Review Article

Cerebral Perfusion Pressure in Neurotrauma: A Review

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It is now well recognized that low cerebral blood flow (and cerebral perfusion pressure (CPP)) is associated with poor outcome after traumatic brain injury. What is less clear is whether altering cerebral blood flow or CPP will lead to clinical improvement. Initial studies indicated that increasing CPP may be beneficial and the Brain Trauma Foundation acknowledged this by incorporating a target of 70 mm Hg in the 1996 guidelines. However, the lack of a demonstrable benefit and the increased complication rate associated with this approach led to a reduction in the CPP goal to 60 mm Hg. More recently, evidence that autoregulation may be disrupted after traumatic brain injury has led some authors to propose an individualized approach to CPP management. Furthermore, with the advent of advanced neuromonitoring techniques, clinicians are able to more closely monitor the effects of hemodynamic manipulations on cerebral metabolism. As yet, there is no strong outcome evidence to support this approach. Until then, the current debate over the optimal approach to CPP management is likely to continue.
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CEREBRAL PERFUSION PRESSURE-GUIDED THERAPY AFTER TRAUMATIC BRAIN INJURY

The impetus for cerebral hemodynamic monitoring in neurotrauma first arose from the original "talk and die" studies that described a group of head-injured patients "who talked and then subsequently died."[1] At necropsy, hypoxic or ischemic brain damage was observed in a variable proportion of patients raising the possibility that systemic or cerebral hypoxia after trauma may have contributed to the poor neurological outcome.[2,3] Data from the studies of Bouma et al., and Jaggi et al., also demonstrated an inverse relationship between cerebral blood flow (CBF) and neurological outcome after traumatic brain injury (TBI).[4,5] The Traumatic Coma Data Bank study reaffirmed the importance of hypoxia and hypotension in determining outcome from neurotrauma.[6–8] Improved understanding of the pathophysiology of neurotrauma influenced clinical practice in two ways: a) a plethora of monitoring modalities were developed for evaluating cerebral hemodynamics and oxygenation and b) squeezing oxygenated blood through a swollen brain by increasing arterial blood pressure (BP) became the cornerstone of therapy in patients with TBI.

Understanding the physiology of cerebral oxygenation is critical to the development of effective management strategies for limiting cerebral insults after injury. The three main factors determining cerebral oxygenation are CBF, arterial oxygen content and cerebral metabolic rate of oxygen consumption ($CMRO_2$).[9,10] In clinical practice, monitoring of arterial blood gas tensions is routine in most critically ill patients. $CMRO_2$ measurement is not commonplace as it is technically cumbersome and difficult to manipulate in clinical practice. Similarly, the routine measurement of CBF (e.g., nitrous oxide or the Xenon 133 radiotracer) is not practical in the intensive care unit.[11,12] The cerebral perfusion pressure (CPP) is the most frequently used surrogate for CBF measurements. CPP is easily performed, provides a continuous measurement and forms part of the management guidelines of the Brain Trauma Foundation (BTF).[13–15] However, the optimal CPP threshold continues to generate controversy.

This article will review the concept of "optimal CPP," and examine its relationship to CBF, metabolism, brain tissue oxygenation and neurological outcome.

THE BASIC PHYSIOLOGY

Physiological Factors Affecting Cerebral Perfusion Pressure

CPP is the difference between the mean arterial BP (MAP) and the intracranial pressure (ICP). It represents the vascular pressure gradient across the cerebral beds and should be measured at the same level. CBF is

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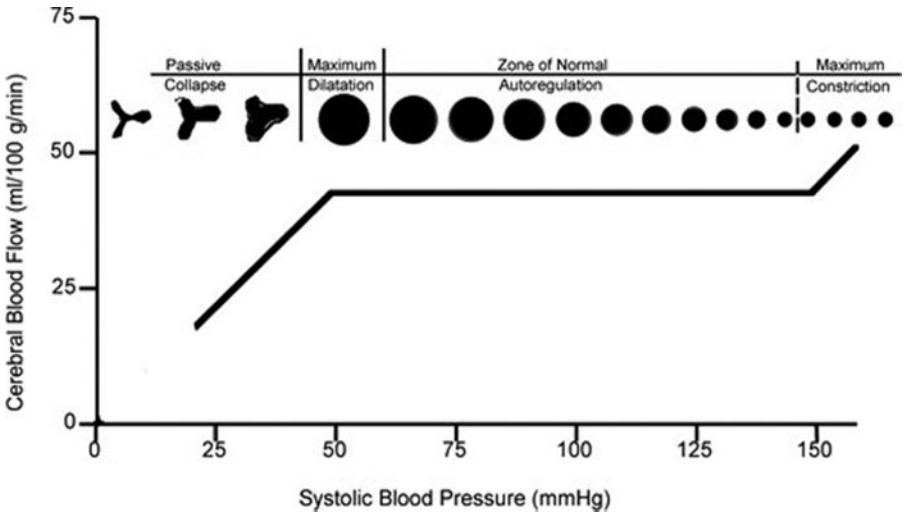

