A brief history of monitoring in neurocritical care

Monitoring in most ICUs between 1960 and 1980 was restricted to clinical examination, heart and respiratory rate, blood pressure, oxygen saturation, body temperature, and central venous pressure. With the advent of the pulmonary artery catheter, monitoring of cardiac output and right-sided cardiac filling pressures became possible, providing new understanding and acting as a guide to therapy for the resuscitation of cardiogenic and septic shock.

Neurologic ICUs (NICUs) at that time focused almost exclusively on the care of postoperative neurosurgical patients, and neuromonitoring was restricted primarily to serial neurologic examination and, in some units, intracranial pressure (ICP) monitoring. These “neuro checks” often did not reveal changes in cerebral function until they were irreversible. The idea was to detect clinical deterioration as soon as possible, enabling prompt efforts to reverse or correct any injurious process. This era can be thought of as the age of clinical neuromonitoring.
Between 1980 and 2000, use of ICP monitoring became more widespread, although even today its use is far from routine, particularly when critically injured patients are admitted to nonspecialty NICUs. The accepted paradigm at this time, which can be thought of as the age of physiologic neuro-monitoring, was to detect and treat increases in ICP before they led to obvious and often irreversible clinical deterioration. Neurocritical care demanded a quick and accurate diagnosis, with monitoring and management based on brain-derived physiologic information to detect secondary injury in its earliest phase. However, at that time, ICP monitoring was the only widely used technique, with jugular venous oxygen saturation monitoring used at only a small number of centers focusing on neurotrauma.

In our view, the future of neurocritical care will bring us into the age of multimodality monitoring and neurophysiologic decision support. Advanced monitoring techniques that can provide real-time information regarding the relative health or distress of the brain, such as brain tissue oxygen tension, signal-processed continuous electroencephalography, and neurochemical analysis using microdialysis will be used to create and maintain an optimal physiologic environment for the comatose injured brain. Rather than using neuromonitoring to alarm the clinician when critical deviations occur, real-time physiologic end points will be used to guide goal-directed therapy, in the same way that targeted therapy to avoid a low venous oxygen saturation in the acute phase of septic shock has been shown to improve survival. Conceptually, rather than reacting to harmful physiologic intracranial events, the idea will be to prevent them altogether with a proactive strategy (Fig. 1).

In the twenty-first century, advanced neuromonitoring techniques and improvements in the surgical, endovascular, and medical management of intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), acute ischemic stroke, and severe traumatic brain injury (TBI) will contribute to improved outcomes from these devastating diseases. Preliminary experiences with real-time monitoring of brain oxygen tension, metabolism, and continuous electroencephalography in patients with severe brain injury already allow prediction of long term-outcome [1–6]. These associations with patient-centered outcomes provide a rationale for using these monitoring techniques as end points for therapy during the acute phase of injury. Future clinical trials will then be needed to demonstrate that goal-directed ICU therapy produces better outcomes. This review provides an overview of the current state of multimodality monitoring in neurocritical care.

Cerebral perfusion and intracranial pressure

Cerebral perfusion and intracranial pressure (CPP) is the driving force of cerebral blood flow (CBF) and is the principal determinant of the autoregulatory response of the cerebral vasculature. Under normal physiologic conditions, a mean arterial pressure (MAP) of 80 to 100 mm Hg and an ICP of
5 to 10 mm Hg generate a CPP of 70 to 85 mm Hg [7]. However, true CPP may vary ±27 mm Hg from measurements with MAP [8]. Accurate MAP measurements require the placement of an arterial pressure catheter. The transducer of the arterial pressure catheter should be positioned at the level
of the foramen of Monroe to accurately measure CPP. Transcranial Doppler (TCD) ultrasonography has been proposed as a noninvasive method to assess the adequacy of CPP [8], but it requires constant adjustment of probe placement by experienced staff.

ICP values can be obtained by inserting ventricular, subdural, epidural, or intraparenchymal microtransducers. The microtransducers have the advantage of low infection and hemorrhage rates, but can have a considerable zero-drift over monitoring periods of a few days and cannot be re-zeroed after insertion. Intraventricular drains connected to external pressure transducers are still the gold standard for ICP monitoring. They provide the most accurate measurements, allow for ICP control by drainage of cerebrospinal fluid (CSF), and can be re-zeroed externally. However, the risk of infection is approximately 10% and increases with longer duration of the monitoring period. Antibiotic coating of intraventricular drains may prevent or delay the onset of infectious ventriculitis [9–12]. Most ICP monitors are MRI-compatible.

ICP waveforms contain additional valuable information regarding compliance of the cerebrospinal system, CBF autoregulation, and CSF absorption capacity (Fig. 2) [9]. Continuous assessment of brain compliance with the Spiegelberg Brain Compliance Monitor and ICP pulse waveform analysis at the bedside may be helpful to predict impending neurologic decompensation and herniation [9].

An interesting approach to noninvasive ICP monitoring is tissue resonance analysis [13]. Unilateral mass effect can be discovered by way of TCD ultrasonography demonstrating depressed ipsilateral mean flow velocities, increased ipsilateral pulsatility index, and reduced ipsilateral-to-

![Fig. 2. Example of intracranial pressure waveforms. P1, percussion wave with a sharp and constant amplitude; P2, tidal wave (ends at the dicrotic notch); P3, dicrotic wave. These waveforms are influenced by arterial and venous pressure, blood volume, CSF volume, and mass lesions.](image-url)
contralateral pulsatility index ratio in ICH with a volume greater than 25 mL [14]. Further studies are needed to evaluate whether ultrasound monitoring of hemispheric mass lesions can complement ICP monitoring by providing information regarding compartmentalized mass effect.

Invasive ICP and CPP monitoring is a standard of care in most neurocritical care units, but the management protocols and therapeutic targets that are used differ considerably. Most brain injuries result in disturbed autoregulation, meaning that CPP and ICP monitoring is necessary to ensure normal cerebral perfusion. Moreover, in patients with depressed mental status (Glasgow Coma Scale score \( \leq 8 \)), ICP monitoring is considered a standard of care given the insensitivity of the clinical examination for detecting clinical deterioration. For example, ICP elevations after SAH may result from CSF outflow obstruction and cerebral edema and cause secondary neurologic injury [15]. ICP control is essential before treatment of the aneurysm and is associated with more favorable outcome by protection against cortical injury and facilitation of surgical exposure of the aneurysm [16].

