Accepted October 2014

REVIEW

Neuromonitoring of patients with severe traumatic brain injury at the bedside

M.J.H. Aries[1, 2], J. van der Naalt[3], W.B. van den Bergh[1], M. van Dijk[4], J.W.J. Elting[3], M. Czosnyka[2], J.G. Regtien[1]

Departments of [1]Critical Care, [3]Neurology and [4]Neurosurgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[2]Department of Clinical Neurosciences, Division of Neurosurgery, University of Cambridge, Cambridge, United Kingdom

Correspondence

M.J.H. Aries – email: m.j.h.aries@umcg.nl

Keywords - **Traumatic brain injury, brain monitoring, intracranial pressure, cerebral perfusion, outcome**

Abstract

Measurement of intracranial pressure (ICP) and arterial blood pressure is used to derive cerebral perfusion pressure (CPP) and to guide targeted therapy of severe traumatic brain injury (TBI) necessitating ICU admission. In this narrative review we discuss the evidence for ICP monitoring, CPP calculation, and ICP/CPP-guided therapy after severe TBI. Despite its widespread use, there is currently no class I evidence that ICP/CPP-guided therapy improves outcomes. Similarly, no class I evidence can currently advise the ideal CPP. 'Optimal' CPP is likely patient-, time-, and pathology-specific and related to cerebral autoregulation status. The fact that *optimal* CPP and autoregulation status varies between individual patients and over time makes it an attractive bedside tool to serve as a (simplified) model to investigate the use of autoregulation status to fine tune or give feedback on clinical treatments in individual sedated patients (*optimal CPP* concept).

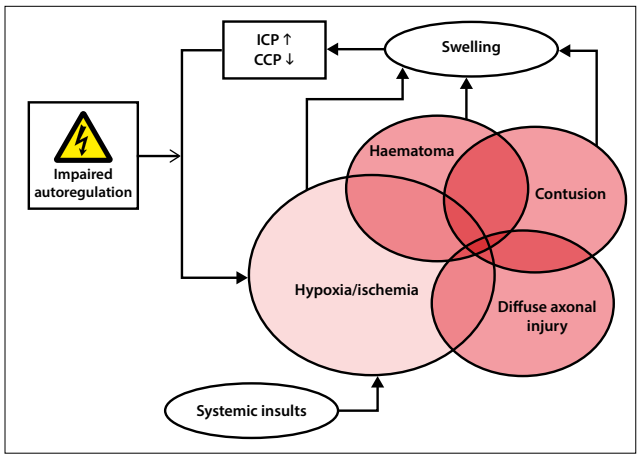
Evidence is emerging for the role of other monitors (representing (local) metabolism, oxygen supply/use, perfusion, neuronal functioning) that enable the intensivist to employ an individualised multimodality monitoring approach in TBI. The management of TBI is likely to become increasingly based on a more comprehensive monitoring and management approach rather than relying on absolute numbers of ICP and CPP in isolation. This will allow individual optimisation of perfusion and therefore of oxygen and energy substrate delivery. We await further robust, high-quality evidence to support the benefits of using more sophisticated monitoring tools during the ICU management of TBI, but for the near future what is more important is to gain a greater understanding of the underlying pathophysiology.

Introduction

Severe traumatic brain injury (TBI) is a major cause of death and disability among youngsters, with an estimated incidence of 25 new cases admitted to hospital per 100,000 people.[1] It constitutes a substantial proportion of ICU admissions, and is a heterogeneous disease in terms of cause, pathology, severity and prognosis, which poses diagnostic and therapeutic challenges.[2] Monitoring of patients with severe TBI in the ICU setting includes both brain specific and systemic monitoring (e.g. invasive arterial blood pressure (ABP), end-tidal CO2, oxygen saturation, cardiac output).[3,4] As most brain trauma patients are sedated and ventilated at the scene, more technically advanced monitoring techniques are desirable on the ICU instead of blurred clinical neurological examinations. Concurrent with the above data, intermittent neuroimaging provides clues to guide initial (surgical) treatment but repeated scanning is associated with transportation risk and radiation.[5] The primary aim of neuromonitoring is to facilitate early detection of devastating secondary insults (e.g. fast growing haematoma), but also to recognise slower developing intracranial complications (e.g. development of gradual brain swelling) before these become clinically evident. Another aim of neuromonitoring is to provide objective parameters to guide individualised therapeutic management and prognostification.[6] Invasive methods are well presented by intracranial pressure (ICP) monitoring, brain tissue oxygenation (PbTiO2), microdialysis, thermal dilution cerebral blood flow (CBF) probes or jugular bulb saturation (SvJO2). Non-invasive methods are transcranial Doppler, continuous EEG and near infrared spectroscopy. Some excellent reviews discussing the pros and cons of these techniques have recently been published.[3,4] The underlying pathophysiology of

