CLINICAL CONCEPTS AND COMMENTARY

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Management of Cerebral Perfusion Pressure after Traumatic Brain Injury

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IN 1996, the Brain Trauma Foundation sponsored the development of guidelines for the management of severe traumatic brain injury (TBI). The method used for development of the guidelines was evidence based, and probably the most significant contribution of the guidelines has been to highlight the remarkable lack of class I evidence available for many current management practices. Recently, revisions to the guidelines were published, and little has been changed in the recommendations.[1] From all of the aspects of management that were reviewed for the guidelines, the authors were only able to provide three standards based on class I evidence (randomized clinical trials) and only eight guidelines based on class II evidence (table 1). Furthermore, the randomized clinical trials that have supported the three guideline standards showed ineffectiveness of certain long-standing management practices (prophylactic hyperventilation, steroid administration, prophylactic anticonvulsants) rather than showing that any practices are beneficial.

One of the most controversial areas of TBI critical care that was highlighted in the review provided by the guidelines is the management of cerebral perfusion pressure (CPP). CPP is the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP). When pressure autoregulation is impaired and when CPP is below the lower limit of pressure autoregulation, cerebral blood flow (CBF) is dependent on CPP. It is important to emphasize that the controversial issue is not hypotension because overwhelming evidence from numerous clinical studies shows that hypotension has adverse consequences for the patient with TBI. Rather, the key controversial issues are what is the minimum level for CPP that is adequate for a brain-injured patient, and does increasing CPP beyond the level that provides adequate perfusion of the brain have an additional beneficial therapeutic effect or does it have a detrimental effect.

The traditional approach to treatment of the brain-injured patient has been to emphasize early surgical treatment of intracranial mass lesions, and meticulous critical care treatment of the patient to avoid causes of secondary injury to the brain and to minimize intracranial hypertension. This general critical care includes tracheal intubation to protect the airway, ventilatory support to prevent hypoxia and hypercarbia, sedation and analgesia, prevention of fever, maintenance fluids to provide normal intravascular volume and electrolytes, nutritional support, and prophylaxis for stress ulcer and for thromboembolism. The goal of this general care is to provide the optimal environment for the brain to recover and to minimize any factors, such as hypoxia, hypercarbia, hyponatremia, or fever, that may aggravate intracranial hypertension. ICP is monitored, and increases of ICP are treated using a stair-step approach, adding or subtracting therapies as needed based on response of ICP (fig. 1A). Usually, the therapies are added in an order that reflects the risk of complications associated with the use of the therapy. A typical protocol might start initially with cerebrospinal fluid (CSF) drainage and neuromuscular blocking agents. If additional treatment is required, osmotic agents are added. Barbiturate coma is reserved for intracranial hypertension refractory to these other treatments in a patient who is hemodynamically stable and who is potentially salvageable. The aim of all of these efforts is to control ICP.

Recently, however, several groups have advocated different overall strategies to the management of TBI. These approaches emphasize different aspects of the pathophysiology of TBI and are based on a favorable clinical experience by the individuals advocating the management protocol. None of these newly proposed approaches have been demonstrated to improve outcome after TBI over the traditional ICP management approach.

One novel strategy, called CPP management, has been advocated by Rosner *et al.*[2] This approach is based on a physiologic concept called the vasodilatory cascade, diagrammed in figure 1B. According to this hypothesis, a reduction in CPP—either a decrease in arterial blood pressure, an increase in ICP, or both—stimulates the cerebral vessels to dilate in an attempt to maintain CBF. This is the normal pressure autoregulatory response to a decrease in CPP. Because the increase in cerebral blood

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Table 1. Recommendations From Guidelines for the Management of Severe
Traumatic Brain Injury (TBI; from reference 1)

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Standards based on Class I evidence:

1. If ICP is normal, avoid chronic prolonged hyperventilation therapy ($PaCO_2$ < 25 mmHg).
2. Administration of steroids does not improve outcome or reduce ICP.
3. Prophylactic use of anticonvulsants does not prevent late posttraumatic seizures.