With autoregulatory failure, sufficient brain perfusion is even more dependent on CPP (Fig. 3). A minimum CPP threshold of 60 mm Hg is generally accepted, but the question remains which CPP is optimal for each
individual patient at different times [9,17]. Hypoxic and ischemic events have been observed despite maintaining a CPP of > 70 mm Hg in patients with TBI [18]. On the other hand, once the CPP reaches the lower threshold of the autoregulatory breakthrough zone, hyperemia and secondary increase in ICP may result [7]. Current management of patients with severe brain injury resulting in intracranial hypertension should be directed at ICP and CPP management. To balance the issue of hypo- and hyperperfusion, additional guidance can be provided by monitoring of jugular venous oxygen saturation, microdialysis (eg, lactate/pyruvate ratio), global or regional CBF, and brain tissue oxygen pressure [7,18–20].

Cerebral blood flow

Cerebral blood flow can normally be maintained over a certain range of CPP. This relationship is nonlinear in injured brain as a consequence of disturbed autoregulation [21]. Therefore, direct monitoring of CBF would be helpful for managing patients with severe brain injury. The Kety-Schmidt Technique, the gold standard of CBF measurement, involves direct measurement of arterial and jugular venous concentrations of an inert, freely diffusible indicator such as nitrous oxide and calculation of global CBF from the uptake rate of the indicator into cerebral tissue [22,23]. CBF can be estimated with use of radioisotopes such as krypton-85 or xenon-133 combined with compact scintillation detectors and microprocessors [24,25], the still-developing indocyanine green dye dilution technique using noninvasive near-infrared spectroscopy [26], and the thermodilution method. Thermodilution CBF measurements are based on bedside recording of a temperature difference between the site of constant injection of a blood compatible fluid with a lower temperature into the jugular bulb and 25 mm downstream from the injection site [27]. Other techniques that assess CBF include xenon-enhanced CT scanning [28], single photon emission CT (SPECT), oxygen-15-positron emission tomography (PET), perfusion CT, or perfusion-weighted magnetic resonance (MR) imaging [29].

Alternatively, CBF can be estimated continuously and invasively by way of laser Doppler flowmetry and thermal diffusion limited to a specific region of interest (Bowman Perfusion Monitor). Laser Doppler flowmetry assesses the volume or concentration and the velocity of red blood cells in a small sample volume (1 mm³), which generates a flow signal; this yields a qualitative estimate of local CBF [30]. Some laser Doppler flowmetry probes are compatible with MRI. Most of the probes are susceptible to artifacts. The thermal diffusion method provides a quantitative estimate of regional CBF in milliliters per 100 g per minute by using thermal diffusion based on the tissue’s ability for dissipation of heat [31]. The MRI compatibility of the Bowman Perfusion Monitor is uncertain.

In comparison with xenon-enhanced CT, a cutoff for CBF of 15 mL/100 g/min was identified as a threshold for diagnosis of symptomatic vasospasm
in SAH for the thermal diffusion method (Table 1) [32]. In small prospective series, both ischemia rebound hyperemia related to temporary arterial clip placement during aneurysm surgery could be identified with a thermal diffusion probe [33]. A study of SAH and TBI patients found a correlation between CBF obtained by the thermal diffusion method and PBO₂, indicating that tissue oxygen levels were determined by regional CBF [34]. This kind of real-time continuous perfusion assessment provides exciting new perspectives into regional cerebral autoregulation, especially if directly time-correlated with ICP and CPP.

Transcranial Doppler evaluation of cerebral autoregulation

The autoregulatory reserve of the cerebral vasculature can be assessed with TCD ultrasonography using several methods [35]:

- observation of alterations of flow velocity (FV) in the middle cerebral artery (MCA) during titration of MAP with vasopressors and calculation of the rise of autoregulation as percentage increase in vascular resistance (CPP/FV) divided by the percentage rise in CPP [36];
- cerebrovascular reactivity to carbon dioxide assessed by way of TCD ultrasonography provides information about the functional status of cerebral vasoreactivity and has been found to correlate with outcome after head trauma [37], but may increase ICP when the cerebral autoregulatory reserve has been exhausted [38];
- a stepwise decrease in arterial blood pressure by deflation of compressed leg cuffs during continuous TCD MCA FV recording can reveal the absence of normal pressure autoregulation [36];
- in the transient hyperemic response test, short-term compression of the common carotid artery normally results in a decrease in ipsilateral MCA FV, followed by transient hyperemia as a result of distal vasodilatation. The presence of the hyperemic response correlates with better outcome after head injury [39];
- with observation of the phase shift between continuously monitored MCA FV and superimposed respiratory and arterial blood pressure waves, a phase shift of zero suggests absent autoregulation, whereas a phase shift of 90° indicates intact autoregulation [40];
- the moving correlation coefficient between mean CPP and mean FV is positive when autoregulation is disturbed and zero or negative when autoregulation is intact (positive coefficients were linked to worse outcome in head trauma patients) [41]; or
- simultaneous recording of flow velocities in both MCAs combined with noninvasive beat to beat finger blood pressure measurements can allow for assessment of diurnal variations of FV, regional autoregulation, and the dependency of FV on cardiac output and stroke volume [42].
### Table 1
Multimodal monitoring reference values for cerebral health and pathologic conditions

