Cerebral Perfusion Pressure Based Management of Traumatic Brain Injury

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Citation

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Abstract

Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Traditionally, management of traumatic brain injury (TBI) depended mainly on ICP control strategies. Based on the evidence that cerebral ischemia plays a major role in causing poor neurological outcome in traumatic brain injury (TBI) and cerebral blood flow autoregulation is shifted rightward in these patients, Rosner and colleagues suggested a treatment protocol that advocated maintaining a CPP higher than 70 mmHg, by controlling intracranial hypertension and increasing MAP by using hypervolemia and vasoactive agents, if required. Following the initial studies that showed better outcomes than other contemporary series, a number of studies tried to define the critical CPP in TBI. The threshold values suggested by these studies varied widely between 50 mmHg and higher than 70 mmHg. While there is no controversy about the adverse effects of low CPP, the major concerns in CPP-based therapy are a possible increase in brain oedema with a decrease in intracranial compliance and the systemic complications associated with the interventions used to achieve high CPP. There is no major evidence to suggest that high CPP increases ICP or decreases intracranial compliance. One major randomized trial comparing CPP-based and ICP-based strategies showed a major reduction in the incidence of cerebral ischemia with cerebral blood flow (CBF)-targeted therapy. But the same study also documented a five-fold increase in acute respiratory distress syndrome in patients managed by CPP-based strategy, and similar outcomes between the treatment groups. Following this, the brain trauma foundation (BTF) lowered the suggested CPP threshold to 60 mmHg from its original recommendation of 70 mmHg. Current research is focusing on the possibility of defining the optimal CPP for any given patient based on more objective measures of cerebral oxygenation, metabolism and CBF autoregulation. Critical thresholds of CPP in children remain ill-understood.

INTRODUCTION

An ongoing debate on ideal management of intracranial dynamics in patients with traumatic brain injury has resulted in two major schools of thought: the cerebral perfusion pressure (CPP)-based management as proposed by Rosner and colleagues and the intracranial pressure (ICP)-based management as proposed by the Lund group. While the former advocates high cerebral perfusion pressures, the latter supports aggressive ICP control and modest CPP values. The following is a brief review of the rationale and the current status of CPP-based strategy in the management in traumatic brain injury (TBI).

PHYSIOLOGICAL BASIS OF CPP-BASED MANAGEMENT

CPP is the difference between mean arterial pressure (MAP) and ICP. It represents the pressure under which the brain is perfused. In the management of patients with cerebral pathology, CPP is generally used as a correlate of global cerebral blood flow (CBF).

Traditionally, management of severe head injury has depended on rigorous control of raised ICP. Early studies in TBI documented improved outcome with aggressive ICP control ([1,2]). However, pathological studies have shown evidence of ischemia in about 90% of patients who died of TBI ([3]) implicating ischemia as a major cause of unfavorable outcome. Ultra early evaluation of CBF following head injury has documented lowest CBF values during the first six hours following injury, with about a third of them having CBF values less than 18 ml/100g/min, a threshold that represents cerebral ischemia ([4]). Cerebral perfusion early after injury has been correlated with the long-term neurological outcome ([5]). In studies where episodes of cerebral oxygen desaturation have been monitored by jugular venous oxygen saturation, a good correlation has been found between the number of episodes of cerebral oxygen desaturation and the long-term neurological outcome ([6,7]). In a serial evaluation of CBF in 125 patients monitored

by transcranial Doppler, and Xe133, a triphasic CBF response has been noticed with hypoperfusion occurring on the day of injury and a prolonged delayed hypoperfusion from day 4 through day 14 ([8]). Based on the evidence of the critical role played by cerebral ischemia in causing poor neurological outcome, it has been postulated that maintenance of optimal CBF is necessary to protect the brain from secondary insults.

