Medical Complications After Subarachnoid Hemorrhage

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KEYWORDS

• Medical complications • Subarachnoid hemorrhage
• Fever • Anemia • Blood transfusion • Hyperglycemia

SCOPE OF THE PROBLEM

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with high disability and mortality rates.[1–3] Poor clinical grade on admission,[1,4–10] age,[1,4–9] large aneurysm size (>10 mm),[1,4,8] and aneurysm rebleeding[1,6,11] have the strongest impact on outcome after SAH. Delayed cerebral ischemia (DCI) from vasospasm, which affects 20% to 45% of patients, is also associated with poor neurologic outcome and mortality[12,13] and has traditionally been the primary focus of postoperative management.

In addition to the direct effects of the initial hemorrhage and secondary neurologic complications, SAH predisposes to medical complications that can have an impact on outcome[14] and increase hospital length of stay.[15] In the placebo arm of the Cooperative Aneurysm Study investigating the effects of nicardipine, the five most frequent non-neurologic complications were anemia, hypertension, cardiac arrhythmia, fever, and electrolyte abnormalities. The proportion of deaths directly attributable to medical complications (23%) was comparable to that of vasospasm (23%) and rebleeding (22%).[16] Advances in aneurysm treatment and neurologic intensive care, with increasing emphasis on aggressive treatment of poor-grade patients, have in all likelihood increased the relative importance of medical complications after SAH.

PHYSIOLOGIC DERANGEMENTS AFTER SUBARACHNOID HEMORRHAGE

Abnormalities of oxygenation, glucose metabolism, and hemodynamic instability within 24 hours of onset can potentially exacerbate the initial brain injury caused by SAH. Claassen and colleagues created a SAH–Physiologic Derangement Score (SAH-PDS), range 0–8, from the most abnormal measurements of physiologic variables (listed in **Table 1**) within 24 hours of admission after SAH. The SAH-PDS was independently associated with death or moderate-to-severe disability (**Fig. 1**) and was found superior to the Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) score and the systemic inflammatory response syndrome (SIRS) score for quantifying the immediate impact of physiologic derangements on outcome after SAH.[1] Interventions to correct these abnormalities, such as tight blood pressure control, brain tissue oxygen tension–directed therapy, or continuous insulin infusion, are reasonable therapeutic options given the current state of knowledge and are promising targets for future safety and feasibility trials.

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Table 1
Components of the subarachnoid hemorrhage physiologic derangement score

Physiologic Derangement	Pathophysiology	Points
Arterioalveolar gradient >125 mm Hg	Oxygen deficits from neurogenic pulmonary edema, aspiration pneumonia, or neurogenic stunned myocardium with pump failure	3
Serum bicarbonate <20 mm Hg	Lactic acidosis due to acute severe peripheral vasoconstriction and skeletal muscle glycolsysis	2
Serum glucose >180 mg/dL	Elevated blood glucose exacerbates ischemic brain injury, increases the risk of infection and critical illness myopathy, or may be a marker of severe brain injury	2
Mean arterial pressure of <70 or >130 mm Hg	Hypotension may be related to neurogenic stunned myocardium or vasodilatory shock triggered by brainstem compression, and can aggravate ischemic injury when autoregulation is impaired. Hypertension reflects the initial severity of brain injury and may provoke autoregulatory breakthrough and aggravate intracranial hypertension	1
Maximum score		8

Data from Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832.

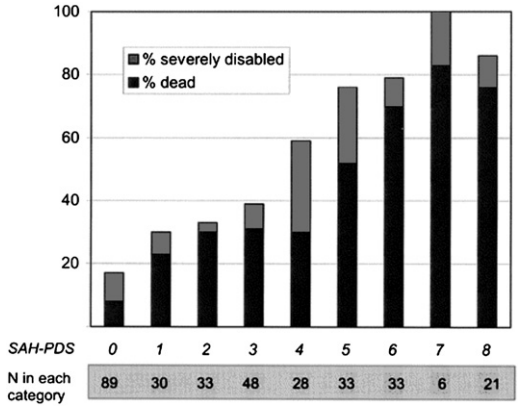

Fig. 1. Percentage of patients who are dead or severely disabled at 3 month by physiologic derangement score (SAH-PDS). (*Modified from* Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832; with permission.)