<table>
<thead>
<tr>
<th>Multimodal monitoring device</th>
<th>Physiologic parameter</th>
<th>Normal range</th>
<th>Pathologic condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous EEG</td>
<td>Brain activity</td>
<td>Alpha/delta ratio $&lt;50%$</td>
<td>Alpha/delta ratio $&gt;50%$</td>
</tr>
<tr>
<td></td>
<td>Epileptiform discharges</td>
<td>No epileptiform discharges</td>
<td>Epileptiform discharges</td>
</tr>
<tr>
<td></td>
<td>Reactivity to stimuli</td>
<td>No reactivity</td>
<td></td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>Mean blood flow velocity</td>
<td>FVm MCA: 30–75 cm/s</td>
<td>MCA FVm 140–200 cm/s; intermediate probability of vasospasm after SAH</td>
</tr>
<tr>
<td>ultrasound</td>
<td>Pulsatility index</td>
<td>FVm ACA: 20–75 cm/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO₂ reactivity</td>
<td>FVm PCA: 15–55 cm/s</td>
<td>MCA FVm $&gt;200$ cm/s; high probability of vasospasm after SAH</td>
</tr>
<tr>
<td></td>
<td>Lindegaard index</td>
<td>FVm/VA: 13–66 cm/s</td>
<td>CO₂R: $&lt;2%$ increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pi: 0.9–1.2</td>
<td>Isilateral-to-contralateral Pi ratio $&gt;1.25$; suspicious for compartmentalized ICP and mass effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO₂R: $\geq 2%$ increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LgI $&lt;3:1$</td>
<td>LgI $&gt;3:1$; mild vasospasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LgI $&gt;6:1$; severe vasospasm</td>
</tr>
<tr>
<td>ICP monitor</td>
<td>ICP</td>
<td>$&lt;20$ mm Hg</td>
<td>$\geq 20$ mm Hg</td>
</tr>
<tr>
<td>ICP monitor and arterial</td>
<td>CPP</td>
<td>$\geq 60$ mm Hg</td>
<td>$\leq 60$ mm Hg</td>
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<tr>
<td>blood pressure catheter</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NeuroSensor cerebral blood</td>
<td>CBF(^a)</td>
<td>50 mL/100 g/min</td>
<td>$\leq 20$ mL/100 g/min; loss of neuronal function and threshold for ischemia</td>
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<tr>
<td>flow and intracranial pressure system (Bowman perfusion monitor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular venous oximetry</td>
<td>SjO₂</td>
<td>50%-75%</td>
<td>$&lt;50%$; increased OEF, indicative ischemia</td>
</tr>
<tr>
<td>Brain tissue oxygen monitor</td>
<td>PBO₂(^a)</td>
<td>20 mm Hg in white matter</td>
<td>$&gt;75%$; reduced OEF, indicative of hyperemia</td>
</tr>
<tr>
<td>(Licox, Neurotrend)</td>
<td>Brain tissue carbon dioxide(^a)</td>
<td>35–40 mm Hg in gray matter</td>
<td>$&lt;20$ mm Hg indicative of cerebral hypoxia</td>
</tr>
<tr>
<td></td>
<td>Brain tissue pH(^a)</td>
<td>43–50 mm Hg</td>
<td>$&lt;8$ mm Hg definite hypoxia/ischemia</td>
</tr>
<tr>
<td></td>
<td>Brain temperature(^a)</td>
<td>7.2</td>
<td>$&gt;60$ mm Hg in brain tissue hypercarbia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correlates with core body temperature (normal 37°C)</td>
<td>$&lt;7.15$ indicative of tissue acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$&lt;36.8^\circ$C or $&gt;37.2^\circ$C</td>
</tr>
<tr>
<td>Cerebral Microdialysis</td>
<td>Glucose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1170 ± 900 (1000–4000) µmol/L (1500–2000 µmol/L)</td>
<td>100 ± 200 µmol/L</td>
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<tr>
<td>Lactate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2900 ± 900 (1000–3000) µmol/L (2000 µmol/L)</td>
<td>8900 ± 6500 µmol/L</td>
<td>31 ± 47 µmol/L</td>
</tr>
<tr>
<td>Pyruvate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>166 ± 47 µmol/L (120 µmol/L)</td>
<td>&gt;40 indicative of ischemia and anaerobic metabolism</td>
<td></td>
</tr>
<tr>
<td>Lactate/pyruvate ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10–40 (15–20)</td>
<td>381 ± 236 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Glutamate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 ± 16 (2–10) µmol/L</td>
<td>573 ± 427 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Glycerol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82 ± 44 (10–50) µmol/L</td>
<td>Increased glutamate and lactate: earliest markers of impending ischemia, followed by increased lactate/pyruvate ratio, decreased glucose and increased glycerol</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Suggested thresholds are drawn from a summary of experimental data cited in the text.

cutoff values for VFm and PI represent the standard values of our Doppler ultrasound laboratory.

**Abbreviations:** CO<sub>2</sub>R, CO<sub>2</sub> reactivity; FVm, mean blood flow velocity; MCA, middle cerebral artery; OEF, oxygen extraction fraction; Pi, pulsatility index; Lgi, Lindegaard index; SAH, subarachnoid hemorrhage.

All of these methodologies are capable of qualitative assessment of cerebral autoregulation, but most are not available continuously. None of these methods has an established role in routine clinical practice, which may be due in large part to operator expertise and time required to perform these studies.

**Further applications of transcranial Doppler ultrasonography**

TCD ultrasonography has long been used to support the diagnosis of arterial vasospasm after SAH and to identify patients at risk for development of delayed ischemia. Correlation of increased mean FV in proximal intracranial vasculature with the diagnosis of vasospasm by cerebral angiography has been established [43,44]. Vasospasm is defined by an increase of mean FV above 200 cm/s by TCD ultrasonography and suspected if mean FV ranges from 140 to 200 cm/s. Comparing the highest FV in the MCA with the highest FV in the extracranial internal carotid artery (Lindegaard Index) eliminates the influence of systemically increased blood flow causing hyperemia (see Table 1) [45]. Vasospasm is considered to be present if the Lindegaard index is greater than 3:1 [45]. Detection of high-intensity transient signals, which are thought to reflect microemboli in stroke patients with cardiac valvular disease, patent foramen ovale, and carotid disease, is another application of TCD ultrasonography [46]. TCD studies have shown high specificity for the confirmation of intracranial circulatory arrest in brain death. Brief systolic forward flow spikes with reversed or absent diastolic flow found bilaterally or in three different arteries are accepted TCD criteria for supporting the diagnosis of brain death [47,48].