In normal brain, autoregulation maintains CBF within normal limits over a wide range of CPP. Impairment of autoregulation in a patient with brain injury results in passive increase in CBF when CPP is increased. While this may be one argument in support of CPP-based therapy, the major advantage of CPP therapy seems to lie in its ability to decrease the ICP. According to the hypothesis of vasodilatory cascade, a reduction in CPP – either as a result of an increase in ICP or a decrease in MAP – causes cerebral vasodilation in an attempt to maintain CBF. This normal autoregulatory response increases CBV and ICP resulting in further reduction of CPP. Thus, a vicious cycle of progressive CPP reduction is set up. An increase in arterial pressure, under these circumstances, increases CPP, causes cerebral vasoconstriction and reduces cerebral blood volume (CBV). The associated decrease of ICP enhances the CPP further, thus setting up a favorable cycle of events that progressively improve the CPP and CBF.

CPP-BASED MANAGEMENT STRATEGY

The strategy of CPP-based management as originally employed by Rosner ([9]) consisted of vascular expansion, systemic vasopressors, cerebrospinal fluid (CSF) drainage through ventriculostomy, and mannitol to maintain a CPP of at least 70 mmHg. All patients had an ICP monitor. All patients were mechanically ventilated to maintain an oxygen saturation greater than 90% and a PaCO2 of 35 mmHg. Prolonged hyperventilation was not used as a therapeutic modality. Hyperventilation was used only for short periods to treat acutely elevated ICP. Fluid management was aimed at maintaining euvolemia or moderate hypervolemia. Albumin infusions were used to mobilize the extracellular water into intravascular compartment in patients who were well- or over-hydrated. Packed red cells were transfused with haemoglobin and haematocrit values as targets. Serum sodium and potassium levels were maintained within normal limits.

A CPP of 70 mmHg was targeted initially, by draining CSF until the ICP decreased to 15 mmHg. In addition, CSF was continuously drained whenever CPP dropped to below 70 mmHg. If still the CPP did not increase to 70 mmHg, vasopressors were added. Phenylephrine or norepinephrine with or without dopamine were used to achieve the required MAP. Mannitol in a dose of 0.5 – 1.0 g/kg was used whenever CPP decreased to below 70 mmHg due to ICP elevation. If CPP was maintained at an acceptable level with high but stable ICP, efforts were made to minimize or avoid mannitol. Barbiturates, active hypothermia and decompressive craniectomy were not a part of the protocol.

With the above protocol, Rosner and colleagues demonstrated better neurological outcome compared to the other reported series. The overall mortality in this series was 29% across all Glasgow Coma Scale (GCS) categories. Mortality ranged from 52% for patients with a CGS score of 3, to 12% for those with a GCS of 7; favorable outcomes for the same groups were 35% and 75% respectively. Questions have been raised later regarding the desirability of high CPP values and the ideal CPP threshold.

THE IDEAL CPP THRESHOLD

Studies in patients with TBI seem to suggest that there is a critical CPP threshold, though its actual value remains controversial. Chan et al ([10]) examined the relationship between SjvO2, transcranial Doppler (TCD) flow velocities in the middle cerebral artery, and CPP in 41 patients with severe TBI. The TCD pulsatility index (PI) increased and SjvO2 decreased linearly with CPP values below 70 mmHg; similar correlation did not exist at CPP values higher than 70 mmHg suggesting that at CPP values lower than 70 mmHg, CBF was inadequate to meet metabolic needs. Zauner et al ([11]), in a study using microdialysis, showed that a CPP of 70 mmHg was associated with an increase in brain tissue oxygenation, decrease in brain tissue CO2 to normal levels, elevation of brain glucose concentration, and a reduction of brain lactate levels. In yet another study, cerebral glucose, lactate, glycerol, glutamate, and pyruvate concentrations correlated with CPP; in this study, 70 mmHg was found to be the critical CPP below which irreversible damage occurred ([12]). However, in a similar microdialysis-based study, Reinert et al ([13]) found that only CPP values above 78 mmHg optimized tissue oxygen partial pressure (PtiO2) and decreased the lactate levels. In a prospective trial with standardized protocols, including a targeted CPP of 70 mmHg, survivors had a mean CPP higher than 70 mmHg, while non-survivors had a much lower average of 41 mmHg ([14]).

