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RESUSCITATION AND CRITICAL CARE OF POOR-GRADE SUBARACHNOID HEMORRHAGE

AS OUTCOMES HAVE improved for patients with aneurysmal subarachnoid hemorrhage, most mortality and morbidity that occur today are the result of severe diffuse brain injury in poor-grade patients. The premise of this review is that aggressive emergency cardiopulmonary and neurological resuscitation, coupled with early aneurysm repair and advanced multimodality monitoring in a specialized neurocritical care unit, offers the best approach for achieving further improvements in subarachnoid hemorrhage outcomes. Emergency care should focus on control of elevated intracranial pressure, optimization of cerebral perfusion and oxygenation, and medical and surgical therapy to prevent rebleeding. In the postoperative period, advanced monitoring techniques such as continuous electroencephalography, brain tissue oxygen monitoring, and microdialysis can detect harmful secondary insults, and may eventually be used as end points for goal-directed therapy, with the aim of creating an optimal physiological environment for the comatose injured brain. As part of this paradigm shift, it is essential that aggressive surgical and medical support be linked to compassionate end-of-life care. As neurosurgeons become confident that comfort care can be implemented in a straightforward fashion after a failed trial of early maximal intervention, the usual justification for withholding treatment (survival with neurological devastation) becomes less relevant, and lives may be saved as more patients recover beyond expectations.

KEY WORDS: Antifibrinolytic therapy, Brain tissue oxygen monitoring, Cardiopulmonary resuscitation, Cerebral aneurysms, Electroencephalography, Microdialysis, Subarachnoid hemorrhage

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Recent technological advances and collaborative efforts between neurosurgeons and neurointensivists have reduced the overall aneurysmal subarachnoid hemorrhage (SAH) fatality rate from 50% to nearly 20% (Table 1) (96, 115). Despite this encouraging trend, there continues to be room for improvement in the outlook for poor-grade SAH. While good-grade SAH patients (Hunt and Hess Grades I to III) generally experience favorable outcomes, mortality among poor-grade patients (Hunt and Hess Grades IV and V) remains high and may be heavily influenced by the aggressiveness of care. In the past, many neurosurgeons were reluctant to treat these patients or treated only a select few (57, 102, 117). Recent studies have shown, however, that many poor-grade patients can recover if treated aggressively from the outset (59, 71).

The premise of this article is that early and aggressive cardiopulmonary and neurological support, to a large extent, determines poor grade SAH prognosis. Moving forward, emergency management protocols that focus on rapid resuscitation and amelioration of acute brain injury, coupled with postoperative management that centers on multimodality monitoring to detect and minimize secondary injury, may offer the best chance for further improvements in outcome. To this end, we review current advances in the emergency and intensive care unit (ICU) management of poor-grade SAH, and we pres-

ABBREVIATIONS: BP, blood pressure; **CBF**, cerebral blood flow; **CPP**, cerebral perfusion pressure; **CSF**, cerebrospinal fluid; **CT**, computed tomographic; **DCI**, delayed cerebral ischemia; **EEG**, electroencephalography; **HHT**, hypertensive/hypervolemic therapy; **HTS**, hypertonic saline; **ICP**, intracranial pressure; **ICU**, intensive care unit; **i.v.**, intravenously; **LOC**, loss of consciousness; **LPR**, lactate-pyruvate ratio; **MAP**, mean arterial pressure ; **$PbtO_2$**, brain tissue oxygen pressure; **SAH**, subarachnoid hemorrhage; **TBI**, traumatic brain injury

TABLE 1. Mortality according to the Hunt and Hess grading scale for aneurysmal subarachnoid hemorrhage[a]

Grade	Clinical findings	Hospital mortality (%)	
		1968	2002
I	Asymptomatic or mild headache	11	5
II	Moderate to severe headache, or oculomotor palsy	26	5
III	Confused, drowsy, or mild focal signs	37	10
IV	Stupor (localizes pain)	71	34
V	Coma (posturing or no motor response to pain)	100	52
Total		35	20

[a] Data are from 275 patients reported by Hunt and Hess in 1968 and 580 patients treated at Columbia University Medical Center between 1996 and 2002. Reproduced with permission from Mayer SA, Kossoff SB: Withdrawal of life support in the neurological intensive care unit. **Neurology** 52:1602–1609, 1999 (62).

ent a framework for optimal emergency resuscitation and critical care support of this high-risk subgroup (Table 2).

EMERGENT RESUSCITATION OF POOR-GRADE SAH

As surgical or endovascular aneurysm repair has been made increasingly available to all but the most moribund poor-grade patients, attention has turned to resuscitation strategies that focus on minimizing brain injury during the acute phase of bleeding as the most promising means of improving outcome. Survival and recovery after poor-grade SAH is primarily determined by the extent and severity of the diffuse brain injury that occurs at ictus. An analysis of more than 1000 SAH patients treated at Columbia University Medical Center between 1996 and 2006 reveals that while aneurysm rebleeding and infarction from vasospasm may have been the leading causes of death in years past (98), the direct effect of severe hemorrhage is by far the leading cause of death in the modern era (Fig. 1). Similarly, a population-based study from Cincinnati found that SAH patients dying from the acute effects of severe hemorrhage vastly outnumbered those who died from vasospasm-related brain infarction (14).

In an effort to minimize ongoing cerebral damage and prevent secondary brain injury, emergency management of the poor-grade patient should focus on 3 initial goals: 1) control of increased intracranial pressure (ICP) caused by hydrocephalus and cerebral edema; 2) cardiopulmonary support to optimize cerebral perfusion and oxygenation; and 3) medical therapy to prevent aneurysm rebleeding, including blood pressure (BP) control and seizure prophylaxis. After aneurysm repair, additional attention should be paid to 2 additional goals: 1) the diagnosis and management of cerebral vasospasm and other forms of secondary injury; and 2) the prevention and treatment of medical complications, including fever, anemia, hyperglycemia, hypotension, hyponatremia, and nosocomial infections. A major premise of this article is that multimodality monitoring of continuous electroencephalography (EEG), brain tissue oxygen pressure ($PbtO_2$), and cerebral microdialysis may eventually allow clinicians to move from the reactive model of detecting secondary insults toward a new paradigm in which these measures serve as targets for goal-directed therapy with the aim of creating an optimal physiological environment for the comatose injured brain.

PATHOPHYSIOLOGY OF ACUTE BRAIN INJURY AFTER SAH

A sudden and acute rise in ICP occurs with SAH. If ICP rises to levels approximating mean arterial pressure (MAP), intracranial circulatory arrest occurs, causing a critical global reduction in blood flow to the brain (80, 81). This often coincides clinically with loss of consciousness (LOC), an important prognostic indicator after SAH. LOC has been linked to the development of acute ischemic injury that can be detected by computed tomographic (CT) scan or magnetic resonance imaging at the time of the initial bleeding event—so called "ictal infarction"—as well as the development of global brain edema, an increased risk of vasospasm, and poor long-term outcome (19, 41, 104, 127).

Ischemic Brain Injury in Acute SAH

In contrast to delayed ischemia from vasospasm, which has been the subject of intense experimental and clinical investigation for several decades, ischemic brain injury at the time of the initial bleeding event has received relatively little attention (29). Hadeishi et al. (35) first demonstrated that symmetric, cortical diffusion-weighted imaging abnormalities can occur in poor-grade SAH patients. We have since replicated these findings, with 11 of 14 poor-grade SAH patients (Hunt and Hess Grades IV or V) demonstrating bilateral ischemic injury on diffusion-weighted imaging but not on CT scans (Fig. 2), mainly involving the anterior cerebral artery territories (10 patients), and less often including the thalamus and basal ganglia and middle cerebral artery territories (3 patients each) (127). The prognosis tends to be extremely poor when acute ischemic injury is present on magnetic resonance imaging scans, with death or severe disability as the predominant outcome.

CT evidence of acute infarction after SAH is a less common complication that probably represents a "tip-of-the-iceberg" phenomenon of only the most severe cases of ischemic injury related to intracranial circulatory arrest. In the Columbia University SAH Outcomes Project, so-called "ictal infarction" was present in 3% of 487 aneurysmal SAH patients (104). More than half of these patients had multiple infarcts that tended to be territorial and symmetric. Acute infarction was correlated with LOC at onset, intraventricular hemorrhage, global cerebral edema, poor Hunt and Hess grade on admission, and elevated Acute Physiology and Chronic Health Evaluation II physiological subscore. The mortality rate was 78% in these patients.

TABLE 2. Columbia University Medical Center management protocol for acute subarachnoid hemorrhage[a]

Blood pressure	Control elevated BP during the preoperative phase (systolic BP <160 mm Hg) with IV labetalol or nicardipine to prevent rebleeding.
Rebleeding prophylaxis	Epsilon aminocaproic acid 4 g IV upon diagnosis, followed by 1 g/h until aneurysm repair, for a maximum of up to 72 h after ictus.
IV hydration	Preoperative: Normal (0.9%) saline at 1.0–1.5 mL/kg/h. Postoperative: Normal (0.9%) saline at 1.0–1.5 mL/kg/h, and 250 mL 5% albumin every 2 h if the CVP is ≤5 mm Hg.
Laboratory	Periodically check complete blood count and electrolytes.
Testing	Obtain serial ECGs and check admission cTI to evaluate for cardiac injury; perform echocardiography in patients with abnormal ECG findings or cTI elevation.
Seizure prophylaxis	Fosphenytoin or phenytoin IV load (15–20 mg/kg); discontinue on postoperative Day 1 unless patient has seized, is of poor grade, has focal cortical pathology, or is otherwise unstable.
Vasospasm prophylaxis	Nimodipine 60 mg po every 4 h until SAH Day 21 or discharge.
Physiological	Cooling blankets to maintain T ≤37.5°C.
Homeostasis	Insulin drip to maintain glucose 100–120 mg/dL. Transfuse to maintain hemoglobin >7.0 g/dL (in the absence or active cerebral or cardiac ischemia).
Ventricular drainage	Emergent EVD placement in all stuporous/comatose patients (Hunt and Hess Grades IV and V), as well as lethargic patients with hydrocephalus. Begin trials of clamping EVD and monitoring ICP on Day 3 after placement. Perform ventriculoperitoneal shunting during subacute phase of illness in patients with persistent cognitive dysfunction and ventriculomegaly.
Vasospasm diagnosis	Transcranial Doppler sonography every 1 to 2 days until the tenth day after SAH. CT or MR perfusion scan on Days 4 to 8 after SAH if high-risk.
Therapy for symptomatic vasospasm	Place patient in Trendelenburg position (head down). Infuse 500 mL 5% albumin over 15 min. If the deficit persists, raise the systolic BP with phenylephrine or dopamine until the deficit resolves (maximum 200–220 mm Hg). 250 mL 5% albumin solution every 2 h if the CVP is ≤8 mm Hg or the PADP is ≤14 mm Hg. If refractory, perform invasive or noninvasive cardiac output monitoring and add dobutamine or milrinone to maintain cardiac index ≥4.0 L/min/m2. Transfuse to maintain hemoglobin >10.0 g/dL. Emergency angiogram for possible cerebral angioplasty unless the patient responds well to the above measures.