Application of TCD ultrasonography for diagnostic monitoring requires experienced and skilled operators. Examination of 200 patients is required to be considered adept at the technique [49]. Other limitations of TCD ultrasonography include inadequacy of the acoustic windows (5%–20%), dependency of the accuracy of the flow velocities on the angle of insonation, and anatomic variants [50].

New developments include continuous TCD monitoring, which requires constant readjustment of the probes, and color-coded transcranial Doppler (TCCD). TCCD can visualize the entire circle of Willis, turbulences within the blood vessels, direction of flow, and increased flow velocities. Direct sampling of defined volumes within blood vessels and obtaining angle-corrected flow velocities provide improved accuracy of measurement [49].

**Cerebral oxygenation monitoring**

Monitoring of cerebral oxygenation after brain injury may lead to the detection or prevention of secondary episodes of ischemia. There are four methods of measuring brain oxygenation: jugular venous bulb oximetry,
direct brain tissue oxygen tension measurement, near infrared spectroscopy, and oxygen-15 PET [29].

**Jugular venous oxygen saturation**

Retrograde placement of a jugular venous catheter equipped with an oximeter can provide continuous measurements of jugular venous oxygen saturation (SjvO$_2$). It is advisable to cannulate the dominant internal jugular vein to correctly assess global cerebral oxygenation. The dominant internal jugular vein can be determined by compression of each internal jugular vein, observing the greater ICP rise if an ICP monitor is present. The catheter tip should be positioned in the jugular bulb and the position confirmed by lateral skull radiograph. After the insertion and every 8 to 12 hours the catheter requires calibration [51,52]. Jugular bulb catheters are compatible with MRI.

SjvO$_2$ is the result of the difference between cerebral oxygen delivery (supply) and the cerebral metabolic rate of oxygen (demand), given that arterial oxyhemoglobin saturation, hemoglobin concentration, and the hemoglobin dissociation curve remain stable. It provides an indirect measurement of CBF. If SjvO$_2$ is low (<50% for >10 minutes in duration) it indicates hypoperfusion (decreased supply) or an increase in cerebral metabolism (increased demand) (see Table 1). The arteriovenous difference in oxygen supply (AVDO$_2$ = CMRO$_2$/CBF, CMRO$_2$ = cerebral metabolic rate of oxygen consumption) is a better estimate of the balance between cerebral metabolism and blood flow [21]. Changes in SjvO$_2$ should be confirmed by measuring the oxygen saturation in a blood sample withdrawn from the jugular venous catheter, and the catheter should be recalibrated if the difference is >4% [51]. Jugular venous oximetry is mainly applied in comatose patients (GCS ≤8) with head trauma, where frequent episodes of cerebral venous oxygen desaturation secondary to hypocapnia, hypoperfusion, and increased ICP are found within the first 48 hours [53]. Monitoring of SjvO$_2$ can also be used in the treatment of SAH [54] and during neurosurgical procedures [55].

Reliability of jugular venous oximetry is limited by changes in arterial oxygen content, hemodilution, prone position of the jugular bulb catheter, necessity for frequent calibrations, and infrequent complications related to catheter insertion such as infection, increase in ICP, thrombosis, arterial puncture, and pneumothorax [52]. Jugular venous oximetry reflects global cerebral oxygenation and does not detect regional ischemia in smaller regions of the brain ipsilateral to the catheter or in the contralateral hemisphere [56].

**Brain tissue oxygen pressure**

Brain tissue oxygen tension of a region of interest can be measured continuously with a small flexible microcatheter inserted into brain parenchyma.
The brain tissue oxygen pressure (PBO₂) value is a marker of the balance between regional oxygen supply and use. Depending on the device, either ICP and brain temperature (Licox, Integra Neurosciences) or the tissue partial pressure of carbon dioxide (PBCO₂) and pH (Neurotrend, Johnson & Johnson) can be monitored in addition to PBO₂. The Licox device measures tissue oxygenation through a polarographic technique by means of a Clark electrode, whereas the Neurotrend uses “optimal luminescence” to measure pH, PBCO₂, and PBO₂ [57,58]. The catheter can be inserted directly into a given region of interest, e.g., any hypoperfused area as determined by CT or MRI perfusion studies, and preferably should pass through gray matter into white matter for optimal value referencing and data comparison. The catheter may either be tunneled after craniotomy or placed through a double or triple lumen bolt (Fig. 4). The measured tissue volume is approximately 17 mm³. Normal PBO₂ varies depending on the region being measured; levels are highest in regions with a dense population of neurons such as cortex and hippocampus and lower in white matter [59]. Measured PBO₂ and amplitude of changes are generally lower with Neurotrend compared with Licox device [60]. Licox and Neurotrend probes are generally compatible with MRI, but may cause artifact in the region of interest.

Monitoring of PBO₂ using Licox probes has been validated in comparison with fiberoptic jugular oxygen saturation monitoring, xenon-enhanced CT scanning, and SPECT to determine an ischemic threshold. In a study, CBF levels of 18 mL/100 g/min by xenon-enhanced CT corresponded to a PBO₂ of 22 mm Hg [61]. During episodes of ischemia as determined by SPECT PBO₂ averaged to 10 ± 5 mm Hg compared with 37 ± 12 mm Hg in normal brain [62]. The likelihood of mortality after severe TBI is increased with prolonged periods with PBO₂ reduction <15 mm Hg, or with any value <8 mm Hg [63,64]. In TBI patients, jugular venous oxygen desaturations below 50%, which indicate a marked global reduction in oxygen delivery, were shown to correlate with critically reduced mean PBO₂ level of 8.5 mm Hg [65]. In a study of 24 patients with TBI, PBO₂ was identified...
as the most powerful predictor of outcome in a multivariate model; levels consistently exceeding 35 mm Hg correlated with good recovery, 26 to 35 mm Hg corresponded with moderate to severe disability, and levels below 25 mm Hg correlated with poor outcome [2]. In regions of focal pathology after TBI, SjvO2 monitoring was found to be insensitive to critical PBO2 reductions detected with a Licox probe [66]. In a larger study comparing PBO2 and SjvO2 monitoring, the sensitivity to detect global cerebral ischemia was 64% for PBO2 catheters and 70% for SjvO2 catheters; in 90% of the ischemic episodes, PBO2 and SjvO2 decreased together. The sensitivity for identification of ischemia due to intracranial hypertension or systemic hypotension by the two methods was not different, but SjvO2 was significantly more sensitive during ischemic episodes caused by hypocapnia [51].