FEVER

Fever ($\geq$38.3°C) is a frequent event in patients with SAH (41%–54% [**Fig. 2**])[14,17–21] and in neurocritical care patients in general.[22] In patients with acute brain injury, fever leads to worsening of cerebral edema and intracranial pressure (ICP),[23,24] exacerbation of ischemic injury,[25] increased oxygen consumption,[24] and depressed level of consciousness.[18] Fever after SAH is associated with an increased risk of symptomatic vasospasm,[18–20] an increased length of intensive care unit (ICU) and hospital stay,[15] and death and poor functional outcome at 3 months (**Fig. 3**).[8,14,18–21] Fever after SAH has been shown to have adverse effects on the outcome of good- and poor-grade patients.[18,19] Infection (pneumonia, urinary tract infection, catheter-related bacteremia, upper respiratory tract infection, or meningitis) can be identified in approximately 34% to 75% of febrile SAH patients,[17,20,21] meaning that in the remainder, the cause of fever may be central or neurogenic in etiology. In the Columbia University SAH Outcomes Project, only pneumonia was significantly associated with fever

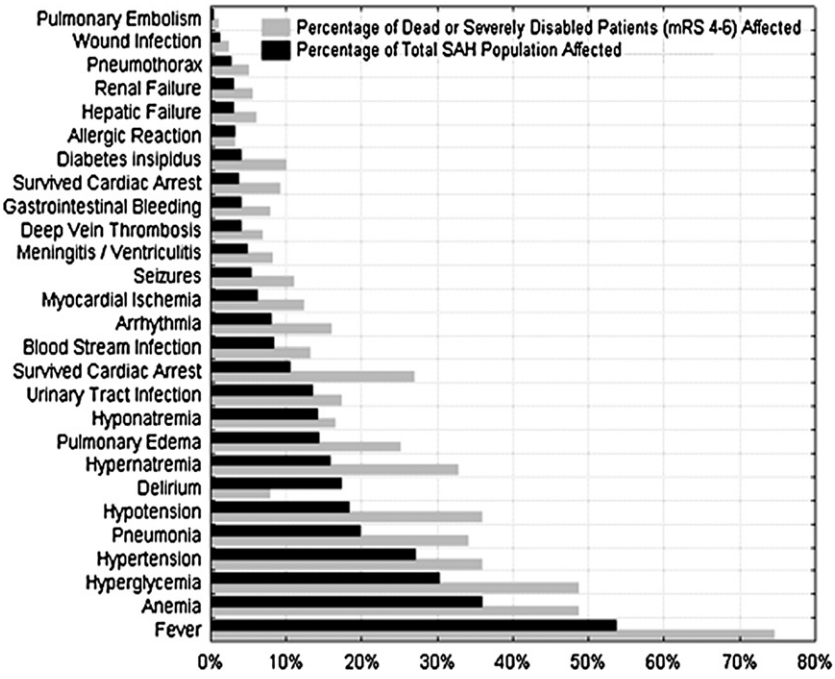

Fig. 2. Frequency of medical complications in the total SAH population (576 patients) and among patients with poor outcome (220 patients, mRS 4–6) at 4 months. (*From* Wartenberg KE, Schmidt JM, Claassen J, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Crit Care Med 2006;34:617; with permission.)

burden.[18] In a cohort of SAH patients, fever was classified as noninfectious in 48% and infectious in only 18% based on rigorous review of cultures and diagnostic studies. Noninfectious fever tended to present earlier in the hospital course (<72 hours after NICU admission).[26] It has been hypothesized that altered rhythmic daily temperature variability may help differentiate central from infectious in SAH patients.[27]

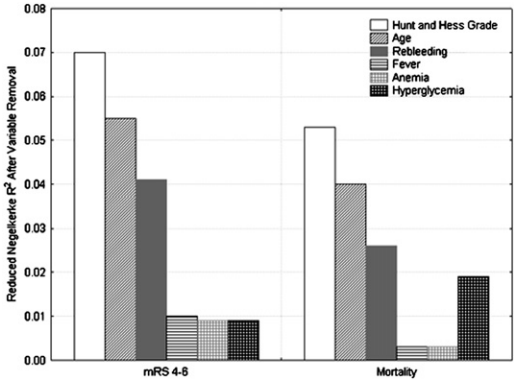

Fig. 3. Attributable risk of individual predictors to poor outcome (mRS 4–6) and mortality (based on Nagelkerke R^2 values). (*From* Wartenberg KE, Schmidt JM, Claassen J, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Crit Care Med 200634:617; with permission.)