Figure 1. Graphic representation of the relationship between cerebral blood flow and mean blood pressure in the normal brain. This may be partially or completely absent following traumatic brain injury leading to a situation where cerebral blood flow becomes dependent on blood pressure.

determined by both CPP and cerebrovascular resistance (CVR) as shown: CBF = CPP/CVR.[9,16,17] CVR (and thus CBF) are affected by a number of physiological variables including arterial carbon dioxide gas tension ($PAco_2$), which has a near linear relationship with CBF within the physiological range (producing a 2%–4% increase of CBF for each millimeter of mercury of $PAco_2$ increase), and cerebral metabolic rate for oxygen and glucose which has a direct relationship with CBF.[18]

Under normal circumstances, the brain is able to maintain a relatively constant CBF of approximately 50 mL per 100 g/min over a wide range of CPP (approximately 60 to 150 mm Hg).[19] This process termed "autoregulation" is a fundamental physiological premise governing the CPP/CBF relationship.

Autoregulation

Autoregulation can be defined as the inherent ability of arteries to vasodilate or vasoconstrict in response to changing perfusion pressure, thereby maintaining a relatively stable CBF (Fig. 1). Metabolic, myogenic, and neurogenic mechanisms have been invoked to explain control of autoregulation.[20–22]

Autoregulation can become impaired or abolished by a variety of insults including trauma, hypoxemia, hypercapnia, and large-dose volatile anesthetics.[23] This is not an all-or-none phenomenon, but is a continuous spectrum of adaptive response in CVR to a change in perfusion pressure and may vary from region to region. In patients with preserved autoregulation, an increase of MAP may be beneficial as the compensatory vasoconstriction mediated by the autoregulatory response would result in a decrease in ICP.[24] Moreover, some TBI patients have a rightward shifted lower limit of autoregulation, necessitating the maintenance of a higher MAP than normal.[25] It has therefore been suggested that evaluation of the cerebral autoregulatory (CA) capacity may facilitate clinical management of these patients.

Several dynamic and static tests for autoregulation are commonly used in patients with neurotrauma including the autoregulatory index, the transient hyperemic response test and the pressure reactivity index. A detailed description of these tests is outside of the scope of this article and the reader is referred to References.[26–29]

There have been a number of clinical studies examining autoregulation after TBI. Czosnyka et al.[30] have demonstrated a correlation between impaired autoregulation and poor neurological outcome in patients with TBI. Autoregulation was noted to be abnormal within the first 2 days after injury and often asymmetrical (different between the two hemispheres). They were able to identify individual thresholds of vascular reactivity for CPP, ICP and ventilator variables. Some authors have suggested that management should be altered depending on the ability to identify a lower inflection point on the CA curve.[31,32] The implication is that CPP should be kept greater than this point when CA is intact, whereas other end-points should be used to titrate CPP when CA is absent (i.e., jugular venous oxygen saturation ($SjVO_2$), cerebral oxygen measurement, etc.).

There are data to support individualizing treatment strategies based on the state of autoregulation. Steiner et al.[32] used the pressure reactivity index to define an optimal CPP for each individual based on the premise that the autoregulatory range varies among patients. Howells et al.[31] compared CPP to ICP-directed therapy in two Groups of patients with TBI. They concluded that ICP-orientated therapy led to better outcomes in pressure-passive patients, whereas hypertensive CPP therapy was better in patients with intact autoregulation.

Is There A Critical Cerebral Perfusion Pressure Threshold in Traumatic Brain Injury?

As autoregulation may be impaired early after TBI, the problem is setting a single goal for CPP in a heterogeneous group of patients with differing levels of autoregulation. Several end-points have been used to define the target CPP, including the relationship

between CPP and CBF, and CPP and brain tissue metabolites. These are discussed briefly below.

The critical threshold of CBF for the development of irreversible tissue damage after TBI is 15 mL 100 g/min.[33] The corresponding figure after ischemic stroke is 5–8.5 mL 100 g/min. As techniques for measuring CBF are largely experimental, most clinicians use CPP as a surrogate. Chieregato et al. demonstrated poor correlation between global CBF and different CPP ranges in severe head injury.[34] This was attributed to preserved autoregulation in their study group. Conversely, Czosnyka et al.[28] demonstrated impaired autoregulation in patients with TBI, making it difficult to derive a relationship between CPP and CBF.