Based on these studies, the cutoff point for cerebral ischemia with PBO2 monitoring seems to be in the range of 8 to 25 mm Hg (see Table 1). A small preliminary nonrandomized study comparing ICP/CPP directed management (ICP < 20 mm Hg, CPP > 60 mm Hg) with PBO2-targeted therapy (PBO2 > 25 mm Hg) in 53 patients with severe TBI was the first to demonstrate a trend toward decreased mortality with PBO2-targeted management strategy [67]. In another study, 52 patients with severe TBI were treated with normobaric hyperoxia for 24 hours within 6 hours after admission. Compared with historical controls, hyperoxia treatment resulted in increased PBO2 levels, reduced levels of glutamate and lactate in cerebral microdialysate that extended beyond the 24-hour treatment window, slightly decreased ICP, and a trend toward higher Glasgow Outcome Scale scores 6 months after injury [68].

Brain oxygen tension measurements have mainly been studied in patients with severe TBI, SAH, and large hemispheric infarctions and in patients undergoing neurosurgical procedures. PBO2 monitoring can provide real-time information regarding autoregulation (Fig. 5 and 6) and has been shown to have a clear impact on the management of patients with TBI and large hemispheric infarction [18,67,69]. Multimodality monitoring, which integrates data from multiple physiologic monitors, is capable of showing strong intercorrelations between PBO2 and various drivers of brain perfusion, including MAP, CPP, and end tidal carbon dioxide (CO2) (see Fig. 6) [2,20,51,59,68,70–80]. Novel methods for correlational data analysis and display may enhance the ability of clinicians to understand complex physiologic relationships and identify optimal physiologic targets (see Figs. 1 and 6). PBO2 monitoring allows for the determination of critical perfusion thresholds [18,20], identification of impaired autoregulation in large hemispheric infarction by means of a pressure oxygen reactivity index (see Fig. 6) [6], and monitoring for ischemia during hyperventilation [81,82], vasospasm [83,84], and hypothermia for severe TBI [85]. It also contributes to better understanding of the pathophysiology of the brain. Appropriate probe placement into the region of interest and probe depth are key for successful monitoring, optimization of cerebral oxygenation and CBF, and prediction of prognosis. PBO2
monitoring may be most useful in brain injury with suspected regional ischemia such as traumatic brain injury, SAH, and ischemic stroke.

Near infrared spectroscopy

Near infrared spectroscopy (rSO₂) is a noninvasive technique to measure regional cerebral oxygen saturation by analyzing the difference of absorption spectra of oxygenated and deoxygenated hemoglobin and cytochrome aa₃. Simultaneous monitoring of transmittance across the brain at two or more wavelengths enables alterations of optical attenuation of the spectra to be converted into changes of cerebral oxygenation [86,87]. Current

Fig. 5. Real-time relationship of the physiological parameters brain oxygen tension (PbO₂), cerebral perfusion pressure (CPP), and intracranial pressure (ICP) over 2 hours in a patient with intracerebral hemorrhage complicated by intracranial hypertension. Note the striking parallel relationship between PbO₂ and CPP, indicative of autoregulatory failure. (From Wartenberg KE, Schmidt JM, Krieger DW. The future of the brain support: Multimodality monitoring. Future Neurology 2006;1(4):473; with permission.)
methods include time-resolved, spatially resolved, and phase-resolved spectroscopy [88]. The change in total hemoglobin is directly related to the change in blood volume [89]. The INVOS system provides a numerical value for oxygen saturation using $rSO_2$; 60% to 80% has been reported as the normal range [90]. NIRO oximeters continuously present values for oxygenated and total hemoglobin concentration, cytochrome aa$_3$, and a tissue oxygen index [91].

Applications of continuous cerebral oxygen saturation measurements with good sensitivity and specificity in adults include detection of changes during carotid cross-clamping during carotid endarterectomy [88,92] and during cardiac surgery [93]. The combination of indocyanine green dye dilution and near infrared spectroscopy might assist in the detection and treatment of cerebral vasospasm causing delayed cerebral ischemic deficit after SAH [94] and in the assessment of perfusion reductions in acute ischemic stroke [95]. The changes of hemodynamics and cerebral oxygenation acquired by rSO$_2$ in ventilated newborns with hypoxic–ischemic encephalopathy were reconstructed to a three-dimensional image using optical tomography to map brain structure and physiology [89].

Infrared spectroscopy is attractive because it is noninvasive and applied simply by attaching pads to the forehead or other regions of interest.
However, concerns have been raised about the limited and variable penetration of infrared light through the skull (2–3 mm, limited to gray matter), contamination by extra- and intracranial sources (mixture of capillary, venous, and arterial blood), and uniform distribution of infrared light in the CSF layer. The degree of scatter of infrared light in adults is unpredictable, especially in the presence of scalp swelling and hematomas [88,96,97]. In a small series comparing rSO₂ of dead and healthy subjects using the INVOS device, 6 out of 18 dead showed rSO₂ values above the lowest obtained values for healthy subjects, raising further doubts about the validity of these measurements [98]. These disadvantages and inconsistent impact of monitoring of decreased oxygenation on neurologic outcome [99–101] have restricted the use of near infrared spectroscopy for adults in the NICU.

