EXPERT OPINION

Subarachnoid hemorrhage: an update for the intensivist

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ABSTRACT

Subarachnoid hemorrhage (SAH) remains a serious condition with high mortality and disability. In the past decades, there have been improvements in the techniques to secure aneurysms both surgical and endovascular techniques aimed at reducing the risk of future bleeding events. Nevertheless, securing the aneurysm is only the starting point in the care of SAH patients. Intracranial and extracranial complications following SAH are common and impact long-term outcomes. Intensive care management of patients with SAH offers the opportunity to reduce morbidity by reducing secondary insults and preventing complications. *(Minerva Anestesiol 2011;77:74-84)*

Key words: Subarachnoid hemorrhage - Intensive Care - Morbidity.

Subarachnoid hemorrhage (SAH) accounts for 6% of total strokes and has an estimated incidence of 8–10 cases per 100 000 people per year. In Italy, the most recent available data from the Health Ministry (hospitalizations in year 2005), recorded 5 300 SAH hospital admissions, with an incidence of 10.9/100 000/year. The most common cause (85%) of non-traumatic SAH is the rupture of an intracranial aneurysm.[1] Aneurysms are saccular or fusiform arterial deformities that are the result of protrusion of the intima through a structural defect in the arterial muscular layer.

It is not completely understood how aneurysms form and grow or when and why subsequent rupture occurs. Recent theories recognize endoglin, an angiogenic growth factor, as one of the factors involved,[2] but the entire process is probably multifactorial. Established risk factors for SAH are smoking, alcohol or cocaine abuse, hypertension and history of SAH in first-degree relatives.[3] Moreover, mechanical stress on the arterial wall plays a role; aneurysms usually develop at vascular bifurcation because of turbulent flow, which most frequently (80-90%) occurs in the anterior portion of the circle of Willis.[4]

Outcome

Overall mortality rate remains very high at approximately 45%. At least 15% of patients die before reaching medical attention, 40% die within 7 days and survivors are often affected by severe disability. Over the past years, intensive care treatment of patients affected by SAH, although different across countries,[5] has led to improved outcomes even in cases previously considered fatal.[6] Survivors with severe neurological disability may rate their quality of life as acceptable and preferable to death,[7] therefore withholding aggressive treatment from these patients should always be evaluated carefully.

Several factors influence survival and disability. A recent retrospective analysis of more than 2 000 cases shows severity of initial hemorrhage, clinically graded by the World Federation of

Neurosurgical Societies (WFNS) score, as the major determinant of case fatality at 60 days.[8] Other factors are size and location of aneurysm, extent of bleeding and clot thickness (assessed by Fisher CT grading scale), comorbidities and occurrence of secondary complications.[9] Cerebral edema due to cerebral hypoperfusion has also been proposed as a factor associated with poor outcome.[10]

Additionally, age plays an important role. Elderly patients have a less favorable outcome compared to younger patients. In patients over 65 years of age, there is a higher mortality rate and a trend towards less independent functional outcome. Additionally, institutional factors and volume load can influence outcome. A cohort study of approximately 13000 patients showed a significant difference in mortality rate when comparing lower with higher case-volume hospitals (<8 *vs.* >19 SAH cases per year).[11] Similar results were obtained after adjusting for age, sex, volume load per year and comorbid conditions.[12] In Italy, patients are often treated in regional low-volume centers; improvement of care could be obtained through centralization in high-volume centers.[13] For example, during a one-year observation in Lombardia, only 9 neurosurgical centers from a total of 24 throughout the region received more than 35 cases/year. Consequently, more than 40% of cases are treated in low-volume centers.

Management

After diagnosis of acute subarachnoid hemorrhage, monitoring of patients' vital signs and neurological status is advisable due to the possibility of sudden deterioration.

In a recent Italian data set on SAH,[14] neurological deterioration was frequent (24%) and mainly occurred in patients with extensive bleeding (*i.e.,* a high Fisher classification) and with pretreatment rebleeding. Neuroworsening has been associated with an unfavorable outcome (46%, 36/78, *vs.* 33%, 83/251). Intensity of care is typically predicted by the severity of neurological dysfunction at the time of presentation [commonly assessed with the Hunt-Hess (HH) Scale [15] or with the WFNS Grading System for Subarachnoid Hemorrhage scale]. ICU admission is highly suggested for patients with ≥3 HH or ≥3 WFNS scores. Less severe patients (1-2 HH) can be managed either in wards or in the ICU depending on the hospital setting.

Management in the ICU setting in the early phase is mainly characterized by prevention of rebleeding, management of hydrocephalus and elevated intracranial pressure (ICP), systemic monitoring and treatment of early physiological derangements. Later, after the aneurysm has been secured, patients require intensive monitoring for identification and treatment of vasospasm, the most risky complication that often leads to delayed cerebral ischemia (DCI) and infarction.

In the past, efforts to improve outcome have been mainly directed at prevention of rebleeding, treatment of acute hydrocephalus and delayed ischemia from vasospasms. In the last decade, SAH was revealed to be a multisystem disease, and medical complications have been identified as factors that can contribute to worse outcomes, thereby expanding intensivists' awareness of this multisystem disease.[16] The specific role of neurointensivists in the management of SAH has been recently examined.[17] A report by Josephson *et al.*[17] discusses a health care system which markedly differs from our Italian system, where SAH patients are managed in intensive care units by trained intensivists. In the analyzed setting, patients had previously been managed by neurosurgeons; initiation of a strategy of routine involvement of a neurointensivist, responsible for managing all aspects of a patient's care, resulted in a significantly reduced length of ICU stay for neurosurgical SAH patients. This approach of involving neurointensivists to manage neurosurgical SAH patients is already standard in our health care system. Nevertheless, in other settings, it merits further consideration as a successful model of care.

