Current concepts of optimal cerebral perfusion pressure in traumatic brain injury

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Abstract

Traumatic brain injury (TBI) consists of varied pathophysiological consequences and alteration of intracranial dynamics, reduction of the cerebral blood flow and oxygenation. In the past decade more emphasis has been directed towards optimizing cerebral perfusion pressure (CPP) in patients who have suffered TBI. Injured brain may show signs of ischemia if CPP remains below 50 mmHg and raising the CPP above 60 mmHg may avoid cerebral oxygen desaturation. Though CPP above 70 mmHg is influential in achieving an improved patient outcome, maintenance of CPP higher than 70 mmHg was associated with greater risk of acute respiratory distress syndrome (ARDS). The target CPP has been laid within 50-70 mmHg. Cerebral blood flow and metabolism are heterogeneous after TBI and with regional temporal differences in the requirement for CPP. Brain monitoring techniques such as jugular venous oximetry, monitoring of brain tissue oxygen tension (PbrO$_2$), and cerebral microdialysis provide complementary and specific information that permits the selection of the optimal CPP. This review highlights the rationale for use CPP directed therapies and neuromonitoring to identify optimal CPP of head injured patients. The article also reviews the evidence provided by various clinical trials regarding optimal CPP and their application in the management of head injured patients.

Key words: Cerebral perfusion pressure, evidence, management protocols, neuromonitoring, optimal, traumatic brain injury

Introduction

The primary aim of managing patients with acute brain injury is to minimize secondary injury by maintaining cerebral perfusion and oxygenation. The inability of the brain to store metabolic substrates, in the face of high oxygen and glucose requirements, makes it very susceptible to ischemic damage. Cerebral perfusion pressure (CPP) has been used as an index of the input pressure determining cerebral blood flow and therefore perfusion. The question whether the management of patients with TBI should be directed towards CPP or intracranial pressure (ICP) as the target is still a matter of debate. An attempt to optimize the

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patient care in terms of one parameter may appear defeating in terms of another. Consequently, laying down specific target for patient management in requisites for overall outcome seems difficult. In the past decade, more emphasis has been directed toward CPP in patients who have suffered traumatic brain injury (TBI). This attention has primarily arisen from study data documenting the occurrence of brain ischemia early after injury and intensive care unit (ICU) based study data documenting the occurrence of reduced CPP and jugular venous desaturation due to increased ICP supporting the concept that relative cerebral perfusion is more important than any potential increase in ICP.[1] Given that CPP is a modifiable target of intensive care in the patient with TBI, a great deal of effort has been expended in optimizing CPP. In fact, this emphasis has been codified into the current Brain Trauma Foundation guidelines for severe TBI[2] (www.braintrauma.org). Nonetheless, considerable uncertainty exists about the optimal level of CPP. This article will address the main evidence for a CPP threshold and attempt to define the optimal CPP for patients with TBI based on this evidence.

CPP in normal brain

Understanding the basic physiology of cerebral oxygenation is important for the development of effective strategies in

management of head injuries. Cerebral oxygenation involves three main factors, namely the cerebral blood flow (CBF), arterial content of oxygen, and cerebral metabolic rate of oxygen consumption. CPP is the surrogate for CBF measurements and is defined as the mathematical difference between mean arterial pressure (MAP) and the pressure in the small cerebral veins just before they enter the dural sinuses. This represents the pressure gradient driving CBF and thereby, oxygen and metabolite delivery. Normal brain autoregulates its blood flow to provide a constant flow regardless of changes in blood pressure. The regulation of CBF is done by altering the resistance of cerebral blood vessels. Cerebral autoregulation is under the influence of myogenic, metabolic, and neurogenic factors; however, how these factors interact is at present poorly understood. Cerebral blood flow is directly related to CPP and inversely to cerebral vascular resistance (CVR). Because CVR is high when intravascular pressure is high, and CVR is low when intravascular pressure is low; CBF remains constant over the wide range of blood pressures. This constancy of CBF is termed autoregulation of CBF. Though classic description of the, CBF-pressure autoregulation of an autoregulatory plateau or a slightly modified with a sloped plateau is widely accepted, a significant variation in intersubject pattern or shape of the circulatory response to hypotension has been reported. It can vary from the classic pattern usually associated with CBF-pressure autoregulation to hyperregulation or peak on one hand and "none pattern" on the other.[3] The variations in CPP at the lower limit of autoregulation is described as "horizontal variations" and the variations of CBF at the lower limit of autoregulation is described as "vertical variations."[4] Given that none pattern is a natural variation in the physiology of cerebral autoregulation, the arbitrary lower limit of autoregulation, a MAP of 50 mmHg, may have serious consequences. The "none pattern", characterized as vasomotor paralysis with loss of autoregulation, can occur as a result of brain damage in conditions such as severe trauma, excessive increases in ICP, subarachnoid hemorrhage, and cerebral ischemia. It is safest to assume that an individual patient has limited autoregulatory capacity to maintain tight control cerebral perfusion.[4]