Given this heterogeneity, interpreting results from clinical outcome studies can be difficult. Researchers have therefore investigated the physiological impact of CPP on a variety of cerebral tissue metabolites. The three metabolic end-points investigated in detail include brain tissue oxygenation, positron emission tomography (PET) scan and cerebral microdialysis. The major limitations of the metabolite approach include the controversy on the ideal area for sampling and the limited ability to extract global conditions from local data. Nevertheless, cerebral metabolite examination provides some indication of the impact that changes in CPP have on brain function.

Cerebral Perfusion Pressure Versus Tissue Oxygenation

Cerebral oxygenation can be assessed both globally using $SjVO_2$ monitoring or locally using brain tissue oxygen tension (PbO_2)probes. $SjVO_2$ (jugular bulb venous oxygen saturation) is a function of the arterial oxygen saturation, CBF and $CMRO_2$. Under conditions of stable cerebral metabolism, changes in $SjVO_2$ reflect changes in CBF. Normal values range from 55%–75%. There is evidence that jugular venous desaturation is associated with poor neurological outcome.[35] However, this technique has not found uniform acceptance among intensivists because of its invasive nature, the difficulty in identifying the appropriate side for cannulation, and erroneous readings resulting from catheter malposition, impaction and thrombus formation.[36] $SjVO_2$ has been found to correlate strongly with tissue Po_2 in the normal brain, but not in the contused brain.[37] It is an index of CBF only if $CMRO_2$ is assumed to be constant.

PbO_2 probes measure the partial pressure of oxygen in the extracellular compartment of the brain, which is the balance between oxygen delivery and consumption and is influenced by changes in capillary perfusion. Hypoxic thresholds vary according to placement of probe and physiological conditions. Positioning is critical as sampling occurs in an area of approximately 15 mm^2 around the probe.

A number of studies have examined the relationship between CPP and cerebral oxygenation. Cruz et al. failed to demonstrate a relationship between CPP and $CMRO_2$, $SjVO_2$ or CBF over a broad range of CPP (60–130 mm Hg).[38] Similarly, Sahuquillo et al.[39] were unable to demonstrate a linear relationship between CPP and low PbO_2. PbO_2 readings less than 15 mm Hg were noted with both normal and supranormal CPPs. Moreover, therapy targeted at improving PbO_2 may not necessarily correlate with CPP. Steifel et al. demonstrated that, although PbO_2-directed therapy led to improved outcomes, CPP was similar between the groups.[40] Not all interventions that increase CPP (i.e., vasopressors, mannitol, and hyperventilation) have equal effects on PbO_2. The effects of vasopressors on cerebral oxygen metabolism are variable. In general, once CPP is less than the autoregulatory range, cerebral oxygenation worsens. The level at which this occurs appears to vary and may represent differences in autoregulation.[41–52] (Table 1).

Cerebral Perfusion Pressure Versus Positron Emission Tomography

PET is an imaging technique that can estimate CBF, cerebral blood volume, $CMRO_2$ and oxygen extraction fraction (OEF). This technology can be used to assess the impact of changes to CPP on cerebral oxygenation.

Johnston et al. investigated whether augmentation of CPP improved CBF and tissue oxygenation as assessed by PbO_2 and microdialysis.[45] They found that CPP changes (70–90 mm Hg) correlated with tissue oxygenation and CBF, but not with microdialysis variables (glucose, lactate, pyruvate, and glycerol). This supports the observation that changes in cerebral oxygen supply do not always correlate with metabolic requirements. The findings of Coles et al. were similar to that of Johnston et al. CPP increases (68–90 mm Hg)[53] were associated with an increase in CBF and decrease in $CMRO_2$ and OEF, mainly in patients with a large ischemic burden. Steiner et al.[54] using PET examined the pericontusional response to increasing CPP in 18 patients with TBI. They found the maximum increase in CBF in the normal brain with minimal increase in the ischemic areas. These studies once again reaffirm the view that, although increasing CPP may improve cerebral oxygenation, the results are by no means universal and vary depending on the area of brain examined.

Cerebral Perfusion Pressure Versus Microdialysis

Cerebral microdialysis (using a catheter ideally placed in the frontal lobe)[55] is a tool for investigating the metabolic status of the injured brain. Interstitial glucose, lactate and pyruvate concentration provide direct information about glucose delivery and utilization, whereas the lactate/pyruvate ratio reflects the intracellular redox state. Furthermore, pH, glycerol (an index of cell membrane breakdown) and glutamate (a measure of cerebral excitotoxicity) can also be measured. Studies examining the relationship between CPP and metabolic end-points have produced conflicting results.

