Multimodal Monitoring in Subarachnoid Hemorrhage

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In severely injured patients, the immediate goal of resuscitation is restoration and maintenance of adequate tissue metabolism by ensuring sufficient delivery of fuel, typically oxygen and glucose, to meet cellular metabolic demands. In neurocritical care, traditional goals of resuscitation—intracranial pressure (ICP), cerebral perfusion pressure (CPP), and the clinical examination—have been extrapolated from those of general critical care. These variables are analogous to central venous pressure, mean arterial pressure, and urine output and are similarly crude. These distant surrogates for cerebral perfusion do not account for dynamic changes in cerebral autoregulation, tissue metabolic rate, cellular fuel use, and microcirculatory dysfunction, all of which impact tissue metabolic health. Although standard, it seems intuitively obvious that a uniform approach of maintaining ICP < 20 mm Hg and CPP > 60 mm Hg is overly simplistic. This approach does not address either significant baseline differences in patient physiology nor the complex, dynamic, and variable pathophysiological changes that ensue after severe brain injury. A more tailored therapeutic strategy that responds to multiple simultaneously measured and more relevant physiological variables is logically appealing. Until recently, however, the requisite individual patient physiology was inaccessible at the bedside.

The emergence of technology that allows for continuous bedside monitoring of cerebral physiology marks a new era in neurocritical care. These monitors facilitate assessment of therapeutic efficacy and may provide more relevant physiological end points for resuscitation. Combining these monitors in a multimodal approach allows for the practice of goal-directed cerebral resuscitation that emphasizes the individual patient’s unique neurological and systemic physiology.

Aneurysmal subarachnoid hemorrhage (SAH) is an example of a disease in which individualized goal-directed cerebral resuscitation using multimodality neuromonitoring might influence therapy and outcome. After initial patient stabilization and aneurysm exclusion from the circulation, care focuses on prevention of secondary neuronal injury. Of those who survive the initial hemorrhage, up to one third develop further brain injury or delayed cerebral ischemia (DCI). DCI accounts for the majority of morbidity and mortality after SAH. Traditional indicators of DCI include worsening clinical examination, angiographic vasospasm, and elevated cerebral blood flow (CBF) velocities by transcranial Doppler (TCD) ultrasonography. However, the agreement of these measures with each other, their sensitivity for DCI, and their correlation with functional outcome are poor. Therefore, there has been growing interest in using real-time monitors of brain physiology to detect evolving secondary injury.

Techniques for measuring cerebral physiology may be classified based on the physiological parameters measured and whether the measure is regional (limited to a small volume of tissue) or global (whole brain). Some technologies are invasive, relying on probes inserted into brain tissue through a burr hole, whereas others use noninvasive scalp detectors. Typically, invasive monitoring is reserved for patients with severe brain injury (eg, Glasgow Coma Scale score < 9). Although these monitors have been studied primarily in patients with traumatic brain injury, there is a small literature on monitoring patients with SAH. In this review we discuss commercially available regional and global continuous (or near-continuous) monitors of brain physiology and their application to patients with SAH. We start with conventional physiological parameters, ICP and CPP, which are distant surrogates for metabolic health, and then cover parameters that progressively approximate tissue metabolic integrity.

ICP and CPP

ICP and CPP (mean arterial pressure–ICP) are surrogates for CBF. If modeled as flow through a rigid tube, then according to Poiseuille’s law, CBF is proportional to CPP and to the radius of the vessel raised to the fourth power and is inversely proportional to blood viscosity. When autoregulation is intact, the primary determinant of CBF is therefore vessel radius and CPP has little impact. Conversely, when autoregulation is absent (vessel radius remains constant), changes in CPP significantly impact CBF.