Alterations of CPP in injured Brain

The homeostatic mechanisms are often lost after head trauma (CVR is usually increased), and the brain becomes susceptible to blood pressure changes.[5] Other factors that may impair autoregulation include hypoxemia, hypercapnia, and large dose volatile anesthetic. CBF normally decreases in response to hyperventilation. This carbon dioxide reactivity is usually, but not always, preserved following head injury. Cerebral ischemia would be further aggravated by the presence of systemic hypotension.

In the absence of intracranial pathology, ICP is low, usually 5 mmHg or less, and CPP changes reflect alterations in MAP. Either a decrease in MAP or an elevation in ICP will deleteriously alter the effective perfusion pressure, the CPP. When elevated profoundly, ICP alters perfusion of cortical and subcortical structures. Historically, maintenance of a CPP greater than 50 mmHg was considered acceptable in head injury patients. However, following trauma, if autoregulation is preserved it is shifted to the right, therefore a higher CPP is needed to maintain adequate CBF. Increasing CPP also minimizes ICP by reducing intracranial blood volume and cerebral edema via autoregulatory vasoconstriction. Rosner, *et al.*, recommended maintaining CPP greater than 70 mmHg in head injured patients to minimize cerebral ischemia and prevent the cascade of events that result from inadequate perfusion.[6] However, autoregulation is often impaired causing an increase in arterial pressure that leads to an increase in CBF, as well as capillary hydrostatic, increased cerebral edema, and intracranial hypertension; the main tenets of this "Lund" approach.[7] Thus, there is a controversy on the optimal CPP following TBI.

Rationale for use of ICP and CCP directed therapy in TBI
ICP directed therapy
Continuous monitoring of ICP has become the cornerstone in neuromonitoring as it reflects the mass effect that predisposes to cerebral injury and herniation. Though there is substantial evidence that ICP monitoring improves outcome,[8,9] there are no randomized trials confirming the benefit of ICP monitoring and treatment in TBI. Large observation studies[10] and retrospective analysis[11] with severe TBI have shown that patients with monitored and controlled ICP had better outcome than those whose ICP was not controlled. They support an ICP of 20 mmHg as the upper threshold beyond which treatment should generally be initiated.[12] But some studies have indicated that despite extremely high ICP, intense, aggressive management of CPP can lead to good neurological outcomes.[1] Moreover, treatment of ICP has adverse effects, and there are several questions about ICP management that have yet to be definitively answered. The risk of infection increases significantly after 3 days of monitoring.[13] In the case of continuous cerebrospinal fluid (CSF) drainage, continuous intraventricular measurement of ICP may become unreliable.[14]

CPP directed therapy
The clinical use of CPP is based on theoretical suggestions that maintaining optimal cerebral blood flow (CBF) is necessary to meet the metabolic needs of the injured brain. The goal is to preserve the ischemic penumbra and avoid exacerbation of secondary insults, such as excitotoxicity,

free radical production, and inflammation. Higher CPP may contribute to various complications and low CPP has concerns of their own. The issue now is to balance CPP and the question of optimal CPP needs to be addressed.

