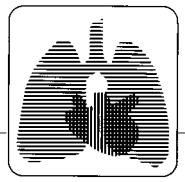

reviews

Hyperventilation in Head Injury*

A Review

Nino Stocchetti, MD; Andrew I.R. Maas, MD, PhD; Arturo Chieregato, MD; and Anton A. van der Plas, MD

The aim of this review was to consider the effects of induced hypocapnia both on systemic physiology and on the physiology of the intracranial system. Hyperventilation lowers intracranial pressure (ICP) by the induction of cerebral vasoconstriction with a subsequent decrease in cerebral blood volume. The downside of hyperventilation, however, is that cerebral vasoconstriction may decrease cerebral blood flow to ischemic levels. Considering the risk-benefit relation, it would appear to be clear that hyperventilation should only be considered in patients with raised ICP, in a tailored way and under specific monitoring. Controversy exists, for instance, on specific indications, timing, depth of hypocapnia, and duration. This review has specific reference to traumatic brain injury, and is based on an extensive evaluation of the literature and on expert opinion. ***(CHEST 2005; 127:1812–1827)***

Key words: cerebral ischemia; hyperventilation; intracranial pressure; traumatic brain injury

Abbreviations: $AVDO_2$ = cerebral arteriovenous difference of oxygen content; CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate of oxygen; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; DPG = diphosphoglycerate; ICP = intracranial pressure; ITP = intrathoracic pressure; LV = left ventricle, ventricular; NO = nitric oxide; $Pbro_2$ = brain tissue oxygen tension; PET = positron emission tomography; RV = right ventricle, ventricular; SjO_2 = jugular bulb oxygen saturation; TBI = traumatic brain injury

Modulation of $Paco_2$ has been used for >40 years,[1] first in neuroanesthesia and subsequently also in neuro-intensive care. Preliminary work has shown that the volume of the swollen brain could be decreased by lowering $Paco_2$. With the realization that raised intracranial pressure (ICP) is a significant, treatable problem in patients with traumatic brain injury (TBI), hyperventilation became a cornerstone in the management of TBI and has remained so for decades. Hyperventilation lowers ICP by the induction of cerebral vasoconstriction with a subsequent decrease in cerebral blood volume.[2] The downside of hyperventilation, however, is that cerebral vasoconstriction may decrease cerebral blood flow (CBF) to ischemic levels. Already in 1942, a slowing of the EEG was observed during active hyperventilation and was interpreted as a sign of cerebral ischemia, thus illustrating the potentially harmful effects of hypocapnia.[3] Over the past decade, relatively more attention has been paid to the adverse effects of hyperventilation and concern seems to exceed enthusiasm. This change in attitude would appear more emotional than data-driven and reflects the lack of conclusive data.

The aim of this review was to consider the effects of induced hypocapnia both on systemic physiology and on the physiology of the intracranial system, with specific reference to TBI. We chose to focus this review on TBI, as much of the research on hyperventilation has been conducted in this field and less information exists on other acute cerebral disorders, such as aneurysmal subarachnoid hemorrhage or

*From the Neuroscience ICU (Drs. Stocchetti and Chieregato), Ospedale Maggiore Policlinico, Milan University, IRCCS, Milan; Department of Intensive Care Medicine (Dr. Chieregato), Ospedale Bufalini, Cesna, Italy; the Departments of Neurosurgery (Dr. Maas) and Intensive Care Medicine (Dr. van der Plas), Erasmus Medical Center, Rotterdam, the Netherlands.

Manuscript received September 23, 2004; revision accepted November 25, 2004.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Nino Stocchetti, MD, Terapia Intensiva Neuroscienze, Padiglione Beretta Neuro, Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy; e-mail stocchet@policlinico.mi.it

stroke. This review is based on an extensive evaluation of the literature, and to this purpose we selected relevant experimental and clinical articles on hyperventilation from among > 5,000 citations found on MEDLINE since 1966. We have indicated explicitly in the text when expert opinion is being expressed rather than available evidence being quoted.

Definition of Hyperventilation

A remarkable confusion exists on terminology. What is usually referred to as hyperventilation is, in fact, hypocapnia. Since a reduction of $Paco_2$ below the normal level (40 mm Hg) is obtained by increasing the alveolar ventilation, hyperventilation became synonymous with hypocapnia. In this review, we will use the less precise (but much more common) term *hyperventilation*. Hyperventilation may be defined as "the induction and/or maintenance of levels of CO_2 tension in the arterial blood below the normal range." In this sense, normal levels of $Paco_2$ should be corrected for barometric pressure at different altitudes.