[a] BP, blood pressure; IV, intravenous; CVP, central venous pressure; ECG, electrocardiogram; cTI, cardiac troponin; po, by mouth; SAH, subarachnoid hemorrhage; T, temperature; EVD, external ventricular drain; ICP, intracranial pressure; CT, computed tomographic; MR, magnetic resonance; PADP, pulmonary artery diastolic pressure.

Acute Vasospasm after SAH

Large animal models have demonstrated that acute angiographic vasospasm often occurs within minutes of the onset of bleeding, with gradual resolution over the following 24 hours (12, 107). In human SAH patients, transcranial Doppler velocity elevations that tend to fall over time (suggestive of resolving spasm) can be detected within 48 hours of onset, and these early accelerations predict subsequent delayed cerebral ischemia (DCI) (Carrera et al., submitted for publication). So-called "ultra-early" angiographic spasm can be detected on admission angiography, and has also been linked to an increased risk of delayed ischemia from vasospasm (9, 90). Preliminary observations using cerebral microdialysis indicate that a massive elevation of the lactate-pyruvate ratio (LPR) occurs during the acute phase of SAH, implicating ischemia with failure of the oxidative metabolism and a shift to anaerobic glycolysis (Fig. 3), but whether this is a consistent phenomenon requires confirmation.

Global Cerebral Edema

CT scans often demonstrate a characteristic form of global brain edema after poor-grade SAH (Fig. 4). The typical findings, which are present on CT scans in more than 20% of poor-grade patients at admission, include effacement of the convexity sulci and disruption of the normal gray-white junction, with "finger-like" projections of lucency extending from the white matter to the cortical surface (19). Global edema is also strongly associated with LOC at ictus and poor clinical grade at admis-

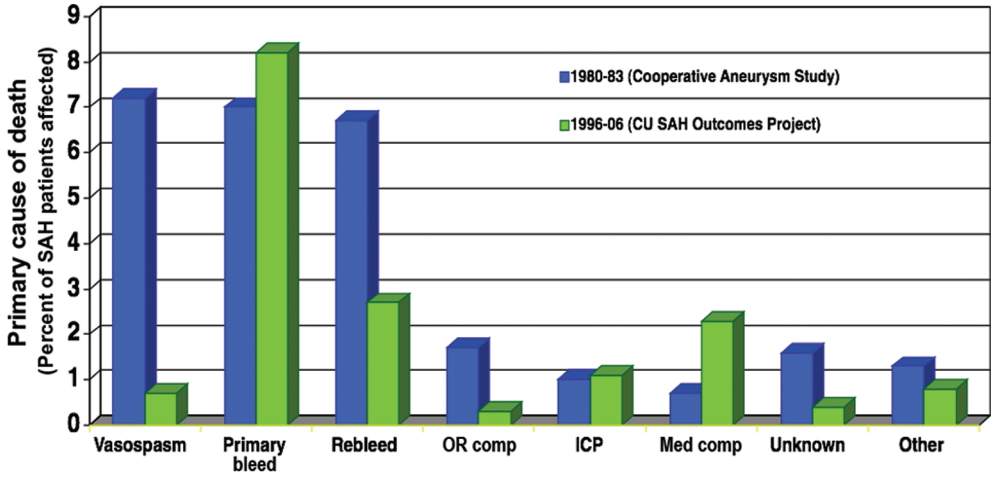

FIGURE 1. *Bar graph illustrating mortality after subarachnoid hemorrhage (SAH) according to the primary cause of death or neurological devastation leading to withdrawal of support. Data are from 3521 patients enrolled in the Cooperative Aneurysm Study between 1980 and 1983 (48), and 1019 patients enrolled in the Columbia University (CU) Outcomes Project between 1996 and 2006. Numbers represent the percentage of all SAH patients who died as a direct consequence of the listed variable. Primary cause of death was based on judgments made by study investigators who served as caregivers. ICP, intracranial pressure; OR, operating room; comp, complication; Med, medical.*

sion, suggesting a transient episode of diffuse cerebral ischemia and secondary reperfusion injury in the pathogenesis of this disorder. It is plausible that the primary locus of initial injury in SAH-related global cerebral edema involves the cerebral microvasculature, leading to endothelial dysfunction, autoregulatory failure, and blood-brain barrier disruption. Global cerebral edema after SAH has been linked to an increased risk of mortality, disability, and cognitive dysfunction among survivors (19, 54).

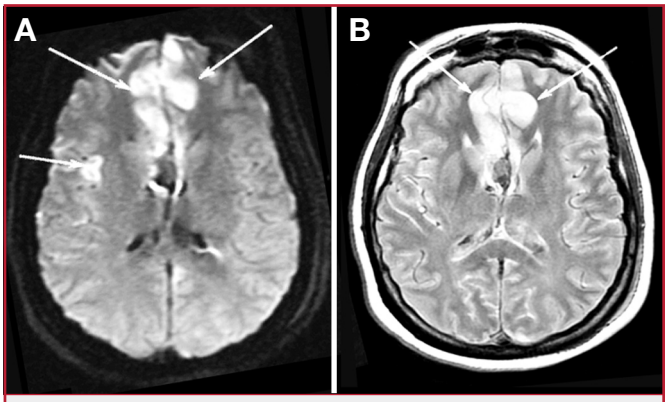

FIGURE 2. *Diffusion-weighted (A) and fluid-attenuated inversion recovery (B) computed tomographic (CT) images demonstrating hemorrhage-related ischemic injury in both anterior and right middle cerebral artery territories (arrows) at admission in a 44-year-old woman with Hunt and Hess Grade V SAH from a left anterior cerebral artery aneurysm that was coiled on Day 3.*

The association of elevated Acute Physiology and Chronic Health Evaluation II scores with CT evidence of ictal infarction raises the possibility that 1 or more acute physiological derangements may modulate global brain injury after SAH (104). This hypothesis is supported by the observation that extremes of BP, hypoxia, metabolic acidosis, and hyperglycemia at admission are independent determinants of poor outcome (24, 32, 71). It is remarkable that the cumulative impact of these acute physiological derangements on outcome is equivalent to that of the admission Glasgow Coma Scale score (24). Further experimental and clinical investigation is needed to gain a better understanding of the pathophysiology of acute global brain injury after SAH, with the hope that the knowledge can be used to positively influence treatment and improve outcome.

ICP CONTROL

External ventricular drainage aids in ICP control, augments brain perfusion, and is generally indicated in all stuporous or comatose SAH patients (Hunt and Hess Grades IV or V), regardless of the presence of acute hydrocephalus, because this complication is almost certain to develop over several hours as a result of arrest of the normal anterograde flow of cerebrospinal fluid (CSF). Beyond CSF drainage or craniotomy for surgical decompression of a space-occupying clot, which is the cornerstone of therapy for ICP, escalating medical therapy in intubated patients includes maximal sedation, optimization of cerebral perfusion pressure (CPP), osmotherapy to reduce cerebral edema, moderate hyperventilation, barbiturate coma, and systemic hypothermia.

Sedation

Intravenous sedation should be administered to SAH patients who are at risk for elevated ICP when they are agitated or have difficulty tolerating endotracheal intubation. Short-acting continuous infusion agents are preferred to allow frequent examinations off of sedation, including daily morning interruptions, which allow for minimization of sedative dosing and more rapid weaning to extubation (55). The preferred agent is propofol at a dose of 50 to 200 μg/kg/min. Prolonged infusions of high-dose propofol to control ICP should be avoided to minimize the risk of propofol infusion syndrome, a

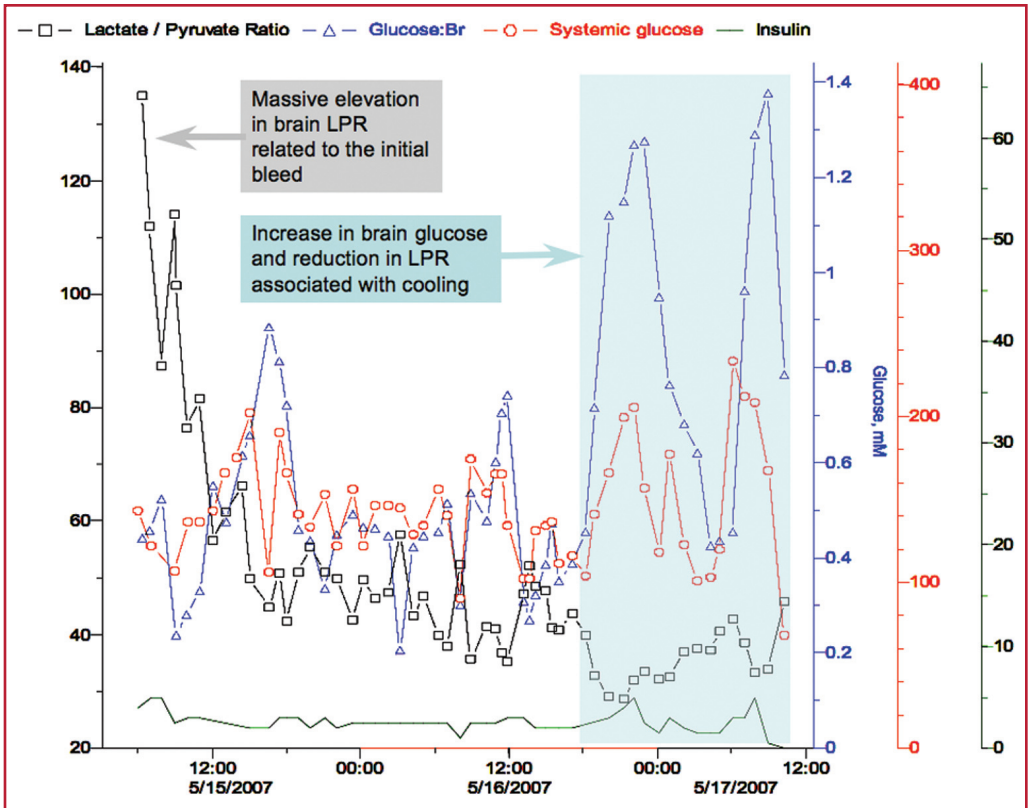

FIGURE 3. *Frequency polygram showing a patient with poor-grade SAH on SAH Day 1 showing massive elevation of lactate-pyruvate ratio (LPR) resulting from lactate concentrations greater than 5 mmol/L and pyruvate concentrations lower than 100 μmol/L. LPR elevation above 40 is considered indicative of ischemic injury sufficient to trigger a significant shift toward aerobic metabolism. Subsequent treatment of fevers with a cooling device was associated with a hyperglycolytic metabolic pattern with an increase in brain glucose levels and both lactate and pyruvate concentrations above normal levels producing a reduction in LPR.*

fatal idiosyncratic reaction characterized by metabolic acidosis, renal failure, and rhabdomyolysis (25). Propofol dosing can be minimized by giving fentanyl (1–3 μg/kg/h) or remifentanyl (0.03–0.25 μg/kg/min) for an added analgesic effect, or midazolam (0.05–0.2 mg/kg/h) for an added anticonvulsant effect, as dictated by the clinical syndrome. The goal should be sedation to a quiet, motionless state while avoiding excessive hypotension.