The "Lund therapy" is a therapeutic approach that focuses on the reduction of ICP by decreasing intracranial volumes.[15] This theory contends that by reducing CPP, there is a reduced risk of promoting vasogenic edema and, therefore, less risk of elevating ICP. However, low CPP causes reduction in cerebral blood flow and predisposes the injured brain to cerebral ischemia and infarction. Within the range of autoregulation, low CPP is associated with increased ICP through compensatory vasodilation in response to decreased perfusion pressure.[16,17] Studies associated with use of microdialysis, jugular venous oximetry, and brain tissue oxygen saturation (PbO$_2$) have found that injured brain that may show signs of ischemia if CPP remains below 50 mmHg and raising CPP above 60 mmHg may avoid cerebral oxygen desaturation.[18-20] These studies suggest that the critical threshold for CPP lies between 50 and 60 mmHg and CPP of less than 50 mmHg be avoided.[21] Rosner and Daughton have shown that a CPP above 70 mmHg is influential in achieving an improved patient outcome.[22] Therefore the concept of prophylactically elevating CPP to avoid brain ischemia and to maintain an ideal CBF has gained support. Subsequently, the randomized controlled trials demonstrated that maintenance of CPP higher than 70 mmHg was associated with five times greater risk of acute respiratory distress syndrome (ARDS).[23] Moreover CPP values higher than 70 mmHg did not offer any outcome benefits.[24] Accordingly, CPP above 70 mmHg has been recommended to be avoided. The CPP to target has been laid within 50-70 mmHg. The cerebral injury following trauma is heterogeneous and therefore the optimal CPP at which cerebral oxygenation is best maintained needs to be identified.

Optimal threshold for CPP following TBI

The individual parameters of CPP (blood pressure and ICP) have been shown to be critically related to outcome from TBI. Systemic hypotension is highly associated with poor outcome.[25,26] As well, elevated ICP predicts increased mortality and less recovery.[25] However, the critical CPP threshold is still debatable.

Role of neuromonitoring to determine optimum CPP

The response of brain to injury is heterogenous. Considerable uncertainty exists about the optimal level of CPP required to restore the cerebral oxygenation. The role of neuromonitoring in determining the optimal CPP for patients with TBI is investigated.

Invasive cerebral monitoring
ICP monitoring

Measurement of ICP is the mainstay of both ICP and CPP directed therapy of TBI. It allows measurement of absolute ICP, calculation of CPP, and identification of optimal CPP.[27] While various methods are available for the measurement of ICP, the "gold standard" is the intraventricular catheter placed in the lateral ventricle. However, placement may be difficult in cases of severe brain swelling and there is also a risk of ventriculitis and hemorrhage.[13] Transducer tipped systems can also be placed in the brain parenchyma or subdural space through a skull bolt or during surgery, with minimal infection and complications. Inaccuracies can occur due to presence of transtentorial and interhemispheric pressure gradients after head injury[28] and zero drifts.

Although it is slowly becoming integral in the management of TBI in most centers, there still exists no Class I evidence supporting its efficacy and its use is still not universal.[29] A host of studies lend support to the fact that ICP monitoring can act as an early warning system that allows appropriate therapy to be instituted.[9,10] However, a few including a recent randomized controlled trials with severe TBI has shown that maintaining monitored ICP at 20 mmHg or less was not superior to care based on imaging and clinical examination.[30,31]