Cardiac and pulmonary care

Cardiac abnormalities are common after SAH, even in non coronary-disease patients. Some patients (20-30%) present with acute cardiac enzyme elevation, and an increase in troponin I, which occurs in more severe patients, correlates with poor outcome.[18] Patients with high tro-

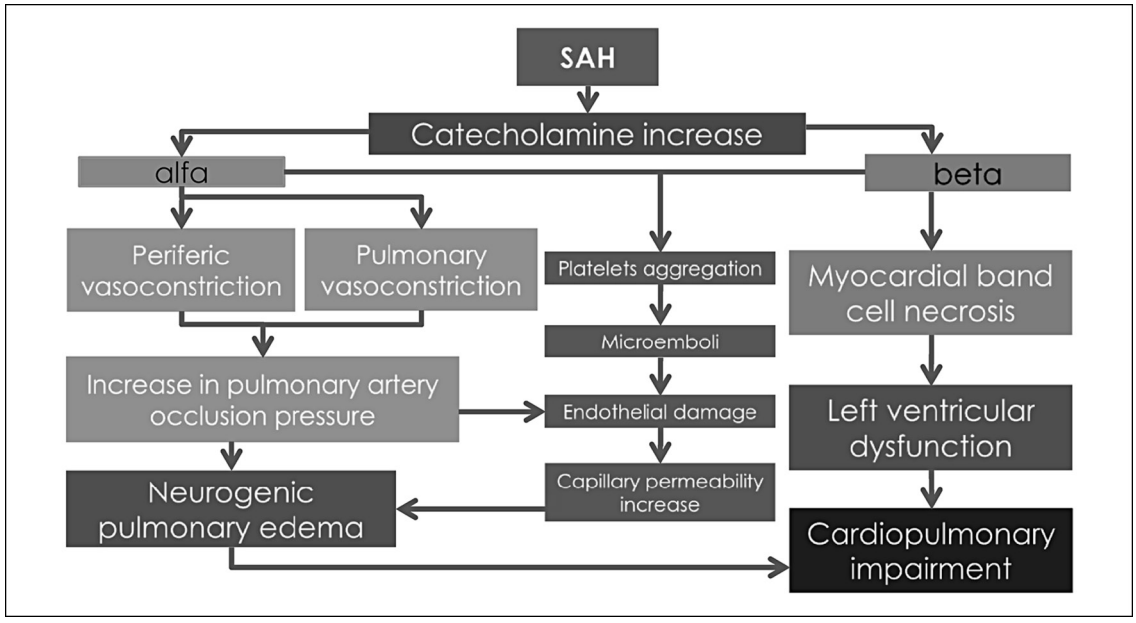

Figure 1.—Cardiopulmonary modifications of subarachnoid hemorrhage (modified from Macmillan *et al.*[22]).

ponin I are more prone to left ventricular (LV) dysfunction, which may lead to congestive heart failure and pulmonary edema that resembles Tako-Tsubo syndrome, a transient cardiac dysfunction first described in the Japanese population.[19]

Oxygenation is impaired in many patients, often without an identified cause.[20] Pulmonary edema is documented in up to 10% of patients but is not always classifiable as cardiogenic because pulmonary capillary pressure can be normal. The underlying mechanism of non cardiogenic pulmonary edema in SAH patients can be an alteration in vascular permeability. These patients are at risk for the so-called "neurogenic stunned myocardium", a reversible impairment of the left ventricle that worsens 19-60 hours after the onset of edema that rarely presents regional wall-motion abnormalities.[21]

Current theories recognize catecholamine release as the main cause of cardiopulmonary sequelae after SAH.[22] An increase in pulmonary capillary pressure results in pulmonary edema, and acute myocardial stress leads to microscopic alteration of myocardial fibrillae known as "contraction-band necrosis". This type of damage, typically subsequent to intracranial bleeding, may be responsible for release of troponin that is related to a decrease in pulmonary function in the absence of cardiogenic edema;[23] its resolution can explain why LV impairment resolves in a few days without sequelae (Figure 1).

Transient arrhythmias are also frequent (25-75%); within one day of surgery bradycardia, ST and T-wave abnormalities are typically present.[24] Clinically important arrhythmias such as ventricular tachycardia and atrial tachyarrhythmias are present in 5% of cases and are associated with increased length of stay and poor outcome after SAH.[25]

Practical hints:

— At admission, a chest x-ray and an ECG should be recorded along with plasma troponin levels.

— If cardiac enzymes are positive, then echocardiographic evaluation of ventricular function should be considered.

— ECG, pulse oximetry and arterial blood pressure monitoring is prudent for all patients, even if they are admitted to a ward.

Fever

Fever (body temperature >38.5 °C) is common (40%) in SAH patients, particularly in

the postoperative period. Fever is frequently non-infectious. The most common cause of non-infectious fever in the neuro-ICU setting is SAH,[26] which is due to a local inflammatory response following hemorrhage that leads to dysregulation of hypothalamic temperature control centers and systemic activation of inflammatory pathways.