CPP Optimization

If ICP remains elevated after maximal sedation, attention should be directed to optimizing CPP, which is defined as MAP minus ICP. Extremes of BP (MAP <70 or >130 mm Hg) have been linked to poor long-term outcome after SAH (24). Under circumstances of reduced intracranial compliance, extremes of BP can aggravate intracranial hypertension (Fig. 5). Low CPP can trigger reflex vasodilatation when pressure autoregulation is intact (cerebral vasodilatory cascade physiology), whereas excessively high CPP can cause breakthrough cerebral edema and microcirculatory vasodilation via hydrostatic forces (perfusion pressure breakthrough) (93, 108). Evidence-based targets for CPP management after SAH do not exist. Before aneurysm repair, however, it is reasonable to maintain CPP as low as possible above 60 to 70 mm Hg to minimize the risk of rebleeding. In the postaneurysm repair phase of ICU care, higher BPs are desired to ensure adequate cerebral perfusion in the face of vasospasm. Invasive intracranial monitoring with brain tissue oxygen probes and microdialysis can provide real-time physiological end points for CPP optimization in comatose patients.

Osmotherapy

Osmotherapy is crucial for managing elevated ICP. In addition to infusion of 0.5 to 1.5 g/kg of 20% mannitol solution, ICP or symptomatic intracranial mass effect can be treated with hypertonic saline (HTS) solutions, including bolus therapy with 23.4% saline via a central venous line (0.5–2.0 mL/kg), or 2% or 3% sodium/chloride-acetate solution at 1.0 mL/kg/h as a maintenance fluid (40, 84). The beneficial effects of HTS on cerebral perfusion in poor-grade SAH patients was recently demonstrated by Tseng et al. (116): 23% HTS at a dose of 2.0 mL/kg decreased ICP by 60% with peak effect 30 minutes after dosage and a duration of 3 to 6 hours. Importantly, cerebral vascular resistance was reduced and cerebral blood flow (CBF) increased with HTS therapy, which may be important given the evidence that microcirculatory disturbances play a role in the pathogenesis of acute brain injury after SAH.

Hyperventilation

After CSF drainage, sedation, CPP optimization, and osmotherapy, further increases in ICP can be controlled with controlled hyperventilation. As is the case with severe traumatic brain injury (TBI), concern is justified that hyperventilation to partial pressure of carbon dioxide levels well below 30 mm Hg may lead to excessive vasoconstriction and exacerbation of ischemic injury (72). Use of brain tissue oxygen or jugular bulb monitoring can provide reassurance that any given level of hyperventilation is not compromising cerebral perfusion, which would be expected to result in reduced jugular bulb mixed venous oxygen saturation or tissue oxygen tension.

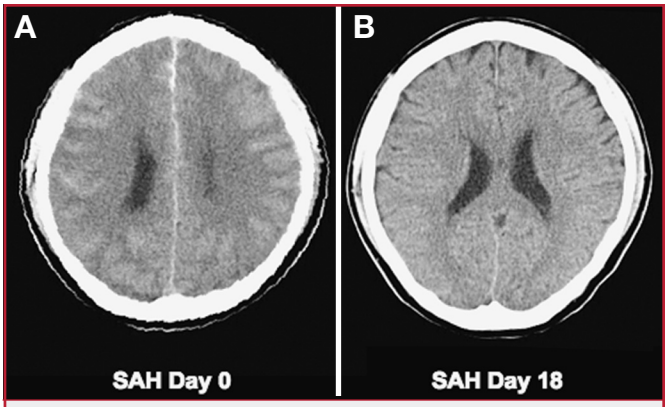

FIGURE 4. A, *admission CT scan (SAH Day 0) showing global edema in a 55-year-old man with a Hunt and Hess Grade V SAH from a left anterior communicating artery aneurysm that was clipped. Note the complete effacement of all convexity sulci and presence of "finger-like" extensions of white matter lucencies to the cortical surface.* **B**, *a follow-up scan on SAH Day 18 showed complete normalization of the CT findings. (Reprinted with permission from 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*** *33:1225–1232, 2002 [19].)*

Pentobarbital and mild to moderate hypothermia (33, 82) are essentially last-ditch interventions for ICP control. Experience with these therapies in poor-grade SAH is extremely limited, and consideration of these interventions should probably prompt a reexamination of definite surgical options (i.e., hematoma evacuation) if aggressive intervention is warranted.

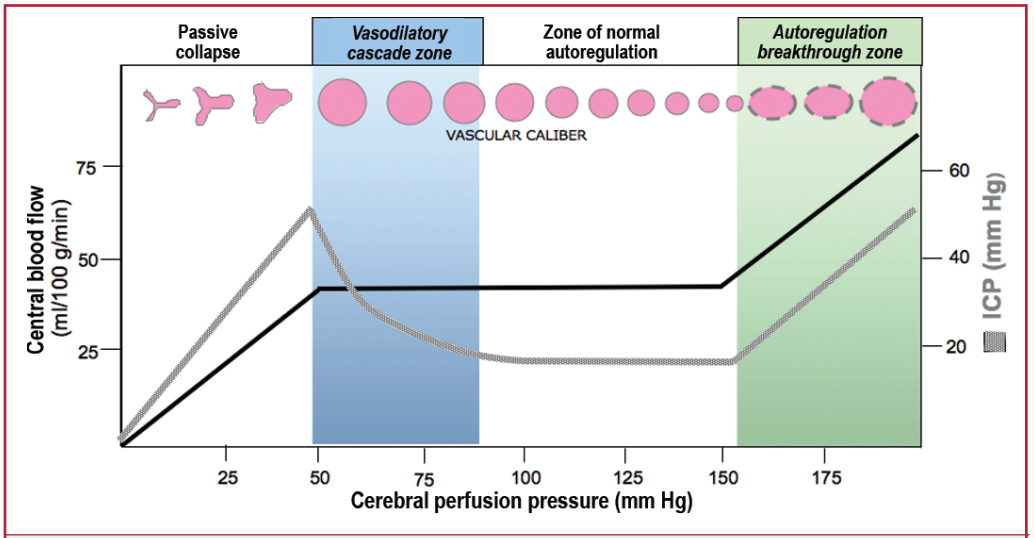

FIGURE 5. *Relationship of ICP to cerebral perfusion pressure (CPP) in states of reduced intracranial compliance. In both the vasodilatory cascade zone and the perfusion pressure breakthrough zone, increased cerebral blood volume leads to an increase in ICP. (Adapted with permission from Rose JC, Mayer SA: Optimizing blood pressure in neurological emergencies.* ***Neurocrit Care*** *1:287–299, 2004 [98].)*

ACUTE CARDIOPULMONARY SUPPORT

Neurogenic pulmonary and cardiac complications are common during the acute phase of SAH and may critically hamper brain perfusion and oxygenation. Hypotension and hypoxemia at admission have been shown to have powerful deleterious effects on the outcome of severe TBI (10), and it stands to reason that the same should be the case in patients with poor-grade SAH. In an analysis of physiological derangements that determine poor outcome after SAH, the presence of an arteriolar-alveolar gradient exceeding 100 mm Hg at admission had the most powerful effect, followed by extremes of BP (20). We hypothesize that the brunt of acute brain injury-related processes occurs during the prehospital phase, when ICP is highest, and before circulatory and oxygenation deficits can be aggressively treated.

Neurogenic Myocardial Stunning

Electrocardiogram changes are common after SAH (64, 65, 76, 87), and in a subset of affected patients, severe cardiac dysfunction or pulmonary edema may occur at the onset of hemorrhage. Postmortem studies in these patients have confirmed an association between a myocardial contraction band necrosis and pulmonary edema, cardiogenic shock, and acute coma or sudden death after SAH (65). Neurogenic myocardial stunning manifests clinically as left ventricular dysfunction on echocardiography (53). Fulminant cardiogenic shock coupled with neurogenic pulmonary edema may occur, but even more common are milder forms of acute hypoxia and relative hypotension (65, 121).

Cardiac Troponin Elevation

Troponin elevations are frequently encountered after SAH, and the magnitude of acute cardiac injury is highly correlated with outcome (60, 76). Even minor abnormalities in enzyme level in the range of 2 to 10 ng/mL are associated with an increased risk of echocardiographic left ventricular dysfunction, pulmonary edema, hypotension requiring pressors, DCI from vasospasm, and death or severe disability at discharge (76). These findings point to the importance of screening echocardiography and either invasive (i.e., pulmonary artery catheter) or noninvasive cardiovascular hemodynamic and cardiac output monitoring in SAH patients with acute myocardial injury.

Management of Hypoxia

To improve cerebral oxygenation when an increased

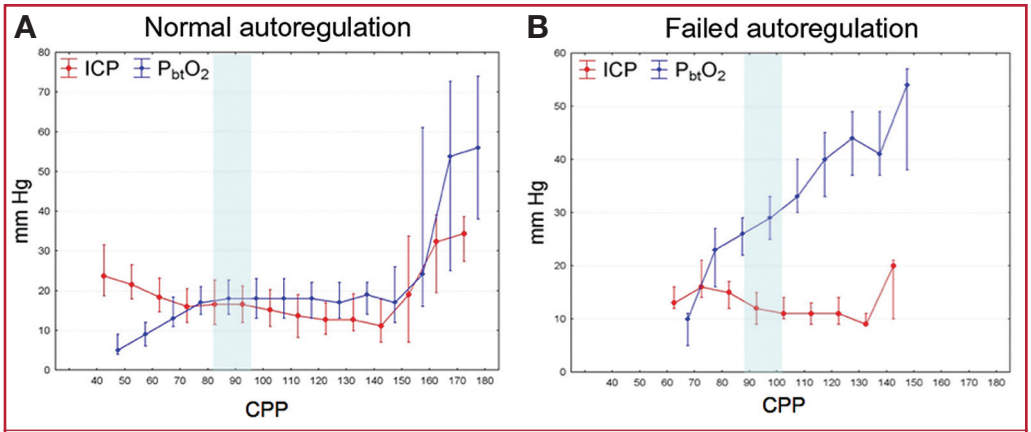

FIGURE 6. *Use of partial pressure of brain oxygen ($PbtO_2$) monitoring for the evaluation of cerebral autoregulation, showing plots of $PbtO_2$ and ICP as a function of cerebral perfusion pressure (CPP).* **A**, *40-year-old man with a 70 mL thalamic hemorrhage. Data displayed are based on 340 hours of monitoring from a probe placed ipsilateral to the hemorrhage. Pressure dependence of oxygen is evident at a CPP less than 80 mm Hg and greater than 130 mm Hg. Autoregulation appears intact within this range.* **B**, *55-year-old man with grade IV SAH owing to an 8-mm anterior communicating artery aneurysm. Head CT revealed thick SAH throughout and global cerebral edema. Data displayed are based on 31 hours of monitoring from a probe placed in the right frontal lobe. Oxygen levels appear dependent on pressure throughout the CPP range. The data indicate that a CPP of 120 to 130 mm Hg is associated with the highest brain oxygen levels without a concurrent increase in ICP. (Reproduced with permission from Wartenberg KE, Schmidt JM, Mayer SA: Multimodality monitoring in neurocritical care.* ***Crit Care Clin*** *23:507–538, 2007 [126].)*

arterio-alveolar gradient is present, pulmonary edema should be aggressively treated with high fractions of inspired oxygen, positive end expiratory pressure to levels of 5 to 15 cm H_20, and careful diuresis to optimize volume status without causing hypovolemia or hypotension. Severe pulmonary edema associated with neurogenic stunned myocardium warrants invasive or noninvasive cardiac output monitoring and administration of inotropes such as milrinone (0.25–0.75 μg/kg/min) or dobutamine (3–15 μg/kg/min), which can improve left ventricular forward flow and minimize pulmonary congestion (52, 73). Milrinone has been shown to result in relatively greater cardiac performance enhancement than dobutamine in SAH-related heart failure, which may relate to the fact that it is a phosphodiesterase inhibitor, and thus may be able to bypass the cardiac beta receptor desensitization that is known to occur with myocardial stunning (73).