Cerebral metabolism

Brain metabolism can be assessed by PET and magnetic resonance spectroscopy, jugular venous oxygen saturation, CBF monitoring, and microdialysis. PET scanning gives a topographic overview of glucose metabolism, and magnetic resonance spectroscopy demonstrates lactate content of a particular cerebral structure qualitatively. The cerebral metabolic rate of oxygen (CMRO₂) represents the product of CBF and AVDO₂ and can be obtained by simultaneous recording of hemispheric CBF (calculated as the average of 16 hemispheric brain regions using the intracarotid ¹³³xenon washout method) and AVDO₂ (obtained by jugular venous oxygen saturation monitoring) [102]. The relationship between CMRO₂ and CBF allows for an estimate of the balance between cerebral metabolism and blood flow, but does not offer the opportunity for simple continuous real-time assessment of cerebral metabolism [56].

With the introduction of cerebral microdialysis, it became possible to monitor neurotransmitters (glutamate), substrates (glucose), metabolites (lactate, pyruvate), and other extracellular neurochemicals (glycerol, acetylcholine, choline) in the extracellular space of specific brain regions in hourly intervals at the bedside (Fig. 7). With microdialysis, a 0.62-mm-wide catheter lined with a polyamide dialysis membrane at the tip is placed into the brain and perfused with Ringer solution or normal saline at ultra-low flow rates (0.1–2.0 μL/min) with a precision pump. Molecules below the cutoff size of the semipermeable membrane (usually 10,000–20,000 daltons) diffuse from the extracellular space into the perfusion fluid, which is collected into vials [103–105]. The diffusion of glucose, lactate, pyruvate, glutamate, acetylcholine, choline, and glycerol from the surrounding brain tissue into the perfusion fluid is approximately 70% at a flow rate of 0.3 μL/min [106]. The vials are changed every 10 to 60 minutes and analyzed by enzyme spectrophotometry or high-performance liquid chromatography at the bedside [103–105]. Recovery of cerebral metabolites into dialysate is maximized.
by increasing the length of the membrane, decreasing the flow rate, and increasing the size of the membrane pores. Semipermeable membranes with a higher limit in size (100,000–300,000 daltons) also allow for the passage of polypeptides and proteins from the extracellular space, such as cytokines, antibiotics, and free phenytoin. Recovery rates for smaller relevant biochemical markers through a membrane with a larger cutoff may be similar to those obtained with the standard microdialysis catheter (cutoff 20,000 daltons) [106–109]. However, microdialysis of larger proteins require slower buffer flow rates, large pore probes, and attention to water loss from the probe [110]. The microdialysis catheter can be placed into the cerebral parenchyma tunneled underneath the scalp through a craniotomy site, through a burrhole, or directly through a bolt fixed to the cranium [103–105]. They are MRI-compatible.

All substances pass the interstitial space between cells and blood capillaries. Monitoring the interstitial fluids provides important information about the biochemistry of neurons and glia potentially subjected to ischemia, hyperemia, trauma, vasospasm, seizures, hemorrhage, and neuurosurgical and medical interventions [104,105]. The catheter should be inserted into areas at risk of ischemia such as the vascular territory most likely affected by vasospasm or brain regions surrounding a mass lesion, or in a standardized location such as the right frontal lobe in diffuse brain injury [105]. A decrease in glucose is thought to signify reduced capillary perfusion, decreased systemic supply, or increased cellular uptake of glucose. In the context of multimodality monitoring, simultaneous measurements of cerebral oxygen tension and cerebral blood flow is thought to clarify whether a decrease in
glucose is due to ischemia (eg, when accompanied by a reduction in CBF and PBO$_2$), or caused by hypermetabolism (normal or increased CBF and PBO$_2$) [2]. Alternatively, an increase in dialysate glucose may be due to hyperemia (increased supply), increased systemic glucose levels, or decreased cellular metabolism. Under aerobic conditions, glucose gets metabolized to pyruvate-producing adenosine triphosphate (see Fig. 7).

During hypoxia and ischemia, the end product of pyruvate is lactate and results in an increase of the lactate/pyruvate ratio [111,112]. The diagnosis of an ongoing ischemic event may be further supported by a simultaneous decrease in CBF and PBO$_2$. Ischemia also results in a release of glutamate. Glycerol is an end product of lipolysis during destruction of cell membranes caused by energy failure. Choline is also released from damaged cell membranes. These changes in the penumbral extracellular milieu often precede the manifestation of definite neurologic deficits. Other substances that can be measured include adenosine, urea, amino acids, nitrate, and nitrite concentrations [59].

Microdialysis monitoring has been shown to be useful in patients with severe TBI with regional or global ischemia [2,105,111–117], SAH and acute or delayed ischemia [71,105,118–120], large hemispheric ischemic stroke [6,121–123], ICH [124], and intraoperatively when episodes of regional ischemia may occur [125–128]. In patients with SAH, metabolic derangements seen by microdialysis are a better predictor of symptomatic vasospasm than TCD ultrasonography and cerebral angiography [118]. Increased lactate/glucose ratios [111,112] as well as reduced glucose along with elevated lactate and hypoxia [2] were found to be predictive of poor outcome after TBI. After ICH, glutamate levels are elevated in the perihematomal zone and decrease with stereotactic aspiration and thrombolysis [124]. Measuring the concentration of antibiotics, anticonvulsants, and other therapeutic agents is another growing field of application for microdialysis [109,129–131].

Microdialysis offers monitoring of brain cell metabolism and is helpful in detecting secondary insults and predicting outcome in patients with severe TBI. Currently, the use of microdialysis is limited more to the observation of trends than the targeting of threshold values for metabolites and neurotransmitters within a small region of interest. However, several catheters can be placed in different locations and monitor cerebral metabolism simultaneously. The microdialysis catheter can be inserted together with the brain oxygen probe, an ICP monitor, or a CBF monitor within a three-lumen cranial bolt (see Fig. 4). If used in combination with PBO$_2$ monitoring, “stunned” brain tissue can be distinguished from brain regions undergoing active ischemic injury.

**Neuroimaging**

Modern imaging techniques provide the opportunity of high-quality diagnosis of disease states and insight into pathophysiology and
hemodynamics of vascular disease. CT and MRI are used frequently for diagnosis of disease states in NICU patients.