There is some evidence that fever can be associated with increased risk of vasospasm and poor outcome,[16] but it remains to be elucidated if it is a worsening factor per se or if it represents a marker of other unfavorable factors.[27] In any case, aggressive control of fever in SAH patients seems appropriate. There are several ways to reduce fever, such as non steroidal anti-inflammatory drugs (NSAIDs) (*e.g.*, paracetamol/acetaminophen), catheter-based methods and cooling blankets. During treatment for fever, it is recommended that the patient avoid shivering, a clinical sign related to reduction in tissue oxygenation.[28] In our institution. we instituted a fever control strategy with Diclofenac sodium (maximum daily dose 75 mg by continuous infusion, titrated according to the temperature target) with very good fever control.[29]

Practical hints:

— Body temperature should be monitored.

— If the patient becomes febrile, then standard microbiological screening along with C-reactive protein (CRP) measurements should be considered. If an infection is identified, then appropriate antibiotic therapy should be started.

— Fever requires prompt symptomatic treatment with cooling, NSAIDs or physical treatments.

Glycemia and metabolism

Persistent severe hyperglycemia, as is well known in ischemic stroke, is associated with increased medical and neurological complications, length of stay, death and severe disability.[30] Hyperglycemia is frequent in patients with a high HH score, which probably represents one aspect of the generalized homeostatic changes after SAH.[16]

Maintaining blood glucose between 130-140 mg/dL is therefore reasonable in SAH patients to avoid hypoglycemia, a life-threatening factor associated with poor outcome.[31]

Practical hints:

— Target blood glucose at 130-140 mg/dL, and infusing insulin when needed.

Fluids

Maintaining normovolemia after SAH is important to avoid cerebral hypoperfusion. It is widely accepted that hypovolemia is associated with DCI and poor outcome[32] and typically presents with electrolyte disturbances. Hyponatremia,[33, 34] often due to cerebral salt wasting syndrome, is frequent (about 30%) and it is related to longer hospital stay[35] and increased rates of cerebral ischemia. Useful treatments are sodium replacement and steroids with mineralocorticoid properties.[34]

Practical hints:

— Evaluate fluid and electrolyte balance daily in the first week.

— Avoid hypovolemia and negative fluid balance in the first week.

— Maintain a normal, stable natremia with sodium infusion if needed.

Surgical treatment - The treatment of choice

After rupture, rebleeding is one of the most important independent determinants of outcome.[36] It is a common complication that mainly occurs in the first few days and in approximately 40% of patients within the first month if the aneurysm is left untreated. Occlusion of the aneurysm is usually performed within the first days after admission (<24-72 hours), although there is no evidence from clinical trials that early occlusion results in better outcome than delayed treatment.[37] Options for treatment of ruptured aneurysms are surgical (clipping) or the endovascular (coiling) approach. Coiling is generally considered to be associated with lower perioperative mortality and morbidity than clipping. After five years, relative risk of death is less for patients who have undergone coiling treatment, but no difference is demonstrated in the probability of good neurological status.[38] Risk of reintervention with coiling is higher than clipping

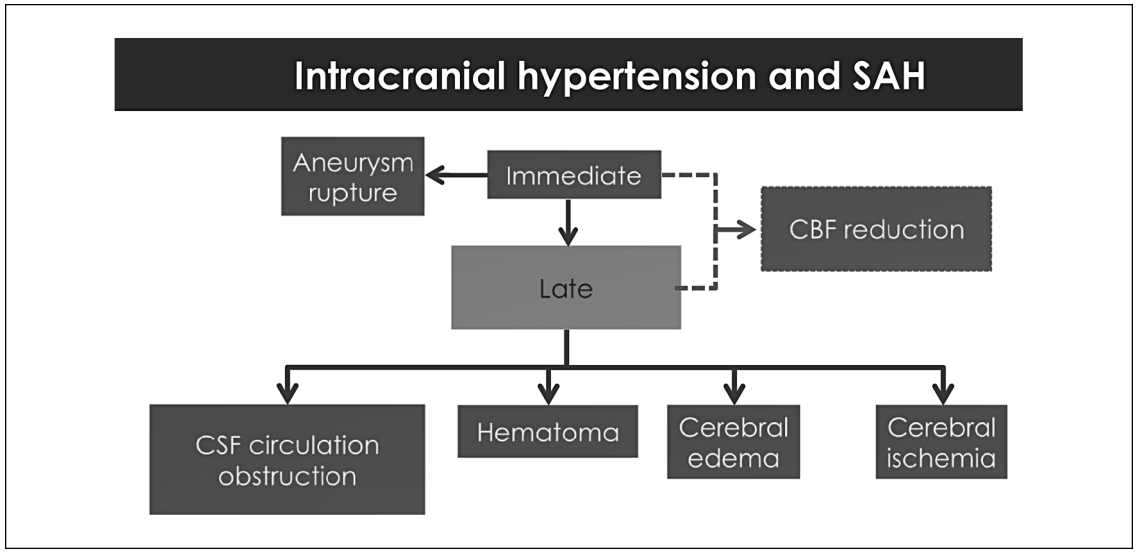

Figure 2.—Events following subarachnoid hemorrhage (modified from Macmillan *et al.*[22]).