Continuous monitoring ICP also enables online calculation of secondary indices and intervention before the onset of intracranial hypertension. Analysis of pathological waveforms[32-34] cerebrovascular reactivity,[35-38] pressure-volume compensatory reserve using indices like pressure volume index (PVI),[39] correlation coefficient (R) between the amplitude of the fundamental component (A) and mean pressure (P) (RAP),[40,41] and compliance by volume-pressure response (VPR)[42,43] can be calculated. Another ICP-derived index is the cerebrovascular pressure reactivity (PRx), which assesses cerebrovascular reactions by observing the response of ICP to slow spontaneous changes in arterial blood pressure (ABP) by calculating the correlation coefficient between time-averaged data points of ICP and ABP. A positive PRx is associated with passive behavior of a nonreactive vascular bed. A negative value of PRx reflects a normally reactive vascular bed. Changes in PRx guide the treatment of patients. The PRx plotted against CPP shows a U-shaped curve. This indicates that in the majority of patients there is a value of the CPP at which pressure reactivity is optimal. This optimal perfusion pressure can be estimated by plotting and analyzing the PRx-CPP curve in a sequential time-moving window. This potentially useful method is used in an attempt to refine CPP-oriented therapy.[38] The PRx may be useful for defining age-specific and possibly patient-specific optimal targets for CPP after TBI.[36]

Jugular venous oximetry (SjVO$_2$)

Continuous monitoring of SjVO$_2$ performed though the fibreoptic catheter placed in the dominant internal jugular bulb can be used to estimate the balance between global cerebral oxygen delivery and utilization.[44,45] Under conditions of stable cerebral metabolism, changes in SjVO$_2$ reflect changes in CBF.[46] SjVO$_2$ has a prognostic value after neurotrauma and a fall in SjVO$_2$ to below 55% is associated with a poor outcome.[47] CPP level below 60 mmHg was associated with abnormal arteriovenous lactate difference (AVDL) and SjO$_2$.[48] SjVO$_2$ helps to determine the optimal CPP required for the maintenance of cerebral oxygenation. There are several limitations of being a global measure with limited sensitivity to regional changes.[49] SjVO$_2$ does not decrease by <50% until more than 13% of the brain becomes ischemic.[50]

Brain tissue oxygen tension

Continuous measurement of brain oxygen tension can be measured by an invasive probe with sensor using polarographic Clarke type electrode[51] or fibreoptic technology.[52] Normal PbrO$_2$ is in the range of 35-50 mmHg.[53] Ischemic thresholds of between 5 and 20 mm Hg have been suggested.[54-56] Reduced PbrO$_2$ has been associated with a poor outcome after neurotrauma.[57]

Optimal CPP can individualized by monitoring the levels of brain oxygenation. A number of studies have examined the relationship between CPP and cerebral oxygenation. After TBI, PbrO$_2$ increases with CPP and the ceiling of this effect is higher in the areas of focal ischemia The increase in PbrO$_2$ relative to an increase in arterial PO$_2$ is termed brain tissue oxygen reactivity. It is believed that this reactivity is controlled by an oxygen regulatory mechanism (CBF autoregulation), and that this mechanism may be disturbed after brain injury. Soehle and colleagues introduced the concept of 'autoregulation', defined as the ability of the brain to maintain PbrO$_2$ despite changes in CPP,[58] thereby identifying appropriate individual CPP targets. Following these findings, manipulation of PbrO$_2$ by altering PO$_2$ (by increases) or altering the CPP (by MAP increases, ICP decreases, or both) have been investigated with the view to therapy optimization and potential prognostication.[58,59] While some studies showed a relationship between CPP and cerebral metabolic rate of oxygen (CMRO$_2$), Sahuquillo, *et al.*, could not demonstrate a direct relationship between CPP and PbrO$_2$.[60] The PbrO$_2$ readings varied with both normal and supernormal CPP. Stiefel, *et al.*, demonstrated that although PbO$_2$ directed therapy led to improved outcomes, CPP was similar between the groups.[61] CPP and ICP are not surrogates for PbrO$_2$. Evidence that guided therapy using brain tissue oxygenation in addition to ICP and CPP monitoring leads to better outcomes after TBI is also increasing.[62-67]

Cerebral microdialysis

Cerebral microdialysis catheter placement in the vulnerable area after TBI provides on line analysis biochemical changes such as glucose, lactate, pyruvate, glycerol, glutamate, and pH. The use of cerebral microdialysis in TBI can predict poor outcome, assist in clinical decision-making and management of CPP.[20] An increase in the lactate-pyruvate ratio above established thresholds is associated with poor outcome in neurotrauma.[68,69] Biochemical changes of microdialysis occur before low CPP is detectable.[70] Nordstrom demonstrated that lactate in the injured brain increased both when CPP was less than 50 mmHg as well as more than 70 mmHg.[20] Stahl, *et al.*, showed that reducing CPP led to normalization of microdialysis constituents only if CPP was more than 50 mmHg and significant ischemia developed below this threshold.[71] Although increased CPP with vasopressors improved CBF and oxygenation it failed to demonstrate any significant change in microdialysis indices.[63,72] There is no clear consensus on relation between CPP and microdialysis.

