Medical management of intracranial hypertension after head trauma: matching treatment to cause

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Abstract. Intracranial hypertension after severe head injury may be caused by the swelling of brain tissues, the mass effect of expanding haematomas, or, rarely, the obstruction of cerebrospinal fluid outflow. Although the latter two causes usually require a neurosurgical intervention, tissue swelling is mostly managed medically. Tissue swelling results from intracellular fluid accumulation (cytotoxic oedema), fluid extravasation (vasogenic oedema), or hyperaemia with vascular engorgement. Accordingly, there are distinct strategies that can be applied to reduce intracranial pressure. These include (1) treatment aimed at reducing cerebral hyperperfusion by metabolic suppression and hyperventilation, (2) treatment aimed at reducing cerebral hypoperfusion and cytotoxic oedema by augmenting cerebral perfusion pressure and osmotherapy, and (3) treatment aimed at reducing fluid extravasation by decreasing cerebral perfusion pressure, and infusing colloids and vasoconstrictors. In this manuscript I discuss the rationale of each therapeutic strategy in relation to the status of cerebral flow-metabolism coupling, pressure autoregulation, blood-brain barrier permeability, and the temporal changes in cerebrovascular physiology observed after brain trauma.

Introduction
After severe traumatic brain injury, basic rules of resuscitation must be applied to correct hypoxemia and shock. If intracranial mass lesions are present, these should be evacuated promptly. However, recommendations for subsequent medical treatment in the intensive care unit are less clear. In this setting there are no interventions that have been evaluated in randomized clinical trials and were shown to improve neurological outcome from head injury. In fact, guidelines by the Brain Trauma Foundation provide just three standards of care (supported by class I evidence) [1]. These are based on trials showing the ineffectiveness of some long-standing management practices (i.e., prophylactic hyperventilation, steroid administration, and prophylactic anticonvulsants). Accordingly, the use of intracranial pressure (ICP) monitoring to guide therapy also remains unsupported by good clinical evidence [1,2]. Monitoring is nonetheless routinely used in about 75% of specialist neurosurgical centres [3], and to many doctors ICP data have become central to management of head-injured patients.

Traditionally, the medical management of raised ICP is characterized by a stepwise approach [4]. The first step typically includes the use of analgesia and sedation, head of bed elevation, initial slight hyperventilation, and cerebrospinal fluid drainage if indicated. The second step includes mannitol or hypertonic saline infusions, and more aggressive hyperventilation (preferably with concomitant monitoring of jugular venous saturation). The third step includes rescue therapies such as high-dose barbiturate infusions, and possibly decompressive craniectomy or hypothermia. Thus, interventions are traditionally chosen in the order of an increasing risk of complications.

Pathophysiological considerations are generally deemed less important for selecting any particular therapy. However, brain tissue swelling after head trauma may result from an increase in cell volume (cytotoxic oedema), interstitial fluid volume (vasogenic oedema), blood volume (vascular engorgement), or a combination of these factors. The distinction between these processes is important to treat intracranial hypertension rationally rather than empirically. Unfortunately, the relative importance of each of these factors is difficult to ascertain and thus has been a matter of debate [5]. As a consequence, treatment protocols for severely head-injured patients differ widely. In this respect, a distinction has recently been made into ICP-targeted, cerebral perfusion pressure (CPP)-targeted, and brain volume-targeted management [6].

In this manuscript I will briefly review the pathophysiology of traumatic brain injury with respect to its relevance for therapy. The rationale of each therapeutic strategy in relation to the status of cerebrovascular reactivity, blood-brain barrier permeability, and the temporal changes in pathophysiology observed after brain trauma will then be discussed.

Pathophysiology
Primary and secondary neuronal injury
Neuronal cell death after severe head injury may result from the primary traumatic insult or from secondary injury processes. The primary damage is the result of acceleration-deceleration forces (especially in the coronal plane) that ensue from impact during falls and motor vehicle accidents. The resulting tissue deformation causes axonal dysfunction and injury, brain contusions, and epicraniar, subdural, subarachnoid, or parenchymatous haemorrhages. This macroscopic injury is associated with microscopic changes and metabolic derangements, including ischemic cytotoxic oedema, astrocyte swelling with microvascular occlusion or dysfunction, and blood-brain barrier disruption [7,8]. These initial injury processes are closely linked with early gene activation, resulting in the subsequent recruitment of inflammatory cells and repair mechanisms (Figure 1).