(10%),[39] primarily because of incomplete occlusion due to the anatomic shape and dimension of the aneurysm.[40] Conversely, risk of rebleeding at eight years does not appear to be dependent on the type of treatment.[41] In summary, endovascular treatment, when feasible, seems to perform better than clipping in terms of outcome. The optimal approach requires the availability of both treatment strategies and expertise (surgical and endovascular) in the same institution. The treatment choice for the individual patient is principally dependent on the anatomic properties of the aneurysm and its position. A discussion of the case by neurosurgeons, interventional neuroradiologists and intensivists should provide the optimal treatment plan for the patient. If the patient is awake and cooperative, then the options should be presented to the patient.

Practical hints:

— A prompt neurosurgical evaluation after the first CT scan and angiography (digital subtraction angiography or CT angiography) is mandatory to plan the best treatment strategy for the aneurysm.

— Availability of both endovascular and neurosurgical procedures, tailored to the individual case, offers a better possibility of successful treatment of the aneurysm.

Elevated intracranial pressure

Intracranial pressure (ICP) can be elevated after SAH due to cerebral edema or infarction, impaired cerebrospinal fluid (CSF) reabsorption and residual hematomas (Figure 2). Positioning of external ventricular drainage is recommended in patients with a higher WFNS score or acute hydrocephalus,[9] both for ICP monitoring and control by CSF withdrawal (Figure 3).

The usual treatment of increased ICP is based on head elevation, sedation, mechanical ventilation (aimed at maintaining a $PaCO_2$ of 35 mmHg), control of temperature and electrolytes, and administration of intravenous osmotic fluids (Figure 4). Second level therapy includes hypothermia, high dose barbiturates and decompressive hemicraniectomy. Decompression may prolong short-term survival[42] and improve cerebral glucose utilization;[43] however, even if it appears promising, differences in outcome have not yet been established. Therefore, timely cerebral decompression, *i.e.*, immediately upon evidence of untreatable increased ICP or impending herniation, seems a reasonable option for controlling elevated ICP in patients with a favorable attended outcome.

Practical hints:

— In severe patients (WFNS≥3), ICP monitoring is required.

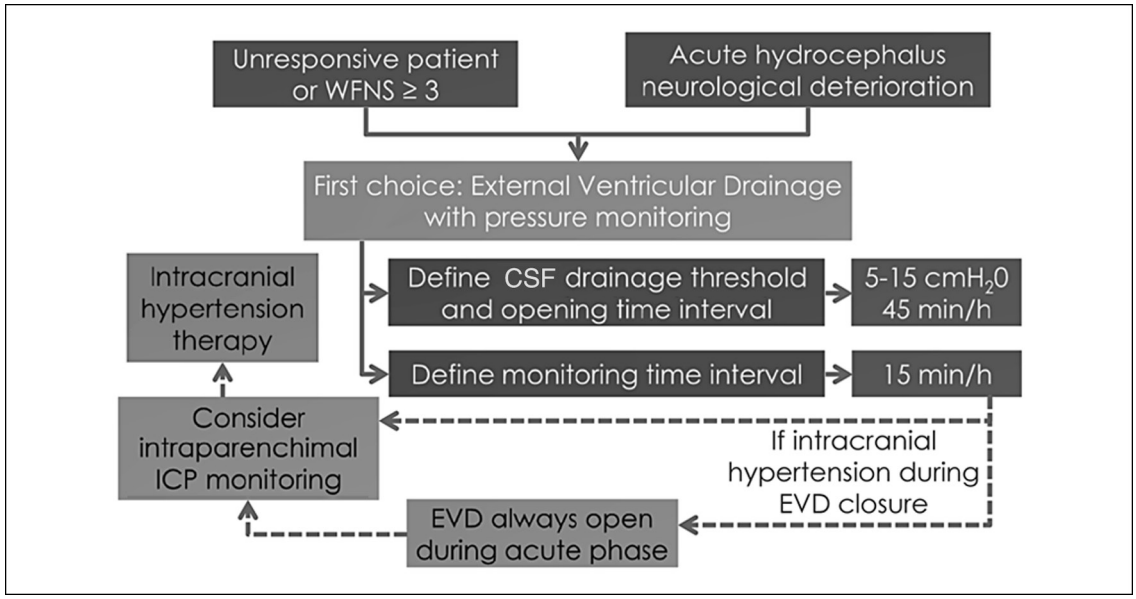

Figure 3.—Management of ventricular drainage during intracranial hypertension.

— A ventricular catheter is the recommended ICP monitoring device, offering the possibility of treating hydrocephalus by draining CSF.

— Controlling elevated ICP in intensive care patients is the standard of care.

Vasospasm and ischemia

Cerebral vasospasm, a phenomenon occurring in up to half of treated patients (usually 3 to 14 days after SAH) consists of intracranial vessel narrowing. As a consequence, regional cerebral blood flow (rCBF) is reduced, leading to neurological deficits and cerebral infarction visible on a CT scan. This phenomenon is known as DCI. The molecular mechanisms responsible for this process are not completely understood, although the by-products of hemoglobin breakdown, endothelin and nitric oxide are likely factors.[44]

Delayed cerebral ischemia can worsen prognosis in SAH patients after the early phase, accounting for about a quarter of deaths.[24] At onset, cerebral ischemia presents clinically with a decrease in the level of consciousness, typically occurring 4 to 12 days after hemorrhage. Specific neurological signs can be followed by cerebral infarction shown on CT scans some days later. Therefore, early diagnosis is important but remains difficult.