Risk factors for fever burden in the Columbia University SAH Outcomes Project patient group included poor Hunt-Hess scale grade at admission, loss of consciousness at ictus, thick cisternal clot, intraventricular hemorrhage, and aneurysm size greater than or equal to 10 mm.[18] Fever is also a common component of the SIRS, which has been shown to predict poor outcome in SAH patients.[28] Brain stem herniation, hydrocephalus treated with external ventricular drainage, cerebral infarction, respiratory failure, anemia requiring transfusion, and hyperglycemia are neurologic and medical complications with a significant association with fever burden.[18,19] In one study, coiling as method of aneurysm repair was related to a higher fever burden than clipping or no repair, for reasons that are unclear.[19]

Fever control can now be achieved by means of core temperature–controlled surface or endovascular cooling devices. Feasibility studies have demonstrated safe and effective fever control in febrile SAH patients refractory to acetaminophen treatment using the Celsius Control System (Innercool, San Diego, California),[29] and a single-center randomized trial showed a 75% reduction in fever

burden with the systemic surface cooling system Artic Sun temperature management system (Medivance, Louisville, Colorado) compared with regular water-circulating cooling blankets.[30] This confirms the results of a previous multicenter fever control trial comparing a catheter-based heat exchange system, the CoolGard/CoolLine system (Alsius, Irvine, California) plus standard fever management (using acetaminophen, ibuprofen, and cooling blankets) to standard therapy alone, in which a 64% reduction in fever burden was shown.[31] Induction of normothermia with ice packs and external surface cooling devices in poor-grade SAH patients significantly reduced episodes of metabolic crisis in the brain assessed by microdialysis markers of metabolic stress (lactate/pyruvate ratio) and ICP.[32]

With all forms of cooling, the main barrier to achieving target temperature is insufficient control of shivering, which increases the systemic rate of metabolism and resting energy expenditure and may potentially adversely affect cerebral oxygenation and ICP.[29,33] Shivering is a natural mechanism that allows the body to create heat if the body temperature falls below the hypothalamic set point. Potentially effective antishivering interventions are listed in **Table 2**. Treatment guidelines almost universally advocate maintenance normothermia for all febrile patients with SAH, despite little evidence to support this practice in the form of randomized controlled trials. Prospective clinical trials are needed to assess the impact of fever control with systemic surface or intravascular cooling devices on development of vasospasm and outcome after SAH.

ANEMIA

Anemia after SAH most likely results from the combined effects of an SAH-related reduction in red blood cell mass,[34] combined with blood losses due to phlebotomy and invasive procedures[35] and hemodilution from fluid administration. In the Columbia University SAH Outcomes Project,

Table 2
Interventions to relieve shivering during active cooling to achieve normothermia with systemic surface or intravascular cooling devices

Method	Dosage	Mechanism
Basic management		
Acetaminophen	650–1000 mg orally every 6 h	Inhibits prostaglandin synthesis
Buspirone	30–60 mg orally every 8 h	5HT-1A partial agonist
Skin counterwarming	Bair Hugger polar air cooling system (Arizant Healthcare, Eden Prairie, Minnesota)	Vasodilatation
Advanced management for persistent shivering		
Magnesium sulfate	0.5–1.0 g/h for target serum magnesium of 1–2 mmol/L (3–4 g/dL)	Vasodilatation, muscle relaxant
Clonidine	15–60 μg/h (1.5–3 μg/kg/h)	α2-Receptor agonist
Dexmedetomidine	0.2–1.5 mcg/kg/h	α2-Receptor agonist
Meperidine (Pethidine)	25–100 mg IV every 4 h (or 0.5–1.0 mg/kg/h)	Opioid receptor agonist
Fentanyl	50–200 μg/h	Opioid receptor agonist
Advanced management for refractory shivering		
Propofol	75–300 mg/h	Impairs vasoconstriction and shivering threshold
Rocuronium/Vecuronium	Usually not needed and should be avoided because of increased incidence of critical illness polyneuropathy	Paralysis

Data from Wartenberg KE, Mayer SA. Use of induced hypothermia for neuroprotection: indications and application. Future Neurology 2008;3:325.

anemia (defined as hemoglobin <9 g/dL requiring blood transfusion) occurred in 36% of 580 patients and was the second most common medical complication (see **Fig. 2**).[14] Anemia treated with blood transfusion is associated with an increased risk of mortality and poor functional outcome after SAH (see **Fig. 3**).[14,36] Administration of blood during the hospital course after aneurysm surgery has also been associated with an increased risk of asymptomatic and symptomatic angiographically-confirmed vasospasm.[36] In another study, blood transfusions were significantly related to poor outcome among SAH patients with vasospasm.[37] Multimodality monitoring in SAH patients demonstrated local brain tissue hypoxia (partial pressure of brain tissue oxygen [$PbtO_2$] <20 mm Hg) and cell energy dysfunction (lactate/pyruvate ratio >40) when hemoglobin values were less than 9 g/dL; however, the relationship to functional outcome was not investigated.[38]