There are multiple invasive methods of directly measuring ICP. The gold standard is the external ventricular drain, a flexible catheter inserted through brain tissue and into the ventricle. This fluid-filled catheter is coupled to a pressure gauge. Similarly, ICP may be transduced by a catheter placed into the lumbar subarachnoid space (lumbar drain). Fiber-optic intraparenchymal catheters, placed through a bolt into...
brain tissue, also allow for continuous ICP monitoring. Catheters that transduce pressure may also be placed in the epidural, subdural, or subarachnoid space but are less frequently used.

Each device has specific advantages and disadvantages. External ventricular drains are associated with intracerebral hemorrhage (41%, usually clinically insignificant), infection (8%), and possibly increased risk of aneurysmal rebleeding. Fiberoptic intraparenchymal probes are relatively easy to place and have a lower rate of intraparenchymal hemorrhage (2.5%) and infection (4.75%). With prolonged monitoring, baseline drift requires probe replacement, because these probes cannot be recalibrated. Furthermore, these devices are fragile and prone to breakage, compromising accuracy. Because intracranial hypertension (ICP >20 mm Hg) is frequently associated with acute hydrocephalus after SAH, an external ventricular drain is preferred for monitoring ICP because it also allows for CSF diversion.

Although ICP and CPP are commonly monitored cerebral variables in patients with high-grade SAH, guidelines that standardize indications and therapeutic targets such as exist for traumatic brain injury are lacking. Increased ICP occurs in >50% of all patients with SAH, including those presenting with good clinical grades. An ICP <20 mm Hg portends a favorable outcome at 6 months, whereas ICP >20 mm Hg predicts increased risk of death or severe disability regardless of clinical grade. Based on these data, and on extrapolation from patients with traumatic brain injury, common practice is to maintain ICP <20 and CPP >50 to 60 mm Hg. However, when measured with other physiological variables in a multimodal approach, optimal ICP and CPP thresholds may be determined on an individual basis according to the impact on tissue oxygenation and metabolism.

Cerebral Blood Flow
CBF more closely reflects fuel delivery than CPP. TCD measures CBF velocity; although it may be used continuously, it is typically used as an intermittent screening tool for vasospasm in patients with SAH. Invasive probes may be used to quantify regional CBF and continuous electroencephalography (cEEG) may be used to trend CBF.

Thermal Diffusion Flowmetry
Thermal diffusion flowmetry uses a flexible catheter with proximal and distal thermistors that is inserted into brain tissue, typically into white matter (20–25 mm beneath the cortical surface). The distal thermistor heats the surrounding tissue by approximately 2°C, creating a spherical thermal field, and the proximal thermistor lying outside the thermal field measures temperature. The power dissipated provides a measure of the tissue’s ability to transport heat, which is determined by both intrinsic tissue conductive properties and convective properties due to blood flow. By determining the conductive properties of the tissue (from the rate of initial thermal field propagation), and separating it from the total heat transferred, a quantitative measure of regional CBF is derived.

Although thermal diffusion flowmetry is the only method that provides continuous and quantitative information about CBF, the probe only samples a small volume of tissue (approximately 30 mm³). Although blood flow is coupled to metabolic demand in the healthy brain, the two are frequently uncoupled after brain injury. Measurement of regional CBF alone does not indicate whether CBF is adequate for metabolic demand or whether cells are able to properly use oxygen and glucose. The rates of probe-related hemorrhage and infection are unknown but are likely comparable to those of similar invasive probes.

A study in patients with SAH suggests that regional CBF probes may detect decreased blood flow 3 to 9 days after hemorrhage, correlating with the peak risk of vasospasm. Thermal diffusion flowmetry may detect ischemia before it is clinically evident and increased CBF after intra-arterial therapy for cerebral vasospasm.