Pathophysiology

CBF Regulation and CO_2 Reactivity

The CNS, accounting for 2% of body weight (average weight of the brain, 1,300 to 1,500 g), has a high energy requirement. The cerebral oxygen consumption is 3.5 mL per 100 g/min, which corresponds to 20% of total body oxygen consumption. Under normal conditions, CBF is maintained at a constant flow rate of 50 to 60 mL per 100 g/min, with 50 mL of oxygen being extracted every minute from 700 to 800 mL of blood (Table 1). The extraction rate for oxygen is high, and the mean arteriovenous difference of O_2 for the CNS is 6.3 mL per 100 mL of blood. CBF depends on the differential pressure between the arterial and the venous side of the cerebral circulation, and is inversely proportional to cerebral vascular resistance. Pressure on the venous side of the capillary bed cannot be measured, and ICP, which is extremely close to venous pressure, is used for estimating the cerebral perfusion pressure (CPP). CPP is calculated as the difference between mean arterial pressure and ICP.

Table 1—*Normal Values and Ischemia Thresholds for the Main Cerebral Variables

Variables	Normal Value	Threshold for Ischemia
Brain weight, g	1,300–1,500	
CBF	50–60 mL/100 g/min brain tissue	< 18 mL/100 g
OEF	30%	
$AVDO_2$	6.3 mL O_2/100 mL blood	> 9 mL O_2/100 ml blood
SjO_2, %	55–75	< 50
$Pbro_2$, mm Hg	> 20	15
ICP, mm Hg	≤ 10	
CPP, mm Hg	60	< 55–60

*OEF = oxygen extraction fraction.

Normal ICP values in adults are < 10 mm Hg, and a threshold of 20 mm Hg is usually accepted for starting active treatment. A CPP of 60 mm Hg is commonly accepted as the minimum value necessary for adequate cerebral perfusion.[4] Two important concepts are:

1. the Monro-Kellie doctrine; and
2. the volume-pressure curve.

The Monro-Kellie doctrine states that the total volume of the intracranial contents (*ie*, brain tissue, blood, and cerebrospinal fluid [CSF]) remains constant as these are contained within a rigid compartment (the skull), as follows:

$$V_C = V_{brain} + V_{blood} + V_{CSF}.$$

An increase in the volume of one of these compartments can initially be compensated for by the displacement of parts of the other components. Cerebral veins can be compressed, resulting in decreased cerebral blood volume, and the volume of the CSF compartment can decrease due to a combination of increased resorption and the displacement of CSF toward the spinal compartment. As volume increases, compensatory mechanisms are exhausted, and a further increase in volume results in a sharp rise of ICP, leading to the volume-pressure curve depicted in Figure 1.

The high metabolic demands of the brain in combination with the limited storage of substrates necessitate maintaining CBF levels within normal ranges. In physiologic circumstances, this is effected through a number of mechanisms, which are commonly referred to as *autoregulation*. CBF increases with vasodilatation and decreases with the constriction of cerebral arteriolae, termed *cerebral resistance vessels*. These vessels respond to changes in systemic BP (pressure autoregulation), blood viscosity (viscosity autoregulation), and metabolic demand, maintaining CBF levels within limits that are appropriate to meet metabolic demands. Pressure autoregulation is shown in Figure 2.

CBF is functionally coupled to the regional cerebral metabolism as expressed in the Fick equation $CMRO_2 = CBF \times AVDO_2$, in which $CMRO_2$ is the cerebral metabolic rate of oxygen and $AVDO_2$ is the

