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Invasive Monitoring in Traumatic Brain Injury

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Abstract
Purpose of Review This review summarizes the most common trends in invasive monitoring of TBI along with recent developments on the subject.
Recent Findings Even though ICP monitoring has a fundamental role in monitoring TBI patients, recent evidence is favoring CPP-directed care over ICP-directed care. Moreover, brain oxygenation and microdialysis techniques are considered to further improve the outcomes of the patients. As novel monitoring techniques are developing, integration and analysis of monitoring multiple data are required.
Summary Traumatic brain injury management has shown extensive progress along with improvements in monitoring modalities. The main purpose of using multimodal monitoring is to prevent secondary injury and to improve outcomes. A better understanding of the status of the brain facilitates providing the optimal treatment for the patient. Monitoring of intracranial pressure, cerebral autoregulation, and cerebral perfusion pressure, brain oxygenation, and cerebral microdialysis techniques are discussed.

Keywords Traumatic brain injury · Invasive monitoring · Multimodal monitoring · Intracranial pressure

Introduction

Modern traumatic brain injury (TBI) care has been enriched by physiological monitors which assist efforts to optimize treatment. The main goals of multimodal neuromonitoring are to optimize nutrient delivery to the injured brain and to prevent or reduce the severity of secondary insults which can further injure the brain [1]. However, interpretation of relevant data is complex; both training and experience are needed to effectively use advanced neuromonitoring (Table 1) [2]. Data gleaned from these devices are also advancing our understanding of the pathophysiologic mechanisms underlying TBI, paving the way for further advancement in the future [3]. This chapter summarizes the invasive TBI monitoring techniques frequently utilized in the contemporary management of TBI as well as current evidence informing the impact of management guided by these devices on patient outcomes.

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Invasıve Monitoring Modalities for TBI

Intracranial Pressure (ICP)

History of ICP Monitoring

The first and most widely used means of invasive neuromonitoring is the measurement of pressure within the cranium. Intracranial pressure (ICP) was first mentioned by Alexander Monro in 1783 in conjunction with the assertion of four hypotheses: the brain is encompassed in a rigid bone structure, it cannot be compressed, the blood volume inside the cranium is constant, and the venous blood should be drained constantly to be replaced by the arterial blood [4]. Key early contributions to this subject were provided by Quincke. In 1891, he performed the first lumbar puncture (LP) in vivo and his studies included the measurement of ICP, glucose, and protein levels, bacteriological, and cytological analysis in a fashion very similar to what is still performed today. Quincke's experiments and findings remain fundamental to the still-evolving field of cerebrospinal fluid (CSF) physiology and CSF flow dynamics [5, 6].

Intracranial pressure monitoring was performed first by Guillaume and Janny with a U-tube in 1951. However, it was popularized by Lundberg and his colleagues [7, 8]. In 1960, Nils Lundberg developed a device that facilitated catheterization of the frontal horn of the lateral ventricle with a connection to an external transducer for continuous ICP monitoring. Lundberg studied elevations of ICP as well as an analysis of ICP waveforms, particularly as they related to clinical deterioration. Lundberg's description of plateau waves remains very relevant to modern neurocritical care: these waves are characterized by a sudden rapid rise, a period of sustained elevated values, and then a rapid fall [4, 8–10]. In 1972, Douglas Miller published his observations on the correlation between cerebral blood flow (CBF) and autoregulatory status with ICP [11•]. These observations were an early expression of the concept of multimodality monitoring to facilitate a better understanding of cerebral physiology.

Advantages of ICP Monitoring in TBI

Although it provides only a single metric, ICP monitoring provides a wealth of useful information relevant to neurocritical care. ICP monitoring assesses the effect of applied therapies aimed at treating ICP elevation, such as decompressive craniectomy, hyperosmolar medication, and barbiturates. It can also detect ICP changes related to other interventions such as mechanical ventilation (i.e., PEEP settings) and patient positioning [12]. ICP elevation can indicate an expanding intracranial hematoma that requires drainage; moreover, it can also imply pressure elevation from other mechanisms such as swelling or hydrocephalus which can impede the inflow of arterial blood to the cranium. In its most extreme form, when ICP exceeds intra-arterial pressure, brain death will occur as blood cannot flow to the brain [12].