Noninvasive cerebral monitoring

Transcranial doppler (TCD)

Currently a lot of work is being done to investigate the application of TCD as a noninvasive estimation of ICP or CPP.[73] Use of the dimensionless TCD-pulsatility index (PI) permit the early identification of patients with low CPP and high risk of cerebral ischemia.[74] Although this work is in its early stages, there has been limited success in correlating CPP derived from TCD with invasive CPP measurement.

It has also been used to test autoregulatory reserve by monitoring changes in CBF velocity in response to changes in MAP.[75] By continuous recording of the flow velocity in the middle cerebral artery (FVmca), the autoregulatory 'threshold' or 'break point' (the CPP at which autoregulation fails) can be easily detected, providing a target CPP value for treatment.[73,76] A decline in autoregulation is associated with poor outcomes.[77] Critical closing pressure (CCP) is calculated from pressure-flow velocity plots from TCD and by linear extrapolation to zero flow. The driving pressure gradient for cerebral perfusion is the difference between MAP and CCP (CCP = zero flow pressure). Therefore, determination of the difference between MAP and CCP should provide an appropriate monitoring of the effective CPP (eff).[78]

Near infrared spectroscopy

Cerebral oximetry records regional saturation of the brain using near infrared spectroscopy (NIRS) and provides a noninvasive method to continuously monitor brain oxygen imbalance. Tentative ischemic thresholds have been described, but clinical data on application of NIRS after TBI is still limited.[79] In patients with neuronal injury, the knowledge

of the status of cerebrovascular autoregulation can help to optimize the management of the CPP. NIRS shows promise for the continuous assessment of cerebrovascular reactivity[80] and cerebral autoregulation in adults.[81] NIRS-based index of cerebrovascular reactivity, called total hemoglobin reactivity (THx) was found to have significant correlation with standard measurements of PRx which requires invasive ICP monitoring. There was a significant agreement with the optimal CPP and ABP assessed with THx and PRx. THx may be of diagnostic value to optimize therapy oriented toward restoration and continuity of cerebrovascular reactivity, especially in patients for who direct ICP monitoring is not feasible.[80] The clinical significance of this new information will need further validation studies.

Evidence for CPP management in TBI

The evidence for CPP in the management of TBI is varied, some supporting increase in CPP and against the rising CPP. The studies have used physiological variables and clinical variables to define the end point. Much of the definition of the former can come from simple physiologic monitoring; the latter requires clinical evidence from controlled trials using outcome as their dependent variable.

Evidence supporting increasing CPP

Physiological indices

When physiological indices are used as dependent variables, there is evidence that low CPP is associated with unfavorable physiological values. Various physiological monitoring parameters have been used to define the optimal CPP [Table 1]. It is important to differentiate physiologic thresholds representing potential injury from clinical thresholds to treat.

Evidence from clinical indices

When CPP per se is evaluated in terms of human clinical outcome, low CPP is frequently found to correlate with poor outcome. Several retrospective and prospective studies have demonstrated clinical benefit of monitoring and maintenance of CPP. But the threshold CPP varies among the studies [Table 2]. Some of these studies, however, were retrospective data analyses without risk adjustment for other parameters.

There is no single optimal CPP following TBI. Moreover, there are no Class 1 study data that indicate an optimal CPP threshold. The aforementioned evidence points to different thresholds of CPP above which physiological markers of injury are decreased, but no single study has involved a clear test of any single CPP threshold in a randomized controlled manner. These studies support CPP as a valuable monitoring parameter in managing patients with severe TBI. It appears that the critical threshold for ischemia generally lies in the realm of 50-60 mmHg and can be further delineated in individual patients by ancillary monitoring.

