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

RESUSCITATION AND CRITICAL CARE OF POOR-GRADE SUBARACHNOID HEMORRHAGE

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical findings</th>
<th>Hospital mortality (%)</th>
<th>1968</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic or mild headache</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, or oculomotor palsy</td>
<td>26</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Confused, drowsy, or mild focal signs</td>
<td>37</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Stupor (localizes pain)</td>
<td>71</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Coma (posturing or no motor response to pain)</td>
<td>100</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>35</td>
<td>20</td>
</tr>
</tbody>
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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 (PbtO2), 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 “ical 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.
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-
tion, 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).

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
fatal idiosyncratic reaction characterized by metabolic acidosis, renal failure, and rhabdomyolysis. 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. 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.
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.

**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
Management of Hypertension

Hypertension 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).

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 euvoolemia, 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 euvoolemia 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/m² (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 PbtO₂, 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, PbtO₂, 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 PbtO₂ 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. PbtO₂ 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). PbtO₂ 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 PbtO₂ levels are typically greater than 25 mm Hg in the gray matter and greater than 20 mm Hg in the white matter (100, 120). Reported PbtO₂ 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).

PbtO₂ 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 PbtO₂ and various drivers of brain perfusion,
including MAP, CPP (Fig. 6), and end tidal CO₂ (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 PbO₂ (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 enterostomy 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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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 convolution) or by electroencephalographic monitoring in a patient who is otherwise comatose and non-convulsive. 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 pO2 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 pO2 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 pO2 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 pO2 monitoring, aimed at detecting adverse systemic or more local changes in brain metabolism, including reduced cerebral perfusion, oxygenation, and glucose delivery.

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This is truly a magnus 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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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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