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GUIDELINES FOR CLINICAL PRACTICE

Contemporary view on neuromonitoring following severe traumatic brain injury

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Abstract

Evolving brain damage following traumatic brain injury (TBI) is strongly influenced by complex pathophysiologic cascades including local as well as systemic influences. To successfully prevent secondary progression of the primary damage we must actively search and identify secondary insults e.g. hypoxia, hypotension, uncontrolled hyperventilation, anemia, and hypoglycemia, which are known to aggravate existing brain damage. For this, we must rely on specific cerebral monitoring. Only then can we unmask changes which otherwise would remain hidden, and prevent adequate intensive care treatment. Apart from intracranial pressure (ICP) and calculated cerebral perfusion pressure (CPP), extended neuromonitoring ($SjvO_2$, $ptiO_2$, microdialysis, transcranial Doppler sonography, electrocorticography) also allows us to define individual pathologic ICP and CPP levels. This, in turn, will support our therapeutic decision-making and also allow a more individualized and flexible treatment concept for each patient. For this, however, we need to learn to integrate several dimensions with their own possible treatment options into a complete picture. The present review summarizes the current understanding of extended neuromonitoring to guide therapeutic interventions with the aim of improving intensive care treatment following severe TBI, which is the basis for ameliorated outcome.

INTRODUCTION

Severe traumatic brain injury (TBI) is associated with a high risk of mortality and persistent deficits, which may preclude successful reintegration, thereby having dramatic consequences not only for the individual patient but also for society due to the tremendous socio-economic burden involved.

To prevent additional damage to the already injured and highly vulnerable brain, especially during the early posttraumatic phase, specific knowledge is essential. An in-depth understanding of interwoven pathophysiologic cascades must be complemented by specific neuromonitoring. Only then can we unmask the presence and extent of typical secondary insults caused by e.g. hypoxia, hypotension, uncontrolled hyperventilation, hypoglycemia as well as hypoventilation, hypertension, and hyperglycemia. Since secondary insults strongly determine quality of survival, it is of utmost importance to prevent these secondary insults. There is increasing evidence which clearly shows that we cannot rely on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) alone to assess additional tissue damage. Therefore, extended neuromonitoring has become indispensable in modern intensive care to unmask otherwise occult signs of cerebral impairment, and during phases of normal ICP. Apart from

diagnosing signs of secondary deterioration, extended neuromonitoring may be helpful in adapting the quality and extent of our therapeutic interventions. In addition to basic neuromonitoring consisting of ICP and CPP, extended bedside neuromonitoring refers to transcranial Doppler/Duplex sonography (TCD), jugular venous oxygen saturation ($SjvO_2$), partial tissue oxygen pressure ($ptiO_2$), and cerebral microdialysis to unmask changes in brain metabolism (glucose, lactate, pyruvate, glutamate, glycerol), and electrocorticography to determine cortical spreading depression (CSD) (Figure 1).

Overall, it is important to refrain from only interpreting one parameter as the different parameters are interwoven and functionally interdependent. Thus, it is important to consider several dimensions simultaneously, integrating e.g. $ptiO_2$, cerebral glucose, CPP, $paCO_2$, and hematocrit. Correct interpretation of these results within the context of the individual situation requires lots of experience in overall clinical management and neuromonitoring. Progressive insight into previously hidden changes which can only be unmasked with extended neuromonitoring is the basis for improved treatment, hopefully resulting in improved outcome following severe TBI.

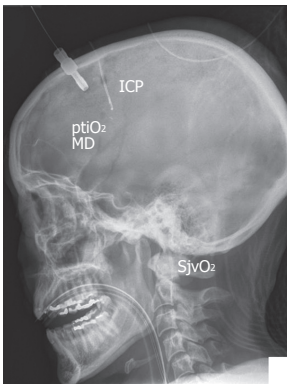

Figure 1 Illustrative lateral X-ray view showing positioning of invasive neuromonitoring to assess intracranial pressure, brain tissue oxygen pressure, brain metabolism using microdialysis, and jugular venous oxygen saturation. ICP: Intracranial pressure; $ptiO_2$: Tissue oxygen pressure; $SjvO_2$: Jugular venous oxygen saturation.