Guidelines based on Class II evidence:

1. All regions should have an organized trauma care system.
2. Avoid or correct immediately hypotension (systolic blood pressure < 90 mmHg) and hypoxia (SpO_2 <90% or PaO_2 < 60 mmHg).
3. Indications for intracranial pressure (ICP) monitoring include Glasgow Coma Score 3-8 with abnormal CT scan or 2 or more of the following adverse features: age > 40 yrs, motor posturing, systolic blood pressure < 90 mmHg.
4. Initiate treatment for ICP at an upper threshold of 20-25 mmHg.
5. Avoid the use of prophylactic hyperventilation ($PaCO_2$ < 35 mmHg) therapy during the first 24 hr after severe TBI.
6. Mannitol is effective for control of raised ICP after severe TBI, in doses ranging from 0.25 g/kg body weight to 1 g/kg body weight.
7. High-dose barbiturate therapy may be considered in hemodynamically stable salvageable severe TBI patients with intracranial hypertension refractory to maximal medical and surgical ICP lowering therapy.
8. Provide nutritional support (140% of resting energy expenditure in nonparalyzed patients and 100% of resting energy expenditure in paralyzed patients) using enteral or parenteral formulas containing at least 15% of calories as protein by day 7 after injury.

ICP = intracranial pressure; $PaCO_2$ = arterial partial pressure of carbon dioxide; SpO_2 = arterial oxygen saturation; PaO_2 = arterial partial pressure of oxygen; CT = computed tomography.
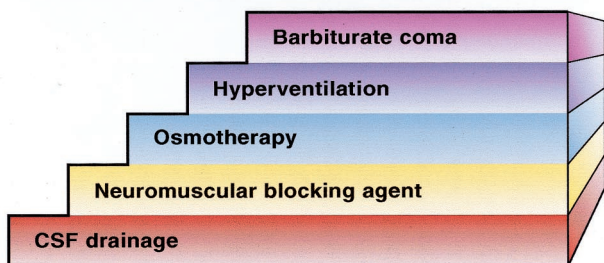
volume that accompanies the vasodilation further reduces CPP by increasing ICP, this sets up a cycle that leads to ever reducing CPP. An increase in arterial blood pressure under this circumstance has been observed to break the cycle and reduce ICP. A detailed description of this approach is given in a recent report of a clinical series.[2] In this series of 158 patients admitted with Glasgow Coma Scale score less than 7, mortality was only 29%, and 59% achieved a good recovery or moderate disability by 6 months postinjury. This approach has been widely adapted, and there was believed to be sufficient value in this practice that it was included in the 1996 Head Injury Guidelines and has continued to be recommended in the 2000 Head Injury Guidelines as a treatment option (supported by class III evidence and expert opinion).[1,3]

Another recent approach, called the Lund therapy, emphasizes reduction in microvascular pressures to minimize edema formation in the brain (fig. 1C). The goals of this approach are to preserve a normal colloid osmotic pressure (infusion of albumin and erythrocytes), to reduce capillary hydrostatic pressures by reducing systemic blood pressures (metoprolol and clonidine), and to reduce cerebral blood volume by vasoconstricting precapillary resistance vessels (low-dose thiopental and
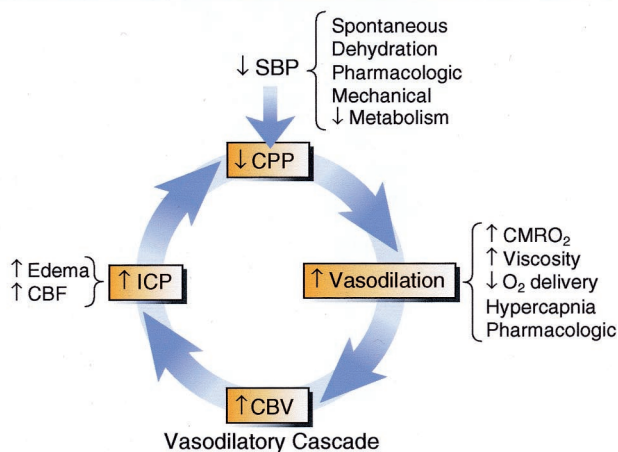
dihydroergotamine). Treatments that would favor increasing transcapillary filtration of fluid are avoided, including cerebrospinal fluid drainage, high-dose (to burst suppression) barbiturates, osmotic diuretics, and high CPP. Decompressive craniectomy, which can also increase edema formation, is reserved as a last resort. A detailed description of this approach is given in two recent publications, including a report of a clinical series in which mortality was 8% and in which 80% of patients recovered with a Glasgow Outcome Scale of good recovery or moderate disability by 6 months postinjury after institution of these measures.[4,5]