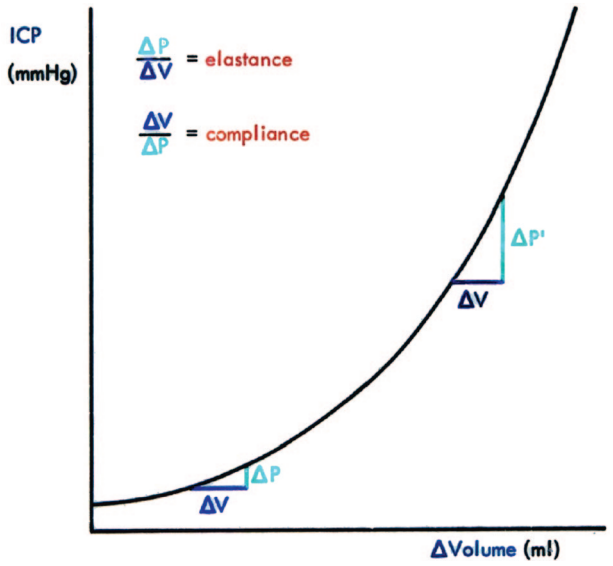

FIGURE 1. Volume-pressure curve, illustrating the exponential increase of ICP following an increase in the volume of the intracranial compartment.

cerebral arteriovenous difference of oxygen content. CO_2 reactivity refers to the response of cerebral vessels and, consequently, of CBF to changes in $PaCO_2$. An increasing CO_2 tension relaxes cerebral arteries *in vitro*.[5] *In vivo*, very localized perivascular changes of $PaCO_2$ or pH can change the vascular diameter, indicating that elements of the vascular wall are responsible for effecting changes in the diameter of vessels. Both vascular cells (*ie*, the endothelium and smooth muscle) and extravascular cells (*ie*, the perivascular nerve cells, neurons, and glia) may be involved. In the clinical situation, CBF changes approximately by 3% for each millimeter of mercury change in $PaCO_2$ over the clinically important range of 20 to 60 mm Hg in patients with TBI.[6,7] Hypoventilation resulting in hypercarbia causes vasodilatation and increased CBF, while hyperventilation results in vasoconstriction and decreased CBF.

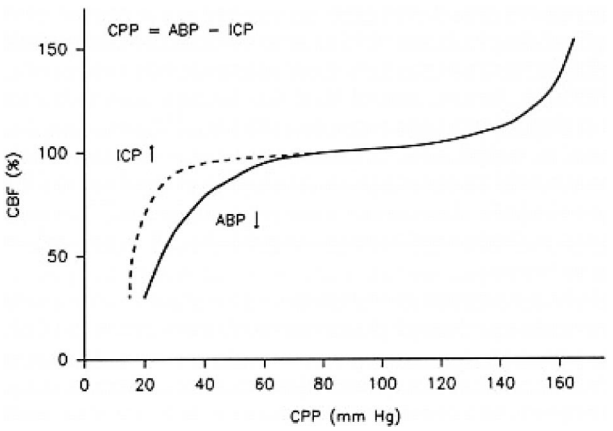

FIGURE 2. The normal autoregulatory curve of CBF vs CPP. CPP is calculated as the mean arterial pressure (arterial BP [ABP]) − ICP. With rising ICP, CBF is maintained at a lower CPP than with declining ABP. Adapted from Miller et al.[148]

The mechanisms underlying the three forms of autoregulation (*ie*, pressure, viscosity, and metabolic) have not been precisely unraveled to date, but, compared to mechanisms underlying CO_2 reactivity, the differences are recognized. Whereas pressure autoregulation seems to be located in the pial arteries, with a diameter > 50 μm, CO_2 reactivity involves smaller pial arteriolae.[8] Different data have been obtained from *in vitro* and *in vivo* experiments. *In vitro*, the middle cerebral artery constricts when it is exposed to raised extracellular pH. In contrast, *in vivo*, large intracranial vessels are not significantly affected by changes in $PaCO_2$.[9] Further, in autoregulation the vascular endothelium-derived nitric oxide (NO) or endothelium-derived relaxing factors are important, but some debate exists about whether these factors are involved in the maintenance of basal CBF or actually couple regional CBF to metabolism. An astrocyte-mediated coupling of synaptic activity to local vasodilation has been proposed and will need further evaluation.[10]

Vessel caliber follows changes in arterial CO_2 by responding to the pH in the perivascular space without molecular CO_2 and bicarbonate ions acting independently on cerebral vessels.[11,12] Nevertheless, changes in pH may exert their effect on smooth muscle tone through second messenger systems or by altering the calcium concentration in vascular smooth muscles directly. Various agents have been identified as potential second messengers, including prostanoids, NO, cyclic nucleotides, potassium, and calcium.