TBI is complex and involves the interaction between changes in cerebral perfusion, cerebral oxygen delivery and metabolism and its compensatory reserves (figure 1).[7]

Figure 1. Determinants of severe traumatic brain injury (TBI) and underlying pathophysiological mechanisms[2].
The different components of TBI with ischaemic damage are superimposed on the primary types of injury (haematoma, contusion, and diffuse axonal injury). Systemic insults, impaired autoregulation and brain swelling contribute to ischaemic damage, which might in turn cause more swelling. ICP = intracranial pressure; CPP = cerebral perfusion pressure



The utilisation of cerebral energy substrates such as glucose and lactate may be severely disturbed or exhausted during admission.[8] Electrophysiological derangements such as seizures and cortical spreading depression may occur after primary injury and contribute to secondary brain injury.[9] The complex cascade of pathophysiological events that follow primary injury is thought to evolve over minutes to weeks to months with substantial regional and temporal heterogeneity.[10] The different aspects of the cerebral pathophysiology are difficult to cover with single neuromonitoring modalities. For example, the first site of salvageable brain tissue is the region immediately surrounding the injury lesion (the 'penumbra'). Deranged local - and not necessarily global - autoregulation, microspasm or micro-vasoparalysis, non-ischaemic metabolic crisis with mitochondrial dysfunction, hyperglycolysis, and also classic ischaemic damage due to reduced oxygen and substrate supply all pose a significant risk of deterioration.[11] Neuromonitoring will only detect these changes if the probe is sited in the specific location at risk. Remote areas of the penumbra may have normal or at least different physiological responses that are unnoticed. Just to guide treatment directed at only one of the many deleterious pathways modulating secondary brain injury is suboptimal and may explain disappointing results of neuromonitoring-guided treatments using single parameters. Therefore, from a pathophysiology perspective, multimodality monitoring is preferred.[12] For example, with solely ICP/cerebral perfusion pressure (CPP) monitoring we will be able to quantify perfusion pressure globally, but this method is unable to assess the exact perfusion in the different tissues at risk.[13] Ideally, choices of therapy are, thus, likely to be best determined by multimodal monitoring at multiple sites that encompasses cerebral haemodynamics, oxygenation and metabolism.[3,4]

Several bedside monitors are available for assessing cerebral function in unconscious patients including ICP/CPP, PbTiO2, near infrared spectroscopy, microdialysis, transcranial Doppler, SvJO2 and continuous EEG monitoring. The 2014 consensus guidelines on multimodality monitoring in neurocritical care strongly recommend ICP and CPP monitoring as part of protocol-driven care in patients who are at risk of elevated ICP based on clinical and/or imaging features. ICP and CPP monitoring – including waveform quality – should be used as a prerequisite to allow interpretation of data provided by the other monitoring devices. New in the guidelines is the recommendation that monitoring and assessment of pressure autoregulation may be useful in broad targeting of cerebral perfusion management goals and prognostication in TBI.[14]

In this narrative review we will discuss the role of ICP/CPP monitoring in the care of patients with TBI, particularly those in coma. We will highlight the upcoming role of continuous bedside monitoring of cerebral autoregulation. More refined monitoring of autoregulatory efficiency is now possible through online calculation of derived indices such as the cerebrovascular pressure reactivity index (PRx) and *optimal CPP* using the commonly available signals of ICP and ABP.

Intracranial pressure

The first ICP measurements date from the 1950s, with an electronic transducer to measure ventricular fluid pressure signals in patients with a diversity of intracranial pathologies.[15] Improvements in technique, safety profile, and development of intraventricular and parenchymal micro-transducers have contributed to the widespread use of ICP monitoring in TBI.[16] ICP monitoring is used not only to manage ICP, but also to calculate CPP, defined by mean ABP minus ICP. Monitoring of ICP and CPP are recommended in the current guidelines for the management of severe TBI.[16,17] Given the recent evidence questioning the utility of ICP-guided therapy using fixed thresholds in adults,[12] different research groups have tried to extend the role of ICP monitoring by defining individualised and up-to-date CPP targets, for example by using autoregulatory indices.[18-22]

