Management of Acute Brain Injury and Associated Respiratory Issues

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Acute brain injury, in the form of trauma, stroke, or spontaneous hemorrhage, occurs commonly and in all age groups. Although the management of these conditions differs considerably, certain physiologic principles are shared by all and are useful in guiding the management of the most severely injured patients. This article reviews basic cerebral physiology and describes the links between physiology and management principles, emphasizing subjects relevant to the respiratory management of patients with acute brain injury. *Key words: acute brain injury, respiratory, intracranial pressure, cerebral blood flow, hyperventilation, lung-protective ventilation, closed head injury, subarachnoid hemmorhage*. [Respir Care 2006;51(4):357–367. © 2006 Daedalus Enterprises]

Introduction

"Acute brain injury" is a broad term that encompasses a wide variety of conditions, including stroke, anoxia, trauma, infection, and spontaneous hemorrhage. Management goals in each of these conditions may differ considerably and are not easily generalizable. However, all forms of acute brain

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Steven Deem MD presented a version of this paper at the 21st annual New Horizons symposium at the 51st International Respiratory Congress of the American Association for Respiratory Care, held December 3–6, 2005, in San Antonio, Texas.

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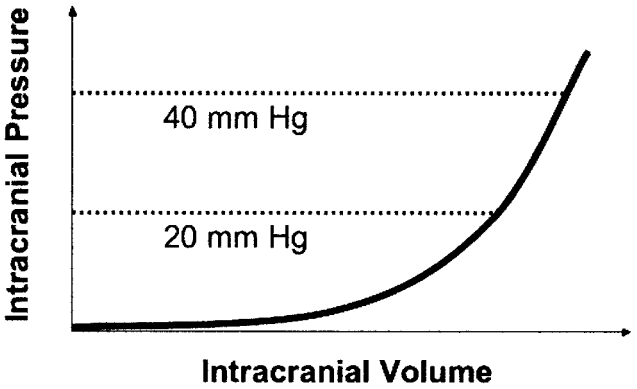

Fig. 1. Intracranial pressure-volume curve. Intracranial pressure changes slowly as intracranial volume increases, until pressure reaches approximately 20 mm Hg, after which pressure rises rapidly with further increase in volume. Brain herniation may occur at intracranial pressure of 40–45 mm Hg.

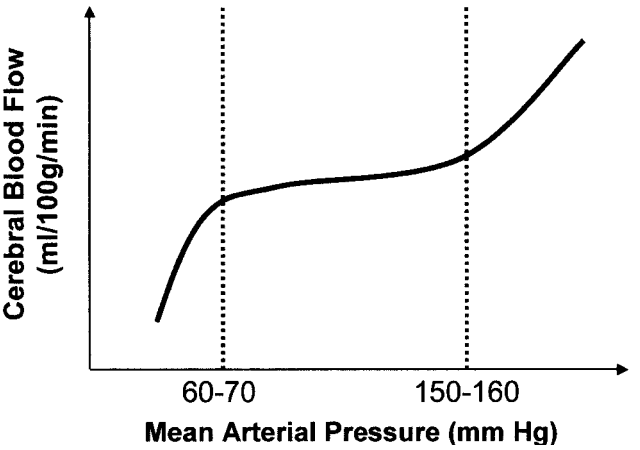

Fig. 2. Blood pressure autoregulation of cerebral blood flow. Cerebral blood flow remains nearly constant between systemic mean arterial pressures of 60–70 mm Hg and 150–160 mm Hg. Above and below these thresholds, cerebral blood flow changes in a linear relationship with mean arterial pressure.

injury share common principles of cerebral physiology that influence interventions to limit progression of injury beyond its initial state. This review will discuss some of these common physiologic principles and emphasize subjects that may impact directly on management of mechanical ventilation. Most of the discussion will center on patients with traumatic brain injury.

Cerebral Physiology

Intracranial Pressure

The intracranial contents consist predominantly of 3 constituents: neural tissue, blood, and cerebral spinal fluid. The rigid skull surrounds the intracranial contents; thus, an increase in the volume of any or all of these constituents can lead to an increase in intracranial pressure (ICP), depending on intracranial compliance. For example, an increase in the volume of cells due to cytotoxic edema or cell proliferation (tumor), or an increase in cerebral spinal fluid due to obstruction of the outflow pathways (hydrocephalus), may increase ICP. Likewise, an increase in cerebral blood volume due to extravasation of blood (trauma or spontaneous hemorrhage) or an increase in cerebral blood flow (CBF) or blood-vessel capacitance may also lead or contribute to an increase in ICP. Conversely, manipulation of these constituents can be used to reduce ICP, as will be discussed in a following section.

Under normal conditions, ICP is $<$ 10 mm Hg. An increase in intracranial volume has little effect on ICP until intracranial compliance can no longer accommodate the increased volume. This typically occurs at an ICP of 15–20 mm Hg (Fig. 1). ICP measurements $>$ 20 mm Hg are consistently associated with poor outcome; thus, 20 mm Hg is a commonly used threshold for initiating therapy.[1,2] Another important ICP threshold occurs at approximately 40–45 mm Hg. At this point, the forces on the brain become so great that herniation of tissue downward through openings in the dura (uncal or tentorial herniation) or skull (foramen magnum or tonsillar herniation) can occur. Herniation of brain tissue is associated with poor outcome, particularly if not corrected immediately.

Cerebral Blood Flow

CBF is controlled by several factors, including systemic blood pressure, cerebral metabolic rate, and P_{aCO_2}. CBF remains relatively constant within a range of systemic mean arterial pressure from 60–70 mm Hg to approximately 150 mm Hg (Fig. 2). More precisely, CBF is determined by cerebral perfusion pressure (CPP), which is determined by the mean arterial blood pressure minus the ICP or jugular venous pressure, whichever is higher. In normal subjects, CBF falls when CPP is below a threshold of approximately 50–60 mm Hg.[3] Thus, an increase in ICP may result in a reduction in CBF and lead to cerebral ischemia if it reduces CPP sufficiently. On the other hand, an increase in ICP that is associated with a simultaneous increase in mean arterial pressure, with a resulting maintained CPP, may not result in a reduction in CBF or cerebral ischemia. Thus, it is important that the ICP be considered in the context of its effect on CPP.