Prostanoids are potent vasodilators, activating adenylate cyclase and increasing cyclic adenosine monophosphate, and are considered to be important regulators of the cerebral circulation in neonates but seem less important in adults. NO, which is produced by a family of NO synthase enzymes in brain vascular endothelial cells, in perivascular nerves, as well as in neurons and glia, increases the intracellular concentration of cyclic guanosine monophosphate, causing vasodilation. Although NO has been shown to act as a vasodilator in response to hypercapnia and acidosis, it cannot account for total vasodilation, as a significant portion (10 to 70%) still occurs when NO synthase is inhibited. The role of NO appears to be complex. It has been hypothesized that a vasodilatory signal is constantly produced by the brain through the synthesis of NO and that an additional signal such as hypercapnia may act on the baseline regulation of the vascular tone. Cyclic nucleotides, such

as cyclic adenosine monophosphate and cyclic guanosine monophosphate, reduce the entry of calcium into vascular smooth muscle, and exert vasodilatory effects either directly or in a permissive role, allowing hypercapnia to exert its vasodilatory effects.

The opening of potassium channels indirectly reduces the influx of extracellular calcium into the cell, reducing vascular smooth muscle tone. In contrast, the disturbance of the calcium homeostasis will lead to increased intracellular calcium concentrations, resulting in vasoconstriction. This constitutes one of the reasons underpinning investigations on the efficacy of calcium channel blockers in patients with TBI.

Systemic Effects of Hyperventilation

The importance of the systemic effects of hyperventilation is often underrecognized. In some reviews,[13] guidelines,[14] editorial comments,[15,16] research syntheses,[17] or systematic reviews[18] little or no attention has been directed to the systemic effects of hyperventilation. Systemic effects are multifactorial and interrelated, affecting multiple sites of the body. Substantial differences exist between active hyperventilation (when the subject voluntarily increases his ventilation) and passive hyperventilation (by means of artificial ventilation). In the former, autonomic flow is markedly affected, while in the latter the effects of CO_2 are combined with those of the complex interaction between artificial ventilation and hemodynamics. Additionally, when hyperventilation is applied for reducing ICP, it is usually combined with a number of concurrent interventions such as sedation, paralysis, and increased fluid input.

Ventilatory and Hemodynamic Effects

Positive-pressure ventilation increases lung volume and intrathoracic pressure (ITP), even when a normal level of arterial P_{CO_2} is maintained, affecting systemic hemodynamics and lung physiology. It is likely that the induction of hyperventilation enhances this effect, as an increase in alveolar ventilation is necessary for inducing hypocapnia.

This may be achieved by increasing the tidal volume and/or the respiratory rate, or by decreasing the dead space. The most appropriate way for inducing hypocapnia has not been determined, but it is usually effected by increasing tidal volume. In stable patients, this has little effect on ITP, but sudden profound hyperventilation may cause marked hemodynamic perturbations,[19] particularly in patients with relative hypovolaemia. An increase in ITP has the following four effects:

1. A reduction of the venous return to the right side of the heart;
2. An increase in right ventricular (RV) afterload (because of the compression of the pulmonary capillaries);
3. A decrease in the size, volume, and compliance of the left ventricle (LV) [the increased RV end-systolic volume causes the interventricular septum to bulge into the left ventricle]; and
4. A decrease of transmural LV pressure output.

The overall effect is that venous return is impaired. This adverse effect can in part be compensated for by an increase in abdominal pressure and intraabdominal vascular pressure due to a more pronounced descent of the diaphragm following an increase in lung volume.[20] Increased abdominal pressure, however, may have an adverse effect on ICP.[21] In the clinical setting, a reduced lung compliance (resulting frequently from the concomitant occurrence of pneumonia, pulmonary contusions, or ARDS) will limit the increase in ITP even if alveolar pressure increases.

The effect of positive-pressure ventilation on RV performance depends on the degree to which venous return (preload) is compromised and pulmonary vascular resistance (afterload) is affected. If compensatory mechanisms are inadequate or if a dysfunction of the RV was already present,[22] the most common and important hemodynamic effect of an increase in ventilation is a decrease in cardiac output due to a decrease in the pressure gradient for systemic venous return.