It is unclear whether anemia after SAH reflects general illness severity[39] or whether the treatment for anemia—blood transfusion—directly contributes to poor outcome. History of blood transfusion was an independent risk factor for intracerebral hemorrhage and mortality after SAH in the Japan Collaborative Cohort Study and Miyako Study.[40–42] Higher hemoglobin values have been associated with a lower risk of cerebral infarction and poor outcome 3 months after SAH in two different SAH cohorts.[43,44] Blood transfusions were related to poor functional outcome but not to mortality in one of these studies[43] and were not considered in the other.[44] Kramer and colleagues investigated the effect of anemia as opposed to blood transfusion on secondary complications and outcome after SAH. Blood transfusion, but not anemia, was an independent risk factor for poor functional outcome and was associated with the development of nosocomial infections but not symptomatic vasospasm.[45] The extent of hemoglobin decline during the first 2 weeks after SAH predicted unfavorable outcome (severe disability or death) and was more pronounced in patients with poor-grade SAH, thick cisternal clot, and intraventricular hemorrhage.[46]

In the Columbia University SAH Outcomes Project, blood transfusions were related to symptomatic vasospasm and were a significant predictor of mortality and poor functional outcome at 3 months; anemia alone did not influence long-term functional outcome in this model.[47] Packed red blood cells (PRBCs) may be depleted of nitric oxide,[48] an endogenous vasodilator that can reverse vasoconstriction of cerebral arteries and arterioles during vasospasm. Thus, transfusion may result in dilution of this active vasodilatory substance and may subsequently worsen microcirculatory flow or predispose to intraoperative cerebral vasoconstriction.[36] Transfusion of PRBCs increases local $PbtO_2$ in the majority of patients with SAH and other severe brain injuries independent of cerebral perfusion pressure and peripheral oxygen saturation.[49] Stored PRBCs, however, have proinflammatory effects and may induce immunodysfunction and neutrophilic and polymorphonuclear cytotoxicity,[50] which may exacerbate the inflammatory component of vasospasm[36] and increase the risk of nosocomial infections.[45] The deformability of stored and transfused erythrocytes is reduced, which may lead to microvascular sludging,[51] and adenosine triphosphate and 2,3 diphosphoglycerate are depleted,[51] resulting in altered oxygen binding and release.[36] Transfused erythrocytes also contain free iron, which can increase oxidative processes in its ferrous form[52] and aggravate ischemia.[36] Storage of PRBCs has been found to generate interleukin 1,-6, and -8 and tumor necrosis factor α,[53] which may augment ischemia and edema formation.[36]

Given the potential detrimental effects of PRBC transfusion, efforts directed at more physiologic transfusion triggers derived from brain multimodality monitoring (**Table 3**)[54] and prevention of anemia after SAH with erythropoietin should be investigated,[55] particularly given its potential neuroprotective properties.[56]

HYPERGLYCEMIA

Hyperglycemia is known to have an adverse effect on outcome in patients with acute ischemic stroke and to increase the likelihood of intracranial hemorrhage after thrombolytic therapy.[57–59] In the authors' SAH population, hyperglycemia exceeding 11.1 mmol/L (200 mg/dL) occurred in 30% (see **Fig. 2**) and was a significant predictor of poor functional outcome and mortality 3 months after SAH[14] (see **Fig. 3**). Depending on the definition, hyperglycemia can be found in 30% to 100% of SAH patients.[14,60–62] When mean daily glucose burden between day 0 and 10 after SAH (defined as the area under the curve above 5.8 mmol/L or 105 mg/dL) was analyzed, hyperglycemia was found to have a stronger association with moderate-to-severe disability (modified Rankin scale [mRS] 4–6) and loss of high-level functional independence than with mortality, suggesting that hyperglycemia may contribute to physical deconditioning.[63] The relationship of admission or sustained hyperglycemia with poor outcome up to 1 year after SAH has also been confirmed in many other studies.[9,60,62,64–67] In the Intraoperative Hypothermia for Aneurysm

Table 3
Suggestion for transfusion practices in neurocritical care patients

Hemoglobin (g/dL)	Packed Red Blood Cell Transfusion
>10	No
<7	Yes
7–10	Yes, if $PbtO_2$ <20 mm Hg or rSo_2 <60% or cardiopulmonary reserve decreased

Abbreviations: $PbtO_2$, partial pressure of brain tissue oxygen; rSo_2, regional oxygen saturation measured by near-infrared spectroscopy.

Data from Leal-Noval SR, Munoz-Gomez M, Murillo-Cabezas F. Optimal hemoglobin concentration in patients with subarachnoid hemorrhage, acute ischemic stroke and traumatic brain injury. Curr Opin Crit Care 2008;14:156.

