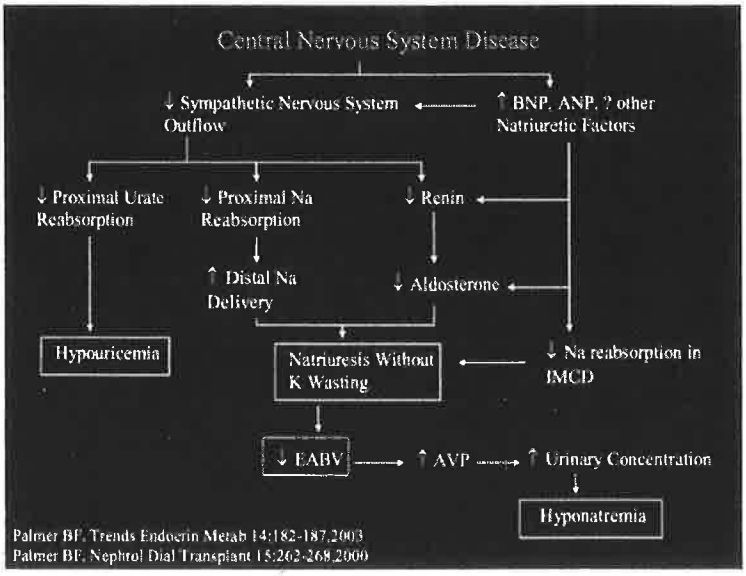


CSW was first described in patients who met criteria for SIADH, but were found to have decreased total blood and plasma volume. Subsequent small series of neurosurgical patients have described development of hyponatremia around day 7-10 after onset of illness with associated negative sodium balance and evidence of volume depletion. Monkey and rat models of SAH demonstrated hyponatremia in association with natriuresis, negative salt balance or decreased body weight. Sham operated animals did not become natriuretic or volume depleted.

The mechanism of natriuresis in CSW is attributed to defective tubular reabsorption of sodium mediated by a natriuretic factor such as brain natriuretic peptide (BNP) and/or disruption of neural input to the kidney. Both atrial natriuretic peptide (ANP) and BNP cause natriuresis that is unrelated to changes in blood pressure. The natriuresis is due to increases in GFR and direct inhibitory effects of sodium transport in the inner medullary collecting duct. ANP and BNP both directly inhibit renin release in the juxtaglomerular apparatus, and aldosterone release from the adrenal gland. Furthermore, these substances decrease autonomic outflow from the brainstem and could synergistically decrease neural input to the kidney. Resultant volume depletion causes a baroreceptor mediated appropriate elevation of ADH and development of hyponatremia. In contrast, secretion of AVP in SIADH is truly inappropriate since the EABV is expanded.

Decreased sympathetic input to the kidney may explain impairment of proximal sodium reabsorption because the sympathetic nervous system alters salt and water handling through various indirect and direct mechanisms. The SNS also plays a role in renin release, so decreased sympathetic input could explain the failure of renin and aldosterone to rise in patients with CSW. Failure of serum aldosterone levels to rise in response to the decreased EABV is felt to account for the lack of renal potassium wasting despite the increase in distal delivery of sodium. For this reason, hypokalemia is not a feature of CSW.

Fig. 6. Proposed Mechanism of Cerebral Salt Wasting



Espiner studied 18 SAH patients' responses in stress hormones, ANP, BNP, and markers of cardiac injury and related them to changes in serum sodium. Intense neurohormonal activation at admission was characterized by increases in AVP, catecholamines and cortisol and associated increases levels of ANP and BNP in serum, but not in CSF. They conclude that the heart is the source of natriuretic peptides in SAH. They also made the observation that during the course of a fall in plasma sodium, there was delayed activation of the RAS system that correlated inversely with declining levels of ANP/BNP.

BNP may be the more likely candidate mediator of renal salt wasting. Berendes studied 10 patients with SAH who underwent surgical clipping as compared with a control group of ten patients who had craniotomy for tumor. Compared with controls, the SAH group demonstrated significantly greater levels of BNP which correlated with both urinary sodium excretion and intracranial pressure. By contrast, there were no differences in circulating concentrations of ANP, digoxin-like immunoreactive substances or plasma renin concentrations. Aldosterone concentrations were suppressed and varied in an opposite direction to that of BNP in the SAH group.