The effects of positive-pressure ventilation on LV function are less important but may also lead to a reduction of cardiac output. This is primarily caused by a reduced venous return as a consequence of decreased LV end-diastolic volume, but also by a reduction of LV diastolic compliance. This may result from a septal shift (*ie*, ventricular interdependence) due to RV dilatation,[23] by pericardial volume limitations[24] or by an increase in lung volume resulting in a direct mechanical compressive effect of the expanding lung on the cardiac fossa.[25,26] These considerations emphasize the importance of maintaining normovolemia in patients with TBI in general and particularly when artificial ventilation is employed.

A beneficial effect of artificial ventilation is the reduction of LV afterload. In fact, LV systolic pressure load is represented more accurately by LV pressure relative to ITP, and an increase in ITP, reducing the transmural LV pressure, decreases the LV afterload. This mechanism may compensate for the reduction in preload and the worsening of LV compliance, thus maintaining a stable cardiac output[27] and may even improve cardiac output when LV end-diastolic volume is preserved.[28]

Respiratory Alkalosis and Electrolyte Disturbances

A fall of $Paco_2$ is associated with a primary decrease in extracellular H^+ concentration.[29] The cellular membranes, particularly the blood-brain barrier, are relatively impermeable to hydrogen ions, but permit a rapid diffusion of CO_2. Therefore, the intracellular hydrogen ion concentration is scarcely influenced by changes in extracellular pH but can be altered by changes in $Paco_2$. The CO_2 passes through the membrane, and, once inside the cell, is able to hydrate and ionize, thus producing hydrogen ions.[30] Following the onset of hyperventilation, a rapid efflux of H^+ occurs within 10 min. In the extracellular fluid, H^+ combines to HCO_3^- to produce CO_2. The extent of this compensatory reaction is, however, not very efficient and, if hypocapnia is prolonged, alkalosis develops.[29]

A more efficient compensatory mechanism is effected by the kidney. A reduction in cellular $Paco_2$ in tubular cells induces an increase in intracellular pH, a reduction of H^+ secretion, and a loss of bicarbonate, together with a decreased excretion of ammonium (NH^{4+}).[29] This response begins within 2 h but is fully effective for 2 to 3 days.[31] In the mammalian nervous system, intracellular pH is one of the most tightly regulated parameters. The maximum change in H^+ concentration that can be tolerated is approximately 0.0005 mmol.[32]

One of the effects of intracellular alkalosis is the activation of glycolysis, which occurs as a consequence of the modulation of the rate-limiting enzyme phosphofructokinase.[33,34] The effect on pH of lactic acid production provides a homeostatic mechanism for generating H^+ ions to rapidly counteract a state of intracellular alkalosis.[32,35,36] The increase of lactate levels during hypocapnia, which develops in the absence of any failure of oxidative metabolism, furnishes H^+ to compensate for the extracellular reduction of H^+. As a consequence of the shift of H^+ from the cellular to the extracellular compartment, an opposite movement of K^+ (and Na^+) from extracellular fluid to the cell occurs. The resulting hypokalemia is, however, typically mild.[29] The increase in cellular phosphorylation causes a rapid shift of phosphate from the extracellular fluid into the cell, with an associated reduction in plasma phosphate concentration.[37] In patients with severe alkalosis, albumin releases H^+, and the binding of Ca^{2+} is increased, resulting in a reduction of the ionized fraction of calcium,[38,37] which may result in clinical symptoms including bradycardia and heart block, or even heart failure and cardiac arrest. Such serious complications are rare unless the concentration of ionized calcium falls to < 0.8 mmol (3.2 mg/dL).[39] It may be supposed that similar effects also pertaining to Mg homeostasis are likely, and in this regard we note that low Mg levels occur frequently following TBI.[40] In our opinion, particular attention should, therefore, be focused on electrolyte concentrations in general following TBI, and in particular if hyperventilation is employed.