Evidence against increasing CPP

Early proponents of CPP management reported improved outcomes for severe TBI patients whose CPPs were higher during their treatment course. Subsequent reports call into question whether there is any marginal gain by maintaining the CPP at an elevated level. There is a growing body of clinical evidence that elevating the CPP above the threshold for ischemia may not be beneficial and may indeed have detrimental cerebral and systemic effects. [Table 3]

At this time, it is not possible to posit an optimal level of CPP to target to improve outcome in terms of avoiding clinical episodes of ischemia and minimizing the cerebral vascular contributions to ICP instability. It is becoming increasingly apparent that elevating the CPP via pressors and volume expansion is associated with serious systemic toxicity, may be incongruent with frequently encountered intracranial conditions, and is not clearly associated with any benefit in terms of general outcome. Based on a purely pragmatic analysis of the randomized, controlled trial; Clifton, et al., noted that a CPP target threshold should be set approximately 10 mm Hg above what is determined to be a critical threshold in order to avoid dips below the critical.[24]

Age based thresholds in pediatric patients

The CBF, $CMRO_2$, and cerebral blood volume (CBV) are thought to be affected in the same manner in children as in adult brain by physiologic and pharmacologic maneuvers. The CPP increases with age, starting from 25 mmHg in

Author/year	Parameter used	CPP threshold	Conclusion
Chan, et al., 1992[82]	$SjVO_{o2}$/TCD	70 mmHg	<70 mmHg: Jugular venous desaturation and increased PI on TCD
Vespa, P et al., 1998[83]	Mmicrodialysis	70 mmHg	<70 mmHg: Increased glutamate
Nordstrom 2003[20]	Microdialysis of injured brain	50-60 mmHg	No benefit of higher CPP
MenzelMenzl, et al., 2003[84]	Pbr O_2	70 mmHg	Transient drop in $PbrO_2$ when CPP decreased to below 70 mm Hg.
Kiening, et al., 1996; Artru, et al., 1998; Bruzzone, et al., 1998[85-87]	Pbr O_2	>60 mmHg	Optimizses Pbr O_2

Table 1: Evidence for a critical CPP threshold from physiological indices

CPP = Cerebral perfusion pressure, $SjVO_2$ = jugular venous oximetry, PI = Pulsatility index, TCD = Transcranial doppler