Nordstrom studied brain tissues with varying degrees of injury.[56] He demonstrated that lactate in the more injured brain increased when CPP $<$50 mm Hg but also when CPP $>$70 mm Hg. There was little change in the normal brain. He surmised that this was due to differences in regional blood flow characteristics. Stahl

Table 1. Studies Comparing CPP with PbO_2

Study	Patients	Method/objective	Results
Johnston et al.[46]	11 TBI patients	Using PET and brain tissue oxygen sensor, cerebral oxygenation assessed following augementation of CPP from 70–90 mm Hg	CPP augmentation resulted in an increase in PbO_2 from 17 ± 8 mm Hg to 22 ± 8 mm Hg. No change in microdialysis parameters
Lang et al.[48]	14 patients with severe TBI	The change in PbO_2 following augmentation of CPP with norepinephrine	A plateau phase for the CPP/PbO_2 relation was noted. The increase in MAP was associated with a decrease in ICP
Stiefel et al.[52]	6 pediatric TBI	Monitoring of PbO_2 with goals of CPP >40 mm Hg and ICP <20 mm Hg	Significant correlation between CPP and PbO_2 Significant negative correlation between ICP and PbO_2
Al-Rawi et al.[41]	40 adult TBI	Paratrend 7 multiparameter sensor inserted to investigate relationship btw PbO_2, pH and CPP	Poor correlation btw CPP and tissue PbO_2 when CPP <60 mm Hg. PbO_2 stable if CPP >60 mm Hg
Bruzzone et al.[42]	7 adult TBI	CPP, $SjVO_2$ and PbO_2 were monitored for 7 d postTBI	Significant positive relationship between CPP and PbO_2 when CPP >60 mm Hg
Marin-caballos et al.[49]	22 adult TBI	Prospective study. PbO_2 measured in uninjured area of brain. Standard management	50% PbO_2 <15 mmHg when CPP <60 mm Hg. This improved although still possible when CPP 60–70 mm Hg
Reinert et al.[51]	20 adult TBI	Prospective observational study of intraparenchymal oxygen and microdialysis catheters	Good correlation between CPP and PbO_2 which peaked at CPP >78 mm Hg. However, no correlation with microdialysis measurements
Fortune et al.[44]	14 adult TBI	$SjVO_2$, ICP and CPP monitored in relation to changes in MAP (eg. after suctioning)	ICP and $SjVO_2$ increased in response to CPP suggesting loss of autoregulation
Kiening et al.[47]	21 adult TBI	$SjVO_2$, ICP, CPP and PbO_2 were monitored for changes in management of TBI	Increasing CPP from 32 mmHg to 67 mm Hg significantly improved PbO_2 by 62% and reduced ICP. Further raising CPP from 68 mm Hg to 84 mm Hg did not alter PbO_2. Hyperventilation normalized ICP and CPP but significantly reduced PbO_2
Meixensberger et al.[50]	53 adult TBI	Compared PbO_2 guided CPP management to historical controls	Found PbO_2 guided CPP management led to less hypoxic events
Chan et al.[43]	41 adult TBI	Monitored CPP, ICP, TCD and $SjVO_2$ following TBI	CPP <70 mm Hg correlated with increase in PI index and decrease $SjVO_2$. This did not occur when CPP >70 mm Hg
Johnston et al.[45]	11 adult TBI	Assess changes in PbO_2 following MAP augmentation with dopamine as compared to norepinephrine. Goal CPP of 65 mm Hg	CPP augmentation with norepinephrine but not dopamine increased brain tissue oxygen

PET = positron emission tomography; TBI = traumatic brain injury; CPP = cerebral perfusion pressure; PbO_2 = partial pressure of cerebral oxygen; MAP = mean arterial pressure; ICP = intracranial pressure; $SjVO_2$ = jugular venous oxygen saturation; TCD = transcranial doppler; PI index = pulsatility index.

et al. demonstrated that reducing CPP led to a progressive normalization of microdialysis constituents as long as CPP was >50 mm Hg but that less than this threshold, significant ischemia developed.[57]

In two separate studies, Johnston et al. attempted to measure the effect of artificially increasing CPP with vasopressors on measures of tissue oxygenation and metabolism including microdialysis.[45,46] Despite evidence of improved CBF and oxygenation, there was no significant change in microdialytic indices. Conversely, Hlatky et al. found a significant increase in microdialysis lactate and pyruvate in a subgroup of patients with TBI who developed focal delayed traumatic injury.[58] This occurred in the absence of global changes in ICP, CPP, and $SjVO_2$.