A recent retrospective case review of 316 patients with SAH admitted to a hospital in Ireland showed an incidence of hyponatremia (defined as less than 130) of 57% compared with 20% in neurosurgical patients undergoing hypophysectomy. Incidence of hyponatremia in SAH patients with aneurysm was 61%, and slightly higher for those undergoing treatment of the aneurysm as compared with those managed conservatively. Patients were screened for the presence of glucocorticoid deficiency and hypothyroidism given the significant incidence (8-32%) of ACTH deficiency in long term survivors of SAH. The etiology of hyponatremia was found to be SIADH in 69%, CSW in 6.5% and hypovolemic hyponatremia in 21%. The authors note that insufficient data on diuresis or natriuresis in some patients may have led to misidentification of some cases of CSW as hypovolemic hyponatremia.

Differentiation of CSW from SIADH is difficult given the similar laboratory values and overlap in clinical presentations with neurological illness. Determination of the ECF volume remains the primary means of distinguishing the two disorders. Along with physical findings of volume depletion, weight loss, and negative fluid balance, laboratory correlates such as hemoconcentration and elevated serum bicarbonate may be useful. Uric acid is normally useful

in distinguishing volume depletion from the volume expanded state in SIADH. However, in CSW serum uric acid levels tend to be unexpectedly low or normal. Hypouricemia and increased fractional urate excretion may be a common feature of intracranial disease. However, increased renal uric acid excretion is a persistent finding after correction of the serum sodium in CSW. Correction of the serum sodium in SIADH leads to normalization of uric acid handling by the kidney.

Only the presence of clear evidence of volume depletion with salt wasting distinguishes CSW from SIADH. In theory, the urine should become dilute after volume expansion with CSW. Few reports can document these features and some have suggested that most patients with purported salt wasting actually excrete sodium physiologically either because of reduced venous capacitance caused by catecholamine mediated vasoconstriction or because of volume expansion with IVF. Patients with SAH are typically given large volumes of isotonic saline, and subsequent high rates of sodium excretion and hyponatremia are not reliable indicators of salt wasting. In surveys of patients in neurosurgical units a positive balance for sodium could be documented in over 90 percent of patients diagnosed with CSW after calculations of all infusions from the time of first medical intervention.

Treatment of CSW includes administration of isotonic saline and in some circumstances, fludricortisone. The exuberant administration of IV fluids in SAH patients is driven by retrospective data showing worsened neurological outcomes in hyponatremic neurosurgical patients who were treated with fluid restriction. Wijdicks et al studied 134 consecutive patients with SAH, 44 of whom had hyponatremia with serum sodium less than 135 mmol/L. Among the 26 hyponatremic patients treated with fluid restriction, cerebral infarctions were observed in 21. Worsening volume depletion in the setting of CSW is hypothesized, and felt to result in decreased cardiac output and more cerebral ischemia from vasospasm. Administration of isotonic fluids to a patient with SIADH may result in further lowering of the serum sodium due to disordered renal water handling but normal renal sodium handling. In order to avoid worsening of the hyponatremia in this setting the osmolality of the fluid given must exceed the osmolality of the urine.

Cardiac manifestation of SAH

One of the first publications recognizing that phenomenon of neurological disease producing cardiac abnormalities was Byers' description in 1947 of patients with ECG abnormalities in the setting of stroke and SAH. Subsequent series have suggested that ECG changes are present in 40-90% of patients with SAH or ICH and up to 20% of those with ischemic stroke. SAH is the most studied entity in this literature, and the ECG abnormalities observed are largely disorders of the repolarization process. Typical changes include QTc prolongation, T wave abnormalities, U waves, ST segment elevation, and ST segment depression. Arrhythmias are also common and run the gamut from harmless premature atrial contractions and sinus arrhythmia to torsades de pointes in the setting of severe QT prolongation.