Intracranial pressure monitoring

ICP can be monitored routinely by two methods in TBI patients: via an intraparenchymal microsensor or an intraventricular catheter. The gold standard method is the latter because it measures global ICP and enables in vivo calibration and therapeutic drainage of cerebrospinal fluid (CSF). Intraventricular monitoring of ICP is complicated by difficulties in catheter placement and the risk

of catheter-associated bacterial ventriculitis.[23] ICP monitoring by use of the extraventricular drainage system is probably only reliable with (temporary) complete interruption of the CSF drainage and maintaining correct reference levels during the measurement.[24] Intraventricular piezo-electric ICP probes combined with an extraventricular drainage option are available but the exact influence of CSF drainage on absolute ICP levels is unknown. Modern microtransducer-tipped and fibreoptic ICP monitoring systems are placed directly into brain parenchyma. While the rate of complications, including infection, is low,[12] the resulting ICP value may not represent global pressure if intraparenchymal pressure gradients exist.[13] Although microtransducer systems are reliable, drift can ensue during long-term monitoring and in vivo calibration is not possible.[23] The assumption that the brain acts like a fluid and that ICP is transmitted equally throughout the intracranial space is disputed in experimental studies that found expanding mass lesions are associated with the development of ICP gradients, especially with expanding subdural haematomas.[25]

The Brain Trauma Foundation recommends ICP monitoring to guide ICP/CPP-directed therapy after severe TBI in all salvageable patients with an abnormal cranial computed tomography (CT) scan, and in those with a normal scan if two or more of the following features are present: age >40 years; unilateral or bilateral motor posturing; or systolic ABP <90 mmHg.[26] We apply these guidelines and when only limited neurological surveillance is possible due to multi-trauma (facial) injuries with extensive CT abnormalities also ICP monitoring is strongly considered, irrespective of the Glasgow Coma Scale. Recent literature from Austria and the Netherlands suggests that only 57% and 46% of eligible TBI patients are being managed with the use of an ICP monitor. The 'worst' and 'best' cases were less likely to receive ICP monitoring.[27,28]

Intracranial pressure management and outcome

ICP monitoring is a standard of care in most trauma centres although there is a wide variability in ICP monitoring.[27,28] ICP as a number associates significantly with mortality, but does not differentiate between severe disability, moderate disability and good outcome.[29] There is little robust evidence for its positive impact on patient outcomes. In earlier studies the effect of combined strategies on ICP was revealed (i.e. sedation, CSF drainage and hyperosmolar therapy) instead of the effect of a single intervention. Mortality after severe TBI is significantly lower in neurosurgical centres compared with non-neurosurgical centres.[30] A meta-analysis published in 2010 concluded that ICP monitoring and aggressive treatment of intracranial hypertension in severe TBI is associated with improved outcomes,[31] whereas some studies have suggested that it might in fact be detrimental.[32,33] These conflicting findings are probably related to important differences between trauma centres such as applying different treatment algorithms, indications and thresholds for ICP monitoring,[34,35] differences in study design and quality of data, and monitoring secondary information such as brain compensatory reserve,[36] brain compliance [37] and cerebrovascular pressure reactivity.[38] In most studies it is difficult to control for confounding factors between groups of patients with and without ICP monitoring.[32]