In contrast with the above evidence in support of CPP values higher than 70 mmHg, some studies have reported lower thresholds. Chambers et al reported threshold values of 55 mmHg for adults and 43 to 45 mmHg for children. At the same time, the same study also suggested that higher CPP values may be more important in adults with mass lesions ([15]). Using pressure reactivity index (PRx) from TCD studies, Steiner et al found the optimal CPP to be between 60 and 85 mmHg ([16]).

Thus, there seems to be a debate on the critical threshold of CPP in patients with TBI. While there is no controversy on the adverse effects of very low CPP, two questions that have emerged from the recent literature are: 1. Is CPP greater than 70 mmHg necessary? 2. Is there is a critical threshold at 60 mmHg?

IS CPP GREATER THAN 70 MMHG NECESSARY?

Some recent evidence suggests that CPP values greater than 70 mmHg do not necessarily achieve the goal of avoiding hypoperfusion and hypoxia. Steiner et al ([17]) evaluated the response of CBF in the pericontusional tissue at 70 and 90 mmHg of CPP. Higher CPP caused only a modest increase in CBF, which does not justify pharmacological elevation of CPP to greater than 70 mmHg. In a study of 18 patients monitored by noninvasive cerebral oximeter, despite demonstration of a CPP greater than 70 mmHg for 90% of the study period, there was a 16% detectable incidence of cerebral hypoxia, supporting the idea that cerebral hypoxia occurs despite what is considered adequate CPP ([18]).

IS THERE IS A CRITICAL THRESHOLD AT 60 MMHG?

A large volume of evidence seems to suggest that there is a critical CPP threshold around 60 mmHg. Using cerebral oxygen extraction as an index of adequacy of CBF, Stochetti et al have shown that a CPP lower than 60 mmHg was associated with inadequate perfusion ([19]). In another retrospective analysis of 74 patients, 60 patients who had a CPP less than 60 mmHg for 75 min suffered poorer outcomes at 6,12 and 12 months ([20]). A significant correlation between CPP and brain tissue oxygen tension was found below a CPP of 60 mmHg ([21]). On the other hand, no correlation was found between CPP and brain tissue oxygen tension at CPP values between 60 and 130 mmHg ([22]).

A 62% increase in brain tissue oxygen tension (Pbto2) was reported when the CPP was increased from 32 to 67 mmHg while no change was noticed when CPP was increased from 68 to 84 mmHg suggesting that a CPP around 60 mmHg provides adequate cerebral oxygenation ([23]). In a post hoc analysis of the Selfotel trial also, the risk of neurological deterioration decreased significantly at a CPP value of 60 mmHg; higher values, did not decrease the risk any further ([24]). Czosnyka et al evaluated CBF autoregulation in head injury by using transcranial Doppler flow velocities and calculating the moving correlation coefficient (Mx). The critical threshold of at which the Mx optimized was 60 mmHg ([25]).

RISKS OF HIGH CPP

The interventions used to achieve high CPP may pose risks to the patients. Robertson et al. ([26]) compared a CBF-targeted protocol (the goals were a CPP higher than 70 mmHg and normocapnic ventilation) with an ICP management protocol (with a target ICP of less than 20 mmHg and a CPP greater than 50 mmHg). Hyperventilation was permitted to treat elevated ICP in the latter group. There was a substantial reduction in ischemic episodes in the CBF-targeted group. This was, however, associated with a fivefold increase in the incidence of acute respiratory distress syndrome (ARDS). Further analysis of the same data ([27]) revealed that the use of epinephrine and high dose dopamine to maintain CPP greater than 70 mmHg was the main risk factor for the development of ARDS.

