Unraveling the complexities of invasive multimodality neuromonitoring

Saurabh Sinha, MD; Eric Hudgins, MD, PhD; James Schuster, MD, PhD; and Ramani Balu, MD, PhD

1Department of Neurosurgery, Perelman School of Medicine; and 2Department of Neurology, Division of Neurocritical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Acute brain injuries are a major cause of death and disability worldwide. Survivors of life-threatening brain injury often face a lifetime of dependent care, and novel approaches that improve outcome are sorely needed. A delayed cascade of brain damage, termed secondary injury, occurs hours to days and even weeks after the initial insult. This delayed phase of injury provides a crucial window for therapeutic interventions that could limit brain damage and improve outcome.

A major barrier in the ability to prevent and treat secondary injury is that physicians are often unable to target therapies to patients' unique cerebral physiological disruptions. Invasive neuromonitoring with multiple complementary physiological monitors can provide useful information to enable this tailored, precision approach to care. However, integrating the multiple streams of time-varying data is challenging and often not possible during routine bedside assessment.

The authors review and discuss the principles and evidence underlying several widely used invasive neuromonitors. They also provide a framework for integrating data for clinical decision making and discuss future developments in informatics that may allow new treatment paradigms to be developed.

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KEY WORDS intracranial pressure; brain oxygen; cerebral blood flow; traumatic brain injury; multimodality monitoring; informatics; precision medicine

ABBREVIATIONS AJVDO2 = arterial to jugular venous difference in oxygen content; BP = blood pressure; CBF = cerebral blood flow; CMRO2 = cerebral metabolic rate of oxygen; CPP = cerebral perfusion pressure; EEG = electroencephalography; ICP = intracranial pressure; PbtO2 = partial pressure of brain tissue oxygen; PRx = pressure reactivity index; SAH = subarachnoid hemorrhage; SjvO2 = jugular venous oxygen saturation; TBI = traumatic brain injury; TDF = thermal diffusion flowmetry.

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allow the repeated, direct sampling of brain interstitial fluid for biochemical measurements. The bundling of multiple monitors together can increase their predictive power, because complementary changes between modalities can be identified. In addition, because distinct secondary injury processes may have unique multimodality monitoring “signatures” (e.g., brain swelling increases ICP and lowers CBF, whereas agitation may increase ICP and CBF concomitantly), individualized therapies targeted to specific clinical situations can be instituted. Invasive multimodality monitoring lifts the veil surrounding the “black box” of the injured brain.

This review provides a framework for understanding how invasive multimodality monitoring can impact the care of patients with acute brain injury. We will outline the physiological principles and evidence supporting many of the most widely used techniques for invasive monitoring in neurocritical care, and we will discuss methods for multivariable data visualization, organization, and analysis.

Matching Metabolic Needs to Supply: A General Framework for Invasive Neuromonitoring

Over the course of the 20th century, 3 overlapping threads facilitated the development and validation of intracranial monitoring as a means to guide care in patients with acute brain injury. First, the ability to continuously record intracranial ventricular fluid pressure established the feasibility of real-time bedside monitoring of intracranial physiology. Second, indicator dilution techniques enabled accurate measurements of cerebral perfusion in humans and demonstrated that elevated ICP leads to reduced CBF. Finally, studies finding that markedly elevated ICP associates with poor outcome, coupled with postmortem studies of patients with traumatic brain injury (TBI) showing extensive ischemic lesions, showed that prolonged intracranial hypertension can reduce cerebral perfusion and cause global ischemia. Taken together, these findings suggested that aggressive ICP control could limit secondary brain injury by improving cerebral perfusion.

Subsequent work showed that abnormalities in CBF and oxidative metabolism are far more complex. After TBI, the initial period of hypoperfusion and increased oxygen demand is followed by a drop in oxygen metabolism (cerebral metabolic rate of oxygen \( \text{CMRO}_2 \)). Unable to use oxygen, the injured brain is forced to compensate by increasing anaerobic glycolysis. Further metabolic stresses create a mismatch between delivery and consumption, ultimately leading to cell death from energy failure. Whether these specific alterations in metabolic supply and demand exist in nontraumatic acute brain injuries is unclear. Nevertheless, viewing mismatches between cerebral oxygen and glucose delivery and metabolic demand as a dominant driver of secondary brain injury remains a useful framework (Table 1).