ECG changes suggest ischemic changes in the subendocardium, but in early studies of patients shown to have regional wall motion abnormalities, coronary angiography showed no obstructive lesions. Use of CK and CKMB was not adequately sensitive or specific in identifying SAH patients with true myocardial injury. More recently, studies of elevated troponin I were found to occur in about 30-40 percent of SAH patients with much better correlation with cardiac dysfunction. Patients with more severe Hunt-Hess grades of SAH are more likely to develop troponin leak and those with elevated troponin are more likely to have ECG abnormalities and clinical evidence of LV dysfunction. Acute troponin elevation also appears to be associated with increased risk of cardiopulmonary complications such as pulmonary edema and hypotension requiring pressors as well as cerebrovascular complications such as delayed cerebral ischemia from vasospasm. There was no increase in risk of complications with increasing absolute value of elevation of troponin. Although any elevated troponin is an independent predictor of poor outcomes, its additional prognostic value beyond the severity of brain injury is limited.

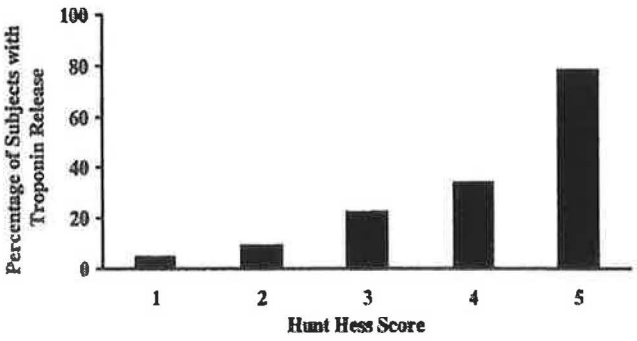


Figure 7. Troponin levels in subarachnoid hemorrhage. Tung P. Stroke 2005; 25:548-51

The neurocardiogenic hypothesis is the most favored current theory of myocardial injury after SAH. In a series of 223 SAH patients, 20% had elevation of troponin greater than 1 mcg/L which correlated most with Hunt-Hess scores greater than two. Animal models suggest that direct release of toxic levels of catecholamines into the myocardium by cardiac sympathetic innervation is a more likely cause of neurocardiogenic injury than is adrenal release of catecholamines into the systemic circulation. The finding that the degree of neurological injury is a strong independent predictor of myocardial necrosis after SAH supports the neurocardiogenic hypothesis.

Contraction band necrosis as a result of direct catecholamine mediated myocardial stunning and myocardial injury is described in patients with SAH. Histological studies of catecholamine injury in cardiac myocytes demonstrate this unique form of myocyte injury characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and intersititial mononuclear inflammatory response that is distinct from the polymorphonuclear inflammation seen with infarction. These changes have been demonstrated in cardiac tissue of up to 50% of patients with fatal SAH. In some studies women are found to produce higher levels of catecholamines and suffer more transient LV dysfunction after SAH. However, most studies of serum catecholamine levels after SAH fail to demonstrate significant or consistent elevation, and the source of the catecholamines is felt to be the neural innervation of the cardiac myocyte. Diastolic dysfunction may also represent a consequence of excessive myocardial norepinephrine discharge as it would lead to increased cytosolic calcium in cardiomyocytes and impede myocardial relaxation.

LV systolic dysfunction occurs in about 10-13 percent of SAH patients, but limited data suggest it is reversible. The cause of the LV dysfunction was historically attributed to CAD, hypertension, coronary spasm or tachycardia. However, experimental models support the theory that excessive release of norepinephrine from myocardial sympathetic nerve terminals is the most likely cause. The most commonly reported pattern of LV dysfunction is dyssynergy of the LV apex. This pattern of wall motion abnormalities is atypical of coronary artery disease but correlates with the sympathetic nerve terminals distribution. One small echocardiographic study of 30 patients with LV dysfunction in SAH suggested a pattern of preserved apical function relative to the base, a pattern also felt to be possibly consistent with neurally mediated cardiac injury. LV systolic dysfunction and low cardiac output states correlate with increased cerebral vasospasm risk.