A final approach has been to try to match the treatment to the underlying pathophysiology. With this approach, it is emphasized that traumatic brain injury is heterogeneous, and each individual patient has a predominant pathophysiologic pattern. In addition, it recognizes that the pathophysiology of traumatic brain injury evolves over time, and treatment that is appropriate in the first few hours after injury may not necessarily be optimal 2 or 3 days after injury. Miller *et al.*[6] proposed that treatment of intracranial hypertension was more successful if the treatment was targeted at the underlying cause, *i.e.*, hypnotic–sedative agents for vascular

A. Traditional ICP-directed management strategy

Barbiturate coma

Hyperventilation

Osmotherapy

Neuromuscular blocking agent

CSF drainage

B. Physiological Basis of the CPP Management Strategy

$\downarrow$ SBP $\left\{\begin{array}{l}\text{Spontaneous} \\ \text{Dehydration} \\ \text{Pharmacologic} \\ \text{Mechanical} \\ \downarrow \text{Metabolism}\end{array}\right.$

$\downarrow$ CPP

$\uparrow$ Vasodilation $\left\{\begin{array}{l}\uparrow CMRO_2 \\ \uparrow \text{Viscosity} \\ \downarrow O_2 \text{ delivery} \\ \text{Hypercapnia} \\ \text{Pharmacologic}\end{array}\right.$

$\left.\begin{array}{l}\uparrow \text{Edema} \\ \uparrow \text{CBF}\end{array}\right\}$ $\uparrow$ ICP

$\uparrow$ CBV

Vasodilatory Cascade

C. Physiological Basis of the Lund Management Strategy

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_p - \pi_i)]$$

P_i $\qquad$ π_i

Interstitial space

Capillary
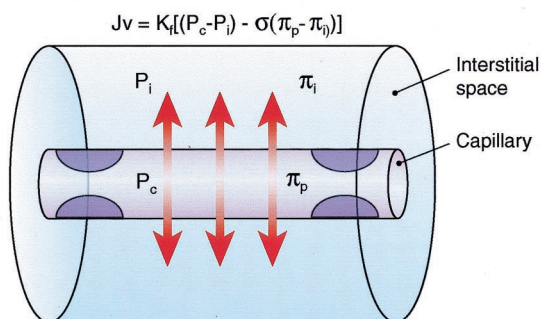
P_c $\qquad$ π_p

Fig. 1. (*A*) The traditional management of traumatic brain injury involves a stair-step addition of treatments as necessary to control intracranial pressure (ICP). CSF = cerebrospinal fluid. (*B*) The cerebral perfusion pressure (CPP) management strategy is based on the vasodilatory cascade (from Rosner *et al.*[2]). Increasing blood pressure breaks the vasodilatory stimulus for intracranial hypertension. SBP = systolic blood pressure; CBF = cerebral blood flow; CBV = cerebral blood volume. (*C*) The Lund strategy is based on knowledge of the forces that govern transcapillary filtration of fluid. Reduction in the hydrostatic pressure in the capillaries reduces edema formation and therefore lowers ICP. J_v = transcapillary filtration of fluid; K_f = filtration coefficient; $(P_c - P_i)$ = hydrostatic pressure difference between plasma and interstitial fluid; $(\pi_p - \pi_i)$ = oncotic pressure difference between plasma and interstitial fluid; σ = solute reflection coefficient.

causes of intracranial hypertension and osmotic agents for edema causes of intracranial hypertension. With regard to management of CPP, this approach reserves the treatment of increasing CPP for the patient who demonstrates a need for this higher CPP to adequately perfuse the brain. This approach most closely follows general critical care principles that emphasize optimizing each individual patient's physiologic status.

