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

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Intensive care of the patient with traumatic brain injury centers on control of intracranial pressure and cerebral perfusion pressure (CPP). The optimal CPP by definition delivers an adequate supply of blood and oxygen to meet the metabolic demands of brain tissue. A great deal of controversy exists regarding the optimal CPP value, with disparate studies providing conflicting evidence for the use of supraphysiological CPP values. No study that accurately assesses the efficacy of normal CPP compared with elevated CPP has been performed, but several studies demonstrate that a CPP threshold exists on an individual basis for patients with TBI. The use of brain monitors of cerebral metabolism and oxygen supply may assist the clinician in the selection of the optimal CPP for an individual patient.

KEY WORDS • traumatic brain injury • cerebral perfusion pressure • cerebral blood flow • intracranial pressure • coma • jugular venous oximetry • microdialysis

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.⁵ 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.

Abbreviations used in this paper: CBF = cerebral blood flow; CPP = cerebral perfusion pressure; ICP = intracranial pressure; ICU = intensive care unit; MABP = mean arterial blood pressure; MR = magnetic resonance; PbrO₂ = brain parenchymal oxygenation; PI = pulsatility index; SjvO₂ = jugular venous oxygen saturation; TBI = traumatic brain injury.

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 colleagues⁴ 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 Vigue, 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 MABP (> 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 MABP.

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 re-

gional 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

Fig. 1. Graph demonstrating matched time samples of CPP, transcranial Doppler ultrasonography-demonstrated PI, and jugular venous oximetry (SjvO₂). As CPP decreases to lower than 70 mm Hg, jugular venous O₂ saturation drops into the ischemic range. (Adapted from Chan, et al., 1992.)

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.³⁴ 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.^{17,21} 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 PbrO_2 to demonstrate a critical CPP threshold. Menzel, et al.,²⁷ noted a concurrent transient drop in PbrO_2 when CPP decreased to below 70 mm Hg. Given that most generally agree that PbrO_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 PbrO_2 and CPP monitoring, a CPP threshold greater than 60 mm Hg was found to be the critical threshold.^{1,2,6,24} Figure 3 features an example decrease in PbrO_2 with a reduction in CPP to below 70 mm Hg.

Finally, the initial study of Rosner, et al.,³¹ 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

Fig. 2. Graph demonstrating an increase in glutamate under conditions of decreasing CPP in normal white matter regions of the brain. (Adapted from Vespa, et al., 1998.)

Fig. 3. Graph demonstrating a decrease in PbrO_2 that occurs during a reduction in CPP to below 70 mm Hg. (Adapted from Menzel, et al., 2003.)

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 colleagues³¹ stimulated much interest and has been followed up by a comparative study by Robertson, et al.,³⁰ 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 hypoxemic 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.¹⁰ 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.¹⁷ 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.²²

Observational studies of CPP within the initial 24 to 48 hours following TBI have been conducted.¹³ In the study by Downard and colleagues,¹³ 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.³⁴ Indeed, recent comparisons between brain PbrO_2 values and CPP indicate that at both extremes of CPP, brain O_2 levels can be lower than in the range of 70 to 80 mm Hg (Fig. 4).²⁹ In the collection of studies by Asgeirsson and coworkers,³ 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.³² 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 (SjvO_2) provides global O_2 saturation values in the brain. Normal SjvO_2 is between 55 and 70%. 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,

Fig. 4. Graph of corresponding values of CPP and brain parenchymal oxygen, indicating that mean brain O_2 levels are highest when CPP is between 70 and 80 mm Hg.

a CPP greater than 70 mm Hg will provide O_2 delivery and CBF in excess of O_2 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,^{7,17,32,35} such as PbrO_2 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 PbrO_2 , and cerebral microdialysis provide complementary and specific information that permits the selection of the best CPP for an individual patient over time.

References

1. al-Rawi PG, Hutchinson PJ, Gupta AK, et al: Multiparameter brain tissue monitoring—correlation between parameters and identification of CPP thresholds. *Zentralbl Neurochir* **61**: 74–79, 2000
2. Artru F, Jourdan C, Perret-Liaudet A, et al: Low brain tissue oxygen pressure: incidence and corrective therapies. *Neurol Res* **20** (Suppl 1):S48–S51, 1998
3. Asgeirsson B, Grande PO, Nordstrom CH: A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. *Intensive Care Med* **20**:260–267, 1994
4. Bouma GJ, Muizelaar JP, Choi SC, et al: Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *J Neurosurg* **75**:685–693, 1991
5. 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* **17**:507–511, 2000
6. Bruzzone P, Dionigi R, Bellinzona G, et al: Effects of cerebral perfusion pressure on brain tissue PO_2 in patients with severe head injury. *Acta Neurochir Suppl* **71**:111–113, 1998
7. Chan KH, Dearden NM, Miller JD, et al: Multimodality monitoring as a guide to treatment of intracranial hypertension after severe brain injury. *Neurosurgery* **32**:547–553, 1993
8. Chan KH, Miller JD, Dearden NM, et al: The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. *J Neurosurg* **77**:55–61, 1992
9. Chesnut RM, Marshall LF, Klauber MR, et al: The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* **34**:216–222, 1993
10. Contant CF, Valadka AB, Gopinath SP, et al: Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg* **95**:560–568, 2001
11. Cruz J, Jaggi JL, Hoffstad OJ: Cerebral blood flow, vascular resistance, and oxygen metabolism in acute brain trauma: redefining the role of cerebral perfusion pressure? *Crit Care Med* **23**: 1412–1417, 1995