Diastolic dysfunction is more common, affecting 71% of patients in a recent prospective study of SAH patients at UCSF and up to 91% of those who suffered pulmonary edema. Although history of hypertension correlates with the presence of diastolic dysfunction, it is observed at a higher prevalence in those with SAH than control patients with hypertension. All patterns of diastolic dysfunction were evident, but the highest odds ratio for pulmonary edema was seen in the restrictive pattern group. The prevalence of diastolic dysfunction is greater as the time from SAH symptom onset to echocardiography increases. This relationship contrasts with the earlier time course of troponin release. The cause of the persistence of diastolic dysfunction over time is not completely understood and may represent a more lasting form or neurocardiogenic injury. Perhaps more plausible is the confounding influence of the use of pressor agents, volume resuscitation and overall higher blood pressure during vasospasm treatment.

Acute elevation of BNP is seen in patients with SAH returning to normal over 1-2 weeks. The source (cardiac or brain) is still debated in the literature. In a prospective study of 57 subjects with SAH by Tung et al found elevated BNP was associated with the presence of regional wall motion abnormalities on echo, systolic and diastolic dysfunction, pulmonary edema, elevated

troponin. This study also suggested that high BNP levels were associated with inpatient mortality. The authors propose this is indirect evidence that the source of BNP is cardiac. Other authors have demonstrated that high BNP levels are associated with risk of cerebral vasospasm. Currently, there are no data that determine the optimal therapeutic interventions in patients with elevated BNP in the setting of SAH.

The role of the immune system and inflammation is an area of interest in current studies of cardiac dysfunction in SAH. Inflammatory cytokines such as TNF alpha and IL-6 are elevated in both blood and CSF after SAH, and have been shown previously to be associated with increased risk of CHF.

In summary, based on the available evidence aggressive treatment of SAH should not be withheld because of cardiac dysfunction. The majority of the manifestations of cardiac abnormalities after SAH are correlated with neurological injury. The neurocardiogenic hypothesis proposes catecholamine mediated injury and may evolve to include the central immune response and inflammation. The use of beta and alpha blocking antihypertensives is rational and supported by small numbers of studies in the setting of SAH. Treatments aimed at improving the patients neurological status are sometimes complicated by cardiopulmonary decompensation, but when successful, are associated with good cardiac outcomes.

Hyperglycemia after SAH

In medical and surgical ICU patients hyperglycemia is common even in nondiabetic patients and has been associated with increased morbidity and mortality. Intensive insulin therapy in ICU patients has been shown to reduce the incidence of sepsis, ARF, blood transfusions, length of ICU stay, and mortality. Hyperglycemia has a detrimental effect in acute cerebrovascular syndrome including infarct expansion, worsened functional outcome, longer hospital stays, higher medical costs, and increased risk of death from ischemic stroke. Elevated glucose with or without diabetes is independently associated with symptomatic hemorrhage after intravenous or intra-arterial thrombolytic therapy for acute cerebral infarction. Van den Berghe et al looked at a small subset of 63 patients with brain injury in their study of insulin therapy in surgical ICU patients (36 had SAH or ICH). Prevention of hyperglycemia with intensive insulin therapy was associated with reductions in intracranial pressure, duration of mechanical ventilation and seizures in critically ill neurological patients, and may improve rehabilitation outcomes.

Frontera and colleagues at Columbia studied the impact of hyperglycemia in 281 patients after SAH. Predictors of hyperglycemia included age greater than 54 years, HH grade 3 or 4, poor APACHE scores and history of diabetes. Multivariate analyses showed glucose burden was associated with increase length of ICU stay, CHF, respiratory failure, pneumonia and brainstem compression from hematoma. After adjustment for HH grade, aneurysm size and age, glucose burden was an independent predictor of poor outcomes and severe disability after SAH. In the same series, elevated BMI and hypertension independently predicted the occurrence of cerebral infarctions. Badjatia and colleagues describe increased risk of symptomatic vasospasm after SAH with hyperglycemia, but the finding was not corroborated in other studies.

Further clinical trials are needed to evaluate the role of strict glycemic control in patients with SAH.