\(^{18}\text{F}\)2-deoxy-d-glucose and oxygen-15 PET is used to obtain a quantitative assessment of brain metabolism and CBF [29,132], but it is not widely available. CBF can be evaluated qualitatively by way of SPECT as well and is more readily available [29].

Xenon-enhanced CT scanning [28], perfusion CT, and perfusion-weighted imaging (PWI) [29] add diagnostic capability to a qualitative image of the cerebral perfusion status which can be assessed by comparison of mean transit time (MTT), CBF, and cerebral blood volume (CBV) between different brain regions. PWI allows for calculation of perfusion maps and the delay of MTT comparing selected locations. Furthermore, MRI detects ischemia early by an increase in signal on diffusion-weighted imaging (DWI) and reduction of the apparent diffusion coefficient within 30 minutes of onset of symptoms. Simultaneous PWI and DWI enable identification of viable areas that lack adequate perfusion and are at risk for infarction. The PWI/DWI mismatch concept has been used in patients with acute stroke symptoms to determine risk and benefit of thrombolysis; however, absolute CBF and CBV values may be more accurate for evaluation of the true perfusion deficit [133].

PET, SPECT, perfusion CT, and MRI are noninvasive methods that assess the cerebral perfusion status and metabolism globally. Most of the time, the imaging facilities are located outside the NICU; consequently, skilled personnel are required to minimize the risk involved with transporting critically ill patient and ventilated patients on continuous drips. Imaging gives a comprehensive evaluation of cerebral perfusion at only one point in time, whereas cerebral autoregulation is a dynamic process. Therefore, supplementation of global one-time assessment of CBF with regional continuous CBF, pBO\(_2\), and microdialysis monitoring at the bedside may be helpful.

**Continuous EEG**

Digital video continuous electroencephalographic monitoring (cEEG) provides prolonged monitoring of brain activity in critically ill patients with altered mental status and at risk for secondary ischemia after acute brain injury. Indications for cEEG include:

1. detection of nonconvulsive seizures or status epilepticus in patients with unexplained fluctuating mental status and after convulsive status epilepticus;
2. characterization of spells such as sudden posturing, rigidity, tremors, chewing, twitching, nystagmus, eye deviation, and agitation, and unexplained changes in heart rate and blood pressure;
(3) assessment of level of consciousness during sedation and paralysis including identification of clinically silent events, management of burst-suppression in anesthetic coma;

(4) detection of ischemia after SAH, during neurosurgical and neuroendovascular procedures, in patients with hemodynamic lesions or at risk for acute ischemia; and

(5) prognostication [134,135].

In a study of 570 hospitalized patients who underwent cEEG monitoring, seizures were seen in 19%, 95% of which were nonconvulsive [136]. Up to 34% of patients in a smaller NICU patient population experienced nonconvulsive seizures, and 76% of these were in nonconvulsive status epilepticus [137]. Nonconvulsive seizures or status epilepticus are associated with increased morbidity and mortality regardless of etiology [138,139], especially after SAH [140–142]. Seizure duration and time to diagnosis are predictors of outcome in patients with nonconvulsive status. Mortality is 36% after 30 minutes in nonconvulsive status, and 75% after more than 24 hours [143]. Seizures occurring after cerebral hemorrhage or brain injury may increase brain edema, midline shift, and intracranial hypertension [144].

Continuous EEG was first applied to monitor for reversible ischemia intraoperatively, during carotid endarterectomy [145,146]. Because certain cEEG patterns such as broad, repetitive slow waves ("axial bursts") are highly correlated with the clinical and angiographic occurrence of vasospasm [147], quantitative analysis was developed to detect delayed cerebral ischemia in SAH by cEEG in awake and comatose SAH patients [148–150] and to predict outcome after traumatic brain injury [151]. Quantitative cEEG allows for evaluation of a large amount of data over long periods of time (raw EEG waveforms) in the form of a summary as compressed spectral array, density spectral array, compressed EEG pattern analysis, bandwidth power trends with ratios of power, geographic power/bandwidth display, burst suppression monitor, and level of sedation monitor in real time. Spectra or power ratios that are easily interpretable with scoring systems or alarms make quantitative cEEG a very useful monitoring tool in the neurologic intensive care unit [134,135,152,153]. Trend analysis of total power (1–30 Hz) [149], variability of relative alpha (6–14 Hz/1–20 Hz) even up to 2 days before clinical changes [150,151], and poststimulation alpha/delta ratio (8–13 Hz/1–4 Hz) [148] were found to correlate with clinical cerebral ischemia or angiographically confirmed vasospasm after SAH and with poor prognosis after SAH and TBI.

Another future application of cEEG may include electrocorticography with observation and measurement of cortical spreading depression, seen in about 50% of patients following an acute brain injury. Transient or prolonged repeated depolarizations of brain tissue surrounding a cortical lesion and slow potential changes (0.005–0.05 Hz) may contribute to expansion of the initial focal injury [154].
Technical requirements such as digital analysis and data reduction; con-
stant fixation of electrodes for agitated, physically moved, and transported
NICU patients; altered cranial anatomy (catheters, monitoring devices,
skull defects, scalp edema); electrical artifacts due to a noisy NICU environ-
ment; availability of 24-hour coverage of experienced electroencephalogra-
phers; availability of networking with real-time and event respond access;
automated alerting systems; and accessibility of remote online analysis
resources currently limit the use of continuous EEG for immediate clinical
decision-making and therapy [135,136,148]. Furthermore, EEG electrodes
interfere with the quality of imaging studies, which are frequently obtained
in NICU patients, and with procedures such as insertion of extraventricular
drains and ICP monitors. Most of the EEG electrodes are not compatible
with MRI.

Power spectrographic displays that compress several hours of recordings
into a single image that reveals certain patterns such as recurrent seizures or
changes of ratios, quantitative analysis, analysis programs at the bedside,
and networking with Web-based links can facilitate the review of large quan-
tities of EEG data by the electroencephalographer and enable a closer–to–
real-time assessment of brain dysfunction [155,156]. Video-assisted EEG
could also allow expert review of documentation of a neurologic assessment.