Effects on Hemoglobin Dissociation Curve and Drug Metabolism

Alkalosis increases the affinity of hemoglobin for O_2 and displaces the dissociation curve to the left. The following two compensatory mechanisms counteract this leftward shift: a rapid increase in lactate production[41]; and the induction of enzymatic activity. The increased intracellular pH activates glycolysis, increases the activity of 2,3-diphosphoglycerate (DPG) mutase and reduces the activity of DPG phosphatase.[30] These enzymatic adjustments lead to an increased concentration of 2,3-DPG, which over a period of several hours may normalize the dissociation curve. The influence of the Bohr effect on O_2 affinity varies inversely with the degree of hemoglobin saturation. Shifts of the dissociation curve are therefore more relevant to the venous side of the circulation. The importance of the Bohr effect on changes in venous cerebral Po_2 has been studied by various authors. Gotoh et al[42] found a decrease of jugular Po_2 due to the Bohr effect of approximately 2.4 mm Hg. Cruz et al[43] reported a moderately disproportional increase in jugular bulb oxygen saturation (SjO_2) relative to jugular bulb Po_2 when pH increased to > 7.6.

Hypocapnia and respiratory alkalosis may also affect the pharmacokinetic metabolism of drugs in many of the following ways: changes in distribution due to variations of the perfusion of organs; changes of ionization of the drug due to a change in blood pH; changes in solubility and transmembrane diffusion; and changes in protein binding. Finally, the urinary excretion of some drugs also may be altered by changes in urinary pH.

Effects on Organ Systems

Hypocapnia decreases perfusion in most of the body organ systems, including the heart,[44] the liver, the gut,[45,46] skeletal muscle,[47] and skin.[48] A reduction in coronary perfusion due to hypocapnia may cause increased risk for cardiac ischemia in patients with preexisting coronary artery disease. Kazmaier et al[44] found a mild increase in systemic vascular resistance and a mild reduction in cardiac index when passive mild hyperventilation was employed in patients with coronary artery disease. Despite the absence of significant changes in coronary perfusion pressure and myocardial blood flow, a reduction in

coronary sinus Po_2 and oxygen saturation have been reported. The risk of coronary spasm is increased during hypocapnia, and in fact active hyperventilation has been used for the noninvasive diagnosis of coronary spasm.[49] The kidney is the main organ involved in the compensatory control of pH during chronic hyperventilation.[50,51] Urinary electrolyte changes (*ie*, an increase in Na^+ or a decrease in K^+) together with a pH increase are part of the compensatory mechanisms in cases of alkalosis.

In the lung, respiratory alkalosis induces vasodilatation of pulmonary vessels[52] and bronchoconstriction.[53,54] The cumulative resulting effect is a reduction in Pa_{O_2} due to a ventilation/perfusion mismatch.[55] In patients with severe head injury, Turner et al[56] found a decrease in Pa_{O_2} from 115 to 99.5 mm Hg after 1 h of hyperventilation. Other clinical research has suggested further adverse pulmonary effects, including increased airway permeability,[57] dysfunctional surfactant levels,[58] and reduced lung compliance.[59] Further, Laffey et al[60] showed in an experimental study that hypocapnic alkalosis may potentiate ischemia-reperfusion-induced lung injury. Ventilation strategies that are commonly employed in patients with TBI include high tidal volume and low positive end-expiratory pressure, and these may increase the risk of worsening acute lung injury,[61–63] both as a consequence of an increase of lung stretch and the reversal of a "protective effect" of hypercapnia. These potentially adverse effects of hyperventilation on pulmonary function are particularly relevant to the treatment of TBI as approximately 20% of patients experience concomitant acute lung injury[64] and the incidence of pneumonia has been reported to be as high 40 to 50%.[65]

Cerebral Effects of Hyperventilation

Hyperventilation and ICP

Hyperventilation has been used in the management of severe TBI for > 40 years since Lundberg et al[66] reported its use to lower elevated ICP in 1959. Hyperventilation reduces ICP by causing cerebral vasoconstriction and a subsequent reduction in cerebral blood volume.[2] Fortune et al[67] showed that decreasing arterial Pc_{O_2} to 26 mm Hg in eight healthy individuals decreased cerebral blood volume by 7.2% and further decreased CBF by 30.7%. Obrist et al[68] showed a beneficial effect of hyperventilation on ICP in 15 of 31 patients with severe TBI but at the same time demonstrated a reduction in CBF in 29 of 31 patients. Several investigators have reported[69,70] that the relationship between Pa_{CO_2} and ICP is not linear, and that the greatest effect is between Pa_{CO_2} values of 30 and 50 mm Hg in humans. In experimental studies over wide ranges of Pa_{CO_2}, a sigmoid relation between ICP and Pa_{CO_2} has been found.[71]