Management of Hypotension

Hypotension in the acute stage of SAH is usually related to cardiogenic shock, although a massive systemic inflammatory response syndrome-like response with vasodilatory shock can occur in moribund poor-grade patients (129). In the absence of ICP measurements, MAP should be maintained between 70 and 90 mm Hg with phenylephrine (2–10 μg/kg/min), norepinephrine (0.03–0.6 μg/kg/min), or dopamine (5–30 μg/kg/min). Norepinephrine (an alpha and beta receptor agonist) is probably the agent of choice because of the tendency of dopamine to cause excessive tachyarrhythmias, and the potential for phenylephrine (a pure alpha agonist) to increase afterload and exacerbate congestive heart failure. Norepinephrine has also been shown to produce more reliable increases in CBF than dopamine in patients with severe TBI (46, 112). In some cases, temporary placement of an intra-aortic balloon pump during the acute phase of resuscitation has been reported to result in good long-term recovery in otherwise completely moribund patients (5, 94).

Management of Hypertension

Acute severe hypertension should be treated aggressively to minimize the risk of rebleeding and exacerbation of cerebral edema and ICP. While a blanket policy of maintaining systolic BP below a standard goal of 120 to 160 mm Hg may be acceptable in good-grade patients, this can be detrimental in comatose patients if ICP is already highly elevated and CPP is compromised. In poor-grade patients, ICP should be monitored and BP targets should be written to maintain a desired CPP target before and after aneurysm repair (generally between 60 and 100 mm Hg, depending on the clinical situation). If an external ventricular drain is used to measure ICP, both the arterial and ventricular CSF pressure transducers should be positioned at ear level to obtain the most accurate measurement of CPP (77). Useful agents to lower BP include labetalol (5–150 mg/h) and nicardipine (5–15 mg/h). Sodium nitroprusside should be avoided because of its unreliable dose-response relationship, which can produce excessive drops in BP, its tendency to produce cyanide and thiocyanate toxicity, and its dilating effects on the cerebral vasculature, which can result in direct increases in ICP (93).

REBLEEDING

Even with aggressive efforts directed toward urgent aneurysm repair, the rate of rebleeding after SAH is nearly 7%, with most rebleeding occurring during the first 72 hours after ictus (74). The most important risk factors for early rebleeding are large aneurysm size and poor clinical grade (74, 97). In the 1994 American Heart Association Guidelines, systolic BP control in combination with bed rest and/or antifibrinolytic therapy were recommended as options to minimize the risk of acute rebleeding (61). Although rebleeding is often attributed to uncontrolled hypertension, vascular shear stress and endogenous fibrinolysis of the clot around the rupture point of the aneurysm may be more important causative mechanisms.

Antifibrinolytic Therapy

When delayed clipping was the preferred method of treating SAH before the 1980s, antifibrinolytic therapy was widely used for the prevention of rebleeding. Previous studies have shown, however, that although antifibrinolytics reduce the incidence of rebleeding, they are associated with an increased risk of ischemic deficits with prolonged infusion (17). Thus, prolonged antifibrinolytic therapy for SAH patients in the United States has largely been abandoned.

A newer approach, however, is to initiate a short course of antifibrinolytic therapy in the emergency department and to continue it until the time of aneurysm repair or for a maximum of 72 hours, when vasospasm begins. A randomized trial of 505 SAH patients found that 1 g of tranexamic acid given intravenously (i.v.) every 6 hours until 72 hours, or until the repair procedure reduced rebleeding from 10.8% to 2.4%, with no increase in delayed ischemic deficits (39). At our center, we have shown that a policy of administering 4 g of epsilon aminocaproic acid i.v. in the emergency department upon SAH diagnosis, followed by an infusion of 1 g/h until the time of aneurysm repair or 72 hours, was associated with a reduction in rebleeding from 11.4% to 2.7%, despite an increase in the risk of deep vein thrombosis (111).

SEIZURE PROPHYLAXIS

All SAH patients should receive seizure prophylaxis upon diagnosis, because acute seizures, although uncommon, may provoke rebleeding. The traditional antiepileptic drug of choice is phenytoin or fosphenytoin (20 mg/kg i.v., followed by 300 mg daily), although levetiracetam given i.v. (2-g load, followed by 1 g every 12 hours) is an increasingly attractive option because of its favorable side effect profile and lack of drug interactions (69, 114). In good-grade patients (Hunt and Hess Grades I and II), antiepileptic drugs can be terminated on postoperative Day 1 with good results (8). In poor-grade patients (Hunt and Hess Grades III to V), those who have had early seizures, or those with focal cortical pathology, it is reasonable to continue prophylactic antiepileptic drugs for approximately 7 days, or until the patient is considered out of the high-risk period. With this management strategy, the risk of convulsive seizures is only 4% (23). Anticonvulsants should be discontinued at hospital discharge if seizures have not occurred because prolonged exposure to these drugs after SAH has been associated with worse functional and cognitive outcomes (75, 95).

MANAGEMENT OF VASOSPASM

Advances in intensive care have substantially reduced the frequency and severity of symptomatic cerebral vasospasm, with the current standard of care including the administration of calcium channel blockers such as nimodipine, strict maintenance of euvolemia, and hypertensive/hypervolemic therapy (HHT) upon the first clinical signs of vasospasm. In recent years, intra-arterial vasodilators and balloon angioplasty have increasingly been viewed as first-line treatments, rather than rescue interventions, for symptomatic vasospasm.

Prediction of Vasospasm

Deterioration or infarction from vasospasm may be predicted using a modification of the Fisher computed tomographic rating scale that accounts for intraventricular as well as thick cisternal blood. The lowest-risk group refers to minimal or thin SAH with no intraventricular hemorrhage (10% DCI risk), whereas the highest-risk group has a thick cisternal clot in combination with bilateral intraventricular hemorrhage (40% DCI risk) (18, 31). Other consistently identified, albeit less robust, predictors of symptomatic vasospasm include poor clinical grade, hypertension, cigarette smoking, untreated hypovolemia, transcranial Doppler velocity elevations, and CT perfusion abnormalities (18, 56, 91).

Vasospasm Prophylaxis

Nimodipine has been shown to reduce the frequency of DCI by approximately 30% in clinical trials (3, 45, 89). This effect is presumably mediated by reduction of calcium entry into ischemic neurons, or by improvement in microcollateral flow. Maintenance of euvolemia and the avoidance of intravascular volume depletion is also an important line of defense against DCI (6, 48, 86). There is no evidence that prophylactic hypervolemic therapy reduces the DCI risk in patients who are already euvolemic (58). Although some institutions use prophylactic hemodynamic augmentation with vasopressors or inotropes in high-risk patients to reduce the risk of DCI, no controlled clinical trials have evaluated the safety and efficacy of this approach.

Medical Treatment of Symptomatic Vasospasm

HHT should be immediately initiated upon the onset of symptomatic cerebral vasospasm (Table 2). Elevated systolic BP, volume loading, and hemodilution to a hematocrit of approximately 30% has been shown to improve CBF in regions of ischemia via 3 mechanisms: 1) elevation of CPP, 2) elevation of cardiac output, and 3) reduction of blood viscosity (92, 109, 128). Clinical improvement in response to HHT in case series is 60 to 70% (47, 86). Phenylephrine is a safe and effective first-line pressor when HHT is instituted for symptomatic vasospasm, as long as left ventricular function is normal (70). For medically refractory patients, we also administer inotropes (milrinone or dobutamine) to maintain the cardiac index above 4.0 L/min/m^2 (73), and transfuse blood to maintain hemoglobin above 10 g/dL (as opposed to 7.0 g/dL, the conventional transfusion trigger for most critically ill patients).

Interventional Treatment of Symptomatic Vasospasm

When HHT alone fails to effectively reverse ischemic deficits as a result of vasospasm, angiography should be performed in a timely fashion. Transluminal balloon angioplasty produces long-lasting dilation of proximal vasospastic arteries in 80% to 100% of patients; clinical improvement in most series ranges from 30% to 80% (13, 132). In the largest series of patients with

symptomatic vasospasm treated with transluminal balloon angioplasty, nearly half improved within 72 hours, one-quarter remained unchanged, and one-quarter deteriorated (78). Early treatment (within 2 hours of the onset of symptoms) has been associated with a higher likelihood of clinical response (98). Complications of transluminal balloon angioplasty include vessel perforation, hemorrhagic infarction, and dissection or thrombosis. Intra-arterial administration of vasodilators such as nimodipine, verapamil, nicardipine, and papaverine is often used when vasospasm of the distal vasculature is found (13, 132). Angiographic improvement occurs in 30 to 100% of patients treated with these agents; clinical improvement is less common, occurring in 30% to 50% (13, 132).

Asymptomatic Cerebral Ischemia in Poor-grade SAH Patients

Poor-grade patients with depressed level of consciousness present a particular challenge regarding the diagnosis of DCI because of the limited use of clinical examination for detecting neurological decline. Clinically "silent" infarction accounts for up to 25% of patients with DCI, and coma is the most important risk factor for asymptomatic infarction (35, 105, 127). Because detection of a new neurological deficit usually triggers the initiation of HHT, angioplasty, and other rescue therapies, it is likely that asymptomatic DCI may often go untreated (105). Even when asymptomatic, cerebral infarction has been associated with poor outcome after controlling for established determinants of outcome (105).

In light of the fact that a substantial amount of ischemic injury may go undetected in poor-grade SAH patients, it is reasonable to perform surveillance catheter angiography between Days 4 and 8 after onset, with the timing of these investigations dictated by the development of transcranial Doppler and CT perfusion abnormalities, with the goal of prophylactically treating any vasospasm that is identified with intra-arterial vasodilators or balloon angioplasty. Others have advocated the routine use of prophylactic HHT in all SAH patients at high risk for developing DCI (86, 92).