Table 2: Evidence for critical CPP threshold from clinical indices

Author/year	Study description	Threshold CPP	Conclusion	Level of evidence
Changaris, *et al.*, 1987,[88]	Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 136 patients with severe TBI.	60 mm Hg	All patients with CPP of 60 mm Hg on the second post-injury day died; more patients had a good outcome than died when CPP was 80 mm Hg	III
McGraw, 1989[89]	Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 221 patients with severe TBI.	80 mm Hg	The likelihood of good outcomes was significantly higher and of death significantly lower if CPP was 80 mm Hg	III
Rosner and Daughton *et al.*, 1990[22]	Prospective study of outcomes in 34 TBI patients who were managed by actively keeping CPP above 70 mm Hg	>70 mm Hg	The mortality rate was 21%, and good recovery rate was 68%	III
Cruz, *et al.*, 1998[44]	Prospective observational study of 6-month outcomes in adults with severe TBI characterized by brain swelling where 178 were treated according to cerebral oxygen extraction and CPP and 175 were treated with management of CPP alone.	70 mmHg	Mortality in the cohort managed according to jugular venous saturation was 9% versus 30% in the CPP group	III
Robertson, *et al.*, 1999[19]	RCT comparing the influence of CPP- versus ICP-targeted management on 6-month outcome in 189 adults with severe TBI	70 mmHg	No difference in outcome. ICP group had more jugular desaturations but these were rapidly managed. CPP group had more systemic complications ARDS was five times greater in the CBF-targeted group	II
Juul, *et al.*, 2000[90]	Retrospective review of the 427 adult patients in the Selfotel RCT of the influence of ICP and CPP on neurological deterioration and 6 month outcome	60 mmHg	CPPs greater than 60 mm Hg had no significant influence on outcome	III
Contant, *et al.*, 2001[23]	Retrospective analysis of the factors related to the occurrence of ARDS in the 189 adults with severe TBI from the RCT comparing CPP- with ICP-targeted		Five-fold increase in risk of ARDS in CPP group strongly related to use of pressors	III
Steiner, *et al.*, 2002[38]	Prospective observation of CPP and outcome at 6 months for 114 adults with moderate or severe TBI	Individualize by PRI	Optimal CPP for each patient was calculated based on the pressure reactivity index. Patients whose mean CPP varied above or below the optimal CPP were less likely to have a favorable outcome	III
Andrews, *et al.*, 2002[91]	Prospective analysis of the influence of quantitative data on secondary insults on 1 year outcome for 69 adults with mild, moderate, and severe TBI		Low CPP and hypotension were powerful predictors of death and poor outcome	III
Clifton, *et al.*, 2002[24]	Retrospective review of 393 patients from the multicenter randomized hypothermia trial, comparing 60 month outcome with ICP, MAP, CPP, and fluid balance	60 mmHg	Poor outcome was associated with CPP of 60 mm Hg No benefit to maintaining CPP of 70 mm Hg	III
Howells, *et al.*, 2005[27]	Prospective observation of 6-month outcome for 131 severe TBI adults who received either ICP (Lund) or CPP-targeted acute care	50-60 mm Hg	Patients with intact autoregulation had better outcomes with CPP elevation. Patients with defective autoregulation had better outcomes with ICP targeted acute care and lower CPPs of 50-60 mm Hg	III

CPP = Cerebral perfusion pressure, TBI = Traumatic brain injury, RCT = Randomized clinical trial, ICP = Intracranial pressure, ARDS = Acute respiratory distress syndrome, CBF = Cerebral blood flow, MAP = Mean arterial pressure

neonates and increasing to 80-90 mmHg in adults. Current guidelines for ICP and CPP thresholds suggest that age-based thresholds should be adopted, but few studies have included the youngest children affected by TBI (those <2 years of age). A retrospective analysis of pediatric TBI concluded that initial CPPs between 40 and 70 mmHg were found to have a better neurological prognosis than those with CPPs either higher or lower than that range.[94] A recent retrospective analysis has shown that despite good ICP control in pediatrics, there was still a 50% incidence of unfavorable outcome, suggesting that there may be unique physiologic parameters that need to be targeted in infants with severe TBI. Data from 22 children (of whom 81% had suffered from inflicted childhood neurotrauma) were analyzed in the first 7 days. Children with unfavorable outcome had more hourly readings of CPP of <45 mmHg compared to children with favorable outcome. There was no difference between the number of hourly readings of ICP of >20 mmHg between the outcome groups. This study suggests a CPP target threshold of 45 mmHg.[95] Monitoring of tissue oxygen, PRx, and