Diagnosis of vasospasm

Diagnosis of vasospasms is usually made when neurological deterioration occurs or when CT scans reveal DCI. This diagnosis is somewhat belated because damage is already present and sometimes irreversible. In a cohort of 508 patients, DCI with neurological deterioration was the only factor related to worsening of quality of life at three months.[45] Thus, great attention is needed to diagnose vasospasms early. Several risk factors can have an effect in leading to spasms: a retrospective study[46] found that occurrence of vasospasms is associated with higher Fisher and WFNS scores.

Transcranial Doppler (TCD) is commonly used to assess early alterations in vascular diameter. It is an operator-dependent technique, and although sensitivity and specificity are variable and dependent on the vessel under investigation, the Expert Committee of the American Academy of Neurology supports the use of TCD on the basis that severe spasms can be identified with fairly high reliability.[47] In a retrospective study of

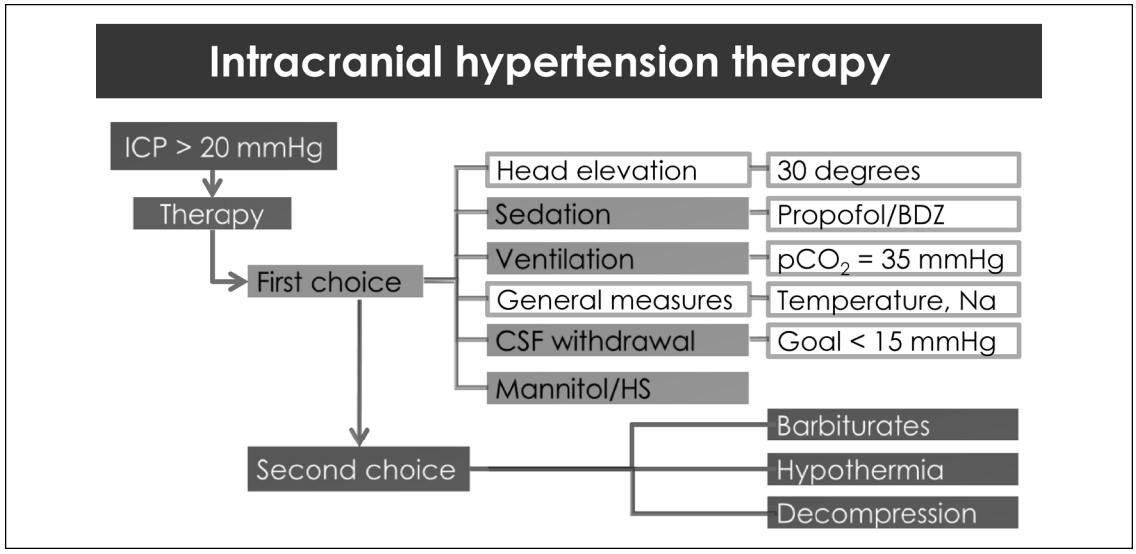

Figure 4.—Intracranial hypertension therapy.

199 patients, independent factors related to the occurrence of DCI were alteration of Doppler velocity within 48 hours from hemorrhage and poor HH grade at admission.[48] In another study of nearly 450 patients, increased TCD flow velocities were related to a mild incremental risk of DCI with maximal sensitivity by day 8. In that study, nearly 40% of patients with DCI never attain a mean blood flow velocity higher than 120 cm/s during the course of monitoring.[49] Doppler is widely used to monitor SAH patients, particularly for median cerebral artery,[47] because of its feasibility. However, it cannot be considered the gold standard diagnostic tool for identifying vasospasms.

Angiography is commonly considered the imaging technique of choice to detect vasospasms. Angiography also allows for local endovascular treatment. Intra-arterial drug injection or ballooning is used to increase vessel diameter, but the latter technique carries significant risk of vascular dissection or vessel rupture and requires an expert neuroradiologist. Moreover, this procedure is only feasible for large vessels, while vasospasms often expand distally. Use of intra-arterial injection of nicardipine or papaverine to dilate peripheral regions has been reported.[50] Endovascular treatment of vasospasms is currently increasing, and its use should be considered where available.[51] Nevertheless, available literature refers mainly to cases reports, and studies on the efficacy of these procedures are not available.

Electroencephalographic monitoring has been suggested for early diagnosis of brain sufferance after SAH, but its use remains limited.[52]

Because tissue damage seems dependent on regional ischemia, attention is now focused on novel techniques that reveal impairment in cerebral blood flow (rCBF). Emerging evidence shows CT perfusion (CTP) as the imaging technique of choice for early assessment of vasospasms.[53] CTP has been proven to be superior to non-contrast CT and CT angiography in diagnosing DCI,[54] and unlike TCD, CTP is predictive of secondary cerebral infarction.[55] CTP is also useful for the diagnosis of altered cerebral blood flow in zones close to the ventricles due to acute hydrocephalus.[56]

Since 2006, after the diagnosis of SAH on the first emergency non contrast CT, both CT angiography to aneurysm detection and CTP are performed at admission in our institution. CTP is repeated on days 5-7 and CT angiography after securing the aneurysm.