MULTIMODALITY NEUROMONITORING

Multimodality monitoring is being increasingly implemented in the critical care of poor-grade SAH patients (101, 120, 126). Given the poor sensitivity of the neurological examination to secondary brain injury, multimodality monitoring combined with newer brain perfusion imaging modalities offers a promising new approach to detecting secondary injury. Advanced monitoring techniques that provide real-time information regarding the relative health or distress of the brain, such as $PbtO_2$, signal-processed electroencephalography, and neurochemical monitoring using microdialysis, can be used not only to detect secondary injury, but theoretically can also be used as end points to create and maintain an optimal physiological environment for the comatose injured brain. As opposed to the traditional reactive paradigm of critical care in which interventions are triggered as soon as a harmful process is detected, goal-directed therapy based on continuous EEG, $PbtO_2$, and microdialysis is a promising and testable proactive approach that may prevent secondary injury from occurring in the first place.

Continuous EEG Monitoring

Patients with poor-grade SAH are at high risk for nonconvulsive seizures and DCI, both of which can be detected with continuous EEG monitoring (21, 22). Continuous EEG monitoring detects seizures in approximately 20% of stuporous or comatose SAH patients, with the vast majority (95%) of these seizures being nonconvulsive and without any clinical correlate (20, 27). Signal-processed continuous EEG displaying reductions in alpha variability or the alpha/delta ratio have been cited as the most sensitive and specific EEG derivatives for detecting DCI after SAH (21, 120). In some cases, continuous EEG changes can precede neurological deterioration by up to 2 days (120). The imperative for continuous EEG monitoring of poor-grade patients is further supported by the observation that many of these patients experience clinically asymptomatic cerebral infarction (105). The presence of periodic epileptiform discharges, the absence of normal sleep architecture and reactivity to stimuli, and nonconvulsive status epilepticus on continuous EEG predicts a poor outcome after SAH (20).

Regional $PbtO_2$ and CBF Monitoring

Probes are available that can measure regional cerebral perfusion; they should be inserted preferably into what is thought to be "tissue at risk," and should pass through gray matter into white matter (25–35 mm deep to the pial surface) for optimal value referencing. $PbtO_2$ monitoring is a robust method for providing continuous measurements of the partial pressure of oxygen in a focal region of brain tissue, and has been shown experimentally to be a reasonable surrogate for CBF if the cerebral rate of oxygen metabolism is stable (37). The Licox monitor (Integra Neurosciences, Plainsboro, NJ) measures tissue oxygenation with a polarographic technique by means of a Clark electrode (26, 124). $PbtO_2$ monitoring allows the determination of baseline critical perfusion thresholds and detection of ischemia as a result of vasospasm or hyperventilation (1, 16, 28, 51, 66, 119). Normal $PbtO_2$ levels are typically greater than 35 mm Hg in the gray matter and greater than 20 mm Hg in the white matter (100, 124). Reported $PbtO_2$ cut points that correspond with cerebral ischemia range from 10 to 25 mm Hg. A newer technology for focal CBF monitoring involves a thermal diffusion microprobe (Bowman Perfusion Monitor; Hemedex Inc., Cambridge, MA). This device provides sensitive, continuous, real-time CBF measured in mL/100 g/min, and has been shown to be well correlated with absolute CBF measurements obtained using xenon-enhanced CT imaging (118).

$PbtO_2$ monitoring can provide real-time information regarding autoregulation (126). When autoregulation is intact, there is little correlation between CPP and brain oxygen tension over a given period of time, because perfusion is maintained at a constant level despite fluctuations in BP. With autoregulatory failure, multimodality monitoring can demonstrate strong correlations between $PbtO_2$ and various drivers of brain perfusion,

including MAP, CPP (Fig. 6), and end tidal CO_2 (2, 50, 67, 68, 126). New methods for correlational data analysis and display may enhance the ability of clinicians to understand complex physiological relationships and identify optimal physiological targets (106). Impaired autoregulation can be detected by means of continuous measurement of oxygen reactivity—essentially the moving correlation coefficient between CPP and $PbtO_2$ (43, 44). In one study, autoregulatory failure as evidenced by more positive oxygen reactivity values was found to be significantly associated with the development of DCI as a result of vasospasm (44). Impaired autoregulation as evidenced by positive oxygen reactivity values has also been correlated with increased mortality after severe TBI (43). Studies on patients with severe TBI have demonstrated the feasibility of goal-directed CPP management based on tissue oxygenation, rather than the conventional CPP target of 60 mm Hg (66, 113).

Cerebral Microdialysis

All substances pass through the interstitial space between cells and blood capillaries. Cerebral microdialysis makes it possible to monitor neurotransmitters (glutamate), energy substrates (glucose), metabolites (lactate, pyruvate), and other extracellular neurochemicals (glycerol, acetylcholine, choline) in the extracellular space hourly at the bedside. The human brain depends almost entirely on glucose and its metabolites to maintain normal metabolism and function (126). Under normal aerobic conditions glucose is metabolized to pyruvate, which generates large quantities of adenosine triphosphate. During hypoxia or ischemia, anaerobic metabolism predominates, adenosine triphosphate production is much less efficient, and the end product of glucose metabolism is lactate, resulting in an increase in LPR (34).

Persistently low and falling brain glucose levels have been associated with mortality and poor functional recover among comatose patients (83, 123). A decrease in brain glucose is thought to signify reduced capillary perfusion, decreased systemic supply, or increased cellular uptake. Failure of mitochondrial oxidative metabolism after injury can lead to a shift toward anaerobic metabolism and a sharp increase the demand for glucose (36, 42, 130). In these conditions, inadequate glucose availability can eventually lead to compromised brain energy metabolism and tissue acidosis, triggering a cascade of cellular injury and death (79, 122). An increased LPR combined with critically low levels of glucose signifies brain energy crisis (122). Other indicators of secondary cellular injury include increased concentrations of brain glutamate, an excitotoxic neurotransmitter, and glycerol and choline, end products of lipolysis during the destruction of cell membranes.

Preliminary microdialysis studies in poor-grade SAH patients have correlated LPR, glycerol, and glutamate elevations with positron emission tomography CBF reductions and symptomatic vasospasm (79, 99, 103). In an observational study of 149 SAH patients, LPR and glutamate elevations were predictive of poor 12-month outcome (101). More research is needed, however, before this technique can be considered a standard of care (88).

MEDICAL COMPLICATIONS

Medical complications occur frequently after SAH and can also contribute significantly to poor outcome. In the placebo group of the Cooperative Aneurysm Study investigating the effects of nicardipine, the most frequent non-neurological complications were anemia, hypertension, cardiac arrhythmia, fever, and electrolyte abnormalities (110). The proportion of deaths directly attributable to medical complications (23%) was comparable to that of vasospasm (23%) and rebleeding (22%). In an update of this study, a multivariable analysis of medical complications in 580 SAH patients found that the most frequent complications were fever, anemia, and hyperglycemia; remarkably, these 3 complications were also significant and independent determinants of poor outcome (125). Other studies have more specifically linked fever and hyperglycemia after SAH to symptomatic vasospasm and poor outcome (7, 30, 32, 85). These findings highlight the potential importance of strict fever control, prevention or treatment of anemia, and normoglycemic management with insulin infusion therapy for improving outcomes after SAH. Clinical trials are needed to determine the optimal management strategies for these conditions.

Finally, infection control strategies are important for reducing morbidity and mortality in all critically ill patients. Comatose neurological ICU patients carry an extremely high risk of pulmonary complications, including some of the highest rates of ventilator-associated pneumonia that have been reported (133). Patient management "bundles" that mandate the application of best medical practices to reduce the risk of catheter-related blood stream infections and ventilator-associated pneumonia should be used routinely in neurosurgical ICUs. Data regarding measures to reduce the risk of external ventricular drain-related ventriculomeningitis, such as the use of prophylactic antibiotics, are conflicting (4, 131). Definite studies are needed before firm recommendations can be made.

END-OF-LIFE CARE

A reconsideration of the therapeutic nihilism that has long shrouded the outlook of poor-grade SAH is an essential component of the paradigm shift that will be required to substantially improve survival. Endotracheal intubation, mechanical ventilation, and cardiovascular support are routinely offered to these patients, essentially ensuring their short-term survival in the ICU. However, for decades, the perception has been that these patients are neurologically unsalvageable, a view that is often used to justify decisions to withhold brain-rescuing neurosurgical interventions such as ventriculostomy and aneurysm repair.

It has become increasingly clear, however, that death after severe brain injury is often the result of a self-fulfilling prophecy (11, 38). It has also become apparent that physicians tend to substantially underestimate the capacity for recovery early in the course of severe brain injury (11). In a Harborview Medical Center study of 159 consecutively admitted Hunt and Hess Grade IV and V patients who were selectively managed with early surgery and aggressive postoperative intensive care,

it was found that attempts to predict poor outcome based on admission clinical and radiographic criteria alone would have resulted in withholding treatment from 30% of patients who ultimately had a favorable outcome (59). Future improvements in poor-grade SAH outcomes must begin with an initial trial of maximal surgical and medical therapy, starting with measures to control ICP and prevent aneurysm rebleeding.

Despite an aggressive approach, outcomes in patients with poor-grade SAH may often be poor. If a satisfactory degree of clinical improvement does not occur within 5 to 10 days despite maximal intervention, this approach does not preclude the right of patients to have life support actively withdrawn if consistent with their wishes (62). When a poor neurological outcome is anticipated, the prospect of continuing long-term support with placement of a tracheostomy and percutaneous enterogastrostomy often triggers decisions to enact do-not-resuscitate status, withdraw life support, and switch the goal from care to comfort. Paradoxically, as physicians become more confident that terminal extubation and comfort care can be implemented in a straightforward fashion, lives may be saved, as the usual justification for withholding potentially brain-saving interventions (survival with neurological devastation) no longer becomes relevant.