The worse outcomes observed in some studies might also be a result of the deleterious effects of the ICP-reducing therapy itself. For example, prolonged hyperventilation has a good effect on ICP reduction, but also reduces CBF significantly.[39] A recent randomised controlled trial in Bolivia and Ecuador found no difference in the combined final clinical outcome score after severe TBI in patients whose treatment was guided by ICP monitoring compared with care only based on frequent head CT scanning and clinical examination (pupil size).[12] Interestingly, those patients not undergoing ICP monitoring received significantly more days of ICP-directed treatment (including hyperventilation, barbiturate coma and hypertonic saline infusion) than those in the ICP-monitored group, although the length of ICU was similar in the two groups. It should be also commented that monitoring of ICP employed in this study was very primitive. Just an end-hour instant ICP value was noted by nurses to guide management. And finally, the mortality was surprisingly high in both groups (around 40%). Another important observational ICP monitoring study treatment was performed in 333 severe TBI patients in the Netherlands. Patients were admitted to one of two centres, with admission to each being determined only by the geographical location of the accident. One centre provided supportive ICU management to maintain very high mean arterial pressure levels (>90 mmHg) and other therapeutic interventions guided by clinical observations and CT abnormalities. Patients admitted to the other hospital underwent ICP monitoring and ICP/CPP-targeted management (maintaining ICP <20 mmHg and CPP >70 mmHg). This study provided no evidence for improved outcomes with aggressive ICP/CPP directed management. Increased levels of therapy intensity (use of sedatives, vasopressors, mannitol infusion and barbiturate coma), and prolonged mechanical ventilation occurred in patients receiving ICP-directed therapy.[32] Clearly, the monitor alone does not affect outcome; it is the management changes implemented as a consequence of the information obtained from the monitor that have the impact. Nowadays, applying CPP levels >70 mmHg during the whole admission does not fit with our understanding of TBI being a dynamic process with an individual time course. Together these two studies have increased, rather than resolved, the controversy over the role of ICP-guided therapy after TBI. Neither study argues that ICP monitoring should be abandoned but, as subsequent comments have highlighted, applying the current fixed ICP/CPP thresholds does not provide a comprehensive picture of changes in cerebral physiology and pathophysiology, and therefore absolute numbers should

probably not be used solely to guide individual and up-to-date treatment.[21,40] In both studies in developing Latin America countries and in the Netherlands, the mortality rate was high, close to 40%! It looks as if in the ICP monitoring group information coming from monitors was not robustly implemented for patient management to achieve mortality rates of around 20-30%, more common in contemporary reports.[12] In addition, using absolute CPP thresholds also makes the ongoing discussion about where the ABP transducer should be referenced relevant. In patients in whom the head of the bed is elevated to promote venous drainage, measuring ABP at the level of the heart results in a calculated CPP that is up to 20 mmHg higher than when ABP is measured at the level of Monro.

Cerebral perfusion pressure

CPP has been the subject of significant research efforts as a modifiable factor influencing outcomes in severe TBI. Current consensus TBI guidelines recommend that CPP should be maintained between 50 and 70 mmHg after TBI, with evidence of adverse outcomes if the CPP is lower or higher.[26,29,41] An argument to favour even higher CPP values is based on the principle of breaching the vasodilatory cascade that accompanies lower CPP values.[42] In addition, a higher CPP also avoids the deleterious effects of systemic hypotension and its known adverse effects on outcomes after TBI.[43] Other studies have suggested that higher CPP values have a substantial risk of acute lung injury after the administration of large fluid volumes and inotropes/vasopressors to maintain CPP.[44] An alternative approach to management (the Lund concept) utilises lower CPP targets, normovolaemia and avoiding vasopressors to minimise increases in intracapillary hydrostatic pressure and subsequent intracerebral oedema.[45] It is likely that an optimal individual CPP threshold exists that changes over time identified by (multimodal) innovative neuromonitoring.