Although there seems to be a relationship between CPP and oxygen metabolism in the injured brain, the optimal level of CPP is difficult to determine. It is also

Table 2. Comparison of CPP Management Protocols

Therapy	Theoretical concept	Goals	Supporting evidence
Management of cerebral volume and perfusion[61,62]	Disruption of BBB leads to leakage of fluid into cerebral tissue worsening ICH. CPP based therapy leads to increased hydrostatic pressure in the setting of deranged autoregulation and an increased ICP	Reduction in capillary hydrostatic cerebral pressure with antihypertensive therapy. Maintenance of COP with 20% albumin CPP 60–70 mm Hg but as low as 50 mm Hg as long as ICP normal	11 pt non-randomised study comparing outcome with that predicted by injury. 53 pt study comparing treatment group with historical controls Both suggested a good outcome with Lund therapy but the lack of a randomized prospective study has limited the universal acceptance of this therapy
CPP based[25]	Autoregulation after TBI is shifted to the right and therefore a much higher CPP is necessary to maintain cerebral perfusion	Maintenance of CPP >70 mm Hg with a combination of albumin, vasopressors and mannitol. CPP could be raised to 80–90 mm Hg if necessary	Non-randomised study of 158 pts comparing outcome to the Traumatic Coma Data Bank Subsequent studies have suggested that there may be significant adverse effects (ARDS etc) associated with CPP >70 mm Hg
CBF/oxygen extraction coupling[40]	TBI leads to reduced cerebral oxygen extraction with consequent relative cerebral hyperperfusion. Optimising hyperventilation improves oxygen extraction coupling with better ICP control	Ventilation is manipulated to optimise $SjVO_2$ and ICP	Prospective randomised study with 178 pts and 175 controls. Groups matched by CT rather then randomisation. Mortality rate in treatment group was 9% and 30% in control There is no data comparing ICP and CPP during the study period. Previous studies suggest hyperventilation leads to worse outcome (although these were not guided by $SjVO_2$)

BBB = blood brain barrier; CPP = cerebral perfusion pressure; CBF = cerebral blood flow; COP = colloid osmotic pressure; ICP = intracranial pressure; $SjVO_2$ = jugular venous oxygen saturation; ARDS = acute respiratory distress syndrome; TBI = traumatic brain injury; ICH = intracranial hypertension.

unclear whether to monitor the injured or normal cerebral tissue. Further studies using multimodal monitoring techniques may clarify the situation.

CONTROVERSIES OF CEREBRAL PERFUSION-TARGETED THERAPY IN NEUROTRAUMA

As noted, optimizing cerebral perfusion continues to generate controversy. Three broad approaches have been proposed: CPP-targeted approach, CBF/ICP-targeted approach, and maintenance of cerebral volume/CPP approach. (Table 2).

Cerebral Perfusion Pressure-Based Therapy

Rosner et al. were among the first to study the effects of aggressively managing CPP.[25] The main tenets of their theory are that autoregulation after TBI is preserved but shifted to the right, therefore a higher CPP is required to obtain adequate CBF. Increasing CPP can also minimize ICP by reducing intracranial blood volume and cerebral edema through autoregulatory vasoconstriction. Thus, by stabilizing CPP at higher levels, they suggested that ICP could be better controlled without ischemia.

To support their theory, they undertook a nonrandomized study of 158 TBI patients presenting with a Glascow Coma Scale (GCS) score of <7.[25] A combination of cerebrospinal fluid drainage, vasopressors (phenylephrine and dopamine) and mannitol was used to keep CPP >70 mm Hg. CPP could be increased to 80–90 mm Hg under certain conditions. The average GCS on admission was five. The mortality rate was 29% with a favorable recovery at 10.5 mo in 59% (Glascow Outcome Scale score 4–5) of patients. This compared favorably with outcomes from the Traumatic Coma Data Bank. During the study, the average ICP was 27 ± 12 mm Hg for the first 10 days and 25 ± 12 mm Hg for the entire course. The mean CPP was greater than 80 mm Hg.

Based on their results, the authors argued that a) the injured brain requires a CPP more than normal before adequate CBF can be attained, b) ICP-based therapy is transient, toxic and should be used sparingly, c) TBI injury shifts the CA curve to the right which explains the finding of dysautoregulation in older studies (i.e., CPP not high enough), and d) autoregulation is not completely absent, therefore increasing CPP will lead to decrease ICP.