When considering the value of ICP monitoring, additional benefits must also be considered. This includes the ability to determine cerebral perfusion pressure (CPP). There is more evidence supporting CPP-directed care than ICP-directed care [2, 12, 13]. In addition, ICP values are required to determine a patient's autoregulatory status. It is now felt that all physicians caring for TBI patients should be familiar with determining patients' autoregulatory status and how to incorporate this knowledge into care strategies [13]. Moreover, it should be remembered that an ICP monitor can provide an important assurance that the ICP is normal, providing reassurance that it is safe for a patient to undergo imaging examinations or other procedures.

Indications for Monitoring ICP in TBI

Several different indications for ICP monitoring have been published. The Brain Trauma Foundation (BTF) guidelines suggest performing ICP monitoring in patients with a Glasgow Coma Score of 3–8 and an abnormal CT scan. It is also recommended in patients who are in a coma, have a normal CT head, and at least two of the following; age > 40, unilateral or bilateral motor posture, and systolic blood pressure < 90 mmHg [12]. It is noteworthy that the evidence supporting these recommendations did not meet a quality threshold for the 4th edition of the BTF guidelines; however, the guideline panel chose to re-state these recommendations of the third edition nonetheless. According to the complementary Milan consensus conference report for clinical applications of intracranial pressure monitoring in TBI, ICP monitoring is recommended for comatose patients in whom cessation of sedation for neurological examination would pose a danger. This group also suggested ICP monitoring in patients with large bifrontal hemorrhagic mass lesions close to the brainstem [14]. The Neurocritical Care Society has also provided recommendations on this topic and they suggest that ICP and CPP monitoring should be performed in patients who are at risk of increased ICP based on clinical and imaging assessments [15].

Although most TBI experts view ICP monitoring as an essential tool in severe TBI care, ICP monitoring remains controversial—in part because it remains without indisputable evidence supporting its use. Meta-analysis and systematic reviews have concluded that ICP monitoring is associated with improved outcomes in severe TBI and that

it is cost-efficient even when used to monitor older patients [14]. On the other hand, BEST-TRIP—a multicenter randomized controlled trial including 324 patients—demonstrated that there were no differences in outcomes 3 or 6 months after an injury related to a treatment protocol involving ICP monitoring or a protocol involving imaging and clinical examination without ICP monitoring [16]. A subsequent meta-analysis published in 2015 concluded that ICP monitoring was not superior to care without ICP monitoring, but notably, most studies published after 2012 have shown lower mortality in patients who underwent ICP monitoring [17].

Clinical Significance

The BTF guidelines recommend treating ICP values above 22 mmHg since values above this level are associated with increased mortality [12]. This recommendation is primarily drawn from a study by Sorrentino et al. [17] that also suggested the threshold for favorable outcome decreased to 18 mmHg in elderly and females [18]. Another recent study examining millions of ICP measurements in hundreds of patients from a single institution concluded that ICP values above 19 mmHg were associated with mortality and that lower values than this threshold were still correlated with outcome [19]. There is also evidence that ICP values higher than 20 mmHg can be tolerated when cerebral perfusion pressure (CPP) is adequate [20•]. It is also interesting to consider emerging literature that raises the possibility that different patients may have distinct optimal ICP treatment thresholds, and that patient characteristics, pathology, and other physiologic parameters may influence this threshold [1, 21].

Technique and Complications

ICP can be measured with either intraparenchymal pressure sensors or fluid-coupled intraventricular catheters (external ventricular drains—EVDs). Intraparenchymal monitors may include either a strain gauge or a piezoelectric system. Strain gauge transducers provide a more precise measurement of intracranial pressure. On the other hand, piezoelectric sensors may provide accurate measurements when ICP values are high (Table 2).

There are important differences between intraventricular and intraparenchymal types of monitoring. Most important is that EVDs can drain CSF and lower ICP, allowing not only the measurement but also the treatment of intracranial pressure elevation. Disadvantages are that EVDs require some skill to successfully cannulate the ventricle and EVDs can also occlude. Although intraparenchymal monitors are easier to place, their measurements are subject to drift over time and they cannot be reset after placement as an EVD can be. Both monitor types are associated with a risk of hemorrhage and infection [22].