CBF is also linked to cerebral metabolic rate; as metabolic rate increases, CBF increases to meet the increased demand for oxygen. Likewise, as cerebral metabolic rate falls, CBF also falls in response to reduced demand. Thus, fever can be detrimental to cerebral hemodynamics by increasing CBF and ICP; conversely, hypothermia can reduce ICP by reducing cerebral metabolic rate and CBF.

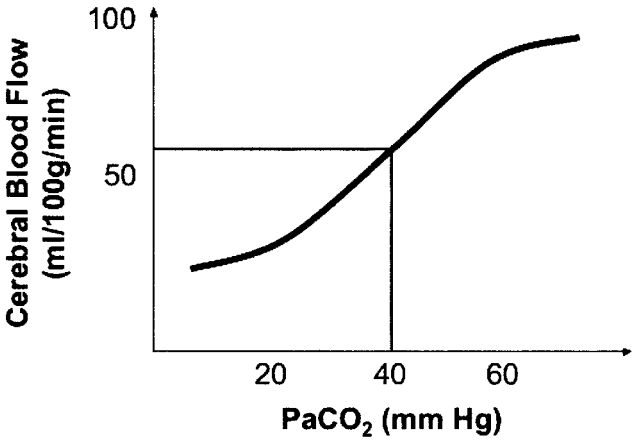

Fig. 3. Regulation of cerebral blood flow by arterial carbon dioxide. Cerebral blood flow changes linearly with P_{aCO_2} between P_{aCO_2} values of approximately 20 and 60 mm Hg. Thus, increases in alveolar ventilation will reduce cerebral blood flow. Clinically, this will reduce intracranial pressure because of reduced cerebral blood volume.

Lastly, CBF is controlled by P_{aCO_2}, and less so by P_{aO_2}. More precisely, it is the perivascular interstitial and vascular intracellular pH that controls CBF. Because CO_2 readily diffuses across the blood-brain barrier and into cells, whereas bicarbonate ion does not, changes in ventilation and, consequently, the P_{aCO_2} result in rapid changes in cerebral perivascular pH and CBF.

The relationship between P_{aCO_2} and CBF is approximately linear between P_{aCO_2} of 20 and 60 mm Hg; as P_{aCO_2} rises, CBF rises also (Fig. 3). Conversely, the relationship between ventilation and CBF is inversely linear; hypoventilation results in an increase in CBF. This relationship can be put to clinical use in the treatment of acute rises in ICP, where hyperventilation results in a rapid reduction in P_{aCO_2} and subsequently CBF. The reduction in CBF reduces cerebral blood volume and ICP.

The effect of changes in ventilation and P_{aCO_2} on CBF is rapidly lost as intracellular pH returns to baseline, by compensatory mechanisms, including transcellular flux of hydrogen and bicarbonate ions and lactate production.[4] These compensations begin within minutes of a step change in ventilation or P_{aCO_2}, and the effect of hyperventilation on CBF is completely lost by 4 hours in normal subjects.[5–7] In patients with traumatic brain injury, the effect of hyperventilation on CBF appears to be more complex, in that ICP returns to baseline prior to recovery of CBF.[8] Thus, hyperventilation is best applied only in short increments while other more sustained treatments to reduce ICP are applied.

P_{aO_2} has little to no effect on CBF until the P_{aO_2} falls to below approximately 60 mm Hg, after which CBF rises in inverse relation to P_{aO_2}.[5]

Cerebral Oxygen Transport

Cerebral oxygen transport is determined by the same principles that determine systemic oxygen transport, with the caveat that cerebral rather than systemic blood flow is considered (CBF vs cardiac output). Thus, cerebral oxygen transport (T_{cO_2}) can be expressed by the following equation:

$$T_{cO_2} = CBF \times ((\text{hemoglobin} \times S_{aO_2} \times 1.34) + 0.003 \times P_{aO_2})$$

in which S_{aO_2} is blood oxygen saturation. It is evident that dissolved oxygen plays a minor role in cerebral O_2 transport, whereas the other factors are equally weighted.

Cerebral oxygen extraction is quantitated by the ratio of cerebral oxygen consumption (cerebral metabolic rate for oxygen) and cerebral oxygen transport. The brain typically extracts 30–40% of the delivered oxygen. An increase in cerebral oxygen extraction suggests inadequate oxygen transport, high cerebral metabolic rate, or a combination of the two.

Cerebral oxygen extraction can be assessed by measuring the oxygen saturation and oxygen content of jugular venous blood (S_{jO_2} and C_{jO_2}, respectively). In addition, cerebral oxygenation can be assessed by direct measurement of brain-tissue P_{O_2} (P_{brO_2}).

To measure S_{jO_2}, the jugular vein is cannulated in a retrograde fashion and a catheter tip is positioned in the jugular bulb, where the vein exits the skull. The S_{jO_2} reflects the amount of oxygen that has been extracted as the blood passes through the majority of brain tissue (global monitor). The S_{jO_2} normally resides in the range of 60–70%; if S_{jO_2} falls below approximately 55%, cerebral oxygen extraction is high, implying that the brain is at risk for ischemia. In the event of a low S_{jO_2} (high cerebral O_2 extraction), efforts to improve cerebral O_2 transport may be beneficial, including increasing CBF, hemoglobin, S_{aO_2}, and (less so) P_{aO_2}. Conversely, a high S_{jO_2} ($> 75–80\%$) implies "luxury perfusion" of the brain with relatively high CBF. In this event, hyperventilation may be reasonably applied to attempt to reduce ICP. A management strategy using S_{jO_2} to optimize cerebral physiology has been reported to improve outcome in traumatic brain injury, although the level of evidence is low.[9]