Regional cerebral blood flow (rCBF) monitoring using thermal-diffusion (TD) flowmetry, a novel tool for the real time bedside evaluation of regional blood flow, appears promising.[57]

Bedside monitoring of TD-rCBF and cerebrovascular resistances, calculated as the ratio between rCBF and CPP, allows for the detection of symptomatic vasospasms. In ten patients with vasospasms, the TD-rCBF decreased from 21±4 to 9±1 mL/100 g/min, whereas in the four other patients, the TD-rCBF value remained unchanged (mean TD-rCBF=25±4 compared with 21±4 m/100 g/min). A comparison of the results of TD-rCBF and Xe-enhanced CT studies, as well as the calculation of sensitivities, specificities, predictive values, and likelihood ratios, identified a TD-rCBF value of 15 ml/100 g/min as a reliable cutoff for the diagnosis of symptomatic vasospasms. In addition, TD flowmetry is characterized by a more favorable diagnostic reliability than transcranial Doppler ultrasonography. Therefore, thermal-diffusion flowmetry represents a promising method for bedside monitoring of patients with SAH to detect symptomatic vasospasms.

Medical treatment for vasospasm

Triple H

Classic therapy for vasospasm relies on the so-called triple-H: hypertension, hypervolemia, hemodilution.[58] Since the middle of the 1970s, triple-H therapy in an intensive-care setting has been shown to improve outcome and is an accepted means of treatment, although a randomized controlled trial has never been undertaken. Recommendations from the literature are not conclusive; prolonged hypotension and hypovolemia are to be avoided, but there is no evidence that prophylactic hyperdynamic therapy or hemodilution are helpful.[9]

Hypertensive hypervolemic therapy is widely accepted. Because autoregulation is often impaired in SAH patients, CBF can become passively dependent on blood pressure and intravascular volume. It was recently demonstrated that vasopressor-induced elevation of mean arterial pressure causes a significant increase in regional cerebral blood flow[59] and brain tissue oxygenation in all patients with subarachnoid hemorrhages. Volume expansion resulted in a slight effect on regional cerebral blood flow only but reversed the effect on brain tissue oxygenation. In view of the questionable benefit of hypervolemia on regional cerebral blood flow and the negative consequences on brain tissue oxygenation together with the increased risk of complications, hypervolemic therapy as part of triple-H therapy should be applied with the utmost caution.[60]

Severe vasospasms can be refractory to standard therapy: in a recent retrospective study, a lack of response after administration of fluids or pressors was related to a higher risk of death and disability, suggesting urgent endovascular intervention in non-responders.[61]

Nimodipine

Currently, only nimodipine, a dihydropyridine, has been shown to affect the clinical outcome of patients with SAH. Randomized trials have demonstrated that treatment with nimodipine is effective in reducing the incidence of DCI and cerebral infarctions.[62] Even if intravenous administration permits more reliable and stable plasma concentration of nimodipine, a randomized trial in 106 patients showed no difference in terms of outcome depending on the route of administration (oral *vs.* intravenous).[63] Experimental models also suggest the effectiveness of intra-arterial administration.[64]

Clazosentan

Endothelin has been proposed to be one of the molecules involved in the development of vasospasms. In view of these pathogenetic considerations, Clazosentan, an endothelin receptor antagonist, has been studied as a promising new drug for the prevention of vasospasms. A randomized double-blind trial in 413 patients[65] showed a dose-dependent reduction in angiographic vasospasms in comparison with a placebo. Together with a relative risk reduction, the treatment group had more side effects (anemia, hypotension, pulmonary complications). Two trials (CONSCIOUS II and III) are ongoing in SAH patients to confirm early results and to evaluate the efficacy of this medication in this setting.

Magnesium

The use of magnesium in SAH patients to prevent vasospasms and DCI is under debate. In the MESH trial,[66] magnesium treatment tended to decrease the occurrence of DCI and poor outcome but was not statistically significant. The type of treatment (endovascular vs. surgical) does not influence the effects of magnesium. A recent meta-analysis of the literature found that poor neurological outcome is less likely in patients treated with magnesium, but there was no improvement in mortality.[67] Further evidence is required on the neuroprotective role of magnesium in SAH.

Statins

Meta-analysis of the literature suggests that statins are associated with a reduction in DCI and show a trend toward lower mortality.[68] However, their routine use is still under debate.

Practical hints:

— Vasospasm has to be investigated during the first week.

— Neurological signs are a late herald of the phenomenon. Early identification and treatment offer better possibilities for controlling vasospasms.

— Hypertensive hypervolemic therapy appears to be the best available strategy for avoiding neurological deficits due to vasospasm.

Conclusions

SAH is a life-threatening condition that is often followed by severe neurological sequelae. Early diagnosis, surgical treatment in a high case-volume center, careful monitoring and treatment of intra- and extracranial complications are key factors for a good outcome.