Surgery Trial population, glucose concentration at the time of aneurysm clipping did not have an impact on mortality at 3 months but influenced physical impairment measured with the National Institute of Health Stroke Scale, neuropsychologic outcome, and intensive care unit (ICU) length-of-stay.[68] In a smaller study of poor-grade SAH patients, early clinical improvement was seen in patients with an admission glucose level less than 180 mg/dL (10.0 mmol/L).[69,70] Elevated blood glucose concentrations on arrival at the hospital were associated with aneurysm rebleeding in another SAH patient cohort.[71] Increased glucose levels, however, have not always been found to be significant predictors of poor functional status after SAH.[66,72,73]

A retrospective study of 352 SAH patients at Massachusetts General Hospital identified hyperglycemia (mean inpatient blood glucose value $\geq$140 mg/dL) in 73% of patients and found an association with symptomatic vasospasm and increased ICU length of stay.[74] The risk of symptomatic vasospasm was also increased with hyperglycemia in a cohort of 244 SAH patients.[75] These findings are in contrast to an analysis of 175 patients in which elevated admission glucose was not predictive of DCI, despite an association with poor outcome at 3 months.[76]

Acute brain injury may lead to a transient generalized stress response, which may explain the high frequency of hyperglycemia after SAH in patients who do not have a history of diabetes mellitus.[62–64,72,75,77] Hyperglycemia was significantly linked to a history of diabetes mellitus, older age, poor clinical grade, brainstem compression from herniation, higher APACHE-2 physiologic derangement scores, and pulmonary decompensation (congestive heart failure, respiratory failure, and pneumonia) in the authors' study.[63] Hyperglycemia is thus just one aspect of a generalized stress response after SAH which can be triggered by a variety of different perturbations.[78] Activation of the sympathetic nervous system increases glucagon, corticosteroids, and somatotropin secretion and decreases insulin release, all of which cause stress-related hyperglycemia.[60,62,79] When this acute metabolic response is persistent, hyperglycemia predicts the occurrence of symptomatic vasospasm, DCI, and poor long-term functional outcome.[64,66,74,75]

The proportion of SAH patients with known diabetes mellitus is relatively low (<10%).[63,80–82] Although hyperglycemia after SAH could simply reflect pre-existing impaired glucose tolerance, previous multivariate analyses have shown that the relationship between hyperglycemia and poor outcome is independent of other known predictors.[1,9,14,60,62–64,66,76] In a study utilizing monitoring of cerebral metabolism with microdialysis, SAH patients with an acute focal neurologic deficit from the initial hemorrhage or procedural complications had systemic hyperglycemia associated with low cerebral glucose levels and elevated lactate/pyruvate ratios (indicating cerebral metabolic crisis) and worse functional outcome at 6 months.[83] In another microdialysis study, episodes of hyperglycemia were frequent in patients with an acute neurologic deficit or DCI and were accompanied by elevated cerebral glycerol levels (a marker of cellular membrane degradation).[84] Blood glucose elevations have also been related to increased lactate/pyruvate ratios, which argues for increased anaerobic glycolysis with saturation of normal aerobic glucose metabolism.[67] This process may exacerbate tissue injury from ischemia.[60,62,76,79]

Strict glucose control has been associated with reduced ICP, duration of mechanical ventilation, hospital length of stay, use of vasopressors, frequency of seizures, and diabetes insipidus in critically ill neurologic patients.[85] Intensive insulin therapy has also been shown to reduce mortality in critically ill surgical ICU patients[86] and in medical ICU patients admitted for more than 2 days.[87] The first randomized trial of management of poststroke hyperglycemia with 24-hour glucose-potassium-

insulin infusions failed to demonstrate a benefit on mortality or disability 90 days after stroke.[88] Glycemic control in this study, however, was poor and the duration of treatment to short. A small trial of 55 patients with SAH demonstrated the feasibility and safety of continuous insulin infusion for glucose values exceeding 7 mmol/L with glucose assessments performed every 2 hours.[89] Retrospective analyses of changes in clinical practice through introduction of insulin protocols in SAH patients showed that achievement of tight glycemic control significantly reduced the likelihood of poor outcome at 6 months[73] and have identified hypoglycemia (<60 mg/dL) as an independent predictor of mortality at discharge.[90]

Balanced against the potential benefits of tight glycemic control is evidence that normalization of hyperglycemia can lead to critical brain tissue hypoglycemia after severe grain injury. Intravenous (IV) insulin therapy for a target glucose of 140 mg/dL (7.8 mmol/L) resulted in critical decreases of cerebral glucose measured with microdialysis at 3 hours after initiation of treatment in 79% of SAH patients, predominantly in men and in the elderly.[91] At 8 hours after start of insulin infusion, cerebral glycerol increased reflecting tissue damage or cellular distress.[91] Another microdialysis study of patients with SAH and other form of brain injury demonstrated a link between high insulin dosages, brain tissue hypoglycemia, elevated lactate/pyruvate ratios, and increased mortality at discharge.[92] Reductions of cerebral glucose has been found related to peri-ischemic cortical depolarizations.[93]

Bilotta and colleagues conducted the first randomized trial of intensive insulin therapy (target glucose 80–120 mg/dL) versus standard insulin therapy (target glucose 80–220 mg/dL) in 78 SAH patients. Rate of infection was the primary outcome measure and was significantly reduced from 42% to 27% in the intensive insulin group. Mortality at 6 months and the frequency of vasospasm were comparable in the two groups.[94] More safety trials of intensive insulin therapy in SAH with cerebral glucose monitoring and efficacy studies exploring long-term outcomes are needed.