P_{brO_2} is measured by directly placing an electrode in brain parenchyma, typically on the injured side. The P_{O_2} is measured continuously in an area that extends approximately 1.4 cm around the tip of the probe (local monitor). P_{brO_2} is normally 25–30 mm Hg. A fall in P_{brO_2} suggests a fall in cerebral oxygen transport relative to oxygen needs, similar to a fall in S_{jO_2}. The critical level of P_{brO_2} is in the

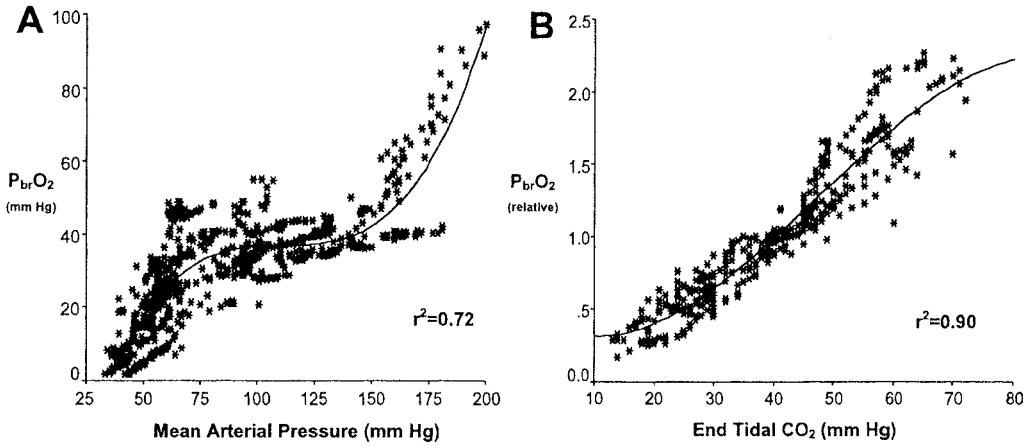

Fig. 4. A: Pressure autoregulation of brain-tissue P_{O_2} (P_{brO_2}). P_{brO_2} varies with mean arterial pressure in a sigmoidal relationship in the mean arterial pressure range of 60–150 mm Hg, similar to the relationship between cerebral blood flow and mean arterial pressure. B: CO_2 reactivity of brain-tissue oxygen. P_{brO_2} is linearly related to the partial pressure of end-tidal CO_2 (P_{ETCO_2}) over the P_{ETCO_2} range 20–60 mm Hg. P_{brO_2} is indexed to pre-run baseline values. (From Reference 11, with permission.)

range of 10–15 mm Hg, and values below this threshold are associated with worse outcome.[10] P_{brO_2} varies with systemic blood pressure in a pattern that mirrors the CBF/blood-pressure autoregulation curve, with P_{brO_2} remaining relatively stable in the mean arterial pressure range of 70–150 mm Hg, and falling when mean arterial pressure is $<$ 60 mm Hg (Fig. 4A). P_{brO_2} varies in a linear relationship with P_{aCO_2} (see Fig. 4B), so hyperventilation should be avoided in patients with low P_{brO_2}.[11,12] Somewhat surprisingly, increasing the P_{aO_2} by increasing the fraction of inspired oxygen (F_{IO_2}) improves P_{brO_2} (Fig. 5).[13,14] This suggests that dissolved O_2 may play a greater role in local O_2 delivery than is predicted by the O_2-transport equation. However, there is no evidence from randomized controlled trials that managing patients using P_{brO_2}-monitoring improves patient outcomes.

Management of Patients With Acute Brain Injury

Management Guidelines and Levels of Evidence

Somewhat surprisingly, few high-quality studies have demonstrated that physiologic management of patients with acute brain injury improves outcomes. Most of the reported trials have been small, uncontrolled, and retrospective.[15] Indeed, there are no randomized prospective trials that clearly describe any outcome benefits from ICP monitoring or management. The Brain Trauma Foundation published guidelines in 2000, updated in 2003, that distill the available literature on management of traumatic injury and provide useful recommendations for clinicians.[1,16] However, these documents rely heavily on expert opinion and low levels of evidence. The principles of managing acute brain injury are outlined below.

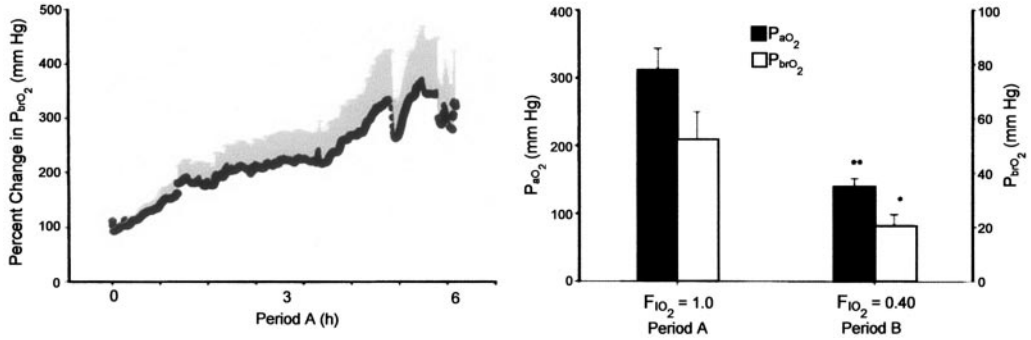

Fig. 5. Left Panel: Mean percentage change in brain-tissue P_{O_2} (P_{brO_2}) during a 6-hour "oxygen challenge" of hyperoxia in 20 subjects with traumatic brain injury. The fraction of inspired oxygen (F_{IO_2}) was increased from 0.4 to 1.0 at time zero. Right Panel: P_{aO_2} and P_{brO_2} in subjects ventilated with F_{IO_2} of 1.0 (period A), followed by F_{IO_2} of 0.40 (period B). * There was a significant difference between period A and period B in both P_{aO_2} ($p < 0.001$) and P_{brO_2} ($p < 0.001$). F_{IO_2} has a large effect on P_{brO_2}. (Adapted from Reference 13, with permission.)