Continuous Electroencephalography
Cerebral hypoperfusion causes characteristic changes in brain electrical activity, including loss of fast activity, increased slowing, and background attenuation. Electroencephalographic abnormalities arise when CBF (normally 50–70 mL/100 g/min) decreases to 25 to 30 mL/100 g/min, well before neuronal death occurs (10–12 mL/100 g/min). Using fast Fourier transform, raw electroencephalographic data are compressed into quantitative cEEG. Software facilitates interpretation through a bedside graphical display (Figure 1). This permits clinicians to recognize worrisome changes, prompting more detailed review of the raw waveforms by trained electroencephalographers. Although the ideal electroencephalographic parameters to detect ischemia are unclear, most studies use some ratio of fast to slow activity.

cEEG in some ways is an ideal monitor; it is noninvasive, provides continuous regional and global data, and is widely available. However, it does not allow for quantification of blood flow. Furthermore, ischemia may not be the sole cause for changes in brain electrical activity. Exogenous artifacts due to electronic devices, patient movement, static charges generating alternate current fields, electrode dislodgement, and generation of a huge data set represent challenges to cEEG use in the intensive care unit.

cEEG has been used in patients with SAH to detect DCI. In 1 study, all clinical ischemic events were associated with electroencephalographic trend changes. These changes frequently preceded clinical neurological deterioration and, in 5 cases, detected asymptomatic ischemia identified by CT. Decreased α variability preceded TCD or angiographic evidence of vasospasm by ≥2 days in 10 of 19 patients. A decrease in the α/δ ratio also correlated with both clinical and radiographic DCI in poor-grade patients. When used prospectively, a blinded reviewer predicted clinical deterioration and response to therapeutic interventions after DCI onset using cEEG. A recent study suggested that intracortical electroencephalography may be superior to scalp electroencephalography for vasospasm detection. Collectively, these studies suggest that cEEG may have a role in guiding management in SAH, although larger, prospective studies are needed. Recent recommendations suggest that cEEG moni-
toring be considered in patients with poor-grade SAH who fail to improve clinically or experience unexplained neurological deterioration.31

Cerebral Oxygenation

Cerebral oxygen delivery is determined by CBF and arterial oxygen content. Global brain oxygenation may be assessed by jugular bulb oximetry, whereas regional oxygenation may be assessed with a Clark-type electrode (Licox) and with near-infrared spectroscopy (NIRS).

Jugular Bulb Oximetry

Jugular venous oxygen saturation (SjvO₂) may be used to determine the adequacy of oxygen supply relative to cerebral metabolic demand. According to the Fick principle, the arteriovenous difference in oxygen content (a measure of oxygen extraction) is proportional to cerebral metabolic demand and inversely proportional to CBF. SjvO₂ normally ranges between 60% and 70%. Low SjvO₂ signifies inadequate delivery relative to demand. This may be due to anemia or decreased CBF (eg, from intracranial hypertension or systemic hypotension) or it may be due to excessive cerebral metabolic demand (such as occurs with seizures or fever). Conversely, a high SjvO₂ signifies that oxygen delivery exceeds metabolic requirements. This occurs when CBF is excessive (hyperemia) or when cerebral metabolic demand is decreased, for example, due to sedatives, hypothermia, or O₂ extraction failure (shunt) from dead or dysfunctional cells.

Retrograde percutaneous cannulation of the internal jugular vein with a spectrophotometric catheter allows for continuous SjvO₂ measurement.20 The catheter tip must lie in the superior portion of the jugular bulb. If too low, the catheter measures saturation of blood from the facial veins admixed with blood from the brain. If too high, the skull base might interfere with spectrophotometric measurements. Proper tip position is confirmed with a neck/skull radiograph.32

Although SjvO₂ has been studied most extensively in traumatic brain injury, a few studies have examined its use in SAH. In patients with coma from various etiologies, including SAH, vasospasm was an important cause of desaturation (SjvO₂ <50%).33 In 4 of 14 patients with SAH with clinical vasospasm, all exhibited increased cerebral oxygen extraction ≥24 hours before clinical symptoms.34 After hemodynamic augmentation, clinical symptoms and cerebral oxygen extraction improved. Some propose that the addition of SjvO₂ monitoring to TCD data might help to distinguish elevated flow velocities due to vasospasm (decreased SjvO₂) from those due to hyperemia (increased SjvO₂).20