Secondary neuronal injury occurs in the period following the initial insult and has consistently been associated with the presence of tissue ischemia [9]. Ischemic cell death involves the release of excitatory amino acids, intracellular calcium overload, oxidative stress mediated by free radicals, and the activation of inflammatory
processes [10]. The inflammation is mediated by the production of pro-inflammatory cytokines in the brain and the upregulation of adhesion molecules, resulting in the early influx of neutrophils, the later recruitment of lymphocytes and macrophages, and fever [11].

**Pressure autoregulation and flow-metabolism coupling**

Because the brain lacks a large storage capacity for oxygen and glucose, it is in need of a constant nutritional supply. Failure to achieve sufficient blood flow quickly results in ischaemia with the potential for additional cell destruction. In normal brain tissue there are endogenous mechanisms that control arteriolar vessel diameter, and thus cerebrovascular resistance, on a regional level in order to keep blood flow matched to alterations in perfusion pressure and metabolic demand. The two components of this autoregulatory system are typically considered separately. First, pressure autoregulation refers to the capacity of the brain to maintain capillary hydrostatic pressure (due to arterial hypertension) may be an important contributing cause of brain oedema [13,19].

**Temporal changes in pathophysiology**

There are sequential changes in cerebrovascular physiology after head trauma that are closely linked to the primary and secondary injury processes described above. In many patients, CBF shows a triphasic pattern (Figure 1) [20]. Early after head injury (within 12 hours), global CBF is typically reduced, sometimes to ischemic levels [21]. Between 12 and 24 hours post injury, CBF increases and the brain may exhibit supernormal flow. While several authors refer to this phenomenon as hyperaemia, the absence of a reduction in cerebral oxygen extraction in many patients suggests that metabolism and blood flow remain coupled, and a more appropriate label would be hyperperfusion [8].

Blood-brain barrier permeability

In normal brain tissue capillaries are impermeable to salts and proteins, and fluid exchange across the blood-brain barrier is completely determined by plasma osmolality. If blood-brain barrier permeability is increased, however, the capillary filtrate contains small solutes and fluid accumulation within the brain becomes dependent on the hydrostatic and oncotic pressure differences across the capillary wall (i.e. Starling equation for peripheral tissues) [17]. Brain water will not accumulate significantly if cerebrovascular permeability is only transiently increased, but with prolonged permeability changes, vasogenic oedema may develop over a period of days [18]. In this situation, an increased capillary hydrostatic pressure (due to arterial hypertension) may be an important contributing cause of brain oedema [13,19].
Cytotoxic edema is believed to result from the loss of a cell’s ability to regulate its ionic gradients, causing a massive increase in osmolality with breakdown of cellular structure [4]. Cerebral vasodilatation makes vascular engorgement an increasingly important contributor to intracranial hypertension from 24 hours onwards. Capillaries also appear to become leaky between the second and fifth days post injury, and extravasation of fluid (vasogenic edema) then worsens brain swelling. Unfortunately these patterns are not consistent or predictable, and different mechanisms may operate concurrently within a single patient at any given time [8].

**Clinical management**

**Goal-directed concepts**

Goal-directed treatment in the intensive care unit refers to clinical management that, as a primary therapeutic end-point, aims to maintain physiological variables strictly within predefined target ranges. If a variable cannot be kept within that target range, a predefined algorithm is used to select appropriate interventions. In this setting, it is possible to set apart several conceptually distinct approaches (Table 1) [6]. These include (1) controlling ICP through reduction of cerebral blood volume, (2) maintaining CBF through augmentation of CPP, and (3) decreasing brain water content through reduction of fluid flux from the capillaries (also known as the ‘Lund concept’). It is important to note that therapy in clinical practice often reflects a combination of these goals. Nonetheless, the classification is useful, because it relates interventions to specific physiological aims, and clarifies which assumptions concerning the status of cerebrovascular reactivity and blood-brain barrier function are required for rational therapy.

**1. ICP targeted treatment**

This is the traditional approach to treatment of severe head injury. It focuses on early surgical evacuation of intracranial mass lesions and meticulous treatment of intracranial hypertension, using a stepwise approach to reduce cerebral blood volume. Although osmotherapy clearly also has an important role in this setting, for the purpose of the discussion, I will only consider interventions that are specific to the ICP targeted concept in this paragraph. These include (1) the use of deliberate hypocapnia and (2) cerebral metabolic suppression therapy. Both measures aim at reducing hyperaemia or vascular engorgement and rely on the assumption that metabolic autoregulation is largely preserved after injury. The use of osmotic diuretics will be discussed in relation to the CPP targeted approach (see below). However, it is important to note that the ICP lowering effect of mannitol is at least partially mediated through metabolic autoregulatory vasodilatation in response to a decrease in blood viscosity following the infusion of this agent [22]. In this respect, mannitol also has its conceptual place in an ICP targeted approach.