CARDIAC COMPLICATIONS

Hypertension treated with continuous IV medication (27%) and hypotension requiring pressors (18%) are common medical complications after SAH, whereas life-threatening arrhythmia (8%), myocardial ischemia (6%), and successful resuscitation from cardiac arrest (4%) rarely occur (see **Fig. 2**).[14,95] The development of clinically relevant arrhythmias, mostly atrial fibrillation or flutter, is associated with older age, a prior history of arrhythmia, hyperglycemia, brainstem herniation, myocardial infarction, a longer NICU length of stay, and poor functional outcome.[95] Electrocardiographic (ECG) abnormalities are found frequently in SAH patients (92%) and encompass ST segment alterations (15%–67%), T-wave changes (12%–92%), prominent U waves (4%–52%), QT prolongation (11%–66%), conduction abnormalities (7.5%), sinus bradycardia (16%) and sinus tachycardia (8.5%).[95–99] Although the majority of these abnormalities do not directly contribute to morbidity or mortality,[97] ST-segment depression has been linked to DCI and poor 3-month outcome.[98]

Neurogenic stunned myocardium is the most severe form of cardiac injury after SAH. It is caused by excessive release of catecholamines from the cardiac sympathetic nerves triggered by the bleeding event and is characterized histologically by myocardial contraction band necrosis.[100] The clinical syndrome of severe acute stunned myocardium is characterized by transient lactic acidosis, cardiogenic shock, pulmonary edema, widespread T-wave inversions with a prolonged QT interval, and reversible left ventricular wall motion abnormalities.[100] Echocardiography and myocardial scintigraphy were performed in 42 SAH patients with stunned myocardium and demonstrated normal myocardial perfusion in all patients, with functional sympathetic denervation and myocardial necrosis in those with regional wall motion abnormalities.[101] In a prospective study of 300 SAH patients undergoing echocardiography and troponin I monitoring, 26% had evidence of regional wall motion abnormalities which persisted through day 9 after SAH. Catecholamine levels obtained on admission were not significantly related to left ventricular dysfunction[102] but might not have been obtained early enough.

The most important risk factor for neurogenic stunned myocardium is poor clinical grade.[102–104] Other predictors of cardiac dysfunction after SAH include older age,[103,105] adrenoreceptor polymorphisms,[106] and prior cocaine or amphetamine use.[102] Tachycardia[102] and troponin I elevation[102,103,105] are almost universally found at in conjunction with neurogenic myocardial stunning. A recent meta-analysis suggested that cardiac abnormalities on ECG, echocardiography, and troponin measurements are related to DCI, poor outcome, and death up to 6 months after SAH.[107,108]

Minor cardiac enzyme elevations occur frequently after SAH, but their significance has been unclear. An analysis of 253 SAH patients

deemed at risk for myocardial injury on the basis of acute ECG changes revealed admission cardiac troponin I elevation in 68%. Troponin levels peaked at 1.7 days, and left ventricular wall motion abnormalities were identified by echocardiography in 22%. Higher Hunt-Hess scale grade on admission, intraventricular hemorrhage or global cerebral edema on admission CT, loss of consciousness at ictus, and more severe admission physiologic derangements were predictive of increased cardiac troponin I levels.[109] The association with intracranial pathology underlines a neurogenic mechanism of cardiac injury. Troponin I elevation was associated with a significantly increased risk of abnormal left ventricular wall motion abnormalities on echocardiography, pulmonary edema, hypotension requiring vasopressors, DCI, and cerebral infarction from any cause. Troponin I elevation also independently predicted severe disability and death at hospital discharge.[109]

Another prospective study found peak troponin I levels of greater than 1.0 μg/L in 20% of 223 SAH patients. In this study, female gender, larger body surface area, Hunt-Hess scale grade greater than or equal to 3, higher heart rate, lower systolic blood pressure, higher doses of phenylephrine, higher left ventricular mass index (increased oxygen demand), and shorter time from SAH symptom onset were independently associated with troponin I elevations within 2 days after symptom onset.[104] This again emphasizes the importance of the initial brain injury as a cause of cardiovascular dysfunction and demonstrates the adverse effects of myocardial injury on cardiac performance. Further research is required to test cardio- and neuroprotective intensive care management strategies, which may improve outcome after SAH.