Specialized Care

Several studies have documented the importance of specialized neurocritical care units and the involvement of intensivists in improving the outcomes of patients with acute brain injury.[17–20] In addition, protocolized care appears to improve outcomes in this population, just as it does in other aspects of critical care.[19]

Cerebral Blood Flow

In general, acute brain injury is associated with focal, regional, or global cerebral ischemia, depending on the mechanism of injury. In traumatic brain injury, global CBF is often low, particularly in the first 24 hours after injury.[21] Thus, an important management tenet is to preserve CBF to avoid secondary injury to vulnerable brain tissue, and most therapeutic strategies focus on this principle. This is most commonly achieved by maintaining adequate CPP, which in turn is accomplished by reducing elevated ICP and avoiding low blood pressure. In addition, other perturbations that may increase secondary brain injury, such as hypoxemia, hyperglycemia, seizures, or fever, must be avoided or treated aggressively.

However, the response of CBF after acute brain injury is complex and variable. In some patients with acute brain injury, total CBF may be relatively high (hyperemia) despite focal or regional ischemia, and is associated with elevated ICP and poor outcome.[22] Thus, somewhat paradoxically, some management strategies may be employed that actually reduce CBF in order to protect cerebral homeostasis. Various treatment strategies will be discussed below.

Hyperventilation

As mentioned previously, hyperventilation rapidly reduces ICP by reducing CBF. However, hyperventilation in acute brain injury is controversial because:

1. The effect of hyperventilation on ICP is lost relatively quickly, whereas the effect on CBF may be more sustained (Fig. 6).[8]

2. The reduction in ICP at the cost of reduced CBF may exacerbate cerebral ischemia. This is of particular concern in the first 24 hours after brain injury, when CBF may already be low. Furthermore, a study published in the early 1990s found worse long-term outcome in patients who underwent aggressive, prophylactic hyperventilation.[23] On the other hand, more recent studies have not found critical reductions in CBF associated with short periods of hyperventilation.[24,25] Based on these observations, it seems prudent to avoid prolonged periods of hyperventilation, but to consider its use for short-term treatment of increased ICP. If sustained or frequent hyperventilation is considered as a therapeutic option, monitoring of S_{jO_2} or P_{brO_2} may assist in titrating ventilation. Hyperventilation should clearly be avoided if S_{jO_2} and/or P_{brO_2} are low,[26] but may be considered if there is evidence of high CBF (hyperemia; $S_{jO_2} >$ 75%). Unfortunately, the evidence is poor regarding either benefit or harm from hyperventilation to treat elevated ICP.[27,28]

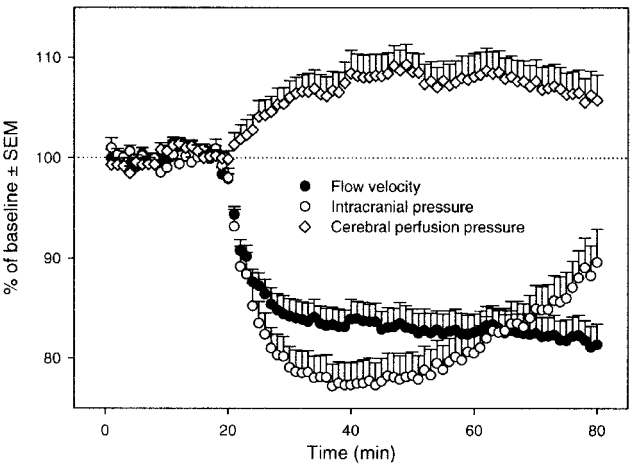

Fig. 6. The relationship between cerebral blood flow and intracranial pressure in acute traumatic brain injury. Hyperventilation is initiated at the 20-min point. After approximately 60 min of hyperventilation, intracranial pressure returns to near-baseline values, whereas cerebral blood flow continues to fall. (From Reference 8, with permission.)

Blood Pressure Management

Even brief periods of hypotension are associated with poor outcome in patients with traumatic brain injury, and this is probably true in other forms of acute brain injury as well.[29–31] For example, even a modest reduction in blood pressure is associated with adverse outcomes in stroke.[32] Thus, it is clearly desirable to avoid hypotension in patients with acute brain injury, and generally desirable to keep blood pressure above the lower limit of CBF autoregulation. On the average, this corresponds to a mean arterial pressure of approximately 70 mm Hg if ICP is normal, or a CPP of approximately 60 mm Hg. If treatment of elevated ICP is insufficient to increase CPP to the desired level, then efforts to drive blood pressure higher using intravascular volume expansion or vasopressors are often initiated. Efforts to increase CPP above 60 mm Hg do not appear to be helpful, and may result in other complications, including acute respiratory distress syndrome (ARDS).[2,33,34] The risk of ARDS is strongly associated with the use of high concentrations of vasopressors to increase CPP, rather than positive fluid balance.[33] Ideally, patients with traumatic brain injury should be kept in a

state of euvolemia, because volume depletion is associated with worse outcome.[31]

Efforts to increase cerebral oxygen transport by increasing CPP and CBF may be beneficial in increasing S_{jO_2} and P_{brO_2}, particularly if CPP is low or CBF autoregulation is disrupted.[10–13] Maneuvers to improve CBF might include:

1. Normalization of P_{CO_2}
2. Increasing CPP through ICP reduction (without hyperventilation), volume expansion, or vasopressors

In addition, reducing cerebral metabolic rate with sedation, aggressive fever control, or hypothermia may reduce cerebral oxygen extraction and prevent ischemia, as discussed below.

Surgical Decompression and Cerebral Spinal Fluid Drainage

In the event of an increase in intracranial volume due to hemorrhage, an obvious way to relieve pressure on the brain is to remove the blood clot by surgical decompression. In cases of severe brain swelling, the surgical cranial defect may be left open until the patient has recovered from the acute injury. Removing cerebral spinal fluid by placing a drainage catheter into the ventricles (ventriculostomy) can also decompress the brain, and is commonly used in cases of traumatic brain injury or mechanical ventricular obstruction.