**Deliberate hyperventilation** - Hyperventilation (arterial pCO$_2$ 3.5-4.5 kPa) rapidly reduces intracranial blood volume through a pH-dependent constriction of precapillary resistance vessels. Because cerebrovascular carbon dioxide reactivity is retained more in relatively healthy brain tissue compared with severely injured areas or the penumbra zone [23], blood flow reductions should theoretically be less pronounced in areas that are most vulnerable to hypoxic-ischaemic insults. Nonetheless, prolonged hyperventilation is probably of limited value for controlling ICP and may even be harmful. First, the reduction of CBF and blood volume during sustained hypocapnia is only transient (4-12 hours), because compensatory reductions in cerebral extracellular fluid bicarbonate levels restore pH over time [24]. Second, there are data to suggest that aggressive hyperventilation can reduce global or regional CBF to below ischemic thresholds and adversely affect patient outcome [25,26]. As a consequence, a case has been made for the continuous monitoring of jugular venous oxygen saturation when using prolonged hyperventilation.

Table 1. Conceptual approaches to intensive care management of traumatic brain injury

<table>
<thead>
<tr>
<th>Pathophysiological targets</th>
<th>ICP targeted</th>
<th>CPP targeted</th>
<th>Volume targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumptions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>carbon dioxide reactivity and flow-metabolism coupling preserved</td>
<td>pressure autoregulation preserved (may be shifted to the right)</td>
<td>pressure autoregulation impaired; blood-brain barrier disrupted</td>
</tr>
<tr>
<td>Goal for ICP</td>
<td>&lt;20 mm Hg</td>
<td>not considered</td>
<td>&lt;25 mm Hg</td>
</tr>
<tr>
<td>Goal for CPP</td>
<td>not considered</td>
<td>70-80 mm Hg</td>
<td>50-60 mm Hg</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>crystalloids; maintain normovolemia</td>
<td>crystalloids + colloid; may use hypervolemia</td>
<td>albumin, plasma, red cells; use furosemide to obtain negative fluid balance</td>
</tr>
<tr>
<td>Vasoactive drugs</td>
<td>none</td>
<td>catecholamines</td>
<td>dihydroergotamine</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>use labetalol if systolic blood pressure &gt;160 mm Hg</td>
<td>use vasoactive agents to increase blood pressure</td>
<td>use metoprolol and clonidine to decrease blood pressure</td>
</tr>
<tr>
<td>Head position</td>
<td>15-30° head elevation flat</td>
<td>flat</td>
<td>flat</td>
</tr>
<tr>
<td>Cerebrospinal fluid drainage</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Osmotherapy</td>
<td>yes;</td>
<td>yes;</td>
<td>no;</td>
</tr>
<tr>
<td>Sedation / stress reduction</td>
<td>use mannitol or hypertonic saline</td>
<td>use mannitol or hypertonic saline</td>
<td>preserve colloid onotic pressure</td>
</tr>
<tr>
<td>Cerebral metabolic suppres-</td>
<td>use benzodiazepines, propofol, morphine</td>
<td>use benzodiazepines, fentanyl, clonidine</td>
<td>use low-dose thiopental, benzodiazepines, fentanyl, clonidine</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>yes;</td>
<td>yes;</td>
<td>no;</td>
</tr>
</tbody>
</table>

CPP=cerebral perfusion pressure; ICP=intracranial pressure. 1 Also known as the ‘Lund’ concept.
Reductions in venous saturation below 55% or increases in arterial to jugular venous differences in oxygen content to greater than 9 ml/100 ml (4 mmol/L) indicate that global cerebral blood flow may be inadequate and that hyperventilation should be reversed [8]. Nonetheless, it remains uncertain whether this approach can effectively prevent locoregional brain ischaemia during periods of pronounced hypocapnia.

**Metabolic suppression therapy** - A reduction of cerebral energy metabolism causes lasting cerebral vasoconstriction and reduction of ICP, provided that flow-metabolism coupling is preserved [27,28]. High-dose intravenous barbiturate infusions (e.g., thiopental sodium 10 mg/kg loading dose followed by 3-20 mg/kg/h continuous infusion, further titrated to maintain approximately 6 bursts/min on EEG) have traditionally been used for this purpose for periods of up to 15 days [29]. More recently the use of propofol has also been advocated. Even at doses that abolish cortical electrical activity, evidence suggests that cerebrovascular carbon dioxide reactivity—and thus presumably flow-metabolism coupling—remains unaffected by the use of these agents [18,30]. However, this coupling may not be perfect, and if systemic haemodynamics become compromised the decrease in CBF may exceed the corresponding decrease in metabolic demand, with a widening of the cerebral arteriovenous oxygen content difference [27]. In addition, prolonged high-dose barbiturate treatment is often associated with pulmonary, cardiovascular, and infectious complications [29], whereas high-dose propofol infusions impose a significant lipid load and appear to be associated with severe adverse cardiac effects and mortality [31].