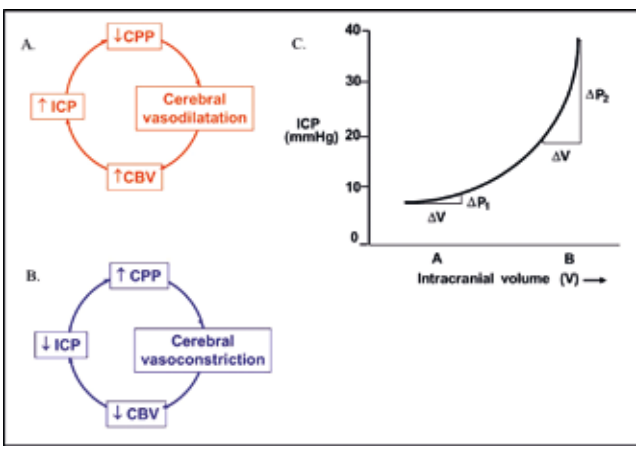
Optimal cerebral perfusion pressure

In determining *optimal CPP* at the individual level, one should be familiar with cerebrovascular reactivity and cerebral autoregulation. In the healthy brain, CBF is suggested to remain constant over a range of ABPs (50–150 mmHg) through autoregulatory mechanisms within the brain. Reactive cerebral arterioles keep CBF constant by active dilatation (with ABP decrease) and constriction (with ABP going up).[46] The 'safe' broad autoregulation plateau is confined by both lower and upper limits where CBF passively follows changes in ABP/CPP. However, the lower limit of autoregulation in a healthy non-anaesthetised adult may be notably higher than the widely applied 50 mmHg (hypertension) and there are suggestions that the autoregulation plateau is very small in various pathological situations. This may have profound implications, especially in the context of monitoring and management of CPP in individual TBI patients. Passive vascular reactivity puts the brain at risk of ischaemia as well as hyperaemia. Methods to indicate the upper and lower limits are therefore essential to protect the brain against inappropriate fluctuations in CBF in the face of changing ABP/CPP. Continuous monitoring of global CBF at the bedside is however not possible.[47] For monitoring, several studies have used ICP (as a surrogate of vascular calibre and reactivity) to continuously monitor the impact of spontaneous fluctuations in ABP/CPP on cerebrovascular physiology and indications of lower and upper limits of autoregulatory efficiency. Cerebrovascular pressure reactivity is a key component of autoregulation and may be impaired in various intracranial pathologies.[47] In patients with continuously monitored ICP the comparison of slow waves of ICP and ABP/CPP can contain information about cerebrovascular pressure-reactivity (PRx). In theory, with good cerebrovascular reactivity, a change in ABP/CPP should provoke inverse, reactive change in cerebral blood volume (CBV). With a steep pressure-volume curve – as is the case with higher ICP levels – the change in CBV should produce correlated changes in mean ICP (figure 2).

Figure 2. Relationship between cerebral perfusion pressure, brain volume and intracranial pressure.

With decreasing cerebral perfusion pressure active vasodilatation will cause an increase in cerebral blood volume (figure 2A) and with steep pressure volume curve characteristics (ΔP2, figure 2C) an obvious increase in intracranial pressure will be noticed. With increasing cerebral perfusion pressure active vasoconstriction will cause a decrease in cerebral blood volume and a decrease in intracranial pressure (figure 2B). ICP = intracranial pressure; CPP = cerebral perfusion pressure; CBV = cerebral blood volume.

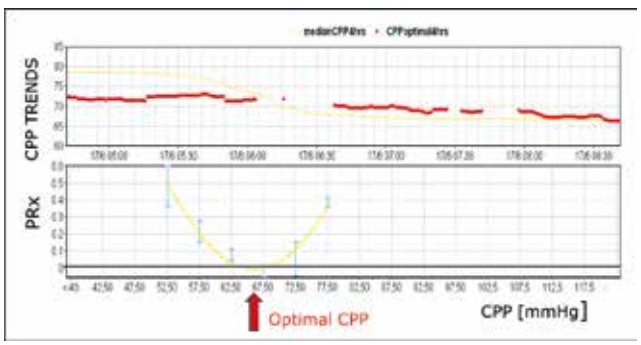
Figure originally constructed by Rosner et al.42 and kindly provided by David Menon (Cambridge).



Therefore, a negative correlation coefficient between changes in mean ICP and ABP/CPP signifies good pressure-reactivity of cerebral arterioles (negative PRx values), which is a condition necessary for intact pressure autoregulation. Conversely, with disturbed reactivity, changes in ABP/CPP produce passive,

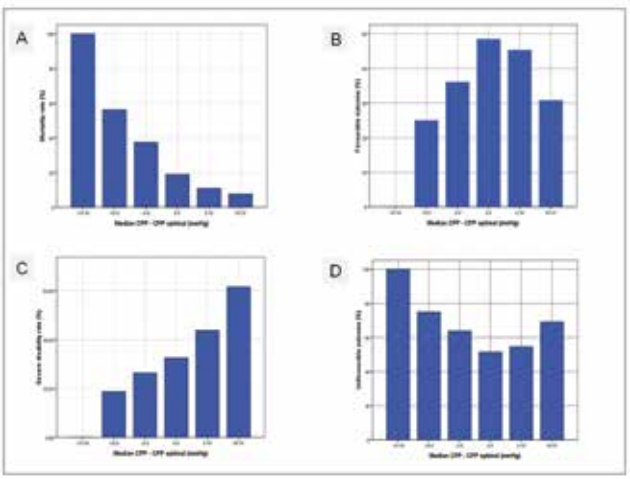
positively correlated changes in CBV; therefore, correlation between ABP/CPP and ICP slow waves is positive (positive PRx values). The Pearson correlation coefficient is calculated from a time window of 5 minutes, and this window may be moved in time to yield repeated measurements. In this way, the PRx index, being a secondary parameter, can be displayed as a time trend alongside the primary modalities as mean ICP, ABP and CPP.[48] PRx correlates with standard measures of based on transcranial Doppler and positron emission tomography, and abnormal values are predictive of poor outcomes after TBI.[47] However, PRx is highly variable (noisy) and requires averaging over time (minimal 30 minutes in normal clinical situations) in order to provide meaningful and reliable values. One useful way of 'averaging' PRx is to divide its values into different bins according to corresponding predefined CPP ranges. It turned out that, as an added benefit of this approach, with only a few hours of ABP and ICP recordings, plotting the PRx index against associated CPP bins frequently produces a U-shaped curve with both hypoperfusion (low CPP) and hyperperfusion (high CPP) associated with worsened cerebrovascular reactivity.[49] With dedicated curve fitting software the lowest point of the individual autoregulation curve can be marked as the 'optimal' CPP (CPPopt) value, corresponding to the CPP where individual pressure autoregulation is the most effective (equivalent to the middle point of the Lassen autoregulation curve) (figure 3).