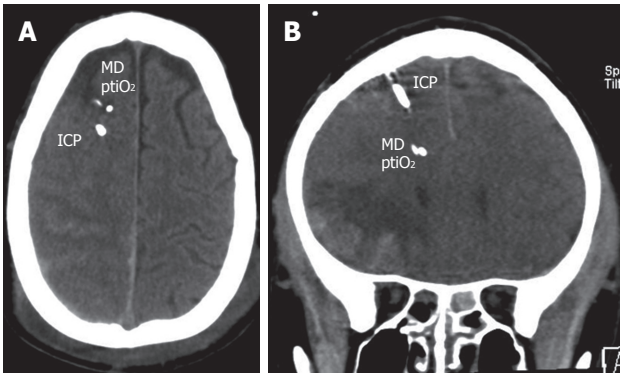

Figure 2 Illustrative examples showing positioning of intracranial pressure, microdialysis catheter, and brain tissue oxygen pressure sensor in the more severely injured hemisphere (A) and within close proximity of a contusion (B). ICP: Intracranial pressure; $ptiO_2$: Tissue oxygen pressure.

BASIC NEUROMONITORING

ICP and CPP

Increased intracranial volume reflected by elevated ICP is the primary parameter used to judge cerebral deterioration during pharmacologic coma. A persistent increase in ICP can induce and maintain a vicious circle[1]. It is important to acknowledge that a normal ICP does not guarantee absence of pathologic processes, especially in conditions in which the ICP cannot be assessed adequately e.g. following craniectomy, CSF leakage, subdural air entrapment, or even sensor malfunctioning. New data clearly show that metabolic and functional alterations unmasked by extended neuromonitoring precede increases in ICP[2].

A very simple measure to indirectly estimate global cerebral perfusion is to calculate CPP = mean arterial blood pressure (MABP) - ICP. A "normal" CPP, however, does not guarantee sufficient cerebral perfusion and oxygenation. To define an optimal CPP leading to optimal cerebral perfusion, other parameters e.g. $ptiO_2$, $SjvO_2$, brain metabolism (e.g. glucose, lactate, lactate to pyruvate ratio) and flow velocity must be integrated. Using extraventricular drainage combined with pressure recording allows us to combine diagnostic and therapeutic options by measuring ICP and draining cerebrospinal fluid to reduce elevated ICP, respectively. Extraventricular drainage, however, is associated with an albeit small risk of additional injury to periventricular structures, hemorrhages, and local infections[3].

Jugular venous oxygen saturation and arterio-jugular venous differences

To assess global cerebral perfusion, oxygen consumption, and metabolic state analysis of $SjvO_2$, various metabolic indices (e.g. oxygen-glucose index, lactate-oxygen index, lactate-glucose index), oxygen extraction ratio, and arterio-jugular venous lactate difference have proven helpful at the bedside[4,5]. $SjvO_2$ correlates directly with perfusion and correlates inversely with cerebral oxygen consumption. Thus, $SjvO_2$ can be used to guide therapeutic interventions, including modulation of MABP and CPP, controlling hyperventilation, guiding oxygen administration, and influencing the extent of pharmacologic coma and hypothermia.

Tissue oxygenation- $ptiO_2$

Measuring $ptiO_2$ not only reflects local changes, but also unmasks cerebral consequences of systemic influences e.g. blood pressure, oxygenation, and anemia. This, in turn, allows us to guide the type and extent of therapeutic interventions[6,7]. Similar to changes in $SjvO_2$, $ptiO_2$ values indirectly reflect cerebral perfusion and oxygenation[8], while low $SjvO_2$ and $ptiO_2$ values unmask reduced cerebral perfusion with cerebral ischemia at $SjvO_2 < 50\%$ and $ptiO_2 < 10$ mmHg. High $SjvO_2$ (> 80%) and $ptiO_2$ values (> 30 mmHg) unmask impaired oxygen consumption en-

countered under conditions of hyperemia/ luxury perfusion.

It is important to correct ptiO2 values < 10 mmHg (Licox®) within 30 min to prevent hypoxia-induced increase in glutamate[9,10], neuropsychologic deficits[11], and poorer outcome with increased mortality[12].