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REFERENCES

1. Al-Rawi PG, Hutchinson PJ, Gupta AK, Piechnik SK, Pickard JD, Kirkpatrick PJ: Multiparameter brain tissue monitoring-correlation between parameters and identification of CPP thresholds. **Zentralbl Neurochir** 61:74–79, 2000.
2. Al-Rawi PG, Zygun D, Tseng MY, Hutchinson PJ, Matta BF, Kirkpatrick PJ: Cerebral blood flow augmentation in patients with severe subarachnoid haemorrhage. **Acta Neurochir Suppl** 95:123–127, 2005.
3. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert DP, Hundley MB, Johnson RK, Strom JA, Transou CR: Cerebral arterial spasm—A controlled trial of nimodipine in patients with subarachnoid hemorrhage. **N Engl J Med** 308:619–624, 1983.
4. Alleyne CH Jr, Hassan M, Zabramski JM: The efficacy and cost of prophylactic and perioprocedural antibiotics in patients with external ventricular drains. **Neurosurgery** 47:1124–1129, 2000.
5. Apostolides PJ, Greene KA, Zabramski JM, Fitzgerald JW, Spetzler RF: Intra-aortic balloon pump counterpulsation in the management of concomitant cerebral vasospasm and cardiac failure after subarachnoid hemorrhage: Technical case report. **Neurosurgery** 38:1056–1060, 1996.
6. Awad IA, Carter LP, Spetzler RF, Medina M, Williams FC Jr: Clinical vasospasm after subarachnoid hemorrhage: Response to hypervolemic hemodilution and arterial hypertension. **Stroke** 18:365–372, 1987.
7. Badjatia N, Topcuoglu MA, Buonanno FS, Smith EE, Nogueira RG, Rordorf GA, Carter BS, Ogilvy CS, Singhal AB: Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. **Crit Care Med** 33:1603–1609, 2005.
8. Baker CJ, Prestigiacomo CJ, Solomon RA: Short-term perioperative anticonvulsant prophylaxis for the surgical treatment of low-risk patients with intracranial aneurysms. **Neurosurgery** 37:863–871, 1995.
9. Baldwin ME, Macdonald RL, Huo D, Novakovic RL, Novakovia RL, Goldenberg FD, Frank JI, Rosengart AJ: Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. **Stroke** 35:2506–2511, 2004.
10. Barrow D (ed): *Complications and Sequelae of Head Injury.* Park Ridge, AANS, 1992.
11. Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, Longstreth WT Jr: Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. **Neurology** 56:766–772, 2001.
12. Bederson JB, Levy AL, Ding WH, Kahn R, DiPerna CA, Jenkins AL 3rd, Vallabhajosyula P: Acute vasoconstriction after subarachnoid hemorrhage. **Neurosurgery** 42:352–362, 1998.
13. Brisman JL, Eskridge JM, Newell DW: Neurointerventional treatment of vasospasm. **Neurol Res** 28:769–776, 2006.
14. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A: Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. **Stroke** 25:1342–1347, 1994.
15. *Deleted in proof.*
16. Charbel FT, Du X, Hoffman WE, Ausman JI: Brain tissue PO(2), PCO(2), and pH during cerebral vasospasm. **Surg Neurol** 54:432–438, 2000.
17. Chwajol M, Starke RM, Kim GH, Mayer SA, Connolly ES: Antifibrinolytic therapy to prevent early rebleeding after subarachnoid hemorrhage. **Neurocrit Care** 8:418–426, 2008.
18. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, Connolly ES, Mayer SA: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: The Fisher scale revisited. **Stroke** 32:2012–2020, 2001.
19. 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** 33:1225–1232, 2002.
20. Claassen J, Hirsch LJ, Frontera JA, Fernandez A, Schmidt M, Kapinos G, Wittman J, Connolly ES, Emerson RG, Mayer SA: Prognostic significance of continuous EEG monitoring in patients with poor-grade subarachnoid hemorrhage. **Neurocrit Care** 4:103–112, 2006.
21. Claassen J, Hirsch LJ, Kreiter KT, Du EY, Connolly ES, Emerson RG, Mayer SA: Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. **Clin Neurophysiol** 115:2699–2710, 2004.
22. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ: Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. **Neurology** 62:1743–1748, 2004.
23. Claassen J, Peery S, Kreiter KT, Hirsch LJ, Du EY, Connolly ES, Mayer SA: Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. **Neurology** 60:208–214, 2003.
24. Claassen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N, Fitzsimmons BF, Connolly ES, Mayer SA: Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. **Crit Care Med** 32:832–838, 2004.
25. Corbett SM, Montoya ID, Moore FA: Propofol-related infusion syndrome in intensive care patients. **Pharmacotherapy** 28:250–258, 2008.
26. De Georgia MA, Deogaonkar A: Multimodal monitoring in the neurological intensive care unit. **Neurologist** 11:45–54, 2005.
27. Dennis LJ, Claassen J, Hirsch LJ, Emerson RG, Connolly ES, Mayer SA: Nonconvulsive status epilepticus after subarachnoid hemorrhage. **Neurosurgery** 51:1136–1144, 2002.
28. Dings J, Meixensberger J, Roosen K: Brain tissue pO2-monitoring: Catheter stability and complications. **Neurol Res** 19:241–245, 1997.
29. Doshi R, Neil-Dwyer G: A clinicopathological study of patients following a subarachnoid hemorrhage. **J Neurosurg** 52:295–301, 1980.
30. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, Kreiter KT, Ostapkovich ND, Kowalski RG, Parra A, Connolly ES, Mayer SA: Fever after subarachnoid hemorrhage: Risk factors and impact on outcome. **Neurology** 68:1013–1019, 2007.
31. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, MacDonald RL, Mayer SA: Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified fisher scale. **Neurosurgery** 59:21–27, 2006.

32. Frontera JA, Fernandez A, Claassen J, Schmidt M, Schumacher HC, Wartenberg K, Temes R, Parra A, Ostapkovich ND, Mayer SA: Hyperglycemia after SAH: Predictors, associated complications, and impact on outcome. **Stroke** 37:199–203, 2006.
33. Gasser S, Khan N, Yonekawa Y, Imhof HG, Keller E: Long-term hypothermia in patients with severe brain edema after poor-grade subarachnoid hemorrhage: Feasibility and intensive care complications. **J Neurosurg Anesthesiol** 15:240–248, 2003.
34. Goodman JC, Valadka AB, Gopinath SP, Uzura M, Robertson CS: Extracellular lactate and glucose alterations in the brain after head injury measured by microdialysis. **Crit Care Med** 27:1965–1973, 1999.
35. Hadeishi H, Suzuki A, Yasui N, Hatazawa J, Shimosegawa E: Diffusion-weighted magnetic resonance imaging in patients with subarachnoid hemorrhage. **Neurosurgery** 50:741–748, 2002.
36. Harris LK, Black RT, Golden KM, Reeves TM, Povlishock JT, Phillips LL: Traumatic brain injury-induced changes in gene expression and functional activity of mitochondrial cytochrome C oxidase. **J Neurotrauma** 18:993–1009, 2001.
37. Hemphill JC 3rd, Knudson MM, Derugin N, Morabito D, Manley GT: Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. **Neurosurgery** 48:377–384, 2001.
38. Hemphill JC 3rd, Newman J, Zhao S, Johnston SC: Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. **Stroke** 35:1130–1134, 2004.
39. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE: Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: A prospective randomized study. **J Neurosurg** 97:771–778, 2002.
40. Himmelseher S: Hypertonic saline solutions for treatment of intracranial hypertension. **Curr Opin Anaesthesiol** 20:414–426, 2007.
41. Hop JW, Rinkel GJ, Algra A, van Gijn J: Initial loss of consciousness and risk of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. **Stroke** 30:2268–2271, 1999.
42. Hovda DA, Yoshino A, Kawamata T, Katayama Y, Becker DP: Diffuse prolonged depression of cerebral oxidative metabolism following concussive brain injury in the rat: A cytochrome oxidase histochemistry study. **Brain Res** 567:1–10, 1991.
43. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J: Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. **Crit Care Med** 34:1783–1788, 2006.
44. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J: Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. **Stroke** 38:981–986, 2007.
45. Jan M, Buchheit F, Tremoulet M: Therapeutic trial of intravenous nimodipine in patients with established cerebral vasospasm after rupture of intracranial aneurysms. **Neurosurgery** 23:154–157, 1988.
46. Johnston AJ, Steiner LA, Chatfield DA, Coles JP, Hutchinson PJ, Al-Rawi PG, Menon DK, Gupta AK: Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. **Intensive Care Med** 30:791–797, 2004.
47. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP: Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. **Neurosurgery** 11:337–343, 1982.
48. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL: The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. **J Neurosurg** 73:18–36, 1990.
49. Kassell NF, Torner JC, Jane JA, Haley EC Jr, Adams HP: The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. **J Neurosurg** 73:37–47, 1990.
50. Kett-White R, Hutchinson PJ, Al-Rawi PG, Gupta AK, Pickard JD, Kirkpatrick PJ: Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. **Neurosurgery** 50:1213–1222, 2002.
51. Kiening KL, Härtl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR: Brain tissue pO2-monitoring in comatose patients: Implications for therapy. **Neurol Res** 19:233–240, 1997.
52. Knudsen F, Jensen HP, Petersen PL: Neurogenic pulmonary edema: Treatment with dobutamine. **Neurosurgery** 29:269–270, 1991.
53. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A: Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: Neurogenic stunned myocardium. **J Am Coll Cardiol** 24:636–640, 1994.
54. Kreiter KT, Copeland D, Bernardini GL, Bates JE, Peery S, Claassen J, Du YE, Stern Y, Connolly ES, Mayer SA: Predictors of cognitive dysfunction after subarachnoid hemorrhage. **Stroke** 33:200–208, 2002.
55. Kress JP, Hall JB: Sedation in the mechanically ventilated patient. **Crit Care Med** 34:2541–2546, 2006.
56. Lasner TM, Weil RJ, Riina HA, King JT Jr, Zager EL, Raps EC, Flamm ES: Cigarette smoking-induced increase in the risk of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. **J Neurosurg** 87:381–384, 1997.
57. Lee KC, Huh SK, Park HS, Shin YS, Lee KS: Management of poor-grade patients with ruptured intracranial aneurysm. **Keio J Med** 46:69–73, 1997.
58. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA: Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. **Stroke** 31:383–391, 2000.
59. Le Roux PD, Elliott JP, Newell DW, Grady MS, Winn HR: Predicting outcome in poor-grade patients with subarachnoid hemorrhage: A retrospective review of 159 aggressively managed cases. **J Neurosurg** 85:39–49, 1996.
60. Manavalan P, Richardson D, Rayford R, Talley JD: ECG and cardiac enzymes changes associated with subarachnoid hemorrhage. **J Ark Med Soc** 93:592–593, 1997.
61. Mayberg MR, Batjer HH, Dacey R, Diringer M, Haley EC, Heros RC, Sternau LL, Torner J, Adams HP Jr, Feinberg W: 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. **Circulation** 90:2592–2605, 1994.
62. Mayer SA, Kossoff SB: Withdrawal of life support in the neurological intensive care unit. **Neurology** 52:1602–1609, 1999.
63. Mayer SA, Swarup R: Neurogenic cardiac injury after subarachnoid hemorrhage. **Curr Opin Anaesthesiol** 9:356–361 1996.
64. Mayer SA, Bernardini GL, Solomon RA, Brust JC: Subarachnoid hemorrhage, Rowland LP (ed): *Merritt's Textbook of Neurology, 11th Ed.* Baltimore, Lippincott, Williams, and Wilkins, 2005, pp 328–338.
65. Mayer SA, Fink ME, Homma S, Sherman D, LiMandri G, Lennihan L, Solomon RA, Klebanoff LM, Beckford A, Raps EC: Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. **Neurology** 44:815–820, 1994.
66. Meixensberger J, Jaeger M, Väth A, Dings J, Kunze E, Roosen K: Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. **J Neurol Neurosurg Psychiatry** 74:760–764, 2003.
67. Meixensberger J, Vath A, Jaeger M, Kunze E, Dings J, Roosen K: Monitoring of brain tissue oxygenation following severe subarachnoid hemorrhage. **Neurol Res** 25:445–450, 2003.
68. Menon DK, Coles JP, Gupta AK, Fryer TD, Smielewski P, Chatfield DA, Aigbirhio F, Skepper JN, Minhas PS, Hutchinson PJ, Carpenter TA, Clark JC, Pickard JD: Diffusion limited oxygen delivery following head injury. **Crit Care Med** 32:1384–1390, 2004.
69. Michelucci R: Optimizing therapy of seizures in neurosurgery. **Neurology** 67:S14–S18, 2006.
70. Miller JA, Dacey RG Jr, Diringer MN: Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. **Stroke** 26:2260–2266, 1995.
71. Mocco J, Ransom ER, Komotar RJ, Schmidt JM, Sciacca RR, Mayer SA, Connolly ES Jr: Preoperative prediction of long-term outcome in poor-grade aneurysmal subarachnoid hemorrhage. **Neurosurgery** 59:529–538, 2006.
72. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. **J Neurosurg** 75:731–739, 1991.
73. Naidech A, Du Y, Kreiter KT, Parra A, Fitzsimmons BF, Lavine SD, Connolly ES, Mayer SA, Commichau C: Dobutamine versus milrinone after subarachnoid hemorrhage. **Neurosurgery** 56:21–27, 2005.
74. Naidech AM, Janjua N, Kreiter KT, Ostapkovich ND, Fitzsimmons BF, Parra A, Commichau C, Connolly ES, Mayer SA: Predictors and impact of