PULMONARY COMPLICATIONS

Pulmonary dysfunction with a disturbance of gas exchange (increased alveolar-arterial oxygen gradient) occurs in up to 80% of SAH patients.[110] Pulmonary complications did not have an independent impact on neurologic outcome at 3 months in the authors' study but remained common and troubling. The most frequent pulmonary complications included pneumonia (20%), pulmonary edema (14%), pneumothorax (3%), and pulmonary embolism (0.3%) (see **Fig. 2**).[14] A previous analysis linked pulmonary events to an increased frequency of symptomatic vasospasm after SAH, but this may reflect fluid overload related to more aggressive hypertensive-hypervolemic therapy.[111]

Pulmonary complications have been independently linked to prolonged ICU and hospital length of stay and poor functional outcome and mortality in several studies.[1,16,110,112,113] A recent study found that bilateral pulmonary infiltrates developed in 27% of 245 SAH patients, mostly due to neurogenic pulmonary edema, aspiration pneumonia, and pulmonary edema complicating neurogenic stunned myocardium. Only pulmonary infiltrates developing later than 72 hours after ictus were predictive of death or poor functional outcome. Pulmonary infiltrates were also associated with poor neurologic grade on admission, symptomatic vasospasm, and prolonged length of hospital stay. Adult respiratory distress syndrome was present in 11% of patients but was not found to be an independent predictor of poor outcome.[113]

Other investigators have linked the delayed onset of pulmonary edema with cardiac dysfunction,[114] presumably reflecting the effects of aggressive volume resuscitation over time. The relationship of pulmonary edema and cardiac dysfunction with ischemic ECG changes, myocardial enzyme elevation, and the requirement of catecholamines for blood pressure stabilization was also confirmed by another group.[115] Adult respiratory distress syndrome and acute lung injury after SAH has been associated with troponin I elevations, length of ICU and hospital stay, and poor short-term (2-week) but not long-term outcome.[15,116] Acute lung injury in SAH patients has also been associated with poor Hunt-Hess scale grade, PRBC transfusion, and severe sepsis.[112]

A review suggested that use of a pulmonary artery catheter during the vasospasm period in SAH targeting an optimal pulmonary artery wedge pressure (10–14 mm Hg) may decrease the incidence of pulmonary edema and sepsis and decrease mortality.[117] The role of newer noninvasive hemodynamic monitoring systems that can provide measurements of stroke volume variability, extravascular lung water, global end-diastolic volume, and other novel measures deserves further study.

ELECTROLYTE ABNORMALITIES

Hyponatremia occurs in 20% to 40% of SAH patients. It may be the result of the syndrome of inappropriate excretion of antidiuretic hormone (SIADH), cerebral salt wasting, or both. Hypomagnesemia (40%), hypokalemia (25%), and hypernatremia (20%) are also common after SAH.[118–120] In the authors' study, hyponatremia (<130 mEq/L) occurred in only 14% (see **Fig. 2**), which might be explained by the standard administration of

isotonic saline solutions and strict avoidance of free water in te management protocol.[14] Hyponatremia did not have any prognostic significance in the authors' study[14] nor has it in others.[120,121]

Although SIADH and cerebral salt wasting are often conceptualized as mutually exclusive, it is most likely that SAH patients experience a physiologic shift that favors both of these derangements simultaneously. In a prospective study investigating hyponatremia and volume status in poor-grade SAH patients, hypovolemia and increased natriuresis were identified as the underlying cause consistent with cerebral salt wasting syndrome.[122] Atrial and brain natriuretic peptide levels were initially increased as a consequence of the bleeding event, and renin and aldosterone levels tend to be suppressed by the acute sympathetic response. This can result in excessive sodium excretion and hyponatremia unless these losses are replaced by with isotonic crystalloid fluid resuscitation. Adrenomedullin, a vasorelaxant peptide, can also induce natriuresis, is elevated in the cerebrospinal fluid of SAH patients, and has been correlated with the occurrence of hyponatremia and delayed ischemic deficits.[123]

A surge in arginine vasopressin levels also occurs as a direct consequence of the initial bleeding event, resulting in SIADH physiology. As a result, free water tends to be retained if it is given, resulting in dilutional hyponatremia. In one SAH cohort treated with hypotonic fluids, hyponatremia presented in 57% of patients.[121] A Japanese group conducted a randomized, placebo-controlled trial of IV hydrocortisone (300 mg every 6 hours for 10 days) to maintain serum sodium greater than 140 mmol/L and central venous pressure of 8 to 12 cm H_2O. Sodium excretion and urine volume were significantly decreased, and plasma osmolarity was more often in the normal range in the hydrocortisone compared with the placebo group. This treatment had no impact on symptomatic vasospasm or functional outcome at 30 days, however. In addition, hyperglycemia, hypokalemia, and hypoproteinemia complicated the use of hydrocortisone.[124] Conivaptan is an arginine vasopressin receptor antagonist (V_{1A}/V_2) approved for the treatment of euvolemic and hypervolemic hyponatremia.[125] Initial reports of it use in neurocritical care patients with hyponatremia have yielded promising results.[126]