Patients with coagulopathies are at the risk of intracranial hemorrhage (ICH) caused by multiple punctures of the brain parenchyma and if a coagulopathy is suspected, invasive monitoring could be avoided [23]. However, there is uncertainty over the management of ICP in ICH, and ICP principles in TBI are empirically applied [24].

The risk of infection with a ventricular catheter is shown to increase after 5 days. Infection may occur both by retrograde colonization of the catheter or contamination during the insertion of the catheter [25]. However, antibiotic-impregnated ventricular catheters have substantially decreased the incidence of catheter-related CSF infections [26].

At this time, evidence does not support the superiority of either intraparenchymal monitors or EVDs. A recent systematic review suggested that even though mortality and functional outcomes after intraventricular and intraparenchymal ICP monitoring were equal, intraventricular catheters were associated with a higher rate of complications, mainly infections (i.e., meningitis) [27]. In another retrospective study, ICP monitoring with the early placement of EVDs (at the first 6 h) in severe TBI was associated with greater in-hospital mortality than intraparenchymal monitors during the same early placement time. This study also concluded that patients with intraparenchymal monitors had shorter ICU stays and better neuropsychological and functional outcomes at 6 months; however, more controlled analysis of the appropriate timing and indication for the use of EVDs in severe TBI are required [28].

Moreover, in the latest consensus summary statement on multimodality monitoring, both modalities are suggested to be equal in accuracy and reliability. However, in the case of hydrocephalus, an external ventricular drain is recommended to extract CSF [15].

Non-invasive ICP Monitoring

Less invasive monitoring of ICP is highly desirable. Such technology could help to determine which patients require invasive monitoring and it is expected that such technologies could replace the use of invasive monitoring in the future. Two promising ways of assessing intracranial pressure non-invasively include optic nerve sheath diameter ultrasound measurements as well as transcranial doppler ultrasonography. While these techniques and technologies are improving, none are as accurate as invasive methods as yet. As such, they are generally viewed as complementary and are likely to be preferred in patients who have a contraindication to invasive interventions, such as

coagulopathy [29], or those in whom the indications for invasive monitoring have not been strictly met (see Tables 1 and 2).

Cerebral Autoregulation and Cerebral Perfusion Pressure

Cerebral autoregulation is defined as the brain's ability to maintain its nutrient delivery despite fluctuations in systemic supply such as fluctuations in blood pressure or viscosity. Autoregulation is achieved via vasodilation or vasoconstriction of the cerebral arterioles. The consensus of the SIBICC panel is that physicians caring for TBI victims must be able to assess the autoregulatory status and incorporate this information into the plan of care [12, 30]. Management strategies for preserved and non-preserved autoregulation may differ. Patients with preserved autoregulation can benefit from a higher mean arterial pressure and CPP for ICP control; however, in patients with dysfunctioning autoregulatory status, targeting lower mean arterial pressure values may be better [15].

In neurocritical care units, cerebral blood flow responses to fluctuations in blood pressure or cerebral perfusion pressure can be monitored for continuous analysis of cerebral autoregulation. The 'moving correlation coefficient' or PRx method involves analyzing the correlation between MAP and ICP over 5 min intervals. This correlation coefficient range can range from -1 to $+1$. Negative values are associated with normally reacting cerebral vessels. A positive PRx especially values greater than 0.3 indicate a pathological passive and non-reactive cerebral vasculature [31, 32].

Cerebral autoregulatory status may also be determined via measuring the cerebral blood flow velocity via transcranial Doppler and near-infrared spectroscopy [33]. The burden of dysfunctional autoregulation is known to predict unfavorable outcomes and can also be used for determining the optimal cerebral perfusion pressure range [34].