aneurysm rebleeding after subarachnoid hemorrhage. **Arch Neurol** 62:410–416, 2005.
75. Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, Connolly ES, Mayer SA, Fitzsimmons BF: Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. **Stroke** 36:583–587, 2005.
76. Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C, Fitzsimmons BF, Connolly ES, Mayer SA: Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. **Circulation** 112:2851–2856, 2005.
77. Nates JL, Niggemeyer LE, Anderson MB, Tuxen DV: Cerebral perfusion pressure monitoring alert! **Crit Care Med** 25:895–896, 1997.
78. Newell DW, Eskridge JM, Aaslid R: Current indications and results of cerebral angioplasty. **Acta Neurochir Suppl** 77:181–183, 2001.
79. Nilsson OG, Brandt L, Ungerstedt U, Säveland H: Bedside detection of brain ischemia using intracerebral microdialysis: Subarachnoid hemorrhage and delayed ischemic deterioration. **Neurosurgery** 45:1176–1185, 1999.
80. Nornes H: The role of intracranial pressure in the arrest of hemorrhage in patients with ruptured intracranial aneurysm. **J Neurosurg** 39:226–234, 1973.
81. Nornes H: Cerebral arterial flow dynamics during aneurysm haemorrhage. **Acta Neurochir (Wien)** 41:39–48, 1978.
82. *Deleted in proof.*
83. Oddo M, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA: Impact of tight glycemic control on brain glucose metabolism after severe brain injury: A microdialysis study. **Crit Care Med** 36:3233–3238, 2008.
84. Ogden AT, Mayer SA, Connolly ES Jr: Hyperosmolar agents in neurosurgical practice: The evolving role of hypertonic saline. **Neurosurgery** 57:207–215, 2005.
85. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, Rordorf G, Schwamm LH, Koroshetz WJ, McDonald CT: Fever in subarachnoid hemorrhage: Relationship to vasospasm and outcome. **Neurology** 56:1299–1304, 2001.
86. Origitano TC, Wascher TM, Reichman OH, Anderson DE: Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. **Neurosurgery** 27:729–740, 1990.
87. Parekh N, Venkatesh B, Cross D, Leditschke A, Atherton J, Miles W, Winning A, Clague A, Rickard C: Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. **J Am Coll Cardiol** 36:1328–1335, 2000.
88. Peerdeman SM, van Tulder MW, Vandertop WP: Cerebral microdialysis as a monitoring method in subarachnoid hemorrhage patients, and correlation with clinical events-a systematic review. **J Neurol** 250:797–805, 2003.
89. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, Disney LB, Khan MI, Grace M, Holness RO: Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. **J Neurosurg** 68:505–517, 1988.
90. Qureshi AI, Sung GY, Suri MA, Straw RN, Guterman LR, Hopkins LN: Prognostic value and determinants of ultraearly angiographic vasospasm after aneurysmal subarachnoid hemorrhage. **Neurosurgery** 44:967–974, 1999.
91. Rabinstein AA: The blood and the vessel: Prediction of cerebral vasospasm after subarachnoid hemorrhage. **Neurology** 66:622–623, 2006.
92. Romner B, Reinstrup P: Triple H therapy after aneurysmal subarachnoid hemorrhage. A review. **Acta Neurochir Suppl** 77:237–241, 2001.
93. Rose JC, Mayer SA: Optimizing blood pressure in neurological emergencies. **Neurocrit Care** 1:287–299, 2004.
94. Rosen CL, Sekhar LN, Duong DH: Use of intra-aortic balloon pump counterpulsation for refractory symptomatic vasospasm. **Acta Neurochir (Wien)** 142:25–32, 2000.
95. Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JI, Goldenberg FD, Macdonald RL: Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. **J Neurosurg** 107:253–260, 2007.
96. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL: Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. **Stroke** 38:2315–2321, 2007.
97. Rosenørn J, Eskesen V, Schmidt K, Rønde F: The risk of rebleeding from ruptured intracranial aneurysms. **J Neurosurg** 67:329–332, 1987.
98. Rosenwasser RH, Armonda RA, Thomas JE, Benitez RP, Gannon PM, Harrop J: Therapeutic modalities for the management of cerebral vasospasm: Timing of endovascular options. **Neurosurgery** 44:975–980, 1999.
99. Sarrafzadeh A, Haux D, Kuchler I, Lanksch WR, Unterberg AW: Poor-grade aneurysmal subarachnoid hemorrhage: Relationship of cerebral metabolism to outcome. **J Neurosurg** 100:400–406, 2004.
100. Sarrafzadeh AS, Haux D, Lüdemann L, Amthauer H, Plotkin M, Küchler I, Unterberg AW: Cerebral ischemia in aneurysmal subarachnoid hemorrhage: A correlative microdialysis-PET study. **Stroke** 35:638–643, 2004.
101. Sarrafzadeh AS, Kiening KL, Unterberg AW: Neuromonitoring: Brain oxygenation and microdialysis. **Curr Neurol Neurosci Rep** 3:517–523, 2003.
102. Sasaki T, Sato M, Oinuma M, Sakuma J, Suzuki K, Matsumoto M, Kodama N: Management of poor-grade patients with aneurysmal subarachnoid hemorrhage in the acute stage: Importance of close monitoring for neurological grade changes. **Surg Neurol** 62:531–537, 2004.
103. Säveland H, Nilsson OG, Boris-Möller F, Wieloch T, Brandt L: Intracerebral microdialysis of glutamate and aspartate in two vascular territories after aneurysmal subarachnoid hemorrhage. **Neurosurgery** 38:12–20, 1996.
104. Schmidt JM, Rincon F, Fernandez A, Resor C, Kowalski RG, Claassen J, Connolly ES, Fitzsimmons BF, Mayer SA: Cerebral infarction associated with acute subarachnoid hemorrhage. **Neurocrit Care** 7:10–17, 2007.
105. Schmidt JM, Wartenberg KE, Fernandez A, Claassen J, Rincon F, Ostapkovich ND, Badjatia N, Parra A, Connolly ES, Mayer SA: Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. **J Neurosurg** 109:1052–1059, 2008.
106. Schmidt JM, Wartenberg K, Wong A, Kesavabhotla K, Mukherjee V, Sheth S, Fernandez A, Frontera J, Temes R, Rincon F, Wazari A, Parra A, Palestrant D, Badjatia N, Connolly ES, Mayer SA: Graphical correlation analysis of brain tissue oxygen and intracranial pressure data for cerebral perfusion pressure optimization: a pilot study. **Neurocrit Care** 6:213–268, 2007.
107. Sehba FA, Bederson JB: Mechanisms of acute brain injury after subarachnoid hemorrhage. **Neurol Res** 28:381–398, 2006.
108. Sekhon LH, Morgan MK, Spence I: Normal perfusion pressure breakthrough: The role of capillaries. **J Neurosurg** 86:519–524, 1997.
109. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N: Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. **Lancet Neurol** 2:614–621, 2003.
110. Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC: Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. **Crit Care Med** 23:1007–1017, 1995.
111. Starke RM, Kim GH, Fernandez A, Komotar RJ, Hickman ZL, Otten ML, Ducruet AF, Kellner CP, Hahn DK, Chwajol M, Mayer SA, Connolly ES Jr: Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. **Stroke** 39:2617–2621, 2008.
112. Steiner LA, Johnston AJ, Czosnyka M, Chatfield DA, Salvador R, Coles JP, Gupta AK, Pickard JD, Menon DK: Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. **Crit Care Med** 32:1049–1054, 2004.
113. Stiefel MF, Spiotta A, Gracias VH, Garuffe AM, Guillamondegui O, Maloney-Wilensky E, Bloom S, Grady MS, LeRoux PD: Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. **J Neurosurg** 103:805–811, 2005.
114. Szaflarski JP, Meckler JM, Szaflarski M, Shutter LA, Privitera MD, Yates SL: Levetiracetam use in critically ill patients. **Neurocrit Care** 7:140–147, 2007.
115. Tamargo RJ, Walter KA, Oshiro EM: Aneurysmal subarachnoid hemorrhage: Prognostic features and outcomes. **New Horiz** 5:364–375, 1997.
116. Tseng MY, Al-Rawi PG, Pickard JD, Rasulo FA, Kirkpatrick PJ: Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. **Stroke** 34:1389–1396, 2003.
117. Ungersböck K, Böcher-Schwarz H, Ulrich P, Wild A, Perneczky A: Aneurysm surgery of patients in poor grade condition. Indications and experience. **Neurol Res** 16:31–34, 1994.
118. Vajkoczy P, Roth H, Horn P, Lucke T, Thomé C, Hubner U, Martin GT, Zappletal C, Klar E, Schilling L, Schmiedek P: Continuous monitoring of regional cerebral blood flow: Experimental and clinical validation of a novel thermal diffusion microprobe. **J Neurosurg** 93:265–274, 2000.