Figure 3. Optimal cerebral perfusion pressure.
Plotting the cerebrovascular pressure index PRx over a period of 4 hours shows a U-shaped curve (yellow). The valley of the curve represents the CPP value for best autoregulation (arrow). This optimal CPP can be displayed automatically at the bedside and followed over time (trend). The U-shape curve indicates that both low and high blood pressures are not well tolerated by the injured brain. CPP = cerebral perfusion pressure; PRx = Pressure Reactivity Index.



Recently, we demonstrated in a single-centre retrospective study in more than 300 TBI patients that using a moving calculation window of four hours an individual optimal CPP value could be updated automatically every minute in 55% of recording time.[50] Deviation from calculated optimal CPP was associated with unfavourable outcome, indicating that both hypoperfusion and hyperperfusion should be avoided. Interestingly, hypoperfusion was associated with higher mortality and hyperperfusion with higher severe disability rate (figure 4).[49,50]

Figure 4. Optimal cerebral perfusion pressure and outcome
Graphs of the relationship between mortality rate (GOS 1), unfavourable outcome (GOS1-3), severe disability rate (GOS 3) and difference between continuous calculation of median CPP and optimal CPP using a moving window of 4 hours (n=299). A. The mortality increases steadily when median CPP is increasingly more below the threshold of optimal CPP and decreases slightly with increasing values above *optimal CPP*; B. This graph shows the asymmetrical inversed U-shaped curve between favourable outcome and the difference between the median CPP minus *optimal CPP*; C. A nearly linear relationship between median CPP above the *optimal CPP* threshold and severe disability rate can be seen; D. A U-shaped curve demonstrating that the smallest incidence of unfavourable outcome was associated with median CPP around optimal CPP. CPP = cerebral perfusion pressure; GOS = Glasgow Outcome Scale



A prospective observational study found that, below the optimal CPP, decreases in CPP were paralleled by decreasing PbTiO2 values.[51] Until more prospective validation data are available, PRx and optimal CPP treatment cannot be considered to be a routine monitoring and management tool. However, a recommendation for its use was made in the 2014 brain monitoring guidelines (weak recommendation, moderate quality of evidence).[14] A multicentre feasibility trial to use optimal CPP guided treatment in TBI patients is currently in preparation. To incorporate the problem of using just a single monitoring modality in the complex TBI pathophysiology, also studies to compare *optimal CPP* monitoring and management results with other neuromonitoring modalities (e.g. more focussed on the micro-environment) should be designed. First to collect additional physiological proof of concept and secondly to expose its limitations.[4,52] Also in subarachnoid haemorrhage and intracranial haemorrhage patients the concept of impaired

pressure reactivity and *optimal CPP* has recently been the subject of research.[53,54]

Conclusions

Monitoring and management of ICP and CPP is currently the cornerstone in the care of comatose patients with severe TBI admitted to the ICU. However, class I evidence for the utility of these measures is lacking, and many important questions regarding ICP/CPP-directed management protocols remain unanswered. The difficulties in performing randomised controlled trials of ICP monitoring and treatment have undoubtedly contributed to the paucity of class I evidence in this area. The best study design would be one whereby all participants underwent ICP monitoring, with some randomised to receive targeted therapy and others not, but the ethical justification of such a study would clearly be challenging.

The management of TBI is, therefore, likely to become increasingly based on a more comprehensive multimodal monitoring and management approach rather than relying solely on absolute ICP/CPP values. This will allow individual optimisation of oxygen and energy substrate delivery guided by multimodal monitoring.

What next?