Reduction of Cerebral Water/Edema

Reducing intracranial volume by osmotic therapy is the cornerstone of ICP management. The most commonly used osmotic agent is mannitol. Mannitol does not cross the blood-brain barrier, and it acts to draw water out of brain cells. The kidney subsequently excretes this water, where mannitol acts as an osmotic diuretic. Hypertonic saline also reduces brain water and ICP by osmosis, without inducing diuresis. Thus, it has appeal in the management of patients who may be volume-depleted, as in after acute trauma. Hypertonic saline may also be more effective, on an equimolar basis, than mannitol in reducing ICP.[35] No placebo-controlled trials have documented outcome benefits of either mannitol or hypertonic saline in acute brain injury, although some data suggest that high-dose mannitol (1.4 g/kg) is more effective than a low dose (0.7 g/kg) in traumatic brain injury.[36]

Sedation

Short-acting and titratable agents such as propofol or midazolam are ideal for sedation of patients with acute brain injury, as they allow frequent neurologic examination during periods of sedation interruption. These agents have the added benefit of reducing CBF by reducing cerebral metabolic rate, and may therefore reduce ICP. In cases of refractory high ICP, more potent longer-acting agents such as barbiturates are occasionally employed. Based on one small randomized trial, barbiturates do appear to reduce mortality in patients with refractory high ICP.[37] However, high-dose barbiturates are typically used as a last resort because of their prolonged effect and profound cardiovascular and respiratory depression. Prolonged infusion of high-dose propofol has been associated with the development of cardiovascular collapse and death in patients with acute brain injury, and should be avoided.[38]

Fever Control and Hypothermia

Fever occurs in the majority of critically ill patients with acute brain injury, and is associated with greater morbidity.[39,40] In patients with stroke, fever is associated with approximately 20% higher mortality.[41] Thus, prevention of fever and maintenance of normothermia may improve outcomes in patients with acute brain injury. Unfortunately, fever control in this patient population is often difficult. Acetaminophen, ibuprofen, and air cooling blankets are largely ineffective in controlling fever.[42,43] Newer water-circulating surface-cooling devices that closely approximate the skin and intravascular cooling devices do appear to be more effective than conventional methods, although both are associated with an increased incidence of shivering.[44,45] Moreover, the effect of aggressive fever control on outcome in patients with acute brain injury has not been determined.

Hypothermia reduces cerebral metabolic rate, CBF, and ICP, and may have additional protective effects during acute brain injury.[46] Mild therapeutic hypothermia (temperature 32–34°C) has been employed in patients with severe traumatic brain injury, stroke, and after cardiac arrest (anoxia). A large prospective randomized trial of therapeutic hypothermia after traumatic brain injury found no evidence of improved outcomes in the hypothermic group.[47] The trials of hypothermia in stroke patients have been small and uncontrolled, although the early results are encouraging.[46] The major benefit identified thus far of therapeutic hypothermia is in patients with anoxic brain injury after cardiac arrest. Two prospective randomized trials found that mild hypothermia for 12–24 hours after cardiac arrest improved neurologic outcome and decreased mortality.[48,49]

Hyperoxic Therapy for Low P_{brO_2}

As mentioned earlier, P_{brO_2} increases with increasing F_{IO_2} and P_{aO_2}. Consequently, hyperoxic therapy is frequently initiated in an effort to correct a low P_{brO_2}. However, there is no evidence that this strategy improves outcome, and there is a theoretical risk of oxygen-induced

lung injury when $F_{IO_2} > 0.60$ is used for an extended period.[50] Exposure of human subjects, including those with coma or neuromuscular disease, to 100% oxygen for several days produced evidence of lung injury, with pulmonary dysfunction and multilobar opacities on chest radiographs.[51,52] Thus, the use of $F_{IO_2} > 60\%$ for more than a few hours should be discouraged, at least until there are outcome data to support the safety and benefit of this practice.

Additional Considerations in the Management of Acute Brain Injury

As alluded to earlier, hyperglycemia is a potential source of secondary brain injury. Hyperglycemia is associated with poor outcome in patients with traumatic brain injury,[53,54] stroke,[55–57] and after cardiac arrest.[58] Retrospective analysis of a small subgroup of patients with neurologic injury from a large randomized trial of intensive insulin therapy in critically ill patients suggested that tight glucose control is associated with reduced ICP, less vasopressor use, fewer seizures, and better long-term neurologic outcome.[59,60] There have been no large randomized trials of glucose control in patients with acute brain injury, but the above evidence suggests that tight control is warranted in this population. The appropriate goal level for glucose is not clear, but may be < 110 mg/dL, which is the threshold used in the previously mentioned trial of intensive insulin therapy in critically ill patients.[60]

Seizures occur frequently after acute brain injury and are potentially harmful in that they increase cerebral metabolic rate, CBF, and ICP. However, there is little to no evidence that seizures are independent determinants of increased mortality after trauma, stroke, or subarachnoid hemorrhage. In addition, although prophylactic administration of anticonvulsants does reduce the incidence of seizures in patients with post-traumatic brain injury and subarachnoid hemorrhage, there is no evidence that this improves other outcomes.[61]

For many years, high-dose corticosteroids have been sporadically administered to patients with traumatic brain injury, based on experimental data indicating a protective effect from this therapy. However, a recent large prospective multicenter randomized placebo-controlled trial showed that high-dose methylprednisolone in patients with acute traumatic brain injury increased mortality at 2 weeks and 6 months, and increased the risk of the combined end point of death and disability at 6 months.[62,63] That study convincingly refuted a role for high-dose corticosteroids in traumatic brain injury.

Patients with acute brain injury are at risk for all the medical complications of critical illness that other patients are subject to, including stress gastritis and bleeding, venous thromboembolism, and intensive-care-unit (ICU) acquired infections. Preventing complications of critical illness with semirecumbent positioning, prophylaxis against gastrointestinal bleeding and thromboembolism, and careful attention to infection-control practices, should be routine. In addition, patients with traumatic brain injury are highly catabolic. Institution of early enteral nutrition is probably beneficial in patients who will be unable to eat for an extended period, although the level of evidence supporting this practice is low.