119. Väth A, Kunze E, Roosen K, Meixensberger J: Therapeutic aspects of brain tissue pO2 monitoring after subarachnoid hemorrhage. **Acta Neurochir Suppl** 81:307–309, 2002.
120. Vespa P: Continuous EEG monitoring for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: "To detect and protect." **J Clin Neurophysiol** 22:99–106, 2005.
121. Vespa PM, Bleck TP: Neurogenic pulmonary edema and other mechanisms of impaired oxygenation after aneurysmal subarachnoid hemorrhage. **Neurocrit Care** 1:157–170, 2004.
122. Vespa P, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, Glenn TC, McArthur DL, Hovda DA: Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. **J Cereb Blood Flow Metab** 25:763–774, 2005.
123. Vespa PM, McArthur D, O'Phelan K, Glenn T, Etchepare M, Kelly D, Bergsneider M, Martin NA, Hovda DA: Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: A microdialysis study. **J Cereb Blood Flow Metab** 23:865–877, 2003.
124. Wartenberg KE, Mayer SA: Multimodal brain monitoring in the neurological intensive care unit: Where does continuous EEG fit in? **J Clin Neurophysiol** 22:124–127, 2005.
125. Wartenberg KE, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapkovich N, Parra A, Connolly ES, Mayer SA: Impact of medical complications on outcome after subarachnoid hemorrhage. **Crit Care Med** 34:617–624, 2006.
126. Wartenberg KE, Schmidt JM, Mayer SA: Multimodality monitoring in neurocritical care. **Crit Care Clin** 23:507–538, 2007.
127. Wartenberg KE, Sheth SJ, Schmidt JM, JA F, Temes RE, Ostapkovich ND, Parra A, Palestrant D, Badjatia N, Khandji A, Mayer S: Acute hemorrhage-related ischemic injury on diffusion-weighted magnetic resonance imaging in patients with poor grade subarachnoid hemorrhage. **Neurology** 66 [Suppl 2]:A109, 2006.
128. Wu CT, Wong CS, Yeh CC, Borel CO: Treatment of cerebral vasospasm after subarachnoid hemorrhage-a review. **Acta Anaesthesiol Taiwan** 42:215–222, 2004.
129. Yoshimoto Y, Tanaka Y, Hoya K: Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. **Stroke** 32:1989–1993, 2001.
130. Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP: Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: Evidence of a hyper- and subsequent hypometabolic state. **Brain Res** 561:106–119, 1991.
131. Zabramski JM, Whiting D, Darouiche RO, Horner TG, Olson J, Robertson C, Hamilton AJ: Efficacy of antimicrobial-impregnated external ventricular drain catheters: A prospective, randomized, controlled trial. **J Neurosurg** 98:725–730, 2003.
132. Zwienenberg-Lee M, Hartman J, Rudisill N, Muizelaar JP: Endovascular management of cerebral vasospasm. **Neurosurgery** 59 [Suppl 3]:S139–S147, 2006.
133. Zygun DA, Zuege DJ, Boiteau PJ, Laupland KB, Henderson EA, Kortbeek JB, Doig CJ: Ventilator-associated pneumonia in severe traumatic brain injury. **Neurocrit Care** 5:108–114, 2006.

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COMMENTS

It is a pleasure to review a concise, interesting, and useful overview of aneurysmal subarachnoid hemorrhage (SAH). Komotar et al. recommend routine seizure prophylaxis, a common practice, but there is evidence that antiepileptic drugs are associated with worse outcomes after SAH (1). We administer anticonvulsants only when a seizure has been recorded clinically (and, by computed tomographic scanning, clearly distinguished from an episode of aneurysm rebleeding, which often resembles a generalized convulsion) or by electroencephalographic monitoring in a patient who is otherwise comatose and nonconvulsive. We agree with the authors that short-term antifibrinolytic treatment to reduce acute rebleeding before early aneurysm repair is sensible and supported by the literature, and we also administer it. In their brevity, the authors have omitted discussion of balloon angioplasty as well as either intra-arterial or intracisternal vasodilator administration for vasospasm reversal, but, of course, balloon angioplasty is frequently performed with sometimes dramatic, but more generally mixed, results.

The authors argue that brain recovery might be optimized by better brain monitoring, aimed at detecting adverse systemic or more local changes in brain metabolism, including reduced cerebral perfusion, oxygenation, and glucose delivery. Microdialysis and, recently, cerebral tissue oximetry are among the approaches to this problem, but both procedures are invasive, measure changes in very small territories, and, in the case of dialysis, are technically demanding. We are still awaiting the type of rapid, global, noninvasive, and informative cerebral monitoring used with good results by Dr. McCoy ("Bones") in *Star Trek.* In the meantime, we routinely perform cerebral angiography during the early vasospastic interval, Day 5 or 6, in comatose or deeply sedated patients. In these patients, we dilate moderately or severely narrowed arteries that can be safely reached with the balloon catheter (in addition to keeping the patient's blood volume replete and hypertensive).

Finally, we have witnessed a recent impulse for some practitioners to take a chance and coil ruptured aneurysms in even very sick patients, avoiding the difficulty of getting beneath an "angry" brain, and then hoping for the best while applying the philosophy and techniques discussed in this article. Performing surgery has always raised the bar, so to speak, in our expectations and predictions of a reasonable recovery before initiating arduous, dangerous, and expensive interventions. These are lessons learned the hard way by aggressive neurovascular surgeons. When we consider our added roles as health care managers, professionals, and doctors who must care for whole families as well as the patient, these lessons should not be forgotten.

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1. Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JI, Goldenberg FD, Macdonald RL: Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. **J Neurosurg** 107:253–260, 2007.

This is truly a magnum opus, albeit a verbose one, on management of the poor-grade SAH patient. It is interesting to consider the advances that have been made and to use this review as a list of the studies needed to determine whether the proposed management schemes are beneficial or not. I still remain relatively pessimistic about outcome in poor-grade SAH patients. Mortality can be reduced, but the survivors are often substantially impaired, and much of this may be attributable to brain injury occurring very early after the SAH.

In terms of the recommendations, controlling intracranial pressure as well as the importance of brain shift, potential rapid changes in pressure when compensatory measures have been exhausted, and the role of cerebral perfusion pressure were recognized as early as the 1970s (1, 2). Cerebral oxygenation was measured using positron emission tomography, but the real-time values obtained currently have obvious advantages. Prevention of rebleeding has been a goal in such cases for many years, but with early endovascular or surgical treatment of the

aneurysm, it is becoming a non-issue. Improvements have been made in pre- and early hospital care to address these problems immediately (i.e., to obliterate the aneurysm quickly by endovascular and sometimes surgical means), and in subsequent care. How much of the immediate brain injury can be mitigated by interventions occurring in the hours afterward is the key question. Otherwise, this is a problem of preventing aneurysm formation and rupture.

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1. Miller JD, Pickard JD: Intracranial volume pressure studies in patients with head injury. **Injury** 5:265–268, 1974.
2. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ: Significance of intracranial hypertension in severe head injury. **J Neurosurg** 47:503–516, 1977.

Komotar et al. have presented a well-written and useful review, and we appreciate the attempt to formalize critical care strategies. We strongly agree with the idea that more aggressive critical care may offer a survival benefit. Indeed, at our institution, we have found that adopting more aggressive critical care measures goes hand in hand with more aggressive surgical strategies. Thus, the poor-grade SAH patient who is "too sick for treatment" may be a reasonable surgical candidate in light of better perioperative critical care strategies. However, despite the great promise that many of these measures hold, few have been proven to be effective. Vasospasm is the most problematic entity in the treatment of the SAH patient.

From institution to institution, there is a great deal of disagreement as to the effectiveness and/or overall benefit of modalities such as continuous electroencephalography, transcranial Doppler, microdialysis, and intracranial oxygen sensors in improving outcomes. As a result, none of these have been adopted on a widespread basis. As the authors suggest, more work needs to be done to define the benefits. Perhaps, the true benefit of these tools is not as a singular solution but instead as part of a combined approach. We suggest that an index of these measures may be the most sensitive and specific approach in the prevention, diagnosis, and/or treatment of vasospasm in certain patients.

We caution that improved and more aggressive critical care techniques are not a panacea. After all these are just secondary measures. The ultimate goal is to mitigate the initial insult that occurs as a result of the SAH. The keys to doing this are 1) improving the efficiency with which SAH patients arrive to the hospital and receive initial treatment, and 2) developing practical neuroprotection paradigms based on an understanding of the cell and molecular processes at work in the immediate post-SAH period. By focusing on these 2 issues, we may be able to affect the primary injury to the neurovascular unit after SAH. Finally, it should be noted that improving mortality does not necessarily translate into improved quality of life.

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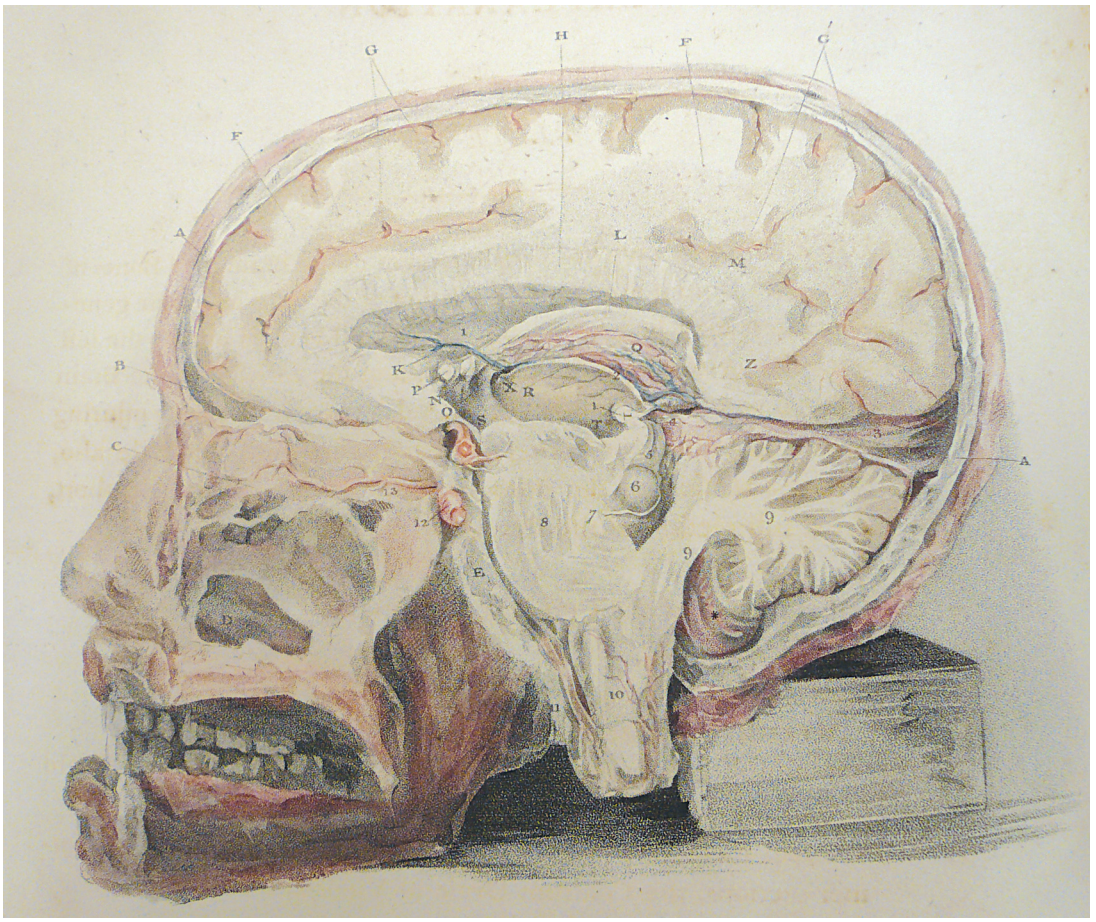

Charles Bell, 1774–1842, ***The anatomy of the brain, explained in a series of engravings. London: C. Whittingham, Dean-Street, Fetter-Lane, 1802.*** *Courtesy, Rare Book Room, Norris Medical Library, University of Southern California, Los Angeles, California.*