Cerebral microdialysis

Changes in cerebral metabolism assessed by measuring glucose, lactate, pyruvate, glycerol, glutamate, and by calculating the lactate to pyruvate ratio, a marker of hypoxic/ischemic metabolic impairment[13,14], both follow as well as precede increases in ICP[2,10]. Pathologic alterations reflected by low glucose and elevated lactate to pyruvate ratio were recently identified to significantly predict mortality following severe TBI[15]. In addition, increased lactate to pyruvate ratio was associated with subsequent chronic frontal lobe atrophy[16], possibly giving rise to subsequent dementia. Overall, metabolic monitoring can also be used to guide therapeutic interventions to correct e.g. hypotension, hyperemia, vasospasm, hyperventilation, fever, epileptic discharges, hypoglycemia, and anemia. The integration of cerebral microdialysis was an integral part of the "Lund concept" allowing a reduction in CPP levels as low as 50 mmHg[17], thereby substantially influencing treatment options. For best results in potentially optimizing our current therapy, metabolic monitoring using cerebral microdialysis must be combined with other parameters e.g. ptiO2, SjvO2, and CPP.

TCD

TCD can unmask conditions of low flow[18], vasospasm, and hyperemia. Each of these conditions, in turn, will require differential therapeutic interventions: vasospasm requires controlled hypertension and normo- to hypoventilation; hyperemia requires controlled hypotension and hyperventilation; low flow requires increased cardiac output especially in conjunction with bradycardia. The cerebral blood flow velocity determined within the large basal cerebral arteries can be used to reflect regional cerebral perfusion, cerebral autoregulation, and CO2-reactivity[19]. In addition, calculating e.g. the pulsatility index and resistance index allow the non-invasive estimation of ICP and CPP[20,21]. This proves helpful when an ICP probe cannot be inserted due to coagulation disorder or if an ICP probe is damaged. This allows us to bridge the time until a new ICP probe can be inserted. However, an ICP probe needs to be replaced as soon as possible since only continuous ICP readings can be used to reliably adapt therapeutic interventions.

CSD

CSD involving neuronal and glial energy-consuming depolarizations[22] as well as a spreading wave of ischemia and vasoconstriction with subsequent vasodilation[23], contributes to the secondary growth of a pre-existing lesion[24,25] and is associated with decreased cerebral glucose, increased lactate to pyruvate ratio, and elevated lactate[26,27]. CSD can be induced by elevated extracellular potassium, decreased cerebral NO levels and reduced blood and brain glucose concentrations[28,29]. CSD requires the introduction of a special sensor which is positioned under the dura directly on the cortical surface. At present, it is unclear which patients with which lesions will profit from the application of these sensors.

LIMITATIONS

Any neuromonitoring technique is limited by certain restraints making compromises indispensable. Similar to ICP, regional metabolic heterogeneity exists even within the same hemisphere depending on the extension of the lesion and the positioning of the probes relative to the lesion[30,31]. Despite the introduction of multiple probes within the supratentorial compartment the infratentorial areas are not assessed. To prevent additional damage, deep structures such as the basal ganglia are not penetrated under clinical conditions. Furthermore, we must also face local changes at different depths along the probes. To avoid inadequate decision-making the catheters and probes should not be positioned within the core of a contusion as this necrotic tissue will always reveal pathologic values. The consensus recommendation is to place the catheters and probes within the pericontusional tissue to successfully unmask progressive lesion growth, metabolic worsening, and impaired perfusion which may be reversible and amenable to treatment options (Figure 2). In the case of diffuse brain injury, the probes should be positioned within the more severely injured hemisphere. Nonetheless, signs of impaired cerebral metabolism are found even in regions without obvious signs of structural damage. This functional impairment can result from increased ICP due to local changes and can be induced by systemic influences due to e.g. hypotension, hyperemia, vasospasm, hyperventilation, fever, epileptic discharges, hypoglycemia, and anemia.

It is important to acknowledge that local and global monitoring does not exclude each other but successfully extends our insight into otherwise occult changes. In this context, ptiO2 and SjvO2 closely reflect each other[6] and arterio-jugular venous glucose differences have been shown to correspond to local changes in cerebral glucose determined by cerebral microdialysis[32]. Despite these limitations, local as well as global parameters should be monitored in patients with severe TBI who are subjected to pharmacologic coma. Categorically omitting neuromonitoring is a mistake as we deprive ourselves of important information, which is decisive in adapting and modulating our therapeutic interventions. At present, it is difficult to define to what extent basic or extended neuromonitoring significantly determines quality of outcome. In theory, we may expect that the substantial increase in our knowledge using neuromonitoring will translate to improved treatment. By strictly integrating SjvO2, ptiO2, microdialysis, and TCD we are able to individualize the extent, aggressiveness, and duration of therapeutic inter-