The application of autoregulation guided CPP treatment protocols *(optimal CPP)* needs to be tested prospectively to improve this innovative method,[49,50] to select the correct patients and test its feasibility. Pilot studies have been conducted and results await publication. The next step will be to combine *optimal CPP* results with other neuromonitoring modalities to understand its benefits and limitations. Also studying the *optimal CPP* concept in different groups of TBI patients would be very useful and maybe limit its role in TBI patients with limited brain swelling, such as those with predominant diffuse axonal injury. Ultimately, a randomised control trial will compare *optimal CPP* guided treatment with current standard TBI treatment. This elaborate research project is complementary to the recently launched CENTER-TBI project implementing comparative effectiveness research between centres around the world (https://www.center-tbi.eu/).[22,55] Clearly, the (multimodal) monitor alone does not affect outcome; it is the management changes implemented as a consequence of the information obtained from the monitors that have the impact.

References

1. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9:231-6.
2. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7:728-41.
3. Feyen BF, Sener S, Jorens PG, Menovsky T, Maas AI. Neuromonitoring in traumatic brain injury. Minerva Anestesiol. 2012;78:949-958.
4. Kirkman MA, Smith M. Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/CPP-guided therapy: a standard of care or optional extra after brain injury? Br J Anaesth. 2014;112:35-46.
5. Picetti E, Antonini MV, Lucchetti MC, et al. Intra-hospital transport of brain-injured patients: a prospective, observational study. Neurocrit Care. 2013;18:298-304.
6. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. Lancet. 2012;380:1088-98.
7. Andriessen TM, Jacobs B, Vos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J Cell Mol Med. 2010;14:2381-92.
8. Vespa P, Bergsneider M, Hattori N et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab. 2005;25:763-74.
9. Strong AJ, Hartings JA, Dreier JP. Cortical spreading depression: an adverse but treatable factor in intensive care? Curr Opin Crit Care. 2007;13:126-33.
10. Coles JP. Regional ischemia after head injury. Curr Opin Crit Care. 2004;10:120-5.
11. Vespa PM. The implications of cerebral ischemia and metabolic dysfunction for treatment strategies in neurointensive care. Curr Opin Crit Care. 2006;12:119-23.
12. Chesnut RM, Temkin N, Carney N, et al. A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury. N Engl J Med. 2012; 27;367:2471-81.
13. Sahuquillo J, Poca MA, Arribas M, Garnacho A, Rubio E. Interhemispheric supratentorial intracranial pressure gradients in head-injured patients: are they clinically important? J Neurosurg. 1999;90:16-26.
14. Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care : A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1189-209.
15. Guillaume J, Janny P. [Continuous intracranial manometry; importance of the method and first results]. Rev Neurol (Paris). 1951;84:131-42.
16. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Recommendations for intracranial pressure monitoring technology. J Neurotrauma. 2000;17:497-506.
17. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Guidelines for cerebral perfusion pressure. J Neurotrauma. 2000;17:507-11.
18. Depreitere B, Guiza F, Van den Berghe G ,et al. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. J Neurosurg. 2014;120:1451-7.
19. Howells T, Johnson U, McKelvey T, Enblad P. An optimal frequency range for assessing the pressure reactivity index in patients with traumatic brain injury. J Clin Monit Comput. 2014. [Epub ahead of print]
20. Elf K, Nilsson P, Ronne-Engstrom E, Howells T, Enblad P. Cerebral perfusion pressure between 50 and 60 mm Hg may be beneficial in head-injured patients: a computerized secondary insult monitoring study. Neurosurgery. 2005;56:962-71.
21. Hutchinson PJ, Kolias AG, Czosnyka M, Kirkpatrick PJ, Pickard JD, Menon DK. Intracranial pressure monitoring in severe traumatic brain injury. BMJ. 2013;346:f1000.
22. Maas AI, Menon DK. Traumatic brain injury: rethinking ideas and approaches. Lancet Neurol. 2012;11:12-3.
23. Zhong J, Dujovny M, Park HK, Perez E, Perlin AR, Diaz FG. Advances in ICP monitoring techniques. Neurol Res. 2003;25:339-50.
24. Birch AA, Eynon CA, Schley D. Erroneous intracranial pressure measurements from simultaneous pressure monitoring and ventricular drainage catheters. Neurocrit Care. 2006;5:51-4.
25. Chambers IR, Kane PJ, Signorini DF, Jenkins A, Mendelow AD. Bilateral ICP monitoring: its importance in detecting the severity of secondary insults. Acta Neurochir Suppl. 1998;71:42-3.
26. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. J Neurotrauma. 2007;24 Suppl 1:S59-64.
27. Mauritz W, Steltzer H, Bauer P, Dolanski-Aghamanoukjan L, Metnitz P. Monitoring of intracranial pressure in patients with severe traumatic brain injury: an Austrian prospective multicenter study. Intensive Care Med. 2008;34:1208-15.
28. Biersteker HA, Andriessen TM, Horn J, et al. Factors influencing intracranial pressure monitoring guideline compliance and outcome after severe traumatic brain injury. Crit Care Med. 2012;40:1914-22.

