What is the optimal threshold for cerebral perfusion pressure following traumatic brain injury?

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In the past decade more emphasis has been directed toward CPP in patients who have suffered TBI. This attention has primarily arisen from study data documenting the occurrence of brain ischemia early after injury and ICU-based study data documenting the occurrence of reduced CPP and jugular venous desaturation due to increased ICP. 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 American Association of Neurological Surgeons' guidelines for TBI. Nonetheless, considerable uncertainty exists about the optimal level of CPP and whether treatments designed to achieve a certain threshold do more harm than good. In this article I will address the main evidence for a CPP threshold and attempt to define the optimal CPP for patients with TBI based on this evidence.

**OVERVIEW**

**Definition of CPP**

Cerebral perfusion pressure is defined as the difference between MABP and ICP, expressed in millimeters of mercury. Typically, it is considered as a global number, reflecting an equal distribution within the intracranial vault. With normal conditions of MABPs of 80 to 100 mm Hg and ICPs of 5 to 10 mm Hg, CPP can be expected to be 70 to 85 mm Hg. With conventional limits of intact autoregulation, CBF remains normal as CPP varies between 60 and 140 mm Hg. Data from experimental studies indicate that CBF declines into the ischemic range when CPP decreases below 50 to 60 mm Hg. With conditions of altered pressure regulation, the lower and upper limits of CPP may shift to the left or right of the normal curve. Detection of such a shift in the lower limit of autoregulation is difficult in normal clinical conditions. After TBI, elevations in ICP can induce reductions in CPP to its lower limits or below the ischemic threshold. Thus an optimal CPP value is not readily apparent following TBI.

**Evidence of Brain Ischemia Following TBI**

The evidence of brain ischemia following TBI comes...
from pathological autopsy series of fatal cases of brain injury and from hyperacute studies of CBF and jugular venous oximetry. Early pathological studies of fatal brain injuries, such as those by Graham, et al.,19 demonstrate ischemic damage in 91% of cases, being severe in 27% and moderate in 43%. This damage was noted to occur mostly in the hippocampus, basal ganglia, and cerebellum. These findings have been reinforced during the last 2 decades.15,20,25 The clinical and pathological correlation in these cases of ischemia indicated that early hypotension was more common. In contrast to the working hypothesis that hypotension elicited ischemia, the cortical watershed (borderzone) areas exhibited less frequent signs of ischemic damage. Data from these pathological series have been quoted often, but also criticized given that they have demonstrated brain cell death, or necrosis, and that ischemia is attributed without clearly documenting ischemia per se. For example, seizures frequently occur in cases of fatal head injury, making the findings of hippocampal damage nonspecific for brain ischemia.25 Indeed, apoptotic cell death is well known to occur after brain injury, and multiple mechanisms other than ischemia have been purported to contribute to cell death.28 Recent MR imaging studies have revealed diffuse shear injuries without the presence of ischemic lesions.16,23,25,26 and diffusion-weighted MR imaging studies obtained in brain-injured patients have demonstrated diffuse axonal injury lesions rather than evidence of stroke like ischemic injury. Hence, cell death may have occurred due to mechanisms other than a pathological lack of blood flow, such as posttraumatic excitotoxicity, shear injury, and so forth. Nonetheless, these pathological series have created a dogma that brain ischemia occurs frequently after TBI.

Additional evidence of brain ischemia has come from early studies of CBF and metabolism following TBI. Early hypotension and hypoxemia occur frequently in the field and in the emergency department.9,33 Chesnut, et al.,9 noted the following: “Hypotension was profoundly detrimental, occurring in 34.6% of these patients and associated with a 150% increase in mortality. The increased morbidity and mortality related to severe trauma to an extracranial organ system appeared primarily attributable to associated hypotension.” Bouma and colleagues performed ultra-early studies of global CBF and oxidative metabolism by using the Kety–Schmidt technique. Within the initial 6 hours of injury, there is greater than a 30% incidence of oligemic CBF and ischemic jugular venous oximetry (measurement of SjvO2) readings in patients with severe TBI (Glasgow Coma Scale score ≤ 8). Similar studies have been repeated by De Deyne and colleagues,12 and Vigué, et al.,36 have confirmed an incidence of early jugular venous desaturation between 30 and 35%. Early desaturation occurs mostly due to elevated ICP despite adequate MAP (≥ 80 mm Hg). Thus, elevated ICP (mean 35 ± 9 mm Hg) was responsible for the low jugular venous saturation values. Ultra-early ischemia was successfully treated by reducing ICP and hyperventilation and increasing MAP.