Cerebral Blood Flow/Oxygen Extraction Coupling Theory

Cruz argued that patients with TBI present with pathologically reduced levels of cerebral oxygen consumption as indicated by reduced cerebral oxygen extraction leading to relative cerebral hyperperfusion.[59] As cerebral hyperperfusion has been associated

with worse outcome, optimized hyperventilation may improve CBF/oxygen extraction coupling, normalizing ICP. He further argued that Rosner et al. did not assess CBF, cerebral blood volume or oxygen extraction when determining vasodilatory cascade, only ICP and BP, leading to the erroneous conclusion that autoregulation is intact in most patients.

Cruz et al. performed two nonrandomized studies to examine the CBF/oxygen extraction-coupling hypothesis. In the first, they investigated 66 adults with severe TBI.[38] There was no correlation between CPP and CBF, atriovenous oxygen content difference and cerebral oxygen consumption. Furthermore, reduced CBF was associated with normal OEF supporting reduced cerebral metabolism and luxury perfusion.

Cruz subsequently prospectively compared the outcome of patients undergoing monitoring and management of oxygen extraction with CPP (CPPe) (n = 178) versus CPP alone (n = 175).[59] The mortality rate in the extraction group (9%) was significantly less than the CPP group (30%). The duration of ICP monitoring was only 6.5 days in the CPPe group versus 10.5 in the CPP group and the CPPe group had overall better outcome. There are, however, no data comparing CPP and ICP during the study period. Cruz argued that TBI leads to relative hyperperfusion after 12 hrs. Furthermore, CPPe shortens the period of hyperemia and thus the length of time needed for monitoring.

Management of Cerebral Volume and Perfusion

The Lund approach is based on the observation that in normal individuals, the blood–brain barrier creates an osmotic gradient between the cerebral tissue and the intravascular compartment, regulating the movement of fluid across the membrane.[60] However after head injury, blood–brain barrier permeability increases reducing the effectiveness of the brain's normal volume-regulating mechanisms. Consequently, forces other than the crystalloid transcapillary force control brain volume (e.g., capillary hydrostatic and plasma oncotic pressure). Furthermore, autoregulation is often impaired causing an increase in arterial pressure which leads to an increase in CBF and capillary hydrostatic pressure, worsening cerebral edema and intracranial hypertension.

The main tenets of the Lund approach include

1. Reduction of capillary hydrostatic pressure by reducing systemic pressure using β – blockade, α antagonist and angiotensin II inhibition
2. Maintenance of normovolemia and colloid osmotic pressure with 20% albumin and blood
3. Prevention of cerebral vasoconstriction by maintaining cerebral oxygenation and avoiding hyperventilation and cerebral vasoconstrictors

There have been four small nonrandomized studies evaluating Lund therapy in adults after TBI.[61–64] Asgeirsson et al. described a case series of 11 severely injured patients with a GCS <8, impaired cerebral reactivity to hyperventilation and computed tomography scan consistent with diffuse injury.[61] Nine patients had good/moderate disability and two died. The authors suggested that similar groups have shown mortality rates of 100%.

Another study by Eker et al. compared Lund therapy in a group of 53 patients with severe TBI, GCS <8 and ICP >25 mm Hg with historical controls who were treated according to conventional principles.[62] Patients were managed according to the above principles and, although a CPP of >60 mm Hg was preferable, 50 mm Hg was acceptable where necessary to maintain ICP <25 mm Hg. Eight percent of patients died and the neurologic conditions of 13% remained severely damaged, compared with 47% and 11%, respectively, for the control group.

According to the authors, despite not being randomized, patients were well matched to historical controls and comparable to results from other units. CPPs as low as 50 mm Hg were well tolerated in their patients and led to decreased cerebral swelling. Overall, the outcomes were good compared to similar cohort studies.

The advocates of the Lund protocol suggest a) outcomes from CPP-targeted therapy are worse than Lund therapy, b) hypotension as a predictor of poor outcome is largely due to hypovolemia whereas they maintained normovolemia, c) optimal CPP should be individualized depending on age, ICP, plasma oncotic pressure and CVR, and d) an increase in ICP can be counteracted by early initiation of therapy.

BRAIN TRAUMA FOUNDATION AND CEREBRAL PERFUSION PRESSURE GUIDELINES

There is good evidence that CPP is low after TBI.[65,66] Certainly postmortem data suggest that cerebral ischemia is common in those who die. Several studies have documented worsened outcome in TBI patients who have experienced episodes of hypotension (systolic BP <90 mm Hg) in the first few hours after injury.[6,67–71] Thus, continuous monitoring and manipulation of CPP has become an integral part of the management of TBI.