A summary of the similarities and differences in the details of management with these various approaches is given in table 2. All of the approaches have some physiologic basis for their use. However, except for the strategy of individualizing treatment, each approach focuses on only one or two aspects of what is a complex problem. The final outcome of the patient at 6 months after a severe traumatic brain injury sums the age and the underlying genetic and physiologic makeup of the individual, the severity of the primary injury, and the events that occur during prehospital care, emergency room resuscitation, surgical treatment of the injury, early hospital care in the intensive care unit, later hospital care on the wards, and rehabilitation. Although acute care after TBI is usually available regardless of financial resources, extensive rehabilitation is often dependent on insurance issues, so socioeconomic factors may also play a role in the final outcome. No study has shown superiority of any one of the approaches on the overall outcome of the TBI patient.

The definition of what characteristic defines an adequate CPP varies with the management approach. Advocates of the Lund therapy consider the minimum CPP that does not result in cerebral ischemia to be optimal. This group argues that a high CPP only serves to increase edema in the injured brain. Advocates of the Rosner CPP approach, in contrast, argue that CPP should be kept above the lower limit of autoregulation. Above this threshold, changes in CPP do not alter cerebral perfusion because the brain is able to compensate adequately for the pressure changes. It is sometimes argued that the brain "knows" what CBF is appropriate as long as CPP is kept within the autoregulatory range. However, there are two flaws in this approach. First, pressure autoregulation is not the primary regulatory mechanism that normally couples CBF to metabolic requirements.[7] It does not logically follow that keeping CPP in the autoregulatory range will necessarily provide an adequate perfusion of the brain. Second, the Rosner CPP approach assumes that pressure autoregulation is intact but that the lower limit of autoregulation is just shifted to a higher CPP. More recent studies using dynamic testing of pressure autoregulation have suggested that pressure autoregulation is not an all-or-none phenomenon but rather can present with various degrees of impairment.[8]

In an attempt to define a minimal threshold for CPP after TBI, a number of clinical studies have examined the relation between CPP and CBF or between CPP and a

Table 2. Differences in Management Approaches to the Head-injured Patient

Differences In Management Approaches to the Head-injured Patient			
Approaches to the Critical Care Management of Traumatic Brain Injury			
Traditional	**CPP management [2]**	**Lund therapy [4,15]**	**Individualized therapy [6]**
General Management:			

Head position
Sedation
Treatment of systemic
  hypertension
Nutritional support
	15-30° elevation
	morphine + lorazepam
	Treat SBP > 160
	mmHg, using labetalol
	Yes, avoid
	  hyperglycemia
		Flat
		No
		No
		
		No
			Flat
			low dose thiopental
			metoprolol + clonidine
			
			Yes, avoid
			hyperglycemia
				whatever position gives best CPP and ICP
				morphine + lorazepam
				Ischemia/hypoperfusion pattern, do not treat
				Adequate perfusion, may treat with labetalol
				yes, avoid hyperglycemia

Treatment of Intracranial Hypertension			
Neuromuscular blockade Hyperventilation CSF drainage Osmotherapy Barbiturate coma	Yes Yes Yes Yes Yes	Yes No Yes Yes No	No No No No No	yes Ischemia/hypoperfusion pattern, don't use Adequate perfusion, may use Yes Hypoperfusion/edema pattern, yes Hyperemia/vascular engorgement pattern, no Hypoperfusion/edema pattern, no Hyperemia/vascular engorgement pattern, yes
Management of Cerebral Perfusion Pressure			