Somatosensory-evoked potentials (SSEPs), brain stem auditory-evoked
response, and long latency cortical auditory-evoked responses are valuable
tools for prognostication in comatose NICU patients. The bilateral absence
of the N20 cortical component of SSEPs obtained in patients with hypoxic–
ischemic encephalopathy after cardiopulmonary resuscitation is associated
with poor neurologic recovery [157]. Normal SSEP conduction times for
the components N13 and N20 bilaterally obtained within 48 hours of admis-
sion to the hospital signify a good neurologic outcome after severe brain
trauma at 12 months in 60% of patients. If any cortical potential is delayed,
the chances for a satisfactory recovery of neurologic function are less than
30%. With absent SSEPs, the most likely outcome is death or disability
[158]. Combined continuous EEG and SSEP monitoring has recently be-
come available [159]. Long latency cortical auditory-evoked responses are
more sensitive for detection of severity and extent of cerebral dysfunction
in traumatic brain injury compared with brain stem auditory-evoked re-
sponses [160].

Multimodality monitoring

The true richness of multimodal neuromonitoring lies not in the addition
of new metrics but in the analysis of relationships among these metrics. Dur-
ing rounds in the NICU with multimodality monitoring, a physician may be
confronted with more than 200 variables [161]. Unassisted human beings,
however, are not able to judge the degree of relatedness between more
than two variables [162]. Computer-assisted graphical analysis can play
a role in the intensive care unit to reap the benefits of intensive neuromonitoring [163–170]. Understanding these relationships may allow earlier identification and treatment of critical patient conditions, ideally before permanent secondary injury can occur.

Several groups have examined the relationships among physiologic metrics to monitor dynamic cerebral autoregulation and pinpoint patient-specific physiologic targets using varying statistical techniques [163–167,171,172]. This research is grounded by the fact that cerebrovascular pressure reactivity can be determined by observing the response of ICP to changes in MAP [168]. With intact pressure reactivity, spontaneous increases in MAP lead to vasoconstriction and a reduction in cerebral blood volume within 5 to 15 seconds, subsequently decreasing ICP. However, if pressure reactivity is disturbed, the absence of vasoconstriction in response to elevations in MAP results in passive increases in cerebral blood volume and ICP. If MAP decreases, the opposite occurs (see Fig. 3) [169]. Additionally, intracranial pressure, cerebral perfusion pressure, and regional cerebral blood flow have been found to be dynamically correlated to decreased brain tissue oxygen [18–20].

Dynamic analysis of these metrics may yield new tools to maintain adequate cerebral oxygenation. Steiner and colleagues [168] analyzed the relation of MAP and ICP to identify a CPP target and demonstrated that patients with a mean CPP closer to their “optimum” CPP target had a better outcome. However, this method failed to identify a target CPP for 40% of patients. An assumption of autoregulatory failure is that the cerebral vasculature is unresponsive to changes in blood pressure, effectively eliminating the negative correlation normally observed between MAP and ICP that is used to indicate a CPP target. This likely accounts for why a target could not be identified in most cases. Soehle and colleagues [165] evaluated the relationship between CPP and PBO₂ to quantify autoregulation dysfunction. An increased correlation among the two parameters is related to worsening autoregulation dysfunction. Furthermore, SAH patients with elevated CPP and PBO₂ correlations were at significantly greater risk for infarction from vasospasm than those with intact autoregulation [170]. We reported preliminary results on the feasibility to generate a CPP target by monitoring the correlation of MAP to PBO₂ simultaneously with the correlation of ICP to PBO₂ and identifying the observed CPP when these relationships change (see Fig. 6) [173]. Though in need of further study, the primary advantage of using brain oxygenation data to identify a patient-specific CPP target is that such a target should be identifiable regardless of autoregulation status.

Complex multidimensional data analysis has been studied to identify complication specific data patterns to good effect. Gather and colleagues [174] applied graphical modeling techniques to physiologic data collected in an ICU revealing distinct partial correlation patterns among physiologic parameters such as heart rate, arterial pressure, SpO₂, and central venous pressure for distinct clinical states, including congestive heart failure,
pulmonary hypertension, and use of vasopressors. In the future, multidimensional data analysis might also be used to generate compound patient-specific physiologic targets—for example, generating targets MAP and end tidal CO$_2$ that will produce the lowest ICP without adversely impacting PBO$_2$. Dynamic analysis of neuromonitoring data has a bright future and will continue to have an increasing role in physician decision support at the bedside.

Summary

Traditional monitoring in the NICU relegates physicians and nurses to treating patients reactively, only after the patients have declined neurologically and a physiologic process has become abnormal. Real-time monitoring of brain oxygen tension, brain temperature, ICP, CPP, CBF, and cerebral metabolism—in addition to TCD ultrasonography, cEEG, and cardiovascular parameters—gives the neurointensivist immediate insight in the physiologic and metabolic state of brain regions at risk for ischemia and injury and enhances the potential of early effective interventions to reverse pathologic states on an individual basis. Specifically, the combination of ICP/CPP monitoring, complemented by brain oxygen tension and lactate/pyruvate ratio monitoring, may distinguish areas of the brain at risk that might respond to manipulations of MAP or CPP.

Initial research using this information at the bedside has enabled proactive treatment of patients in the form of patient-specific physiologic targets. Ideally, multimodal analysis of physiologic data will enable neurointensivists to optimize a patient’s physiology, minimizing the impact of neurologic derangement, and ultimately transforming the NICU treatment model. To get there, more research and actual application of these techniques is needed to confirm reference values for brain health and to standardize clinical management (see Table 1). Optimization of CPP and ICP, hyperventilation, hyperosmolar therapy, hypothermia, weaning from liberation from ventilation, diagnosis and treatment of vasospasm, and temporary occlusion of arteries during radiologic or surgical interventions can be guided by these novel technologies. Clinical informatics tools and decision support research will be needed to reduce the quantity and increase the quality of information neurointensivists must sift through when managing their patients. Multimodal monitoring should become the standard of every NICU and offers tremendous potential.

References