The ideal CPP is controversial.[72] CBF requirements and autoregulation are different in injured compared to noninjured cerebral regions leading to varying susceptibility to ischemia. The initial 1995 BTF recommendations advocating a CPP of 70 mm Hg have been criticized as they were not based on randomized controlled trials (RCTs) and maintenance of CPP was often not the primary focus[13,14,25,67,72–78] (Table 3). Subsequent studies have challenged this approach based on several lines of evidence: a) the higher risk of acute respiratory distress syndrome (ARDS) in patients who are treated with pressors to achieve target CPP[79] (logistic regression suggested that induced hypertension was the main factor leading to ARDS[80]), b) the finding that patients who developed ARDS

Table 3. Summary of CPP Studies from Brain Trauma Foundation Guidelines

Study	Type	Description	Conclusion
Changaris et al.[67], 1987	136 severe TBI retrospective analysis	Analysis of the relationship between 1 yr outcome and initial CPP	Patients with CPP <60 mm Hg on d 2 died Improved outcome if CPP >80 mm Hg
Clifton et al.[74], 1993	46 patients prospective clinical trial	Therapeutic hypothermia where CPP >70 mm Hg	Mortality 35% with 45% good recovery
Fortune et al.[44], 1994	14 patients prospective study	Study of relationship btw $SjVO_2$ and outcome with CPP >70 mm Hg	Mortality 14%
Marion et al.[75], 1993	40 patients prospective clinical trial	Therapeutic hypothermia where CPP >70 mm Hg	Mortality 5% with 50% good recovery
McGraw et al.[76], 1989	221 patients retrospective analysis	Analysis of relationship btw 1 yr outcome and initial CPP	Likelihood of good outcome higher and death lower ($p < 0.001$) if CPP >80 mm Hg
Rosner et al.[77], 1990	34 patients prospective study	Outcome of patients managed with CPP >70 mm Hg	Mortality was 21% with 68% good recovery
Yoshida et al.[78], 1993	32 patients prospective study	Effect of barbiturate therapy on CPP threshold for good outcome	Barbiturates lowered threshold of CPP for good recovery. CPP >70 mm Hg required without barbiturates
Bouma et al.[82], 1990	35 patients prospective study	Study of effect of BP elevation on ICP and CBF	When SBP increased by 30 mm Hg, mean ICP did not increase if autoregulation was intact
Bruce et al.[73], 1973	14 patients prospective study	Effect of increasing BP on ICP and CBF	SBP increased by 30 mm Hg. Average ICP increase was 4 mm Hg and ICP decreased in 3 cases. Minimal increase in patients with defective autoregulation
Robertson et al.[79], 1999	189 patients prospective RCT	Comparing ICP (CPP >50 mm Hg) with CBF (CPP >70 mm Hg) targeted therapy	No difference in 3 or 6 mo GOS or mortality. Incidence of ARDS higher in CBF group
Kiening et al.[47], 1997	21 patients prospective cohort study	Effect of CPP on PbO_2	Elevation of CPP from 32–67 mm Hg improved PbO_2 No increase above this limit
Cruz et al.[59], 1998	353 patients prospective cohort study	Comparing management of cerebral O_2 extraction with management of CPP	Outcome at 6 mo significantly better in the cerebral extraction group
Andrews et al.[72], 2002	69 patients prospective data analysis	Analysis of the influence of quantitative data on secondary insults on outcome	Low CPP and hypotension were predictors of death and poor outcome
Clifton et al.[74], 2002	393 patients retrospective analysis	Review of data from the hypothermia trial	Poor outcome was associated with CPP < 60 mm Hg No benefit to CPP >70 mm Hg
Howells et al.[31], 2005	131 patients retrospective study	ICP based (Lund) compared to CPP based therapy in relation to the state of autoregulation	Patients with intact autoregulation appear to benefit from CPP based therapy while pressure passive patients do better with ICP directed therapy
Juul et al.[81], 2000	427 patients retrospective analysis	Review of data from Selfotel RCT	CPP >60 mm Hg had no influence on outcome
Steiner et al.[19], 2002	114 patients retrospective observation	Review of CPP observations and outcome	Optimal CPP level was calculated using pressure reactivity index. Patients whose mean CPP varied above or below optimal CPP had less favourable outcome

CPP = cerebral perfusion pressure; ICP = intracranial pressure; TBI = traumatic brain injury; RCT = randomised controlled trail; CBF = cerebral blood flow; SBP = systolic blood pressure; PbO_2 = partial pressure of cerebral oxygen; $SjVO_2$ = jugular venous oxygen saturation; GOS = Glasgow outcome score.