Goal for CPP	Not considered, keep
	ICP < 20 mmHg and
	normal BP
		>70-80 mmHg
		(above lower limit of
		autoregulation)
			>50-60 mmHg
			(whatever provides
			adequate perfusion)
				Hypoperfusion/ischemia pattern-increase CPP to
				  improve CBF, especially if autoregulation is
				  impaired
				Adequate perfusion, maintain normal CPP

CPP = cerebral perfusion pressure; ICP = intracranial pressure; SBP = systolic blood pressure; CSF = cerebrospinal fluid; BP = blood pressure; CBF = cerebral blood flow.

measure of cerebral oxygenation, either jugular venous oxygen saturation ($Sjvo_2$) or, more recently, brain tissue Po_2. In a prospective study of 21 patients with severe TBI, increasing CPP from 32 ± 2 to 67 ± 4 mmHg improved brain tissue partial pressure of oxygen (Po_2) by 62%.[9] Increasing CPP above 68 mmHg did not result in an additional improvement in brain tissue Po_2. Below a CPP of 60 mmHg, Bruzzone et al.[10] found a significant relation between CPP and brain tissue Po_2. Between a CPP of 60 and 130 mmHg, another investigator found no relation between $Sjvo_2$ and CPP.[11] Chan et al.[12] found no relation between $Sjvo_2$ and CPP above 70 mmHg, whereas $Sjvo_2$ decreased with CPP below 70 mmHg.

Other studies have examined the relation between different thresholds for CPP and outcome from TBI. The concept for these studies is that if a CPP of 60 or 70 mmHg is a critical value below which additional damage may occur to the injured brain, there should be a significant relation between the length of time that CPP is below this critical threshold and the neurologic outcome of the patient. Clearly, this type of study can only show an association and does not prove that the relation is that of cause and effect. Using the physiologic data collected by the Traumatic Coma Data Bank, Marmarou et al.[13] examined the length of time that ICP, MAP, and CPP were beyond several different threshold levels and found that for MAP and CPP, the thresholds of 80 and 60 mmHg, respectively, were the most closely re-

lated to outcome. Struchen et al.[14] studied 184 patients with severe head injury and found significant relations between the length of time that ICP, MAP, and CPP were beyond the thresholds of 25, 80, and 60 mmHg, respectively, and neurologic outcome measured by both the Glasgow Outcome Scale and the Disability Rating Scale. In both of these studies, the predictive value of the physiologic variables did not seem to be simply a measure of severity of injury, because the relation to outcome remained significant when the models were adjusted for demographic characteristics that indicate severity of injury, such as initial Glasgow Coma Scale score, type of injury, and age. In children, the critical threshold for CPP may be lower. A mean CPP below 40 mmHg has been associated with certain fatality in pediatric TBI, but above 40 mmHg, higher levels for the average CPP do not seem to be correlated with a better outcome.[15]

Based on the available information, it is probably most correct to conclude that after TBI, an adequate CPP is necessary, but not sufficient to guarantee that CBF is adequate. The available clinical studies suggest that a CPP of 60 mmHg provides an adequate perfusion pressure for the majority of adult TBI patients, based on measures of global CBF and cerebral oxygenation.

The Rosner CPP approach argues that it is sometimes necessary to increase CPP higher than 70–80 mmHg to

keep CPP in the autoregulatory range. In fact, the average CPP in their clinical series (Glasgow Coma Scale score 7 group) was 85 ± 12 mmHg (ICP 27 ± 12 and MAP 111 ± 14). The Lund approach argues that a high CPP only induces additional edema formation and aggravates intracranial hypertension. It is not possible to directly compare these two clinical series, which both report excellent outcomes with these different approaches to management of CPP. There are likely many differences in the overall population of patients included in the two studies, which confound the effect of the management strategy.