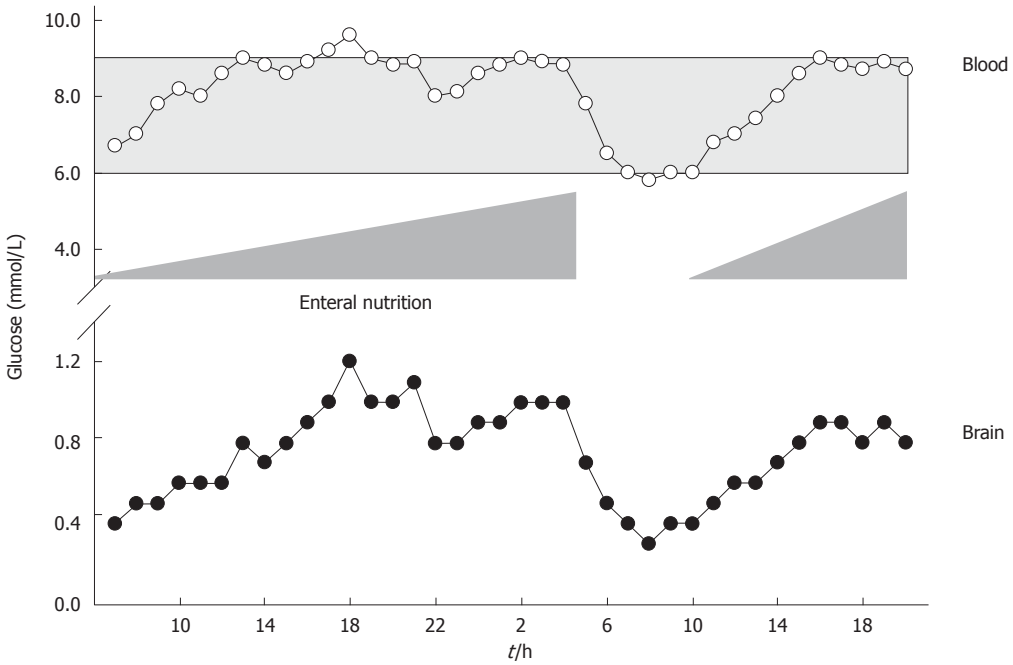

Figure 3 Illustrative case showing the influence of enteral nutrition on arterial blood and brain glucose levels. Based on low brain glucose, enteral nutrition was gradually increased resulting in elevated blood and brain glucose. Due to surgery, enteral nutrition was stopped. This resulted in a decrease in blood and brain glucose. Restarting of enteral nutrition increased blood and brain glucose again.

ventions, thereby reducing the frequency of barbiturate coma, secondary craniectomies, pulmonary dysfunction, and significantly reducing the rate of red blood cell transfusions and associated costs in patients subjected to prolonged pharmacologic coma.

WHAT IS THE IMPACT OF EXTENDED NEUROMONITORING IN ROUTINE INTENSIVE CARE?

While basic neuromonitoring includes neurologic examination, computerized tomography, and ICP, extended neuromonitoring comprises $SjvO_2$, $ptiO_2$, microdialysis, TCD, and electrophysiologic recordings including CSD.

Extended neuromonitoring in daily clinical practice helps to improve our treatment options by characterizing functional influences, defining threshold values, and adapting therapeutic interventions in type, extent and duration. In addition, extended neuromonitoring helps us to prevent induction of additional brain damage due to excessive therapeutic corrections. In this context, aggressive volume administration aimed at improving cerebral perfusion was associated with a sustained risk of acute respiratory distress syndrome[33] and abdominal compartment syndrome[34]. Furthermore, excessive ventilatory support to increase paO_2 can induce additional pulmonary damage[35], aggressive lowering of arterial blood glucose to prevent hyperglycemia-induced cell damage increases the frequency and extent of hypoglycemic episodes[36], and a categorical transfusion regimen to improve cerebral oxygenation may be associated with transfusion-related complications[37].

When only relying on changes in ICP and CPP, we may not only miss important signs of deterioration, but also fail to adequately reduce therapeutic interventions. Based on current evidence, extended neuromonitoring is important to determine optimal CPP, guide oxygenation and ventilation, influence transfusion practice, define optimal blood and brain glucose, and even guide decompressive craniectomy.