### Specific Monitoring Modalities

#### Cerebral Oxygenation

##### Jugular Venous Oximetry

In jugular venous oximetry, the oxygen content of blood is sampled from the cerebral venous circulation to determine the global balance between cerebral oxygen delivery and metabolism. A central venous catheter is inserted into the dominant internal jugular vein and directed toward the skull until it terminates at the jugular bulb. Jugular bulb oxygen content is determined solely by cerebral oxygen consumption, because venous blood at this level has not yet mixed with blood draining from the scalp and face. Correct catheter position is determined by obtaining a lateral skull film and identifying that the tip of the catheter terminates just above the inferior border of the C-1 vertebral body.

The relationship between cerebral oxidative metabolism (i.e., \( \text{CMRO}_2 \)) and CBF can be calculated using the Fick equation: \( \text{CMRO}_2 = \text{CBF} \times \left( \frac{\text{Arterial O}_2 \text{ content} - \text{Venous O}_2 \text{ content}}{\text{Venous O}_2 \text{ content}} \right) \). Rearranging this equation shows that the ratio of \( \text{CMRO}_2 \) to CBF equals the arterial to jugular venous difference in oxygen content (\( \text{AJVDO}_2 \)). Elevated \( \text{AJVDO}_2 \) values signal cerebral metabolic demand in excess of supply, whereas low \( \text{AJVDO}_2 \) values suggest luxuriant perfusion or dead brain tissue.

In practice, the jugular venous oxygen saturation (\( \text{SjvO}_2 \)) is often used as a proxy for \( \text{AJVDO}_2 \). An \( \text{SjvO}_2 \) value \(< 55\%\) suggests high cerebral oxygen demand or hypoperfusion, and a value \(> 45\%\) is associated with increased cerebral glutamate and lactate production. Conversely, a value \(> 75\%\) suggests hyperemia or shunting around metabolically inactive dead brain tissue. Prior studies have shown robust associations between episodes of jugular venous desaturation (\( \text{SjvO}_2 < 50\% \)) and poor outcomes in patients with TBI. Current guidelines from the Brain Trauma Foundation state that jugular venous oximetry monitoring can be considered to guide care and that treatment strategies that maintain \( \text{SjvO}_2 \) values above 50% may improve 3- and 6-month outcomes (Level III recommendation).

In contrast to TBI, patients with poor outcome after diffuse hypoxic ischemic brain injury in general have elevated \( \text{SjvO}_2 \) levels. This may be due to early cortical cell death during reperfusion, which leads to reduced overall oxygen consumption.

The \( \text{SjvO}_2 \) measurements are highly sensitive to catheter position. In addition, whereas \( \text{SjvO}_2 \) measurements accurately reflect the global balance between oxygen delivery and metabolic demand, they may easily miss smaller regional changes from focal injury.

| Condition       | Normal                | Functional Hyperemia (Normal) |
|-----------------|-----------------------|------------------------------|
| Ischemia        |                       |                              |
| Seizure         | Sedation              | Malignant Hypertension       |
| Spreading depolarization | Anesthesia | Luxury Perfusion             |
| Cerebral edema, vasospasm | | Cerebral infarct |

**Table 1. Matching of cerebral metabolic demand to supply**

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Brain Tissue Oxygen Tension

The partial pressure of brain tissue oxygen (PbtO₂) can be measured using catheters directly placed into parenchymal tissue. The most commonly used measurement system (Licox, Integra) uses a Clark electrode, which consists of an oxygen-permeable membrane that surrounds a metallic cathode and anode immersed in electrolyte solution. Oxygen diffuses through this membrane and undergoes a redox reaction, resulting in an increase in current. Oxygen-induced currents rapidly reach steady state, and as a result, changes in current directly reflect fluctuations in oxygen tension.

Unlike jugular venous oximetry, PbtO₂ measurements do not directly report the balance between oxygen metabolism and supply. Rather, PbtO₂ reflects the product of CBF and arterial to venous free oxygen tension difference and provides an aggregate measure of both cerebral perfusion and systemic oxygenation. Despite its complicated dependence on multiple physiological factors, brain hypoxia is an independent predictor of poor outcome in brain-injured patients, and PbtO₂ threshold–based treatment strategies may improve outcomes.

Monitoring devices for PbtO₂ measure local tissue oxygen tension and may not reflect global brain oxygenation. In addition, probe placement can cause local tissue injury, leading to falsely low measurements. Probe function can be assessed by measuring the response to a 100% fraction of inspired oxygen challenge.