Implications of Acute Brain Injury for Respiratory Care

There are several aspects of neurocritical care that have particular implications for the management of respiratory failure and acute lung injury. These include application of the use of lung-protective ventilation, positive end-expiratory pressure (PEEP), liberation from mechanical ventilation, and tracheal extubation.

Lung-Protective Ventilation and PEEP

Acute lung injury and ARDS occur frequently in patients with traumatic and other forms of acute brain injury, and are associated with poor outcome.[34,64–66] Limiting tidal volume to ≤ 6 mL/kg (of predicted body weight) and static airway pressure to ≤ 30 cm H_2O reduces mortality in patients with acute lung injury and ARDS.[67] This strategy, known as lung-protective ventilation, is commonly associated with some degree of hypercapnia and respiratory acidosis, which in the majority of critically ill patients is of little physiologic consequence. However, in patients with acute brain injury and increased ICP there is concern that hypercapnia may contribute to ICP elevation and cerebral ischemia. There is little evidence to suggest that this is true, however. As previously discussed, the evidence supporting hyperventilation as an effective long-term strategy for reducing ICP is weak. The compensatory responses to changes in intracerebral perivascular pH occur rapidly (within minutes to hours); thus, hypoventilation, like hyperventilation, is likely to have only a transient effect on ICP. Unfortunately, there are few data to document either benefit or harm from the application of lung-protective ventilation to patients with acute brain injury. One small study suggested that lung-protective ventilation is safe and results in little change in ICP, despite a small increase in P_{aCO_2}.[68] Given the proven benefits of lung-protective ventilation in the general population of patients with acute lung injury and ARDS and the speculative detriments of lung-protective ventilation and hypercapnia in acute brain injury, it is reasonable practice to cautiously reduce tidal volume to the goal of 4–6 mL/kg and static airway pressure to ≤ 30 cm H_2O, with close observation of ICP and CPP if P_{aCO_2} rises. Increased ICP can be treated with os-

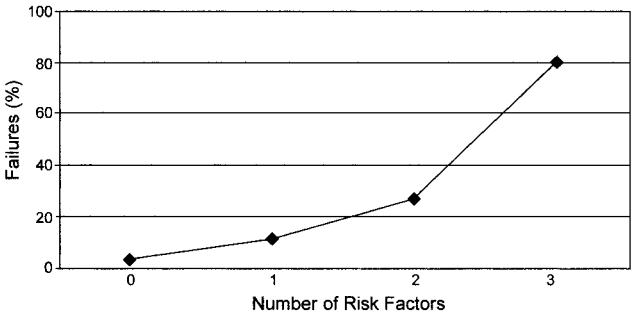

Fig. 7. Cumulative modifiable risk factors and the risk of extubation failure. The risk factors were inability to perform all 4 simple tasks, cough peak flow of ≤ 60 L/min, and secretions of ≥ 2.5 mL/h. The accumulation of risks had a synergistic effect on extubation failure. (Adapted from Reference 82, with permission.)

motic agents, sedation, and/or ventricular drainage if necessary.

PEEP increases intrathoracic pressure and reduces the flow of venous blood to the heart, with a resulting increase in jugular venous pressure. Thus, PEEP can increase ICP, reduce mean arterial blood pressure, and, consequently, reduce CPP. Concerns about the effects of PEEP on ICP and CPP in head-injured patients were initially raised more than 30 years ago.[69,70] However, laboratory and ICU studies with patients have found inconsistent effects of PEEP on ICP and CPP.[68,71–77] The variable effect of PEEP on ICP may in part be dependent on lung and brain mechanical properties.[76,78] For example, patients with relatively normal static lung compliance may be more susceptible to the effects of PEEP on ICP than are those with low compliance.[76] In addition, in some patients ICP may increase because of an increase in P_{aCO_2} as a result of PEEP-induced lung hyperinflation.[78] Patients in whom PEEP induces lung recruitment and improves lung compliance may be less likely to suffer an increase in ICP. Thus, PEEP should be applied cautiously to patients with acute brain injury, but should certainly not be withheld if needed to provide adequate oxygenation. If PEEP increases the ICP, interventions such as osmotic therapy and sedation may be useful to restore adequate CPP. In addition, expansion of intravascular volume may improve CPP by limiting the deleterious effects of PEEP on preload and systemic blood pressure.

Liberation From Mechanical Ventilation and Extubation

Once acute management issues are resolved and elevation of ICP is no longer a major problem, the process of evaluating the acute-brain-injury patient's readiness for extubation should proceed just as it does for other patients with respiratory failure. The ability to breath without support should be tested, ideally using a respiratory-care-driven protocol.[79] After the patient has successfully completed a trial of spontaneous ventilation, special attention must be paid to airway issues, given that these patients may have an altered level of consciousness and/or obtunded airway reflexes due to central-nervous-system injury. There have been few studies on this subject to guide practice, but it appears that depressed level of consciousness should not be the sole reason for delaying extubation of patients with acute brain injury. In a prospective, cohort study of patients with acute brain injury of diverse etiologies, Coplin et al found that depressed level of consciousness was associated with extubation delay but not extubation failure, as defined by the need for reintubation.[80] The presence of a spontaneous cough and a low frequency of tracheal suctioning, but not the presence of gag, predicted extubation success. Furthermore, extubation delay was associated with a greater risk of pneumonia, longer ICU and hospital stay, higher costs, and higher mortality, independent of the presence of coma. Namen et al found that a higher Glasgow Coma Score was associated with successful extubation in patients with acute brain injury; however, that study was seriously compromised by the inclusion of patients who had support withdrawn after extubation, resulting in a large number of "extubation failures" in patients who were likely to have had a low Glasgow Coma Score prior to extubation.[81] Given the high morbidity and cost associated with delayed extubation, it is reasonable that patients with acute brain injury be extubated when they meet usual clinical criteria and have a spontaneous cough and minimal tracheal secretions.