Mild to moderate hypothermia (32-35 °C) has been used to lower ICP for periods of 1-7 days, both as an alternative for and as an addition to the pharmacological suppression of cerebral metabolic demand [32,33]. Hypothermia has also been reported to blunt the cascade of secondary injury processes following head injury if it is started early enough [34]. However, despite encouraging observations in animal models and preliminary clinical studies of traumatic brain injury, hypothermia (33°C for 48 h) failed to improve patient outcome in a large randomized controlled trial, although it did effectively reduce intracranial hypertension [35]. As a consequence, focus has now shifted from the deliberate use of hypothermia towards the strict prevention and reversal of spontaneous hyperthermia.

**2. CPP targeted treatment**

CPP-targeted management was introduced by Rosner et al. in 1995 and is based on the physiological concept of the vasodilatory cascade [36]. According to this hypothesis, a reduction in CPP - either a decrease in arterial pressure, an increase in ICP, or both—stimulates the cerebral vessels to dilate in an attempt to maintain cerebral blood flow constant. Because the increase in cerebral blood volume that accompanies the vasodilation decreases CPP by increasing ICP, this sets up a cycle that leads to further deterioration of CPP. An increase in arterial blood pressure under this circumstance has been observed to break the cycle, restore adequate tissue perfusion, and reduce ICP. Obviously, the CPP targeted concept assumes that pressure autoregulation is preserved. It is further hypothesized that the autoregulation curve has shifted to the right in a majority of patients, rendering the brain vulnerable to low perfusion pressures. Moreover, in order to maximize vasoconstriction, the CPP would conceptually need to be kept at the higher end of the pressure autoregulation plateau. Consequently, this strategy implies that CPP targets are set at much higher levels than the value of 60 mm Hg which is thought to provide mere adequate perfusion for most patients [6,37].

The CPP can be improved by lowering the position of the head relative to the rest of the body, by raising mean arterial pressure, or by reducing ICP. ICP reduction—in its turn—can be obtained using a variety of interventions. However, because the CPP targeted approach assumes that the brain is operating at the lower limit of autoregulation and is thus prone to ischaemia resulting from hyperperfusion, measures to lower ICP by cerebral vasoconstriction (e.g., by hyperventilation) do not fit logically in this concept. Instead, osmotherapy is the more rational choice to treat cytotoxic oedema caused by tissue ischaemia.

**Iatrogenic arterial hypertension** - Augmentation of mean arterial pressure involves intravenous volume expansion to obtain adequate cardiac preload and the continuous infusion of inotropes and vasopressors. However, this practice has been associated with an increased risk of adult respiratory distress syndrome in head-injured patients and possibly cardiac complications [38]. Prolonged high-dose infusions of phenylephrine or noradrenaline to maintain arterial hypertension may also be a priming or triggering factor for development of stress cardiomyopathy or propofol-infusion syndrome in these patients [39]. Although it has been demonstrated that catecholamines have no direct effects on cerebral vessels in healthy patients [40], there are no data on the safety of infusing high doses of vasoactive agents in the presence of a disrupted blood-brain barrier, and it is conceivable that catecholamines cause unintended local vasoconstriction in the injured brain [23].