References

1. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007;369:306-18.
2. Alberts MJ, Davis JP, Graffagnino C, McClenny C, Delong D, Granger C *et al.* Endoglin gene polymorphism as a risk factor for sporadic intracerebral hemorrhage. Ann Neurol 1997;41:683-6.
3. Diringer MN. Management of aneurysmal subarachnoid hemorrhage. Crit Care Med 2009;37432-40.
4. Priebe HJ. Aneurysmal subarachnoid haemorrhage and the anaesthetist. Br J Anaesth 2007;99:102-18.
5. Stevens RD, Naval NS, Mirski MA, Citerio G, Andrews PJ. Intensive care of aneurysmal subarachnoid hemorrhage: an international survey. Intensive Care Med 2009;35:1556-66.
6. Lerch C, Yonekawa Y, Muroi C, Bjeljac M, Keller E. Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5:85-92.
7. Seder DB, Mayer SA. Critical care management of subarachnoid hemorrhage and ischemic stroke. Clin Chest Med 2009;30:103-22, viii-ix.
8. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS *et al.* Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). Eur J Epidemiol 2010;25:261-6.
9. Bederson JB, Connolly ES, Jr., Batjer HH, Dacey RG, Dion JE, Diringer MN *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009;40:994-1025.
10. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke 2002;33:1225-32.
11. Bardach NS, Zhao S, Gress DR, Lawton MT, Johnston SC. Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke 2002;33:1851-6.
12. Cross DT, 3rd, Tirschwell DL, Clark MA, Tuden D, Derdeyn CP, Moran CJ *et al.* Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. J Neurosurg 2003;99:810-7.
13. Citerio G, Beretta L, Stocchetti N. Do we provide optimal care to patients with acute neurological injuries? Minerva Anestesiol 2010;76:155-6.
14. Citerio G, Gaini SM, Tomei G, Stocchetti N. Management of 350 aneurysmal subarachnoid hemorrhages in 22 Italian neurosurgical centers. Intensive Care Med 2007;33:1580-6.
15. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968;28:14-20.
16. Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage: new strategies for prevention and management. Curr Opin Crit Care 2006;12:78-84.
17. Josephson SA, Douglas VC, Lawton MT, English JD, Smith WS, Ko NU. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management. J Neurosurg 2010;112:626-30.
18. Jeon IC, Chang CH, Choi BY, Kim MS, Kim SW, Kim SH. Cardiac troponin I elevation in patients with aneurysmal subarachnoid hemorrhage. J Korean Neurosurg Soc 2009;46:99-102.
19. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M *et al.* Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol 2001;38:11-8.
20. Vespa PM, Bleck TP. Neurogenic pulmonary edema and other mechanisms of impaired oxygenation after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2004;1:157-70.
21. Lee VH, Oh JK, Mulvagh SL, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5:243-9.
22. Macmillan CS, Grant IS, Andrews PJ. Pulmonary and car-