A recent study with medical ICU patients emphasized the importance of cough and secretion volume in determining extubation success. Salam et al quantitated cough using peak expiratory flow, volume of tracheal secretions, and neurologic status, measured with a simple 4-part set of tasks, in medical ICU patients.[82] They found that a cough peak flow of ≤ 60 L/min, secretion volume > 2.5 mL/h, and inability to perform the 4 simple tasks all predicted extubation failure, and a combination of these factors had a synergistic effect on extubation failure (Fig. 7). Patients with all 3 factors present had an extubation failure rate of 80%.

In general, approximately 60–80% of patients with severe acute brain injury can be successfully extubated on the first attempt.[80,81,83] A subset of patients will require tracheotomy for extended airway management; the frequency of this appears to be in part a matter of local preference. In the study by Coplin et al, only 4% of the study cohort underwent tracheotomy,[80] whereas others have reported that approximately a third of patients with acute brain injury undergo tracheotomy at their institutions.[81,83]

Summary

The critical-care management of acute brain injury is based on observational studies and basic principles of cerebral physiology. Unfortunately, there is little high-level evidence to prove that various management strategies either help or harm patients with acute brain injury, and large randomized prospective trials are desperately needed. The outcome of patients with acute brain injury is likely to be improved when management is led by intensivists using protocol-driven therapy. It is important to recognize that theoretical detrimental effects of various ventilatory strategies on cerebral physiology should not preclude the use of therapies that have proven mortality benefits, such as lung-protective ventilation in patients with acute lung injury. Lastly, the presence of coma should not preclude consideration of extubation of patients with acute brain injury, as a high percentage of these patients can be successfully extubated. On the other hand, if the patient has weak cough or large secretion volume, early tracheotomy may expedite discharge from the ICU.

REFERENCES

1. Brain Trauma Foundation. Management and prognosis of severe traumatic brain injury. 2000. http://www2.braintrauma.org/guidelines. *Accessed Jan 19, 2006.*
2. Juul N, Morris GF, Marshall SB, Marshall LF. 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 2000;92(1):1–6.
3. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997;86(6):1431–1433.
4. Maddock RJ. The lactic acid response to alkalosis in panic disorder: an integrative review. J Neuropsychiatry Clin Neurosci 2001;13(1):22–34.
5. Ellingsen I, Hauge A, Nicolaysen G, Thoresen M, Walloe L. Changes in human cerebral blood flow due to step changes in P_{AO_2} and P_{ACO_2}. Acta Physiol Scand 1987;129(2):157–163.
6. Poulin MJ, Liang PJ, Robbins PA. Fast and slow components of cerebral blood flow response to step decreases in end-tidal P_{CO_2} in humans. J Appl Physiol 1998;85(2):388–397.
7. Raichle ME, Posner JB, Plum F. Cerebral blood flow during and after hyperventilation. Arch Neurol 1970;23(5):394–403.
8. Steiner LA, Balestreri M, Johnston AJ, Czosnyka M, Coles JP, Chatfield DA, et al. Sustained moderate reductions in arterial CO_2 after brain trauma time-course of cerebral blood flow velocity and intracranial pressure. Intensive Care Med 2004;30(12):2180–2187.
9. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobinsaturation: management strategies and clinical outcome. Crit Care Med 1998;26(2):344–351.
10. Mulvey JM, Dorsch NW, Mudaliar Y, Lang EW. Multimodality monitoring in severe traumatic brain injury: the role of brain tissue oxygenation monitoring. Neurocrit Care 2004;1(3):391–402.
11. Hemphill JC 3rd, Knudson MM, Derugin N, Morabito D, Manley GT. Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. Neurosurgery 2001;48(2):377–383; discussion 383–384.
12. Kiening KL, Hartl R, Unterberg AW, Schneider GH, Bardt T, Lanksch WR. Brain tissue PO_2-monitoring in comatose patients: implications for therapy. Neurol Res 1997;19(3):233–240.
13. Reinert M, Barth A, Rothen HU, Schaller B, Takala J, Seiler RW. 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 (Wien) 2003;145(5):341–349; discussion 349–350.
14. Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Clausen T, et al. Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. J Neurosurg Anesthesiol 1999;11(4):240–251.
15. Narayan RK, Michel ME, Ansell B, Baethmann A, Biegon A, Bracken MB, et al. Clinical trials in head injury. J Neurotrauma 2002;19(5):503–557.
16. Brain Trauma Foundation. Management and prognosis of severe traumatic brain injury (update 5/1/2003). 2003. http://www2.braintrauma.org/guidelines. *Accessed Jan 19, 2006.*
17. Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. Crit Care Med 2001;29(3):635–640.
18. Mirski MA, Chang CW, Cowan R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. J Neurosurg Anesthesiol 2001;13(2):83–92.
19. Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ. Specialist neurocritical care and outcome from head injury. Intensive Care Med 2002;28(5):547–553.
20. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, et al. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. Crit Care Med 2004;32(11):2311–2317.
21. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg 1991;75(5):685–693.
22. Kelly DF, Martin NA, Kordestani R, Counelis G, Hovda DA, Bergsneider M, et al. Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg 1997;86(4):633–641.
23. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75(5):731–739.
24. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 2002;30(9):1950–1959.
25. Diringer MN, Yundt K, Videen TO, Adams RE, Zazulia AR, Deibert E, et al. No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury. J Neurosurg 2000;92(1):7–13.
26. Imberti R, Bellinzona G, Langer M. Cerebral tissue P_{O_2} and S_{jvO_2} changes during moderate hyperventilation in patients with severe traumatic brain injury. J Neurosurg 2002;96(1):97–102.
27. Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. Cochrane Database Syst Rev 2000;(2):CD000566.
28. Stocchetti N, Maas AI, Chieregato A, van der Plas AA. Hyperventilation in head injury: a review. Chest 2005;127(5):1812–1827.
29. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34(2):216–222.
30. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in