29. Balestreri M, Czosnyka M, Hutchinson P, et al. Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury. Neurocrit Care. 2006;4:8-13.
30. Gabbe BJ, Lyons RA, Lecky FE, et al. Comparison of mortality following hospitalisation for isolated head injury in England and Wales, and Victoria, Australia. PLoS One. 2011;6:e20545.
31. Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. J Neurosurg. 2010;112:1105-12.
32. Cremer OL, van Dijk GW, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med. 2005;33:2207-13.
33. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. J Trauma. 2008;64:335-40.
34. Lazaridis C, DeSantis SM, Smielewski P, et al. Patient-specific thresholds of intracranial pressure in severe traumatic brain injury. J Neurosurg. 2014;120:893-900.
35. Vik A, Nag T, Fredriksli OA et al. Relationship of "dose" of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurg. 2008;109:678-84.
36. Czosnyka M, Smielewski P, Timofeev I, et al. Intracranial pressure: more than a number. Neurosurg Focus. 2007;22:E10.
37. Yau YH, Piper IR, Contant C, Dunn L, Whittle IR. Assessment of different data representations and averaging methods on the Spiegelberg compliance device. Acta Neurochir Suppl. 2005;95:289-92.
38. Czosnyka M, Guazzo E, Whitehouse M et al. Significance of intracranial pressure waveform analysis after head injury. Acta Neurochir (Wien). 1996;138:531-41.
39. Coles JP, Fryer TD, Coleman MR, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. Crit Care Med 2007;35:568-78.
40. Aries MJ, Bergh WM van den. Het meten van de absolute hersendruk zegt onvoldoende. Ned Tijdschr Geneeskd. 8-4-2013, 156.
41. Zweifel C, Lavinio A, Steiner LA, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. Neurosurg Focus. 2008;25:E2.
42. Rosner MJ. The vasodilatory cascade and intracranial pressure. In: Miller JD, Teasdale JM, Rowan JO, Galbraiht SL, Mendelow AD, editors. Intracranial pressure. IV ed. Berlin: Springer Verlag, 1986:137-41.
43. Lingsma HF, Roozenbeek B, Steyerberg EW, Murray GD, Maas AI. Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol. 2010;9:543-54.
44. Robertson CS, Valadka AB, Hannay HJ et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med. 1999;27:2086-95.
45. Grande PO. The Lund concept for the treatment of patients with severe traumatic brain injury. J Neurosurg Anesthesiol. 2011;23:358-62.
46. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL, Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol. 1978;234:H371-83.
47. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. Neurocrit Care. 2009;10:373-86.
48. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997;41:11-7.
49. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med. 2002;30:733-8.
50. Aries MJ, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012;40:2456-63.
51. Jaeger M, Dengl M, Meixensberger J, Schuhmann MU. Effects of cerebrovascular pressure reactivity-guided optimization of cerebral perfusion pressure on brain tissue oxygenation after traumatic brain injury. Crit Care Med. 2010;38:1343-7.
52. Lazaridis C, Smielewski P, Steiner LA et al. Optimal cerebral perfusion pressure: are we ready for it? Neurol Res. 2013;35:138-48.
53. Diedler J, Santos E, Poli S, Sykora M. Optimal cerebral perfusion pressure in patients with intracerebral hemorrhage: an observational case series. Crit Care. 2014;18:R51.
54. Rasulo FA, Girardini A, Lavinio A, et al. Are optimal cerebral perfusion pressure and cerebrovascular autoregulation related to long-term outcome in patients with aneurysmal subarachnoid hemorrhage? J Neurosurg Anesthesiol. 2012;24:3-8.
55. Manley GT, Maas AI. Traumatic brain injury: an international knowledge-based approach. JAMA. 2013;310:473-4.