BTF guidelines suggest that the optimal range of CPP is between 60 and 70 mmHg; however, the threshold values should be individualized based on autoregulatory status [12]. In a distinct approach, the CPP at which PRx is most negative has been conceptualized as the optimal CPP (CPPopt). Preliminary studies suggest that patients in whom the CPPopt is achieved have better outcomes [35]. The downsides of this approach include the fact that the optimum CPP varies over time and can take many hours to calculate [36].

Brain Oxygenation Monitoring

Brain Tissue Oxygenation ($PbtO_2$)

Brain hypoxia is recognized as a key secondary insult following traumatic injury. Measurements of brain tissue oxygenation, therefore, hold promise for detecting and treating cerebral hypoxemia, potentially improving outcomes [37]. Brain oxygenation may be monitored via two invasive modalities: jugular bulb oxygen saturation and brain parenchymal oxygen tension. Near-infrared spectroscopy is a non-invasive bedside monitoring technique that functions percutaneously similarly to pulse oximetry but this remains investigational for TBI at this time [15].

$PbtO_2$ levels are now frequently measured by the insertion of a catheter in the subcortical white matter through a single or multiple lumen bolt. The Licox system from Integra Neurosciences is such a commercially available system. The Neurovent-PTO system from Raumedic is another [38]. This is a triple-lumen catheter inserted via an intracranial bolt which measures $P_{bt}O_2$, brain tissue temperature, and intracranial pressure [39]. As this monitoring modality is invasive, complications are associated with the placement of these devices. In a systematic review, complications were listed as local bleeding around the catheter in 0–3%, and technical complications such as dislocation or defect in 6–14% [38].

The threshold for cerebral hypoxia remains a subject of refinement. Originally the BTF recommended 15 mmHg [39] as the treatment threshold. Subsequently published recommendations from the Neurocritical Care Society suggested 20 mmHg and this is now widely used [15]. A recent large study suggested that 19 mmHg could be a more precise, ideal treatment threshold; however, a benefit was associated with $PbtO_2$ values as high as 33 mmHg [40].

When interpreting $PbtO_2$ measurements, it is helpful to understand that $PbtO_2$ is not directly related to total oxygen delivery or cerebral oxygen metabolism but there is a correlation between $PbtO_2$ and cerebral blood flow with arteriovenous oxygen tension [3]. Moreover, probe location has a strong influence of $PbtO_2$ measures and how $PbtO_2$ responds to interventions [41]. When the tip of the probe is in or near the injured brain, $PbtO_2$ measures tend to be low and do not demonstrate improvement with treatments. It is the senior authors' preference to place $PbtO_2$ monitors in the more normal frontal lobe as it better facilitates titration of treatment.

$PbtO_2$ monitoring has shown encouraging results so far [42] and is currently being investigated in a phase 3 trial. BOOST-II was a randomized control study that compared management solely informed by ICP monitoring and that informed by both ICP and $PbtO_2$ monitoring. Interestingly,

Table 1 Invasive and non-invasive monitoring modalities for TBI

Parameter	Invasive	Non-invasive
ICP	Intraparenchymal probe	Optic nerve sheath diameter (Ultrasound or MRI)
	External ventricular drain	Ophthalmodynamometry
		Transcranial doppler ultrasonography
Cerebral autoregulation and CPP	MAP and ICP (PRx)	Transcranial doppler ultrasonography
		Near-infrared spectroscopy
Brain oxygenation	PbtO2	Jugular venous oxygen saturation (SjvO2)
		Arterio-jugular differences of oxygen (AVDO2)
Cerebral blood flow	Bowman Perfusion Monitor (Hemedex, Cambridge, MA, USA)	Thermal diffusion flowmetry
		Laser doppler flowmetry
Tissue biochemistry	Cerebral microdialysis	MR spectroscopy

Table 2 Invasive ICP monitoring methods

Invasive ICP monitoring methods	Advantages	Disadvantages
External ventricular drainage	Accuracy high	Difficulty in insertion (especially when ventricles are narrow
	CSF drainage and sampling	Risk of infection
	Delivery of intrathecal drugs	Risk of hemorrhage
		Catheter occlusion
Intraparenchymal microsensor	Easy insertion	Accuracy low
	Lower infection risk	Calibration cannot be performed
		No CSF drainage and sampling
Epidural or subdural device	Easy insertion	Accuracy low
	Lower infection risk	Calibration cannot be performed
		No CSF drainage and sampling

both groups had $PbtO_2$ monitors placed, but the measurements were kept concealed in the ICP-only group. In the group with care informed by both $PbtO_2$ values with ICP monitoring, there was a reduction in brain hypoxia as well as improved functional outcomes and lower mortality [42]. The ongoing BOOST-III trial will determine the 6-month neurological outcome comparison between ICP-only and ICP + $PbtO_2$ monitoring. In BOOST-III, placement of the monitor must be completed within 6 h of presentation to the hospital.