Beyond the initial 6 hours, brain ischemia is less common, but has devastating effects if it occurs. Most studies of the early posttraumatic period (after 12 hours) have been undertaken in the ICU by performing global or regional analyses of CBF. Bouma, et al.,4 demonstrated a 4% incidence of brain ischemia 12 to 48 hours after injury. Gopinath and colleagues18 reported that 46 of 116 patients with severe TBI had one or more episodes of jugular venous desaturation, indicating ischemia during the initial 5 days after injury. In this seminal study, SjvO2 decreased to less than 50% due to excessive hyperventilation in 25% of cases and reduced CPP in only 12.5% of cases. The causes of ischemia in these studies were most often excessive hyperventilation, intractable elevation of ICP, and reduction of CPP. Nonetheless, when the total duration of SjvO2 monitoring is factored, there is a less than 1% incidence of brain ischemia during an ICU stay for up to 5 days postinjury. Fandino and coworkers14 detected ischemia in less than 2% of 12,800 cumulative hours of jugular monitoring. Vespa, et al.,35 demonstrated a similar low incidence of brain ischemia (< 2%) by using multiple methods of measuring global (jugular oximetry) and regional brain oxygenation (positron emission tomography) in a multitude of studies performed in the ICU between 12 and 240 hours after injury. Results of several reports have indicated that ischemia occurs with terminal herniation and that many of these events are not reversible. Thus, there is evidence that ischemia does occur infrequently in the context of aggressive care in the ICU, but less frequently than in the initial 12 to 24 hours of care.

**Evidence for a Critical CPP Threshold**

The critical CPP threshold in these early studies is not well described. In a later study by Chan, et al.,8 however, a reduction in CPP to less than 70 mm Hg was associated with jugular venous desaturation and an increase in transcranial Doppler ultrasonography–demonstrated PI. Figure 1 demonstrates the decrement in brain oxygenation that occurs with a decreased CPP to less than 70 mm Hg. A decline in SjvO2, lower than 50% indicates global ischemia, or at least global critical oligemia, and an enhanced
uptake of oxygen by the brain, leading to an increased arterial-venous difference in oxygen content.

Similarly, a reduction in CPP to below 70 mm Hg was found to be related to increased extracellular glutamate in a study in which investigators compared cerebral microdialysis and CPP. In Fig. 2, glutamate increases to excitotoxic levels as CPP falls below 70 mm Hg. In this example, the microdialysis probe is located in normal tissue and is considered to reflect globally representative measure for the entire brain. Experimentally, the concept that an increase in glutamate indicates brain ischemia and neuronal metabolic distress has been well validated. Thus, there is evidence that a reduction in CPP to less than 70 mm Hg results in focal evidence of neuronal ischemia with a subsequent increase in glutamate. This increase in glutamate is not dependent on ICP and is closely linked to reductions in MABP, because the correlation between glutamate and ICP is poor (r = 0.09). Thus, a reduction in CPP to a value lower than 70 mm Hg has been associated with global and regional evidence of brain ischemia.

In addition to jugular oximetry and cerebral microdialysis, other investigators have used \( P_{brO_2} \) to demonstrate a critical CPP threshold. Menzel, et al., noted a concurrent transient drop in \( P_{brO_2} \) when CPP decreased to below 70 mm Hg. Given that most generally agree that \( P_{brO_2} \) reflects the balance of supply and demand of O\(_2\) in the brain, these data indicate that a CPP to lower than 70 mm Hg results in a critical limitation of O\(_2\) supply compared with ongoing demand. In similar studies of combined \( P_{brO_2} \) and CPP monitoring, a CPP threshold greater than 60 mm Hg was found to be the critical threshold.

Finally, the initial study of Rosner, et al., demonstrated that mortality rates were reduced in consecutive patients treated with supramaximal levels of CPP compared with historical controls. In this study, CPP was maintained above 80 mm Hg (mean 83 ± 14 mm Hg) and the mortality and good outcome rates were 29 and 35%, respectively. By comparison, the mortality rates in previous series of similarly injured patients were in excess of 40%. Thus, Rosner and colleagues contend that a CPP above 70 mm Hg is influential in achieving an improved patient outcome. Therefore the concept of prophylactically elevating CPP to avoid brain ischemia and to maintain an ideal CBF has gained support, although this tactic remains unproven by a randomized controlled study.