the Traumatic Coma Data Bank. Acta Neurochir Suppl (Wien) 1993; 59:121–125.
31. Clifton GL, Miller ER, Choi SC, Levin HS. Fluid thresholds and outcome from severe brain injury. Crit Care Med 2002;30(4):739–745.
32. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33(5):1315–1320.
33. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg 2001;95(4):560–568.
34. Robertson CS, Valadka AB, Hannay HJ, Contant CF, Gopinath SP, Cormio M, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med 1999;27(10):2086–2095.
35. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med 2005;33(1):196–202; discussion 257–258.
36. Roberts I, Schierhout G, Wakai A. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev 2003;(2):CD001049.
37. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988;69(1):15–23.
38. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ. Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet 2001;357(9250):117–118.
39. Albrecht RF 2nd, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. Mayo Clin Proc 1998;73(7):629–635.
40. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 2004;32(7): 1489–1495. *Erratum in: Crit Care Med 2004;32(10):2170.*
41. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome : a meta-analysis of studies in patients. Stroke 2000;31(2): 410–414.
42. Dippel DW, van Breda EJ, van der Worp HB, van Gemert HM, Meijer RJ, Kappelle LJ, Koudstaal PJ; PISA-Investigators. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608690]. BMC Cardiovasc Disord 2003;3:2.
43. Mayer S, Commichau C, Scarmeas N, Presciutti M, Bates J, Copeland D. Clinical trial of an air-circulating cooling blanket for fever control in critically ill neurologic patients. Neurology 2001;56(3): 292–298.
44. Diringer MN; Neurocritical Care Fever Reduction Trial Group. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. Crit Care Med 2004;32(2): 559–564.
45. Mayer SA, Kowalski RG, Presciutti M, Ostapkovich ND, McGann E, Fitzsimmons BF, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Crit Care Med 2004;32(12):2508–2515.
46. Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. Intensive Care Med 2004;30(4):556–575.
47. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR Jr, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344(8):556–563.
48. White H, Baker A. Continuous jugular venous oximetry in the neurointensive care unit: a brief review. Can J Anaesth 2002;49(6):623–629.
49. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–563.
50. Lodato RF. Oxygen toxicity. Crit Care Clin 1990;6(3):749–765.
51. Barber RE, Lee J, Hamilton WK. Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. N Engl J Med 1970;283(27):1478–1484.
52. Hyde RW, Rawson AJ. Unintentional iatrogenic oxygen pneumonitis—response to therapy. Ann Intern Med 1969;71(3):517–531.
53. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery 2000; 46(2):335–342; discussion 342–343.
54. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg 1991; 75(4):545–551.
55. Gentile NT, Seftcheck M, Martin R. Blood glucose control after acute stroke: a retrospective study (abstract). Acad Emerg Med 2003; 10(5):432.
56. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, et al; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology 2002; 59(5):669–674.
57. Bruno A, Biller J, Adams HP Jr, Clarke WR, Woolson RF, Williams LS, Hansen MD. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Neurology 1999;52(2):280–284.
58. Mullner M, Sterz F, Binder M, Schreiber W, Deimel A, Laggner AN. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. J Cereb Blood Flow Metab 1997;17(4):430–436.
59. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005;64(8):1348–1353.
60. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345(19):1359–1367.
61. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev 2001;(4):CD000173.
62. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al; CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364(9442):1321–1328.
63. Edwards P, Arango M, Balica L, Cottingham R, El-Sayed H, Farrell B, et al; CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. Lancet 2005; 365(9475):1957–1959.
64. Bratton SL, Davis RL. Acute lung injury in isolated traumatic brain injury. Neurosurgery 1997;40(4):707–712; discussion 712.
65. Holland MC, Mackersie RC, Morabito D, Campbell AR, Kivett VA, Patel R, et al. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. J Trauma 2003;55(1):106–111.
66. Kahn JM, Caldwell E, Hudson LD, Deem S, Rubenfeld GD. Impact of acute lung injury on outcome in patients with subarachnoid hemorrhage (abstract). Am J Respir Crit Care Med 2004; 169(7):A780.
67. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301–1308.

68. Wolf S, Schurer L, Trost HA, Lumenta CB. The safety of the open lung approach in neurosurgical patients. Acta Neurochir Suppl 2002; 81:99–101.
69. Shapiro HM, Marshall LF. Intracranial pressure responses to PEEP in head-injured patients. J Trauma 1978;18(4):254–256.
70. Apuzzo JL, Wiess MH, Petersons V, Small RB, Kurze T, Heiden JS. Effect of positive end expiratory pressure ventilation on intracranial pressure in man. J Neurosurg 1977;46(2):227–232.
71. Aidinis SJ, Lafferty J, Shapiro HM. Intracranial responses to PEEP. Anesthesiology 1976;45(3):275–286.
72. Videtta W, Villarejo F, Cohen M, Domeniconi G, Santa Cruz R, Pinillos O, et al. Effects of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. Acta Neurochir Suppl 2002;81:93–97.
73. Huynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. J Trauma 2002; 53(3):488–492; discussion 492–493.
74. Georgiadis D, Schwarz S, Baumgartner RW, Veltkamp R, Schwab S. Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke. Stroke 2001;32(9):2088–2092.
75. Huseby JS, Luce JM, Cary JM, Pavlin EG, Butler J. Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension. J Neurosurg 1981;55(5):704–705.
76. Burchiel KJ, Steege TD, Wyler AR. Intracranial pressure changes in brain-injured patients requiring positive end-expiratory pressure ventilation. Neurosurgery 1981;8(4):443–449.
77. Frost EA. Effects of positive end-expiratory pressure on intracranial pressure and compliance in brain-injured patients. J Neurosurg 1977; 47(2):195–200.
78. Mascia L, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med 2005;31(3): 373–379.
79. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335(25):1864–1869.
80. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD.Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 2000;161(5): 1530–1536.
81. Namen AM, Ely EW, Tatter SB, Case LD, Lucia MA, Smith A, et al. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med 2001;163(3 Pt 1):658–664.
82. Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med 2004;30(7):1334–1339.
83. Koh WY, Lew TW, Chin NM, Wong MF. Tracheostomy in a neurointensive care setting: indications and timing. Anaesth Intensive Care 1997;25(4):365–368.