Jugular Venous Oxygen Saturation ($SjvO_2$) and Arterio-Jugular Differences of Oxygen ($AVDO_2$)

Jugular venous oximetry may show the amount of oxygen in the cerebral venous circulation and is inserted into the jugular bulb using a central venous catheter to approximate the skull base through the dominant internal jugular vein [43]. This position is ideal for determining cerebral oxygen consumption since the blood draining from the scalp and face has not yet mixed with the cerebral venous blood. The catheter placement may be confirmed by a lateral skull X-ray with the tip of the catheter placed above the inferior border of the vertebral body of the axis [43].

Cerebral oxidative metabolism is directly correlated with cerebral blood flow and arteriovenous differences in oxygen. When $AVDO_2$ increases, the cerebral metabolic demand is low, and when $AVDO_2$ decreases, this may be suggestive of hyperperfusion or tissue death [43]. $SjvO_2$ levels are correlated with $AVDO_2$ and may be useful in detecting ischemia or hyperemia [15]. While the normally accepted $SjvO_2$ value is between 55 and 75%, ischemia cannot be excluded from these normal ranges because the monitor provides a global measurement [44]. At least 13% of the brain must be ischemic for $SjvO_2$ values to be abnormal [45]. Due to poor quality signals caused by contamination with inaccurate placement, clot formation, thrombosis, and inadequate calibration, data may not be

accurate for the total monitoring duration [38]. Per the 4th edition BTF guidelines, a $SjvO_2$ threshold of 50% should be considered a treatment threshold for $SjVO_2$ monitoring (Level III) [12].

Cerebral Blood Flow (CBF)

Given the importance of cerebral hypoxemia discussed above, there has also been strong interest in monitoring cerebral blood flow. Cerebral blood flow decrease may be associated with functional and structural alterations which may result in neuronal death and it has been measured experimentally for determining the threshold for ischemia [12]; however, in clinical practice, evidence is still lacking with respect to a precise threshold for ischemia. Measures for monitoring cerebral blood flow include thermal diffusion flowmetry or Laser doppler flowmetry. Focal blood flow measurements can be obtained at the bedside using the Bowman Perfusion Monitor (Hemedex, Cambridge, MA, USA). It involves placing an intraparenchymal probe which is heated to 2 °C above the baseline brain temperature. As heat loss from the brain is directly proportional to blood flow, flow can be estimated from the input energy needed to maintain the heating of the local brain tissue, as measured by a highly sensitive thermistor [46]. The derived thermal conductivity measurement also allows the calculation of the percent of brain tissue water content near the tip of the probe which can inform regional cerebral edema [46, 47]. As a proof of principle, brain tissue water percentage measured with this technology was higher in patients showing brain edema on CT imaging and this percentage decreased 1–3 h after hyperosmolar bolus therapy [48]. Because of the need for periodic cooling of the brain, CBF measurements made with this technique are discontinuous. For safety, heating of the brain is limited with this technology and can prevent readings from occurring when there is brain hyperthermia.

Cerebral Microdialysis

Cerebral microdialysis provides information on the neurochemical state of the brain as it provides an analysis of chemicals in the brain's interstitial fluid. This information can help to guide therapy such as mean arterial pressure parameters, ventilatory rate, pCO_2 levels, hyperosmolar therapy as well as the potential need for surgical interventions [49]. Moreover, the lactate pyruvate ratio may be used to predict the safe lower limit of CPP values and may help to inform individualizing optimal threshold values for CPP [50].