Table 3: Evidence against increasing CPP

Author/year	Methods	Comment
Rosner and Daughton[22]	CPP 70 mmHg compared with historical controls from trauma data bank	No adjustment for differences between the two populations. One subsequent analysis suggested that the outcome differences disappeared if there was adjustment for the incidence of in-ICU hypotension
Robertson, *et al.*[19]	CBF targeted group: Hypervolemia-hypertension treatment to elevate CPP. ICP targeted group (CPP > 50)	50% fewer hypoxemic events in the CBF targeted group, but no difference in overall outcome. CBF-targeted group experienced worse pulmonary edema and ARDS
Contant, *et al.*[23]	RCT on ICP-based management versus CPP-based management	Five-fold increase in risk of ARDS. Increased administration of epinephrine and dopamine. More likely to develop refractory intracranial hypertension, two times more likely to be vegetative or dead at 6-month follow-up
Juul, *et al.*[90]	International, multicenter, randomized, double-blind Selfotel trial	Did not find a benefit of maintaining CPP greater than 60 mm Hg.
Downard, *et al.*[92]	Children with TBI: Mean CPP in the range of greater than 40-50, 50-60, 60-70, or greater than 70 mmHg	No difference in outcome could be demonstrated. Excessive CPP levels may be associated with hyperemia and harm
Vespa, *et al.*[83]	Microdialysis	A CPP greater than 100 mmHg was associated with an increase in glutamate
Cruz, *et al.*[44]	Prospective study managed based on jugular venous saturation and CPP target CPP of 70 mmHg	Mortality in the cohort managed according to jugular venous saturation was 9 versus 30% in the CPP group
Reinert, *et al.*[93]	$PbrO_2$	At both extremes of CPP, brain O_2 levels can be lower than in the range of 70-80 mmHg
Asgeirsson, *et al.*[7]	$SjVO_2$	Hyperemia occurred with CPP values higher than 70-100 mmHg with the elevation of both jugular venous oximetry and ICP. Advocates normalization or reduction of CPP in the setting of deep sedation rather than selection of a CPP threshold
Sahuquillo, *et al.*[60]	Studied PbO_2 values as a function of CPP in severe TBI patients	Did not find that low PbO_2 values were predictable with low CPPs ranging from 48 to 70 mmHg. Raising CPP did not increase oxygen availability in the majority of cases

CPP = Cerebral perfusion pressure, ICU = Intensive care unit, TBI = Traumatic brain injury, RCT = Randomized clinical trial, ICP = Intracranial pressure, ARDS = Acute respiratory distress syndrome, CBF = Cerebral blood flow, MAP = Mean arterial pressure, $SjVO_2$ = Jugular venous oximetry

autoregulation were found to be useful in determining optimal CPP in pediatric TBI also.[36,96,97] A prospective study is needed to fully determine what goals should be targeted for this vulnerable population.

Selection of the optimal CPP following TBI

Steiner, *et al.*, used an on-line method of measuring cerebral pressure autoregulation and estimated the CPP at which autoregulation appeared most robust in 60% of their patient group.[38] The more closely the mean CPP at which individual patients were maintained approximated the CPP at which their autoregulation was optimal, the more likely that patient was to have a favorable outcome. The use of $SjVO_2$ in conjunction with measuring CPP may provide a method of selecting the optimal CPP for an individual patient. Based on continuous $SjVO_2$ values, a CPP level can be selected that provides adequate O_2 delivery and CBF. In many cases, especially under conditions of deep sedation, a CPP greater than 70 mmHg will provide O_2 delivery and CBF in excess of O_2 demand[7] and may promote hyperemia and therefore raised ICP. Similarly, using other brain monitoring devices,[71,98-100] such as $PbrO_2$ probes and microdialysis probes, optimization of CPP to lower or higher levels may be possible. Nonetheless, the more studies are required to determine how best to integrate additional brain monitors in the decision process about the optimization of CPP. Based on

the currently available evidence Brain Trauma Foundation has made the following recommendations for threshold CPP[21] (www.braintrauma.org).

Recommendations of brain trauma foundation

a. Level I: There are insufficient data to support a Level I recommendation for this topic.
b. Level II: Aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome (ARDS).
c. Level III: CPP of 50 mmHg should be avoided. The CPP value to target lies within the range of 50-70 mmHg. Patients with intact pressure autoregulation tolerate higher CPP values. Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management.

Conclusions

The selection of an optimal CPP following TBI is possible in theory, but in practice many uncertainties remain. Cerebral blood flow and metabolism are heterogeneous after TBI both in space (regional differences) and time (temporal profile). Thus, different regions of the brain may require different levels of CPP and different levels of CPP may be needed at

different time points after injury. Although optimal CPP is essentially an imaginary number, brain monitoring techniques such as jugular venous oximetry, monitoring of $PbrO_2$, and cerebral microdialysis provide complementary and specific information that permits the selection of the best CPP for an individual patient over time.

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