The 22% frequency of hypernatremia in the authors' study almost certainly reflects treatment for cerebral edema with mannitol or hypertonic saline solutions and, therefore, was mostly iatrogenic. Only 4% of the authors' patients experienced diabetes insipidus.[14] The incidence of hypernatremia was 22% in another SAH patient population and had strong associations with left ventricular dysfunction and troponin I elevation,[118] suggesting a contribution to cardiorespiratory compromise. Hypernatremia may be a marker for extracerebral organ dysfunction and treatment of intracranial hypertension.

INFECTIONS

The most common infections during the course of SAH include pneumonia (20%), urinary tract infection (13%), blood stream infection (8%), and bacterial meningitis/ventriculitis (5%) (see **Fig. 2**).[14,127] After adjusting for length of ICU stay, older age, poor clinical grade, and mechanical ventilation are risk factors for pneumonia.[14] Blood stream infections were associated with mechanical ventilation, urinary tract infections with female gender and central line use, and meningitis/ventriculitis with the presence of intraventricular hemorrhage and extraventricular drainage.[127] In the Columbia University SAH Outcomes Project, none of these infections was independently predictive of poor functional outcome and mortality at 3 months.[14] Pneumonia and urinary tract infection, however, were significantly related to the occurrence of DCI[127] and all infectious complications were associated with prolonged ICU and hospital length of stay.[15,127]

SIRS was diagnosed on at least one ICU day in 87% of 276 SAH patients, and was linked to higher clinical grade, higher Fisher grade, elevated admission mean arterial pressure, aneurysm size, and clipping of the aneurysm. The SIRS burden on the first 4 days after SAH was a strong predictor for the development of symptomatic vasospasm and of poor outcome (death or discharge to nursing facility).[128] The extent to which SIRS physiology after SAH results from nosocomial infection is unclear, but it is an important contributing factor. Hospital-acquired infections should be prevented and treated aggressively, and further studies of the associations of infections with neurologic complications are needed.

OTHER RARE COMPLICATIONS

Renal failure, hepatic failure, deep vein thrombosis, and gastrointestinal bleeding occurred at a frequency of less than 5% in the authors' SAH population and had no impact on neurologic outcome (see **Fig. 2**).[14]

A study of 100 SAH patients found that a low ratio between the lowest platelet during the hospitalization and the admission platelet count (<0.7) an independent predictor of symptomatic vasospasm.[129] This may be explained by increased

platelet aggregation and substance release from the platelets resulting in microcirculatory dysfunction.[129] The role of platelet dysfunction in the pathophysiology of vasospasm requires additional studies.

SUMMARY

For years, efforts to improve the outcome of SAH have focused on treatment and prevention of neurologic complications, such as acute hydrocephalus, aneurysm rebleeding, and delayed ischemia from vasospasm. As survival has improved, however, it is increasingly recognized that medical complications also contribute substantially to many of the poor outcomes that result from this disease. Fever, anemia requiring transfusion, hyperglycemia, and neurogenic stunned myocardium seem to have the strongest association with poor outcome after SAH, thus seem to be the most promising candidates for novel treatment strategies.

Given the available evidence, the authors recommend the practice of maintaining normothermia with systemic cooling devices and normoglycemia with continuous insulin infusion monitoring for hypoglycemia, with care to avoid critical brain tissue hypoglycemia in comatose patients undergoing microdialysis monitoring. Phlebotomy should be minimized to prevent severe anemia, and the authors recommend a restrictive blood transfusion policy (a trigger of <7.0 mg/dL) unless active cerebral or myocardial ischemia is present, in which case a transfusion trigger of less than 10.0 mg/dL is reasonable. Measurement of troponin I levels on admission is a sensitive means of identifying neurogenic cardiac injury and identifies patients at risk for cardiopulmonary complications, DCI, and poor outcome. Cardiovascular hemodynamic monitoring may help optimize hypertensive-hemodynamic therapy in patients with neurogenic cardiopulmonary dysfunction. Prevention and treatment of nosocomial infections should be a focus of all neurointensivists. Vasopressin receptor antagonists may aid in combating hyponatremia in SAH patients in the future. Multimodal monitoring pf brain tissue oxygen, microdialysis, cerebral blood flow, and intracortical electroencephalography may become helpful in the assessment, diagnosis, and treatment of medical complications once more experience is gained.

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