experienced a 2.5-fold increase in refractory intracranial hypertension and were more likely to be in a vegetative state or dead at 6 mo postinjury, and c) the demonstration of a plateau in brain tissue Po_2 at a CPP of 60 mm Hg.[48]

The data from Juul et al. examining patients enrolled in the Selfotel trial[81] also suggested that the critical CPP threshold was 60 mm Hg. There was no independent effect on neurologic outcomes for patients who had CPPs higher than 60 mm Hg. Based on

the above data, the BTF revised their guidelines to advocate a goal CPP of 60 mm Hg rather then 70 mm Hg. The 2007 BTF guidelines have further refined their recommendations considering the growing body of evidence that suggests CPP-based therapy should be adapted to reflect the state of autoregulation in a given patient.[15,82] This was largely based on the work of Howells et al. and Steiner et al. as previously described.[31,32] Balestreri et al.[83] subsequently confirmed the dangers of excessively high or low CPP. While continuing to note the dangers of a CPP >70 or <50 mm Hg, the recommendation is to use ancillary monitoring of cerebral oxygenation and metabolism to individualize therapy within the CPP range of 50–70 mm Hg.

Pediatrics

There is little high quality evidence to support CPP-based management in pediatric TBI patients. There are no RCTs. However, a retrospective cohort, class II study by Downard et al.[84] found that mortality rate was significantly associated with a mean CPP <40 mm Hg ($P < 0.01$) and mean ICP >20 mm Hg ($P < 0.001$). There was no incremental reduction in the mortality rate or improved 3-mo Glascow Outcome Scale score associated with mean increases of CPP >40 mm Hg. Several small nonrandomized studies have found similar results.[85–87] The International Brain Injury Association Guidelines have recommended a perfusion pressure of >40 mm Hg in children with TBI.[88] They further noted that a CPP between 40 and 65 mm Hg is an age-related continuum for the optimal treatment threshold.

OUTCOME STUDIES

Few RCTs have examined the relationship between CPP and outcome. Juul et al. examined physiological data from the Selfotel study,[81] a RCT of 427 severe TBI patients randomized to receive either *N*-methyl-D-aspartate antagonists or placebo. They failed to find a relationship between outcome and CPP if CPP >60 mm Hg, but noted a strong relationship between outcome and ICP >20 mm Hg. ICP not CPP was the major risk factor for neurological deterioration.

Huang et al.[89] retrospectively compared three techniques for managing ICP/CPP. The first was ICP based, the second CPP with target >70 mm Hg and the third was CPP with target >60 mm Hg. They found similar results to previous studies. CPP-based therapy improves outcome compared to ICP and CPP >60 mm Hg is comparable to CPP >70 mm Hg with fewer complications. This study has a number of limitations. It is retrospective, the ICP group was hyperventilated to CO_2 <25 mm Hg if needed (in excess of BTF recommendations), and CPP was maintained at 50 mm Hg and the patients managed in a negative fluid balance. Consequently, their data are difficult to interpret.

Several studies have included CPP/ICP data in their analysis. The phase II study of dexanabinol, a synthetic nonpsychotropic cannabinoid included 67 severe TBI adults and found the percentage of patients with a good outcome at 3 and 6 mo was 21% and 14% higher than control.[90] This appeared at least partly due to a significant reduction in percentage of time ICP >25 mm Hg, CPP <50 mm Hg and MAP <90 mm Hg. However, the subsequent phase III study, in 861 patients with TBI found no difference in outcome, ICP or CPP.[91] Cooper et al.[92] examined 229 patients with TBI who received hypertonic saline versus Ringer's solution pre-hospital admission. There was no difference in outcome between the groups despite near significant differences in the duration of CPP <70 mm Hg (9.5 vs 17 hrs in control ($P = 0.06$)).

In summary, there is little evidence from RCTs to support a specific CPP target. It is surprising that, until recently, CPP was not regarded as an important consideration in trial design or data interpretation. Future researchers need to include ICP and CPP data to ensure experimental groups are well matched.

CONCLUSION

Experimental and clinical evidence suggests that a low CPP is potentially harmful after TBI. What is less clear is the optimal CPP for a given patient. Although some would argue that the higher the better, artificially increasing CPP has repeatedly been shown to be harmful and may actually worsen outcome. Further complicating the issue is that optimal CPP may vary from patient to patient and over time as the physiological environment of the injured brain changes, prompting the need for a more individualized approach. This idea has merit but needs further investigation before being adopted as standard of care. Until then, we would suggest following the BTF CPP guidelines target of 50 mm Hg −70 mm Hg as a compromise in the knowledge that CPP is only one aspect in the complex management of TBI.

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