Near-Infrared Spectroscopy

NIRS uses light absorption of oxygen-carrying molecules in the brain to assess cerebral oxygenation. Oxy- and deoxyhemoglobin have characteristic absorption spectra in the near-infrared range (650–1100 nm). When a scalp emitter sends near-infrared light through the skull and into brain tissue, the relative concentration of chromophores is determined by their relative absorption of light (measured by scalp detectors). NIRS interrogates all tissue within the field of view (penetrating to a depth of 2.5 cm), measuring hemoglobin concentration in arterial, venous, and capillary blood. From this, oxygen saturation can be calculated and used to identify cerebral hypoxia.35

NIRS is attractive as a bedside monitoring tool because it is noninvasive, provides continuous data, and is easy to set up and maintain. However, the quality of measurements may be altered by changes in hemoglobin concentration, skull thickness, and alterations in CSF layers. Furthermore, values and interpretation vary across devices, limiting the generalizability of available studies.36

Figure 1. Histogram of EEG α frequencies in a patient monitored after SAH. Relative frequency of α EEG waveforms is shown on the y axis. Initially, α variability (defined as excursions above the baseline >15% at least once per hour28) was good. However, as monitoring progressed, α variability decreased (arrow; no excursions greater than 2%28), suggesting cerebral ischemia. EEG indicates electroencephalography; SAH, subarachnoid hemorrhage.
Experience with NIRS in patients with SAH is limited and has yielded conflicting data. Some studies indicate a correlation between data from NIRS and TCD and suggest that NIRS may be more sensitive than TCD for detecting compromised cerebral oxygenation. In patients with a new focal neurological deficit, NIRS detected decreased cerebral oxygenation in the affected region and a rise in oxygenation after treatment with an inotrope. However, others have found no such correlation.

Table. Cerebral Physiological Monitors Used for SAH

<table>
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<tr>
<th>Physiological Parameter</th>
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<th>Monitor</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tr>
<td>Intracranial pressure</td>
<td>Surrogate for cerebral blood flow; hydrocephalus common after SAH</td>
<td>External ventricular drain</td>
<td>Allows therapeutic CSF drainage</td>
<td>Invasive; risk of aneurysmal rebleeding; infection; catheter-related hemorrhage</td>
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<tr>
<td>Cerebral blood flow</td>
<td>Measures fuel delivery to cerebral tissue</td>
<td>Thermal diffusion flowmetry</td>
<td>Quantitative</td>
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<td>Cerebral oxygenation</td>
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<tr>
<td>Cerebral metabolism</td>
<td>Metabolites generated by anaerobic metabolism indicate cellular hypoxia</td>
<td>Cerebral microdialysis</td>
<td>Most direct measure of cellular health</td>
<td>Invasive; near-continuous; diffusion may delay detection of metabolic change; probes fragile</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; EEG, electroencephalography; CSF, cerebrospinal fluid.

Brain Tissue Oximetry

Partial pressure of brain tissue oxygen (PbtO2) is a complex physiological variable that likely reflects the interaction among oxygen delivery, extraction, and tissue demands. Although the exact determinants of PbtO2 are unknown, it is clear that compromised PbtO2 (<20 mm Hg) is associated with pathophysiological processes, including decreased CBF, low arterial oxygen saturation, lung injury, and anemia.

PbtO2 is measured with an invasive probe that uses a Clark-type electrode. Oxygen diffuses into the probe and is reduced by a cathode creating a measurable electric current that is linearly related to oxygen concentration. The probe is precalibrated and allows for PbtO2 quantification.

Several technical aspects of brain tissue oximetry potentially limit its use in SAH. The probe is placed near, but not within, the injured site, capturing data from a small volume of tissue. Although DCI often occurs in the region of the parent vessel, it may occur elsewhere. Because the probes are implanted, they cannot be easily moved to sample other areas.