Cerebral Blood Flow

Traditional methods for determining CBF provide single snapshot measurements and are therefore unsuitable for use as continuous monitors. In contrast, thermal diffusion flowmetry (TDF) allows for continuous real-time measurement of absolute CBF. Commercially available TDF systems (Qflow probe, Bowman Perfusion Monitor, Hemedex) measure thermal conductivity of brain tissue to quantify CBF. A catheter with 2 thermistors is inserted into parenchymal tissue. The proximal active thermistor heats adjacent tissue, while the distal passive thermistor measures parenchymal temperature. The power required to maintain a temperature difference is directly proportional to perfusion and is used to calculate blood flow.

Cerebral blood flow measured by TDF correlates reasonably well with PbtO₂ measurements in brain-injured patients, and decreases in CBF can be seen in patients with high-grade subarachnoid hemorrhage (SAH) prior to the development of delayed cerebral ischemia.

Because thermal conductivity reflects tissue water content, TDF may also allow real-time measurements of brain tissue edema. A recent study showed a strong association between thermal conductivity and radiographic measurements of brain swelling. Thus, continuous determination of brain water content may provide additional information that can help guide care.

Although promising, invasive CBF measurements may require further validation before becoming widely adopted. For example, TDF monitors require repeated calibration (usually once every 30 minutes for 2–5 minutes), which leads to significant data loss. In addition, significant measurement drift can occur between calibration cycles. Finally, because cerebral perfusion fluctuates in response to cerebral metabolic needs, reduced CBF could simply reflect decreased metabolic demand rather than true ischemia.

Cerebral Biochemistry

Cerebral microdialysis measures biochemical markers of secondary brain damage. A double-lumen catheter surrounded by a semipermeable membrane is inserted into parenchymal tissue. Isotonic artificial CSF is continuously cycled into the inlet lumen and removed from the outlet lumen at a constant rate. Molecules in brain tissue interstitial fluid (such as metabolic byproducts, neurotransmitters, small peptides, and fatty acids) will diffuse across the semipermeable membrane, and the concentration of these analytes in the recovered dialysate can be determined. Commercially available microdialysis systems measure markers of cerebral metabolism (glucose, lactate, and pyruvate); excitotoxicity (glutamate); and cell membrane turnover (glycerol). Calculating the ratio of recovered analytes (such as lactate:pyruvate) normalizes for differences in analyte recovery and facilitates serial comparisons over time.

Hourly sampling is typically used for clinical care; however, rapid sampling and microfluidic methods have been developed that enable essentially continuous measurements.

An elevated lactate/pyruvate ratio (> 40) is a marker of anaerobic cerebral metabolism, and reduced cerebral glucose (< 0.7 mmol/L) similarly suggests a profound mismatch between metabolic demand and supply. These biochemical signatures of metabolic distress both predict poor outcome. They can occur both in response to decreases in cerebral perfusion and when CBF is normal. “Nonischemic” metabolic crises are probably due to injury-associated mitochondrial dysfunction, which reduces the brain’s ability to use oxygen and triggers compensatory hyperglycolysis. Isolated lactate elevations could be due to neuroprotective mechanisms that provide alternative fuel sources for oxidative phosphorylation. Consistent with this view, a prior study showed that patients with SAH who had isolated lactate elevations experienced better than expected outcomes, whereas patients in whom elevated lactate coincided with brain hypoxia fared poorly. Finally, extracellular levels of the excitatory neurotransmitter glutamate also correlate with markers of secondary brain injury and poor outcome. Seizures and reduced CPP are both associated with abnormally elevated glutamate after TBI.

As with other invasive monitors, probe placement can induce local tissue injury, which can cause significant abnormalities in analyte levels that take hours to normalize. In addition, because of low sampling rates (usually 1 per hour) and variability in measurements, actionable changes in biochemical parameters can take hours to develop. The low time resolution of microdialysis is offset by the fact that biochemical changes can occur hours before changes in other monitored parameters can be identified.