In a clinical study of 94 patients with severe head injury, Yoshihara et al[72] found that a blood volume change of only 0.5 mL was necessary to produce an ICP change of 1 mm Hg. Consistent with the concept of the pressure-volume curve (Fig 1), a lower blood volume was necessary to produce a significant ICP change in patients with reduced compliance. Further, it was shown that the effects on ICP were greater during hypercapnia than during hypocapnia. Similar results have also been reported by Stocchetti et al,[73] who calculated a mean (± SD) blood volume change of 0.72 ± 0.42 mL for each millimeter of mercury of change in Pa_{CO_2}. Surprisingly, only a few studies have addressed the important question of whether beneficial effects on ICP remain present during prolonged hyperventilation. Muizelaar et al[12] have stressed that the vasoconstrictive effect will be diminished in prolonged hyperventilation as the pH of the perivascular spaces normalizes after 24 h. They further demonstrated in experimental studies that a rebound vasodilation may occur along with a risk of increasing ICP following the discontinuation of hyperventilation.

Hyperventilation and CBF

A major concern in treating raised ICP by hyperventilation is the risk of inducing cerebral ischemia, either globally or regionally. As in stroke, the risk of ischemic damage is dependent on the extent and duration of low-flow states (Fig 3). In the early posttraumatic phase, both global and regional CBF are markedly decreased,[74,75] and the presence of low

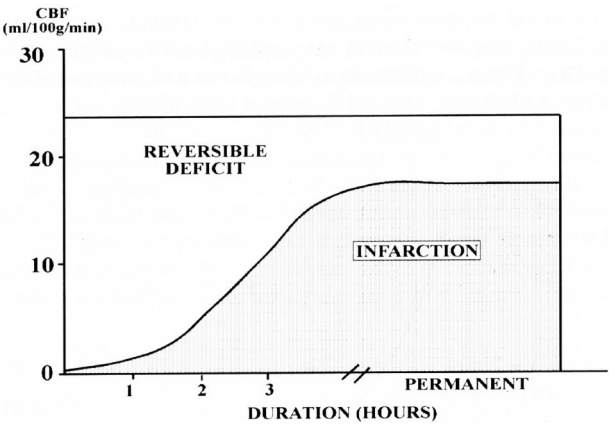

Figure 3. Graph illustrating the relations among decreased CBF, reversible ischemia, and infarction. Adapted from Jones et al.[149]

CBF early following TBI is significantly associated with early mortality and poorer outcome.[76,77] CBF can be measured, directly or indirectly, by a number of methods, none of which, however, are easily available at the bedside in the ICU environment. CBF measurements with radioactive ^{131}Xe were introduced for clinical use in the 1970s, but this technique was later banned from clinical use because of radiation dangers. Following the introduction of faster multislice CT scanners, Xe-CT scans became a standard technique for measuring CBF with the use of stable, nonradioactive Xe during CT scans of the brain. Inhaled Xe, which is freely diffusable from the lungs to the blood, and from the cerebral vasculature to the brain tissue, can be detected in the brain via CT scan because it increases the attenuation of x-rays.[78] Direct measurements of CBF can further be performed with positron emission tomography (PET) scanners, which offer the additional benefit of assessing metabolic parameters. PET scanning is, however, available in only a few research centers; provides, as is also the case in stable Xe-CT scanning, only momentary information; and involves transport from the ICU environment for longer periods of time. Indirect measurements of CBF can be performed with transcranial Doppler ultrasonography techniques, which permit measurements of blood flow velocity through the basal intracranial arteries. Blood flow velocity, however, does not directly correspond to CBF, as no information is available on the diameter of the cerebral arteries.

Using Xe-CT scanning to quantify regional CBF, Bouma et al[77] found CBF values below ischemic thresholds of 18 mL per 100 g of tissue per minute in 31% of TBI patients. In a retrospective analysis of TBI patients with subdural hematomas, Marion et al[13] observed the lowest CBF within the first 24 h following injury ipsilateral to the hematoma. Studies with transcranial Doppler ultrasonography have also shown a low-flow velocity state in the early phase after injury, occurring in 63% of patients.[79]