**Osmotherapy** - Intravenous mannitol has traditionally been used for treatment of cytotoxic oedema after brain trauma. Both conventional-dose (0.25-1 g/kg) and high-dose (1-2 g/kg) repeated bolus infusions may be appropriate in this setting [41]. In addition to its osmotic and diuretic effects, mannitol has antioxidant properties and rheological activity [42]. Decreased blood viscosity after mannitol infusion probably contributes to ICP reduction by stimulating autoregulatory cerebral vasoconstriction [22]. Hypertonic saline is an alternative osmotic agent and may be effective particularly for small-volume fluid resuscitation in head-injured patients with major systemic trauma, and for cases of refractory intracranial hypertension [43,44]. It has an osmolar effect that is potentially slightly greater than that of mannitol given at equimolar doses (blood-brain reflection coefficient 1.00 for sodium chloride compared with 0.90 for mannitol) [23]. In addition, hypertonic saline may improve regional cerebral blood flow by dehydrating cerebral endothelium and erythrocytes. Membrane stabilization, immune modulation and other potentially beneficial effects have also been claimed [44]. Hypersmolar therapy relies on the assumption of a preserved blood-brain barrier. If the reflectance for mannitol or sodium-chloride is seriously compromised (e.g.,in areas of contusion or haemorrhage) the osmotic agents may pass from the blood into the interstitial space, where they might produce reverse osmotic shifts and cause ‘rebound’ intracranial hypertension [45]. Furthermore, hypersmolar therapy is associated with other risks. Mannitol is a potent diuretic and its repeated administration puts patients at risk of dehydration if the fluid balance cannot be maintained. Hypersmolar therapy also has potential renal toxicity, which can possibly be reduced if plasma osmolality is kept below 320 mosm/L [42].
3. Brain volume targeted treatment

The volume targeted ‘Lund therapy’ emphasizes a reduction in microvascular pressures to minimize oedema formation in the brain. Conceptually, this approach assumes that pressure autoregulation is impaired or completely abolished (allowing hydraulic conduction of arterial hydrostatic pressure to the capillaries) and that the blood–brain barrier is open to small solutes (allowing osmotic agents to leak into the interstitial space) [13,17]. As a consequence, the goals of this strategy are to preserve a normal colloid oncotic pressure, to reduce capillary hydrostatic pressures by reducing systemic blood pressure, and to reduce cerebral blood volume by vasoconstricting venous capacitance and precapillary resistance vessels. Treatments that would favour increasing transcapillary filtration of fluid are avoided, including cerebrospinal fluid drainage, high-dose barbiturates, osmotic diuretics, and high CPP.

The clinical protocol presented by the group from Lund, Sweden, utilizes low-dose thiopental and dihydroergotamine infusions to constrict cerebral arterioles and venules, and metoprolol and clonidine to reduce blood pressure, accepting CPP values as low as 50 mm Hg in adults [40]. In addition, packed red cells, plasma, and albumin transfusions are used to preserve normovolaemia and restore plasma oncotic pressure after injury, while avoiding fluid overload by using furosemide and restricted amounts of crystalloid solutions [27]. The head-up position is not used because it would only result in venous collapse where the bridging veins pass through the dura, leaving the intracranial blood volume unaltered [13]. Cerebrospinal fluid drainage and decompression craniotomy are also not routinely performed, because these interventions would decrease tissue pressure and favour capillary fluid filtration, potentially resulting in unwanted brain bulk shifts.

Conclusion

There are at least three conceptually distinct strategies that can be applied to the medical management of intracranial hypertension in severely head-injured patients. Each strategy is based on a particular rationale for cerebral tissue and blood volume regulation, and relies on assumptions about the status of cerebrovascular reactivity and blood-brain barrier integrity after injury. Unfortunately, there is currently no practical method to test these assumptions, or to assess the relative contributions of cytotoxic oedema, vasogenic oedema, and vascular engorgement to the problem of raised ICP.

With the present state of knowledge, one should be extremely cautious in recommending any one particular way of physiological management of severe traumatic brain injury over another. However, considering that there are known temporal changes in cerebrovascular physiology after head trauma, it seems most rational to adapt a CPP targeted approach during the first 24 hours, when cerebral hyperfusion is most commonly observed, whereas a primarily ICP targeted approach seems more appropriate on subsequent days, when inflammation and hyperaemia are prominent. Brain volume targeted therapy according to the Lund protocol is still considered controversial by many experts, despite its successful application by some centres in Scandinavia. Large bi-fronto-temporal decompressive craniectomy with duraplasty has not been discussed in this paper, but its role as rescue therapy in cases of severe refractory intracranial hypertension seems promising [47]. It is currently being evaluated in two randomized clinical trials [48,49]. Finally, it is important to consider that there is large heterogeneity within the head trauma population. It is therefore possible that treatments that are commonly used in the population at large may be ineffective, unnecessary, or even harmful for some patients at some times. When considering any one particular intervention in a head-injured patient, its effects on ICP, CPP, and indices of cerebral oxygenation should preferably be verified in that individual before a decision is made to commence long-term therapy. Possibly, optimal management can thus be offered with a reduced risk of iatrogenic injury.

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References


38. Contant CF, Valadka AB, Gopinath SP, Hannay HI, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension and cerebral perfusion pressure. Available at: www2.braintrauma.org/guidelines/.
43. Polderman KH, Tjong Tjin JR, Peerdeman SM, Vand...