Although PbtO2 monitoring has been studied primarily in patients with traumatic brain injury, limited data in patients after SAH suggest an association between depth and duration of compromised PbtO2 and mortality. Other studies, however, have not shown a relationship with clinical outcome.

Figure 2. Example of multimodal monitoring data obtained from a patient after severe SAH (Fisher Grade IV). Multimodal monitoring of ICP, biochemistry (CMD), and PbtO2 demonstrates that CPP augmentation with a vasopressor increased PbtO2 (blue line) and decreased LPR, suggesting that vasopressor administration improved tissue metabolic health. SAH indicates subarachnoid hemorrhage; ICP, intracranial pressure; CMD, cerebral microdialysis; PbtO2, partial pressure of brain tissue oxygen; CPP, cerebral perfusion pressure; LPR, lactate:pyruvate ratio.
Cerebral Metabolism

Cerebral Microdialysis

During cerebral hypoxia, cells transition from aerobic to anaerobic metabolism, ending in the conversion of pyruvate to lactate. In its extreme, hypoxia results in cell death, prompting glycerol release from the cell membrane. Cerebral microdialysis measures these small molecules using a microcatheter covered in a semipermeable membrane inserted into brain parenchyma. Small molecules move down their concentration gradients into artificial CSF (dialysate) that is pumped through the catheter. The dialysate is recovered periodically (eg, hourly) and analyte concentrations are determined by a bedside analyzer. Cerebral microdialysis therefore provides near-continuous information about brain bioenergetics and cell integrity.

Probe position in the territory of the parent artery is important and, thus, probe insertion must be delayed until after angiography. Because fluid flows through the catheter slowly, measured values may represent events occurring 20 to 60 minutes earlier. Finally, clotting of the probe may limit its functional duration. Although a multitude of small molecules might be measured in the laboratory, the currently Food and Drug Administration-approved device measures only lactate, pyruvate, glucose, glycerol, and glutamate.

In patients with ischemic symptoms after SAH, cerebral microdialysis detected elevated concentrations of glutamate, lactate, glycerol, and a higher lactate/pyruvate ratio in regions of reduced CBF (confirmed by 18F-fluorodeoxyglucose positron emission tomography imaging). Ischemic dialysate patterns (>20% increase in lactate/pyruvate ratio, lactate/glucose ratio, and glycerol concentration) were detected in 17 of 18 patients with SAH who experienced DCI but in only 3 of 24 patients who did not. Ischemic biomarker patterns were detected on average 11 hours before clinical signs. In another study, CPP <70 mm Hg was associated with metabolic crisis (lactate/pyruvate ratio >40), suggesting that cerebral microdialysis may be used to determine a safe lower limit of CPP on a patient-specific basis. Furthermore, the duration of metabolic crisis during monitoring correlated with a poorer outcome at 3 months. However, not all authors have found that ischemic patterns precede clinical deterioration. One study found that lactate/pyruvate ratio changes had a high sensitivity for infarction but low specificity for ischemia. Marked changes in metabolic markers occurred only with extreme clinical changes such as herniation, suggesting that cerebral microdialysis, at least as a single monitor, may not be useful for predicting cerebral compromise.

Conclusions

Advances in technology have made previously unobtainable measures of cerebral physiology readily accessible at the bedside. These advances have brought individualized physiologic goal-directed therapy within reach for patients with severe brain injury. However, study of the clinical use of these tools is in its infancy, especially for patients with SAH. These devices are largely experimental and many require additional technological innovation. User-friendly information systems that can acquire, synchronize, display, analyze, and store the abundant and complex data streams generated by multiple devices must be developed in parallel. Further work is also needed to better understand the determinants and interactions of complex physiological variables (Table). Although no single monitor provides a complete set of information, a multimodal approach paints a more comprehensive physiological picture (Figure 2). The optimal “bundle” or combination of monitors has yet to be determined. Ultimately, individualized goal-directed cerebral resuscitation strategies should be compared with standard management approaches in randomized trials to determine their relative impacts on outcome.

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References


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