diac sequelae of subarachnoid haemorrhage: time for active management? Intensive Care Med 2002;28 (8):1012-1023.
23. Naidech AM, Bassin SL, Garg RK, Ault ML, Bendok BR, Batjer HH *et al.* Cardiac troponin I and acute lung injury after subarachnoid hemorrhage. Neurocrit Care 2009;11:177-82.
24. Solenski NJ, Haley EC, Jr., Kassell NF, Kongable G, Germanson T, Truskowski L *et al.* Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. Crit Care Med 1995;23:1007-17.
25. Frontera JA, Parra A, Shimbo D, Fernandez A, Schmidt JM, Peter P *et al.* Cardiac arrhythmias after subarachnoid hemorrhage: risk factors and impact on outcome. Cerebrovasc Dis 2008;26:71-8.
26. Rabinstein AA, Sandhu K. Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors. J Neurol Neurosurg Psychiatry 2007;78:1278-80.
27. Todd MM, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Bayman EO *et al.* Perioperative fever and outcome in surgical patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2009;64:897-908; discussion 908.
28. Oddo M, Frangos S, Maloney-Wilensky E, Andrew Kofke W, Le Roux PD, Levine JM. Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. Neurocrit Care 2010;12:10-6.
29. Cormio M, Citerio G. Continuous low dose diclofenac sodium infusion to control fever in neurosurgical critical care. Neurocrit Care 2007;6:82-9.
30. Frontera JA, Fernandez A, Claassen J, Schmidt M, Schumacher HC, Wartenberg K *et al.* Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. Stroke 2006;37:199-203.
31. Naidech AM, Levasseur K, Liebling S, Garg RK, Shapiro M, Ault ML *et al.* Moderate Hypoglycemia is associated with vasospasm, cerebral infarction, and 3-month disability after subarachnoid hemorrhage. Neurocrit Care 2010;12:181-7.
32. Solomon RA, Post KD, McMurtry JG, 3rd. Depression of circulating blood volume in patients after subarachnoid hemorrhage: implications for the management of symptomatic vasospasm. Neurosurgery 1984;15:354-61.
33. Cole CD, Gottfried ON, Liu JK, Couldwell WT. Hyponatremia in the neurosurgical patient: diagnosis and management. Neurosurg Focus 2004;16:E9.
34. Rahman M, Friedman WA. Hyponatremia in neurosurgical patients: clinical guidelines development. Neurosurgery 2009;65 (5):925-935; discussion 935-926.
35. Kao L, Al-Lawati Z, Vavao J, Steinberg GK, Katznelson L. Prevalence and clinical demographics of cerebral salt wasting in patients with aneurysmal subarachnoid hemorrhage. Pituitary 2009;12:347-51.
36. Claassen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N *et al.* Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832-8.
37. Rinkel GJ, Klijn CJ. Prevention and treatment of medical and neurological complications in patients with aneurysmal subarachnoid haemorrhage. Pract Neurol 2009;9:195-209.
38. Broderick J. Clipping or coiling: the first step for ruptured aneurysms. Lancet Neurol 2009;8:414-5.
39. Ferns SP, Sprengers ME, van Rooij WJ, Rinkel GJ, van Rijn JC, Bipat S *et al.* Coiling of intracranial aneurysms: a systematic review on initial occlusion and reopening and retreatment rates. Stroke 2009;40:e523-529.
40. Fiehler J, Byrne JV. Factors affecting outcome after endovascular treatment of intracranial aneurysms. Curr Opin Neurol 2009;22:103-8.
41. Schaafsma JD, Sprengers ME, van Rooij WJ, Sluzewski M, Majoie CB, Wermer MJ *et al.* Long-term recurrent subarachnoid hemorrhage after adequate coiling versus clipping of ruptured intracranial aneurysms. Stroke 2009;40:1758-63.
42. D'Ambrosio AL, Sughrue ME, Yorgason JG, Mocco JD, Kreiter KT, Mayer SA *et al.* Decompressive hemicraniectomy for poor-grade aneurysmal subarachnoid hemorrhage patients with associated intracerebral hemorrhage: clinical outcome and quality of life assessment. Neurosurgery 2005;56:12-9.
43. Nagel A, Graetz D, Vajkoczy P, Sarrafzadeh AS. Decompressive craniectomy in aneurysmal subarachnoid hemorrhage: relation to cerebral perfusion pressure and metabolism. Neurocrit Care 2009;11:384-94.
44. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S *et al.* Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol Res 2009;31:151-8.
45. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N *et al.* Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke 2009;40:1963-8.
46. Dupont SA, Wijdicks EF, Manno EM, Lanzino G, Rabinstein AA. Prediction of angiographic vasospasm after aneurysmal subarachnoid hemorrhage: value of the Hijdra sum scoring system. Neurocrit Care 2009;11:172-6.
47. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E *et al.* Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004;62:1468-81.
48. Carrera E, Schmidt JM, Oddo M, Ostapkovich N, Claassen J, Rincon F *et al.* Transcranial Doppler ultrasound in the acute phase of aneurysmal subarachnoid hemorrhage. Cerebrovasc Dis 2009;27:579-84.
49. Carrera E, Schmidt JM, Oddo M, Fernandez L, Claassen J, Seder D *et al.* Transcranial Doppler for predicting delayed cerebral ischemia after subarachnoid hemorrhage. Neurosurgery 2009;65:316-23; discussion 314-23.
50. Hoh BL, Ogilvy CS. Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, and intra-arterial nicardipine. Neurosurg Clin N Am 2005;16:501-16, vi.
51. Pierot L, Aggour M, Moret J. Vasospasm after aneurysmal subarachnoid hemorrhage: recent advances in endovascular management. Curr Opin Crit Care 2010 Jan 21. [Epub ahead of print].
52. Dreier JP, Woitzik J, Fabricius M, Bhatia R, Major S, Drenckhahn C *et al.* Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain 2006;129 (Pt 12):3224-37.
53. Rijsdijk M, van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Global and focal cerebral perfusion after aneurysmal subarachnoid hemorrhage in relation with delayed cerebral ischemia. Neuroradiology 2008;50:813-20.
54. Dankbaar JW, de Rooij NK, Velthuis BK, Frijns CJ, Rinkel GJ, van der Schaaf IC. Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration. Stroke 2009;40:3493-8.
55. Pham M, Johnson A, Bartsch AJ, Lindner C, Mullges W, Roosen K *et al.* CT perfusion predicts secondary cerebral infarction after aneurysmal subarachnoid hemorrhage. Neurology 2007;69:762-5.
56. van Asch CJ, van der Schaaf IC, Rinkel GJ. Acute hydrocephalus and cerebral perfusion after aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol 2010;31:67-70.
57. Vajkoczy P, Horn P, Thome C, Munch E, Schmiedek P. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1227-34.
58. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N.

Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol 2003;2:614-21.
59. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. Crit Care 2010;14:R23.
60. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P *et al.* Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. Crit Care Med 2007;35:1844-51; quiz 1852.
61. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N *et al.* Clinical response to hypertensive hypervolemic therapy and outcome after subarachnoid hemorrhage. Neurosurgery 2010;66:35-41; discussion 41.
62. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM *et al.* Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 1989;298:636-42.
63. Kronvall E, Undren P, Romner B, Saveland H, Cronqvist M, Nilsson OG. Nimodipine in aneurysmal subarachnoid hemorrhage: a randomized study of intravenous or peroral administration. J Neurosurg 2009;110:58-63.
64. Tomassoni D, Lanari A, Silvestrelli G, Traini E, Amenta F. Nimodipine and its use in cerebrovascular disease: evidence from recent preclinical and controlled clinical studies. Clin Exp Hypertens 2008;30:744-66.
65. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S *et al.* Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke 2008;39:3015-21.
66. van den Bergh WM, Algra A, Rinkel GJ, Group MS. Magnesium and aspirin treatment in patients with subarachnoid haemorrhage. Comparison of effects after endovascular and neurosurgical aneurysm occlusion. J Neurol 2009;256:213-6.
67. Zhao XD, Zhou YT, Zhang X, Zhuang Z, Shi JX. A meta analysis of treating subarachnoid hemorrhage with magnesium sulfate. J Clin Neurosci 2009;16:1394-7.
68. Kramer AH, Fletcher JJ. Statins in the management of patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurocrit Care 2010;12:285-96.

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