Electrical Activity

Seizures are common after acute brain injury and are consistently associated with worsened outcome. Early studies evaluating the utility of continuous scalp electroencephalography (EEG) monitoring noted that seizures
occur in approximately 25% of patients with TBI and intracerebral hemorrhage and that the majority of seizures are nonconvulsive, with no clinical manifestations. Nonconvulsive seizures are associated with ICP increases and cerebral metabolic distress after TBI, independently predict hematoma expansion, and are associated with increased risk of hippocampal and cortical atrophy. More recent studies have used intracranial electrophysiological methods, including subdural electrocorticography and intracortical EEG, to monitor brain-injured patients. Subdural electrocorticography strips can be placed intraoperatively in patients requiring acute neurosurgical intervention, whereas depth electrodes for intracortical EEG can be inserted through a bur hole placed at bedside. Intracranial recordings detect seizures with much higher sensitivity than scalp EEG; in patients being monitored with both types of recordings, conventional scalp EEG misses up to 60% of seizures that are subsequently picked up with invasive methods. Seizures identified with invasive recordings produce brain hypoxia and metabolic dysregulation (e.g., cerebral glycopenia and elevated lactate/pyruvate ratio), thus providing a rationale for using intracranial EEG monitoring to guide patient care.

In addition to detecting seizures with higher sensitivity, intracranial EEG allows for the detection of injury-associated spreading depolarizations, which occur over slow time scales (minutes) and are largely undetectable by scalp EEG. Spreading depolarizations are waves of intense depolarization that emanate from foci of cortical injury to produce widespread metabolic distress, cytotoxic edema, and impaired neurovascular coupling. Spreading depolarizations are strong predictors of poor outcome after TBI, ischemic stroke, intracerebral hemorrhage, and SAH. Given that ketamine impedes the occurrence and propagation of spreading depolarizations, monitoring for these deleterious physiological stressors could positively impact patient outcome.

Integrating Multiple Modalities to Guide Patient Care

The true promise of the techniques described in this article lies in their ability to be bundled together to provide complementary information. Streamlining monitor insertion so that multiple monitors can be placed simultaneously and proper data visualization are key prerequisites for the effective implementation of multimodality monitoring–guided care.

Monitor Insertion

The use of a multilumen bolt facilitates the simultaneous placement of multiple monitors through a single insertion site (Fig. 1). Different combinations of monitors can be placed through the same bolt housing, and in general lumens are oriented such that inserted catheters splay out from the insertion site. This ensures that each monitor independently samples a different brain region and reduces the risk that tissue injury around one monitor adversely affects data collected by other monitors.

Data Visualization and Review

Overlaid time series displays enable the simultaneous visualization of multiple physiological trends, which aids in understanding the complex interactions between different brain regions and in guiding clinical decision-making.
In identifying concordant changes across different monitors. An example of a multimodal data display is shown in Fig. 2. Each track shows temporal trends for a specific recorded parameter over a 6-hour window. In addition to raw data, a track showing the cumulative ICP burden (the percentage of time that ICP stays > 20 mm Hg) is also shown. The overlay of multiple physiological trends clearly shows the effect of a spontaneous increase in ICP (denoted in the figure as IC1) on brain oxygen (denoted as IC2) and perfusion. Simultaneous display of raw waveform data (right side of the figure) allows for the identification of data artifacts (such as arterial line flushing).

Bedside trend analysis can help guide patient care; however, the large number of recorded variables makes identification of secondary injury processes difficult on bedside spot checks. Detailed retrospective review at regular intervals by a physician or technician enables identification of worrisome trends, assessment of the cumulative effectiveness of therapeutic interventions, and identification of novel patterns in the data. When conceptualized in this manner, effective analysis of invasive multimodal data becomes analogous to reviewing continuous EEG data.

At our institution, we have adopted such a strategy for periodic retrospective data review (Fig. 3). Data streams from different physiological monitors are recorded and time-synchronized onto a unit (CNS Monitor, Moberg Research) that allows bedside review of physiological trends by members of the clinical team. The recorded data are also automatically archived in real time to a secure server within the hospital network that can be remotely accessed for periodic review. The retrospective identification of specific physiological signatures of secondary injury then prompts communication with the clinical team, thus closing the loop and ensuring that worrisome trends are acted on. This strategy has greatly increased the confidence among clinical staff at our institution in the utility of intracranial monitoring. Future work is required, however, to assess whether this strategy improves physiological end points or patient outcome.