Hypertensive therapy can be expected to increase ICP and cause poor outcome ([28],[29]). The effect of artificial blood pressure elevation on ICP and CBF has been studied by Bouma and Muizelaar. In 35 patients with TBI, they found that elevation of the mean arterial blood pressure from 92 ±10 mmHg to 123 ± 8 mmHg led to only an insignificant increase in ICP in those patients with intact autoregulation ([30]). In the group with defective autoregulation, there was actually a decrease in mean ICP. In 14 patients with severe TBI, Bruce et al found that artificially increasing the systolic blood pressure by 30 mmHg caused an average increase in ICP of only 4 mm Hg, and in 3 cases the ICP actually decreased ([31]). In a subgroup of these patients with defective autoregulation, ICP increased by only 3 mm Hg or less in 4 patients, although it increased by 13 and 27 mm Hg in the other 2 patients. These studies demonstrate that ICP usually changes very little when blood pressure is increased by as much as 30 mm Hg in head-injured patients, regardless of the status of their CBF autoregulation. Thus, moderate increases in blood pressure, as might be needed to maintain

an adequate CPP, should not be expected to cause an increase in ICP in most patients with TBI. The reason for minimal increase in ICP even when there is loss of autoregulation, is not clear. One probable explanation is that, in TBI, the physiologic characteristics of autoregulation may be altered, but the autoregulation itself, may not be completely lost. Those patients considered to have lost autoregulation may, in fact, have their autoregulatory curve shifted to the right. Increasing the blood pressure in these patients might bring them into the autoregulatory range.

In our own data of 27 patients with diffuse axonal injury, where intracranial compliance was monitored by pressure volume index (PVI), maintaining CPP above 70 mmHg did not affect either the ICP or the PVI ([32]).

RECOMMENDATIONS OF THE BRAIN TRAUMA FOUNDATION

Based on the available evidence, the Brain Trauma Foundation (BTF) recommended a CPP threshold of 70 mmHg in their guidelines published in the year 2000 ([33]). But the recent update of the same recommendations advocates a lower threshold of 60 mmHg. They also caution that, in the absence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors should be avoided because of the risk of ARDS ([34]).

COMPARISON OF CPP-BASED MANAGEMENT WITH OTHER THERAPIES

In a recent study, the efficacy of CPP therapy in decreasing ICP was compared with that of hyperventilation and metabolic suppression with propofol. In a group of 33 patients with a median GCS score of 7, hyperventilation (PaCO2 decreased from 35 ± 5 to 27 ± 5 mmHg) was consistently effective in decreasing ICP (ICP decrease from 20 ± 11 to 13 ± 11 mmHg). With propofol, ICP decreased from 20 ± 10 to 16 ± 11 mmHg. Induced hypertension (MAP increase by 14 ± 5 mmHg) was generally ineffective and in some instances significantly raised the ICP. The study concluded that hyperventilation may be preferred over other techniques, provided it is performed in conjunction with monitoring of cerebral oxygenation ([35]). Another study comparing the CBF-targeted and ICP-targeted strategies reported a reduction in the incidence of secondary ischemia by approximately 50%. The treatment strategy, however, increased the incidence of acute respiratory distress syndrome five fold and did not improve the long-term neurological outcome. The interpretation of the results was that the beneficial effects of CPP therapy in decreasing the ischemic events, was offset by the systemic complications associated with CBF-targeted therapy ([26]).

CPP-BASED THERAPY IN PAEDIATRIC HEAD INJURY

The relevance of CPP therapy to paediatric brain injury is not well understood at present. A recent series compared ICP-based and CPP–based management in 17 children under the age of 15 years. The targets were an ICP less than 20 mmHg and a CPP greater than 50 mmHg in the ICP group. In the CPP group, the target CPP was 60 mmHg in children below 2 years of age and higher than 70 mmHg in others. Unimpaired survivals were more in the CPP group (P = 0.08). This study has proven the safety of CPP therapy in children, though the thresholds remain to be defined for any given age group ([36]). Another study based on calculation of pressure time index (PTI) for ICP and CPP identified critical thresholds of CPP as 48, 54 and 58 mmHg for children aged 2-6, 7-10 and 11-15 years ([37]).

ADDITIONAL TARGETS TO OPTIMISE CPP-BASED THERAPY

Of late, there is an emergent opinion that the outcome of TBI may be improved if the CPP target is based on some other relevant pathophysiological correlate rather than using an arbitrary CPP threshold. Pressure reactivity of intracranial dynamics and brain tissue oxygen tension have been explored for their potential to guide CPP-based management.