Pulmonary Complications

Pulmonary complications of SAH include acute lung injury, neurogenic and cardiogenic pulmonary edema, nosocomial or aspiration pneumonias and pulmonary embolism. Many studies question the possible role of hemodynamic augmentation in the development of

pulmonary edema and congestive heart failure in patients with symptomatic vasospasm. As discussed above, diastolic dysfunction may be more common than systolic dysfunction in patients who have pulmonary edema. Pulmonary complications are associated with worse neurological grade, with symptomatic vasospasm and with worse neurologic outcomes.

A recent study of 620 patients with aneurysmal SAH looked at the incidence of acute lung injury as defined by the North American-European Consensus Conference definition. They found it occurred in 27 percent of their study population, and was associated with increased odds of death and longer ICU stays as it has been in studies of other patient populations. Factors that are associated with ALI included sepsis and transfusion as well as neurological grade at admission. The investigators ask the question of whether lung-protective ventilation (LPV) strategies can be safely and effectively used in these patients at risk for elevated ICP and decreased CPP. Of note in their study, PaCO2 was not increased significantly in the patients who did receive LPV. This may be preliminary evidence that LPV can be implemented without affecting minute ventilation and by extension, ICP.

Hydrocephalus

Hydrocephalus occurs in 20% of patients with SAH, and is a necessary consideration in the differential of diminished level of consciousness. Normal CSF circulation may become obstructed by clot in the basal cisterns or at the level of the arachnoid villi. Intracerebral extension of hemorrhage, posterior circulation aneurysm rupture and decrease GCS score on admission can all be predictive of acute hydrocephalus. Acute neurological decline in the setting of enlarging ventricles is an indication for placement of an external ventricular drain (EVD). Placement of such a drain does not appear to increase the risk of rebleeding in patients with unsecured aneurysm if the drainage is performed at moderate pressures (<10cm H2O). The risks of EVD are small, but include infection, particularly when the drain is left in place for extended periods, and prophylactic antibiotics in this circumstance are not of proven benefit. Frequent monitoring of CSF chemistries, cell count and culture may be useful, particularly in the patient with fever. Hydrocephalus may also occur weeks into the recovery after SAH, and should be considered in patients with continued depressed level of consciousness.

Seizure and Epilepsy complicating SAH

Seizures after subarachnoid hemorrhage (SAH) are a feared but uncommon (4% to 10%) complication of the acute bleed or rebleeding, with most occurring soon after the initial event. The incidence of late epilepsy after SAH varies between 7 and 25 percent in different studies. Most patients who seize do so in the perioperative period, and these events are not predictive of future epilepsy. The risk factors include the side of the aneurysm (higher with MCA aneurysm), temporal ICH, brain ischemia and hypertension. In recent studies, seizures after aneurysm surgery are uncommon, especially in patients without the above risk factors, but many clinicians still opt for prophylaxis with phenytoin (Dilantin) or fosphenytoin. The use of Dilantin after SAH remains controversial after a retrospective study of 527 patients showed a strong association between phenytoin exposure and functional and cognitive disability. Other studies have suggested that non-convulsive status epilepticus occurs even in patients on seizure prophylaxis. Thus, EEG evaluation should be pursued in patients with decline in mental status that is not explained by other metabolic disturbance, vasospasm, infection or hydrocephalus. Further studies of the effectiveness of AEDs in the acute and long term settings are warranted.

Neuroendocrine Complications of SAH

Hypothalamic and pituitary injuries are also a possible outcome of aneurysmal SAH. Theoretically, they endocrine disturbance could be caused by compression by the aneurysm, damage from the hemorrhage, ischemia from vasospasm, increased ICP or the surgery

performed to secure the aneurysm. This is particularly true of aneurysms from the Anterior Communicating artery whose branches supply portions of the hypothalamus. There are only small studies of this phenomenon estimating the incidence of neuroendocrine dysfunction at between 6 and 47%. Low insulin-like growth factor compatible with GH deficiency, hypogonadism and cortisol hyporesponsiveness are the most commonly cited abnormalities. During the rehabilitation of these patients, symptoms of fatigue, loss of motivation and other functional limitations could warrant investigation of the hypothalamic pituitary axis. Posterior pituitary injury with resultant diabetes insipidus is also reported in about 4 percent of SAH patients.