One randomized clinical trial has examined the consequences, both beneficial and adverse, of different levels of CPP.[16] This trial compared a CBF-targeted strategy (CPP was kept > 70 mmHg) to a conventional ICP-targeted strategy (CPP was kept > 50 mmHg) in the initial management of acute TBI. The CBF-targeted treatment decreased the duration of time that CPP was less than 60 mmHg from a median of 13 h to 4 h ($P = 0.008$). The CBF-targeted treatment reduced the incidence of secondary ischemic events by approximately 50% ($P < 0.001$). However, this treatment strategy also increased the incidence of acute respiratory distress syndrome fivefold and did not improve long-term neurologic outcome. The interpretation of this study favored by the authors is that the beneficial effect from the CBF-targeted management of reducing secondary ischemic insults was offset by complications associated with maintaining blood pressure at an increased level.

Conclusion

Much more work is needed to answer this controversial question definitively. However, it is clear from the work that has been done to date that neurologic critical care issues such as this can and must be systematically studied in randomized clinical trials. Additional uncontrolled clinical series will never provide a convincing answer. In addition, because the only randomized trial that has compared the consequences of targeting different levels of CPP failed to show a long-term benefit and, in fact, showed a clear detrimental effect (increased incidence of acute respiratory distress syndrome) with a CPP goal of greater than 70 mmHg, there is no compelling reason

to increase CPP beyond that required to adequately perfuse the brain. It seems likely that a CPP of 60 mmHg provides adequate perfusion for most TBI patients. Higher CPP levels should probably be reserved for those TBI patients who demonstrate a specific indication for induced hypertension, such as regional or global ischemia. This recommendation differs from that of the 2000 Head Injury Guidelines but is better supported by the available literature.

References

1. Bullock RM, Chesnut R, Clifton GL, Ghajar J, Marion DW, Narayan RK, Newell DW, Pitts LH, Rosner MJ, Walters BC, Wilberger JE: Management and prognosis of severe traumatic brain injury, part 1: Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000; 17:451–553

2. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: Management protocol and clinical results. J Neurosurg 1995; 83:949–62

3. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care: Guidelines for the management of severe head injury. J Neurotrauma 1996; 13:641–734

4. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH: Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 1998; 26:1881–6

5. Grande PO, Asgeirsson B, Nordstrom CH: Physiologic principles for volume regulation of a tissue enclosed in a rigid shell with application to the injured brain. J Trauma 1997; 42:S23–31

6. Miller JD, Piper IR, Dearden NM: Management of intracranial hypertension in head injury: Matching treatment with cause. Acta Neurochir Suppl (Wien) 1993; 57:152–9

7. Paulson OB, Strandgaard S, Edvinsson L: Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990; 2:161–92

8. Strebel S, Lam AM, Matta BF, Newell DW: Impaired cerebral autoregulation after mild brain injury. Surg Neurol 1997; 47:128–31

9. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR: Brain tissue pO2-monitoring in comatose patients: Implications for therapy. Neurol Res 1997; 19:233–40

10. Bruzzone P, Dionigi R, Bellinzona G, Imberti R, Stochetti N: Effects of cerebral perfusion pressure on brain tissue pO2 in patients with a severe head injury. Acta Neurochir Suppl (Wien) 1998; 71:111–3

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 1995; 23:1412–7

12. Chan KH, Miller JD, Dearden NM, Andrews PJ, Midgley S: 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 1992; 77:55–61

13. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, Foulkes MA, Marshall LF, Jane HA: Impact of ICP instability and hypotension on outcome in patients with severe head injury. J Neurosurg 1991; 75:S59–64

14. Struchen MA, Hannay HJ, Contant CF, Robertson CS: The relation between acute physiological variables and outcome on the GOS and DRS following severe traumatic brain injury. J Neurotrauma 2001; 18:115–25

15. Downard C, Hulka F, Mullins RJ, Platt J, Chesnut R, Quint P, Mann NC: Relation of cerebral perfusion pressure and survival in pediatric brain-injured patients. J Trauma 2000; 49:654–8

16. Robertson CS, Valadka AB, Hannay HJ, Contant CF Jr, Gopinath SP, Cormio M, Uzura M, Grossman RG: Prevention of secondary insults after severe head injury. Crit Care Med 1999; 27:2086–95