Evidence Against a Critical CPP Threshold

The work of Rosner and colleagues stimulated much interest and has been followed up by a comparative study by Robertson, et al., in which patients were randomized to treatment based on maintaining CBF rather than controlling ICP. In the CBF-targeted group, patients received a type of hypervolemia–hypertension treatment designed to elevate CPP, whereas the ICP-targeted group did not. In fact, in the ICP-targeted group, the goal was to maintain CPP above 50 mm Hg. Results indicated that there were 50% fewer hypoxic events in the CBF targeted group (p < 0.001), but no difference in overall outcome. In the ICP-targeted group, however, the mean CPP was greater than 70 mm Hg. Patients in the CBF-targeted group experienced worse pulmonary edema and adult respiratory distress syndrome complications as a result of increased fluid administration. Nonetheless, there was considerable overlap in the actual CPP between the two groups. The CPP was statistically significantly higher in the CBF-targeted group (p < 0.004), with an absolute difference in mean CPP between the two groups of less than 6 mm Hg (78 compared with 73 mm Hg). The total length of time that CPP remained below 60 mm Hg in the CBF-targeted group was less than that in the ICP-targeted group (4 compared with 13 hours, p < 0.001). Equally problematic is the available evidence that CPP does not correlate with actual CBF. Treatment was not adjusted to a CBF threshold per se, although the mean daily CBF was higher in the CBF-targeted group. At present, however, there is no Class 1 evidence supporting the maintenance of CPP above 70 mm Hg.

Observational studies of CPP within the initial 24 to 48 hours following TBI have been conducted. In the study by Downard and colleagues, no difference in outcome could be demonstrated in children who had maintained a mean CPP in the range of greater than 40 to 50, 50 to 60,
60 to 70 or greater than 70 mm Hg. In contrast, excessive CPP levels may be associated with hyperemia and harm. In microdialysis studies, a CPP greater than 100 mm Hg was associated with an increase in glutamate. Indeed, recent comparisons between brain PbrO2 values and CPP indicate that at both extremes of CPP, brain O2 levels can be lower than in the range of 70 to 80 mm Hg (Fig. 4). In the collection of studies by Asgeirsson and coworkers, hyperemia occurred with CPP values higher than 70 to 100 mm Hg. This hyperemia was associated with the elevation of both jugular venous oximetry and ICP. The protocol from these investigators advocates normalization or reduction of CPP in the setting of deep sedation rather than selection of a CPP threshold. This technique involves using metabolic suppression to reduce the rate of oxidative metabolism, in combination with reducing systemic blood pressure and cerebral blood volume simultaneously and increasing osmotic pressure with the aid of albumin. This procedure most resembles standard metabolic suppression with the aid of barbiturate coma, but is modified in permitting a reduction in CPP to levels between 30 and 60 mm Hg. Using this technique, Asgeirsson and coworkers have reported improved outcomes, especially in patients who had been unresponsive to conventional methods of ICP reduction.

**Selection of the Optimal CPP Following TBI**

There is no single optimal CPP following TBI. Moreover, there are no Class 1 study data that indicate a optimal CPP threshold. The aforementioned evidence points to different thresholds of CPP above which physiological markers of injury are decreased (that is, glutamate), but no single study has involved a clear test of any single CPP threshold in a randomized controlled manner. In many ways, the use of jugular venous oximetry in conjunction with measuring CPP may provide the best method of selecting the optimal CPP for an individual patient. The jugular venous oximetry (SjvO2) provides global O2 saturation values in the brain. Normal SjvO2 is between 55 and 70%. Based on continuous SjvO2 values, a CPP level can be selected that provides adequate O2 delivery and CBF. In many cases, especially under conditions of deep sedation, a CPP greater than 70 mm Hg will provide O2 delivery and CBF in excess of O2 demand. Hence, a CPP level above 70 mm Hg with such conditions may promote hyperemia and therefore raised ICP. Similarly, using other brain monitoring devices, such as PbrO2 probes and microdialysis probes, optimization of CPP to lower or higher levels may be possible. Nonetheless, the more study is required to determine how best to integrate additional brain monitors in the decision process about the optimization of CPP.

**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). Cerebral perfusion pressure is by definition monolithic; 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 CPP is essentially an imaginary number, brain monitoring techniques such as jugular venous oximetry, monitoring of PbrO2, and cerebral microdialysis provide complementary and specific information that permits the selection of the best CPP for an individual patient over time.

**References**


![Fig. 4. Graph of corresponding values of CPP and brain parenchymal oxygen, indicating that mean brain O2 levels are highest when CPP is between 70 and 80 mm Hg.](image-url)
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27. Stocchetti N, Furlan A, Volta F: Hypoxemia and arterial hypo-


31. Stocchetti N, Furlan A, Volta F: Hypoxemia and arterial hypo-


Manuscript received November 3, 2003. Accepted in final form November 12, 2003.
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