Rehabilitation

Physical, cognitive, behavioral, and social deficits are relatively common after SAH, and can have a significant impact on effective home, community, and work reentry. Neurologic sequelae often relate to the location of the aneurysm. Cognitive, behavioral, and social sequelae are most frequent in patients with anterior cerebral and communicating artery lesions; however, delayed ischemic dysfunction often accounts for these deficits in patients with lesions in other distributions. Middle Cerebral Artery Aneurysms are associated with higher rates of epilepsy, visual field deficits, hemiparesis and dysphasia.

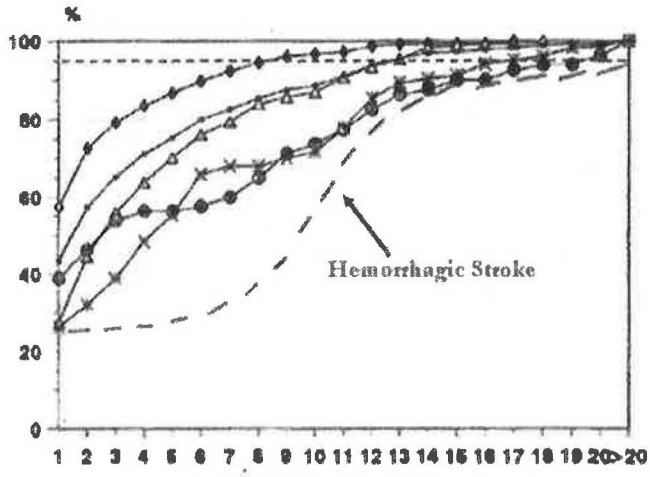


Figure 8. Cumulative rates of achieving best ADL function for patients with ischemic stroke by severity
Jorgensen HS. The Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(5):406-12.

The rehabilitation of patients after SAH is distinct from that of patients with ischemic stroke. Improvements in neurologic function occur more slowly, and prognostic statements about the extent of recovery cannot reasonably be made as early as they can in patients with ischemic CVA. Evaluation by specialists in neurorehabilitation and referral to a specialized center is recommended for most all patients.

Seizure risk after SAH or craniotomy and the use of prophylactic anticonvulsant medications is often a confusing and troublesome issue for the rehabilitation specialist. This situation often is handled by weighing the potential risk of serious medication side effects against the potential seizure risk. Phenytoin (Dilantin) is routinely used for seizure prophylaxis after SAH, but may adversely affect neurologic and cognitive recovery. A recent study at Northwestern of 527 SAH patients treated with Dilantin assessed cognitive outcomes at 14 days and 3 months with the telephone interview for cognitive status. They found that patients in the higher quartiles of phenytoin burden (calculated from levels between days 1 and 14 after hemorrhage) were associated with poorer neurologic and cognitive outcome after SAH. Many clinicians today are

using newer anticonvulsants such as Keppra instead of Dilantin, but available data are limited regarding their comparable efficacy in the acute hospital setting and their potential effects on neurologic recovery.

Follow Up

The annual rate of new aneurysm formation in patients treated for aneurysmal SAH is reported to be as high as 1.8%, especially in patients with history of multiple aneurysms. The probability of new aneurysm formation is about 0.9% per year. This data supports the rationale for late (10 year) angiographic follow up in patients with aneurysms that were treated surgically. Endovascular follow up occurs at more frequent intervals due to the incidence of compaction of the coils. Smoking and female sex were significant independent risk factors for future aneurysm formation. Cessation of smoking is very important for patients with ICA and probably for those with history of SAH.

Conclusions

The management of subarachnoid hemorrhage may lie more in the realm of the neurosurgeon and neurointensivist, but it is fascinating for internists as diagnosticians and as consultants. In the era of hospitalists and intensivist run ICUs, familiarity with this entity will be increasingly important. The last several decades have seen decline in morbidity and mortality with early operative strategies, incredible advances in neuroimaging, endovascular management strategies, and aggressive management of vasospasm. The area of neuroprotective strategies after SAH should be exciting in the coming decade.

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