PRESSURE-REACTIVITY AS A GUIDE FOR CPP-BASED MANAGEMENT

Howells et al studied pressure reactivity as a guide for CPP therapy in two groups of patients: one group treated according to the ICP protocol (ICP < 20 mmHg) and another group treated by a CPP protocol (CPP > 70 mmHg and ICP < 25 mmHg). Among the patients treated by ICP protocol, pressure-passive patients (patients in whom ICP increased with CPP) had a better outcome. Among the patients treated by CPP-protocol, pressure active patients (patients in whom ICP did not change significantly with CPP) had a better outcome. The authors suggest that ICP–oriented treatment could be helpful in patients whose slope of the MAP/ICP regression line is at least 0.13. CPP–therapy is likely to produce better results when the slope is less than 0.13 ([38]).

Other investigations also suggested that CPP management might be optimised by daily trial manipulation of arterial blood pressure to identify the autoregulatory range ([39]). In one study, CPP was manipulated in a range of 51 to 108

mmHg on Days 0, 1, and 2 post-injury while the ICP, autoregulation capacity, and brain tissue partial pressure of oxygen were monitored. When the ICP was normal, there were no major changes in the measured variables as CPP was changed, indicating that the brain was within autoregulatory limits. Conversely, when intracranial hypertension was present, CPP reduction to less than 77 mmHg increased the ICP further, decreased the autoregulation, and decreased the brain tissue partial pressure of oxygen; CPP increase bettered these variables, indicating that the brain was operating at the lower limit of autoregulation. The authors suggest that daily assessment of autoregulatory limits may help to optimize the CPP.

BRAIN TISSUE OXYGEN TENSION GUIDED CPP THERAPY

Some recent evidence points out that CPP therapy guided by direct monitoring of cerebral oxygenation may result in better outcomes compared to CPP therapy with arbitrary thresholds. Cerebral oxygenation has been shown to be directly related to CPP over as wide range of CPP values with a break point around 60-70 mmHg. When the CPP values were higher than 70 mmHg, only 10% of the PbtO2 values were in the hypoxic range, as against 25% and 55% when the CPP was 60-70 mmHg or less than 60 mmHg respectively ([40]). Meixensberger et al reported a series of 93 patients of severe TBI who were managed by an ICP target of less than 20 mmHg and a CPP target greater than 70 mmHg. In 53 of these patients, CPP was manipulated to maintain a PbtO2 greater than 1.3 kPa (10 mmHg). Cerebral hypoxic events were significantly reduced by PbtO2 monitoring. Though statistically not significant, there was a positive trend towards better outcome in patients monitored by PbtO2 ([41]). In another series with ICP and CPP targets of 20 and 60 mmHg respectively, patients who had concomitant PbtO2 monitoring had a significantly lower mortality (44% vs 25%) ([42]).

In survivors of TBI, CPP and ICP do not seem to be related to later neuropsychological functioning ([43]). On the other hand, when a possible relationship between cerebral oxygenation during Day 1-10 after severe head injury and neuropsychological outcome at 2-3 years was investigated, a correlation was found between the performance in neuropsychological tests and cerebral oxygenation. Patients with low brain tissue oxygenation fared worse in neuropsychological testing, especially those concerning intelligence and memory. These observations imply that monitoring and treatment of cerebral hypoxia is crucial for better functional outcome ([44]). Therefore, combining CPP target with a PbtO2 target may be beneficial in improving the long-term functional outcome.

In conclusion, CPP-based management is founded on the premise that high CPP counteracts the cerebral ischemia, which has a major role in the pathophysiology of TBI. This strategy has also been proposed move the CPP in to the autoregulatory range, which is shifted rightward in a patient with TBI. A threshold value of 70 mmHg suggested in the original work is questioned by later studies. The current recommendation of the Brain Trauma Foundation is a CPP of 60 mmHg. Systemic complications have been caused by the techniques used to maintain high systemic arterial pressures required to achieve high CPP values. While there is no controversy about the hazards of very low perfusion pressures, the benefit of CPP values higher than 60 mmHg remains to be confirmed by studies based on objective measures of cerebral oxygenation and metabolism and larger clinical outcome trials.

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