Moving Beyond Simple Trend Analysis: Finding Hidden Patterns

Analyzing trends in multimodality monitoring data allows therapies to be instituted that renormalize physiology. However, our preexisting expectations for the data can severely constrain our ability to find novel physiological signatures of injury, treatment response, and outcome. For instance, because of the rich history of ICP-oriented therapies in neurocritical care, clinicians may focus on ICP elevations while ignoring other concerning patterns. Unbiased analysis methods can aid in finding hidden patterns that can guide patient care.

Pairwise Correlation Analysis

Dependencies between physiological variables can be identified by pairwise correlation analysis. For example, plotting paired values of ICP and PbO2 may reveal a relationship in which higher ICP is associated with lower PbO2.
and suggests that actively reducing ICP can improve brain oxygenation (Fig. 4). In contrast, ICP elevations caused by increases in cerebral perfusion would be expected to increase PbtO₂, producing the opposite relationship.

Calculating the correlation between BP and CBF (or a proxy measurement) can provide a measure of cerebral autoregulation—the ability of the brain to maintain constant CBF in the face of changing CPP. The pressure reactivity index (PRx), which measures time-varying changes in the correlation coefficient between arterial BP and ICP, has emerged as a widely adopted index of autoregulation. Negative correlations between ICP and BP (i.e., negative PRx) suggest intact autoregulation (because elevated BP should trigger vasoconstriction and decreased cerebral blood volume), whereas ICP values that correlate positively with BP (i.e., positive PRx) indicate failed autoregulation. Persistently positive PRx is associated with poor outcome, and maintaining CPP in a range where PRx is minimized (i.e., CPPopt) may improve outcome. The PRx fluctuations can be plotted along with other trends in multimodal data displays (Fig. 2), allowing the effects of different therapies on the autoregulatory state to be assessed. Similar autoregulation indices between CPP and PbtO₂ and CPP and CBF have been constructed, although they have not been validated to the same degree as PRx.

Multidimensional Approaches

Cluster Analysis

Rather than vary smoothly over a broad range of values, variables such as ICP and PbtO₂ may aggregate into distinct groups that signify specific physiological states. Cluster analysis methods can help identify these related groups in an unbiased fashion by calculating a distance metric between data points and then identifying collections of data points that lie close to each other. Although conceptually simple (Fig. 4), the power of cluster analysis is that it can easily be scaled to analyze relationships between large numbers of variables. In previous studies in which this approach was used to analyze physiological data from patients with multisystem trauma and TBI, novel combinations of physiological variables were found that predict infection, death, and poor outcome.

Multivariate Regression Models

Predictive models based on least-squares polynomial data-fitting techniques are simple, efficient, and effective means of developing automated approaches to identify unique physiological signatures that portend poor outcome. Logistic regression modeling is one such multivariate analysis technique that can provide robust detection of worsening trends of intracranial monitoring values. Binomial distributions of independent data variables are created by aggregating large data sets from several patients who have known outcomes. Sufficiently large retrospective data sets will create accurate models that can be used to predict future states of new patients based on aggregates of their monitoring data plotted against the model.

Smart Alarms

Finally, there has been significant interest in the critical care field in developing alarms that provide early alerts about worsening patient conditions. Standard alarms have typically relied on simple and separate thresholds for independent data variables such as heart rate, BP, and ICP.
However, the large variance of clinical data leads to a large number of false-positive alarms that are not clinically relevant. Logistic regression models enable the use of more sophisticated trigger thresholds to alert clinicians toward worsening trends in monitoring data, and consequently the development of “smart alarms” that could provide sensitive and specific detection of early changes in the monitoring data while minimizing false positives.

Conclusions

Invasive multimodality monitoring holds great potential for identifying unique physiological signatures of secondary brain injury so that patient care is individualized. The increasing adoption of invasive multimodality monitoring bundles in neurocritical care units promises to usher in a new era of precision medicine. To realize this goal, however, standardized methods for data visualization and interpretation are required. In addition, the development of novel analytical methods and informatics tools that allow for unbiased assessments of large, multidimensional data sets will be crucial for the successful translation of multimodality monitoring from the realm of clinical research to standard clinical practice.

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Conception and design: Balu, Sinha. Analysis and interpretation of data: Balu, Sinha, Hudgins. Drafting the article: Balu, Sinha, Hudgins. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Balu.

Correspondence

Ramani Balu, Department of Neurology, Division of Neurocritical Care, Perelman School of Medicine, University of Pennsylvania, 3W Gates, 3600 Spruce St., Philadelphia, PA 19104. email: ramani.balu@uphs.upenn.edu.