A microdialysis catheter may be inserted either in the operating room or in the intensive care unit with standard landmarks [49]. Theoretically, the catheter tip should be placed in the pericontusional area; however, recent consensus agrees that the location of the probe tip depends on the diagnosis, type, and location of the lesion [15]. The microdialysis catheter is composed of a dialysis tube and shows the chemical composition of the interstitial fluid. Water and solutes diffuse between the interstitial fluid and perfused solution, which is called the perfusate, and the concentration gradient between these two chambers allows the diffusion of solutes at a constant speed for producing the dialysate [51]. The measurements depend on the membrane pore size, surface area, flow rate of the fluid, the size of the extracellular space, and rate of diffusion for the solute. Therefore, the analysis is defined as the relative recovery [52•]. Hourly or more frequent sampling is applied and detection of metabolic alterations may precede intracranial hypertension, and therefore, this monitoring modality may provide early detection of secondary brain damage [53].

A number of metabolites have been studied and are believed to serve as biomarkers following TBI. Glucose is the main energy source of the brain, and following TBI, low glucose levels are associated with unfavorable outcomes. In a healthy brain, serum glucose concentration and glycemic control are associated with cerebral glucose; however, this correlation may be altered in brain injury. Cerebral glucose levels may decrease in association with secondary insults such as spreading depolarizations [53]. The lactate–pyruvate ratio may increase in many situations. Increased lactate with near-normal pyruvate may indicate mitochondrial failure rather than ischemia. When the lactate pyruvate ratio is increased while pyruvate and oxygen levels are low, ischemia should be suspected. However, an increase in lactate–pyruvate ratio with normal or high pyruvate and normal oxygen levels may indicate mitochondrial dysfunction [53]. Microdialysis has shown predicted relationships with brain oxygenation, helping to support its validity. In one study, focal microdialysis and $PbtO_2$ monitoring were performed in patients who underwent evacuation of subdural hematoma, seventeen of thirty-three patients showed an increase in lactate–pyruvate ratio and reduced $PbtO_2$, while ICP, CPP, and $SjvO_2$ were normal, suggesting that microdialysis monitoring could inform secondary brain insults and guide corrective therapy [54].

Glutamate and glycerol are also showing promise as microdialysis biomarkers. Glutamate is an excitatory amino acid and neurotransmitter and its excess in the brain's interstitial fluid may be observed in ischemia and seizures. Its release is associated with excitotoxicity and has shown an association with outcome and prognosis in TBI [55]. Glycerol levels in dialysate are believed to inform cell membrane breakdown. Glycerol concentrations

may also provide information on the stress response of cerebral tissue [53].

It can be helpful to interpret multiple microdialysis biomarkers in concert. This was effectively demonstrated in an experimental study where transient cerebral ischemia was induced in fetal lambs in utero. This resulted in a rapid increase in lactate/pyruvate ratio along with glutamate. Glucose, pyruvate, and glutamate rapidly decreased after resuscitation; however, lactate and glycerol levels remained elevated [56].

The main limitation against the use of microdialysis is costs and the laboriousness of gathering and interpreting the results from many samples as needed for optimal analysis. Moreover, accurate placement of the probe in the pericontusional area is difficult to achieve reliably; misplacement—in particular ventricular or extradural positioning—may result in inaccurate data. Additionally, the probes are fragile and may be damaged or pulled out of position with head movement, especially if not secured well to the scalp [52].

Microdialysis has provided important information about TBI pathophysiology and continues to be an important tool as new biochemical markers are being investigated and utilized. However, further studies are necessary to clarify whether interventions based on microdialysis data may improve patient outcomes.

Conclusion

Advanced neuromonitoring in TBI has led to a better understanding of the underlying pathophysiologic mechanisms of secondary injury and they facilitate more individualized patient management. These technologies are, however, markedly increasing the complexity of neurocritical care, and strong evidence proving that they positively impact patient outcomes is not yet available. Many experts feel, however, that these monitors improve the quality of patient care, especially when used in combination and by well-trained and experienced practitioners. In the coming years, much work must be done to refine the use of these devices in modern neurocritical care.

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Recent papers of particular interest have been highlighted as:

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