12. De Deyne C, Decruyenaere J, Calle P, et al: Analysis of very early jugular bulb oximetry data after severe head injury: implications for the emergency management? **Eur J Emerg Med** 3: 69–72, 1996
13. Downard C, Hulka F, Mullins RJ, et al: Relationship of cerebral perfusion pressure and survival in pediatric brain-injured patients. **J Trauma** 49:654–659, 2000
14. Fandino J, Stocker R, Prokop S, et al: Cerebral oxygenation and systemic trauma related factors determining neurological outcome after brain injury. **J Clin Neurosci** 7:226–233, 2000
15. Firsching R, Woischneck D, Klein S, et al: Brain stem lesions after head injury. **Neurol Res** 24:145–146, 2002
16. Garnett MR, Blamire AM, Rajagopalan B, et al: Evidence for cellular damage in normal-appearing white matter correlates with injury severity in patients following traumatic brain injury: a magnetic resonance spectroscopy study. **Brain** 123: 1403–1409, 2000
17. Globus MY, Busto R, Dietrich WD, et al: Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. **J Neurochem** 5:1455–1464, 1988
18. Gopinath SP, Robertson CS, Contant CF, et al: Jugular venous desaturation and outcome after head injury. **J Neurol Neurosurg Psychiatry** 57:717–723, 1994
19. Graham DI, Adams JH, Doyle D: Ischaemic brain damage in fatal non-missile head injuries. **J Neurol Sci** 39:213–234, 1978
20. Graham DI, Ford I, Adams JH, et al: Ischaemic brain damage is still common in fatal non-missile head injury. **J Neurol Neurosurg Psychiatry** 52:346–350, 1989
21. Hagberg H, Lehman A, Sandberg M, et al: Ischemia-induced shift of inhibitory and excitatory amino acids from intra- to extracellular compartments. **J Cereb Blood Flow Metab** 5: 413–419, 1985
22. Juul N, Morris GF, Marshall SB, et al: Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. **J Neurosurg** 92: 1–6, 2000
23. Kampfl A, Franz G, Aichner F, et al: The persistent vegetative state after closed head injury: clinical and magnetic resonance imaging findings in 42 patients. **J Neurosurg** 88:809–816, 1998
24. Kiening KL, Unterberg AW, Bardt TF, et al: Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue PO₂ versus jugular vein oxygen saturation. **J Neurosurg** 85:751–757, 1996
25. Kotapka MJ, Graham DI, Adams JH, et al: Hippocampal damage in fatal paediatric head injury. **Neuropathol Appl Neurobiol** 19:128–133, 1993
26. Liu AY, Maldjian JA, Bagley LJ, et al: Traumatic brain injury: diffusion-weighted MR imaging findings. **AJNR** 20: 1636–1641, 1999
27. Menzel M, Soukup J, Henze D, et al: Brain tissue oxygen monitoring for assessment of autoregulation: preliminary results suggest a new hypothesis. **J Neurosurg Anesthesiol** 15:33–41, 2003
28. Raghupathi R, Graham DI, McIntosh TK: Apoptosis after traumatic brain injury. **J Neurotrauma** 17:927–938, 2000
29. Reinert M, Barth A, Rothen HU, et al: Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury. **Acta Neurochir** 145:341–350, 2003
30. Robertson CS, Valadka AB, Hannay HJ, et al: Prevention of secondary ischemic insults after severe head injury. **Crit Care Med** 27:2086–2095, 1999
31. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: management protocol and clinical results. **J Neurosurg** 83:949–962, 1995
32. Stahl N, Ungerstedt U, Nordstrom CH: Brain energy metabolism during controlled reduction of cerebral perfusion pressure in severe head injuries. **Intensive Care Med** 27:1215–1223, 2001
33. Stocchetti N, Furlan A, Volta F: Hypoxemia and arterial hypotension at the accident scene in head injury. **J Trauma** 40: 764–767, 1996
34. Vespa P, Ronne-Engstrom E, Caron M, et al: Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. **J Neurosurg** 89:971–982, 1998
35. Vespa PM, McArthur D, Glenn T, et al: Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. **J Cereb Blood Flow Metab** 23: 865–877, 2003
36. Vigue B, Ract C, Benayed M, et al: Early SjvO₂ monitoring in patients with severe brain trauma. **Intensive Care Med** 25: 445–451, 1999

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