GUIDANCE FOR CPP

Calculating CPP does not guarantee adequate cerebral perfusion. Assessing $ptiO_2$ is indispensable in determining optimal cerebral perfusion as CPP significantly influences $ptiO_2$[38]. $ptiO_2$ can be used to determine the lower still acceptable CPP value[39]. Several studies have convincingly shown that the generally recommended CPP threshold of 60 mmHg is insufficient and that even "normal" CPP values cannot protect from cerebral hypoxia and impaired metabolism[14]. Furthermore, regional heterogeneity is characterized by different requirements reflected by different levels of CPP-dependent $ptiO_2$ values. In this context, normal CPP of approximately 70 mmHg is insufficient for the perifocal tissue compared to normal appearing tissue in which $ptiO_2$ was significantly higher[40]. Advancing from observational to interventional studies, integrating $ptiO_2$ in clinical routine by using a $ptiO_2$-supplemented ICP- and CPP-based treatment protocol significantly kept ICP < 20 mmHg, improved outcome judged by the Glasgow Outcome Scale, and reduced mortality rate compared to the standard ICP/CPP-directed therapy[41,42].

With the help of monitoring brain metabolism using cerebral microdialysis, CPP can be reduced to low values e.g. 50 mmHg without causing additional brain damage[17]. In this context, lactate and the calculated lactate to pyruvate ratio unmask insufficient cerebral perfusion and oxygen delivery leading to energetic and metabolic impairment[17,43]. As shown using the "Lund concept" to treat patients with severe TBI, microdialysis must be included to allow a reduction in CPP providing the therapeutic concept is practiced as published[17]. Improving cerebral perfusion and correcting anemia has been shown to successfully normalize brain lactate to pyruvate ratio, glycerol, and glutamate levels[43]. Whether this is valid for all lesion types is unclear.

GUIDANCE FOR VENTILATORY SUPPORT: OXYGENATION AND VENTILATION

Integrating $ptiO_2$ and $SjvO_2$ in clinical routine can be used to individually define paO_2 and $paCO_2$ targets. These individual targets, in turn, can be used to adjust ventilatory settings, thereby preventing ventilation-induced lung injury and hemodynamic instability.

Oxygenation

Elevating the fraction of inspired oxygen (FiO_2) significantly increased $ptiO_2$[38,44] and reduced cerebral lactate[38]. However, increasing $ptiO_2$ too aggressively by normobaric hyperoxia (FiO_2 1.0) was associated with decreased cerebral blood flow despite improved brain metabolism. This impaired perfusion coincided with poorer outcome 3 mo after TBI. As shown under experimental conditions, increasing oxygen supply alone is insufficient to improve cerebral oxygenation if impaired cerebral perfusion is not corrected adequately[45].

Hyperventilation

Although hyperventilation is an easy and helpful therapeutic intervention to decrease elevated ICP[46], hyperventilation can induce additional secondary ischemic brain damage[47] due to hypocapnia-induced vasoconstriction. This impaired perfusion, in turn, results in metabolic and neurochemical alterations reflected by reduced $ptiO_2$ and $SjvO_2$, and elevated extracellular glutamate and lactate[48]. Interestingly, even small changes in $paCO_2$ within normal limits are detrimental[49]. Consequently, extended neuromonitoring should also be performed in patients during anticipated normoventilation. It is essential to control hyperventilation by using appropriate neuromonitoring techniques to unmask signs of cerebral ischemia due to hyperventilation-induced vasoconstriction, because normal ICP levels achieved by hyperventilation will cause us to miss relevant pathologic processes within the brain. Reduced $SjvO_2$, decreased $ptiO_2$, and signs of metabolic impairment (lactate, glutamate, lactate to pyruvate ratio)[50,51] aid in assessing the lowest possible individual $paCO_2$ level[52-56]. This helps us to avoid active induction of secondary brain damage.

GUIDANCE FOR RED BLOOD CELL TRANSFUSIONS

Cerebral oxygenation is influenced by the number of circulating oxygen carriers, i.e. red blood cells (hematocrit). At present, the optimal hematocrit following severe TBI is controversial. A fast reduction in hematocrit known to significantly reduce cerebral oxygen supply[57] must be avoided. Under controlled critical care conditions with stable CPP and stable oxygenation and ventilation, $ptiO_2$ can be used to define the transfusion threshold[58,59]. Patients with a $ptiO_2$ > 15 mmHg do not profit from red blood cell transfusion[59]. A transfusion of red blood cells in patients with a hematocrit < 30% and a concomitant $ptiO_2$ value below 15 mmHg was able to persistently increase $ptiO_2$ > 15 mmHg[59]. At the same time, CPP must be maintained above 60 mmHg to prevent cerebral hypoxia determined by $ptiO_2$[59]. These data show that $ptiO_2$ can be used to reliably assess the individual transfusion threshold.

GUIDANCE FOR OPTIMAL BLOOD AND BRAIN GLUCOSE

Mitochondrial damage, aggravated oxidative stress, impaired neutrophil function, reduced phagocytosis, and diminished intracellular destruction of ingested bacteria are deleterious consequences of hyperglycemia. Elevated blood glucose > 9.4 mmol/L (> 169 mg/dL) is associated with sustained mortality and morbidity[60,61]. These deleterious consequences can be prevented by normalizing elevated blood glucose levels. Maintaining blood glucose levels within tight limits between 4.4 mmol/L and 6.1 mmol/L (80 to 110 mg/dL)[62], however, is hampered by the risk of hypoglycemia and a strong variation in blood glucose levels[63], which was associated with sustained mortality[62,64,65]. Reducing blood glucose to 4.4-6.1 mmol/L significantly increased extracellular glutamate levels and elevated lactate to pyruvate ratio, reflecting excessive neuronal excitation and metabolic perturbation[66]. Decreased blood glucose and low cerebral extracellular glucose levels were even associated with sustained mortality[67] and induction of CSD at low blood glucose levels < 5 mmol/L[28,68,69]. To define individual blood and brain glucose, void of any deleterious metabolic consequences, extended neuromonitoring is indispensable. In this context, reduced cerebral oxygen consumption, reduced lactate and CO_2 production, increased glucose uptake, elevated cerebral glucose and decreased lactate to pyruvate ratio were observed at arterial blood glucose levels between 6 mmol/L and 9 mmol/L[32]. Based on cerebral microdialysis, insulin should not be given at arterial blood glucose levels < 5 mmol/L as this significantly increased extracellular glutamate and lactate to pyruvate ratio. At arterial

blood glucose levels > 9 mmol/L, insulin administration is encouraged to significantly increase cerebral glucose levels and reduce lactate to pyruvate ratio[32,70]. Based on data obtained by microdialysis, brain glucose should remain above 1 mmol/L since cerebral glucose < 1 mmol/L was associated with increased lactate to pyruvate ratio[32,66,71]. Persistently low brain glucose levels were also associated with electrographic seizures, nonischemic reductions in CPP, decreased $SjvO_2$, increased glutamate levels, and poor outcome[71]. Expanding the assessment of brain glucose from mere monitoring to integration into clinical decision-making allows us to guide adaptation of nutritional support, which is a simple measure to increase both blood as well as brain glucose concentrations (Figure 3). Overall, nutritional support has been shown to improve hormonal status and clinical outcome in patients with TBI[72,73].

GUIDANCE FOR DECOMPRESSIVE CRANIECTOMY

For patients with uncontrollable intracranial hypertension, decompressive craniectomy with dura enlargement has been shown to improve cerebral perfusion, oxygenation, and metabolism[74-78], reflected by increased $ptiO_2$, decreased lactate to pyruvate ratio, reduced glycerol and glutamate levels[79].

Several reports have shown that pathologic neuromonitoring precedes clinical deterioration[75,78,79]. This, in turn, underscores the importance of integrating extended neuromonitoring in clinical routine to support decision-making on when to perform a decompressive craniectomy[78,79].

CONCLUSION

In the contemporary intensive care of patients with severe TBI subject to pharmacologic coma, basic monitoring using only ICP and CPP should be expanded by extended neuromonitoring including e.g. $SjvO_2$, $ptiO_2$, microdialysis, TCD, and electrocorticography. Growing evidence clearly supports the integration of extended neuromonitoring to unmask otherwise occult alterations and to differentially adapt the type, extent, and duration of our therapeutic interventions. By expanding our knowledge and experience, the integration of extended neuromonitoring in daily clinical routine will provide us with the means to improve outcome, which has not been possible by relying on ICP and CPP values alone as practiced in the past.

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