As low CBF is common in the first 24 h after a TBI, there is particular concern for aggravating the risk of ischemia by the institution of hyperventilation.[13] In healthy volunteers, Raichle et al[80] described a 40% decrease in CBF 30 min after decreasing $PaCO_2$ by 15 to 20 mm Hg. The response, however, was transitory, and after 4 h, CBF was restored to 90% of baseline values. Clinical studies in patients with TBI have shown a 3% change in CBF per millimeter of mercury change in $PaCO_2$, but the response was lower in patients with lower CBF levels.[81]

Various clinical studies[68,82–85] have confirmed an adverse effect of hyperventilation on CBF levels in patients with TBI. McLaughlin and Marion[86] further showed increased CO_2 vasoresponsivity in contusions and the surrounding penumbra, and they hypothesized that this possible hypersensitivity in combination with relative hypoperfusion may render such lesions particularly vulnerable to secondary ischemic injury, which may be aggravated by hyperventilation. The ultimate question, however, is whether the observed reduction in CBF following hyperventilation indeed leads to clinically significant ischemia, as evidenced by metabolic studies. Diringer et al,[87] for instance, showed that brief moderate hyperventilation did not impair global cerebral metabolism and oxygen extraction in patients with severe TBIs, despite a clear decrease in global CBF level. Cruz[88] has argued that the decrease in CBF level following hyperventilation is acceptable as long as the metabolic parameters are not deranged.

Hyperventilation and Cerebral Oxygenation

The monitoring of cerebral oxygenation has received considerable attention in view of the significant risk of hyperventilation to decrease CBF levels and possibly to induce/aggravate ischemia. Clinical studies have focused on jugular bulb oximetry and the monitoring of brain tissue oxygen tension ($PbrO_2$).

In jugular bulb oximetry, SjO_2 is monitored either continuously with fiber optic techniques or intermittently from blood sampling. It is therefore a global technique providing information on the oxygen extraction from the cerebral venous blood draining via that particular vein. However, this does not necessarily reflect hemispheric values as cross-flow may exist, with one jugular vein being more dominant.[89] It is generally preferred to measure/sample in the dominant vein.

Under normal circumstances (*eg*, awake or under normal hemoglobin concentration) the SjO_2 ranges from 55 to 70%. Values below 50 to 55% are generally regarded to represent global cerebral hypoperfusion with an increase in cerebral oxygen extraction.[90] Additional information can be obtained by calculating $AVDO_2$ or by determining the oxygen extraction fraction. Some studies[91,92] have shown that forced hyperventilation, although normalizing ICP, can lead to significantly reduced cerebral oxygenation. Other studies,[93,94] however, have described SjO_2 values of $> 55\%$ with a concomitant reduction in ICP. In the experimental situation, Sutton et al[95] found a significant drop in venous oxygen content following hyperventilation in two of six animals studied, accompanied by a decrease in phosphocreatine level, which was rapidly reversible after reestablishing normocapnia.

Cruz and colleagues[88,96–98] investigated the so-

called flow-metabolism coupling and showed that in approximately 20% of patients with elevated ICP blood flow outstrips cerebral metabolic demands. Hyperventilation in this subgroup may lower CBF and improve ICP without reducing cerebral oxygenation. Cruz and colleagues[88,96–98] have proposed the concept of optimizing hyperventilation on the basis of SjO_2-derived parameters, aiming to both normalize ICP and decrease the cerebral extraction of oxygen by manipulating hyperventilation, to $PaCO_2$ values ranging from18 to 30 mm Hg. Cruz et al[88] have claimed that this approach yielded better patient outcomes compared to CPP-directed therapy. However, others[94] have argued that, even with careful SjO_2 monitoring, the risk of inducing iatrogenic ischemia with hyperventilation to $PaCO_2$ levels < 30 mm Hg is too large, and therefore the physician should adhere to CPP-based therapy by maintaining $PaCO_2$ levels at > 30 mm Hg.

In contrast to SjO_2 monitoring, $PbrO_2$ monitoring is a regional technique. Most studies on monitoring $PbrO_2$ also have shown a deleterious effect of hyperventilation on cerebral oxygenation. Continuous $PbrO_2$ monitoring became possible when miniaturized probes, which can be inserted into the cerebral cortex, were manufactured. The first probe was a polarographic, Clark-type sensor, in which a cathode and an anode were contained in a membrane that was only permeable to oxygen. When oxygen diffuses from the tissue into the probe, it generates an electric current between the cathode and anode that is proportional to the oxygen tension. Subsequently, additional technologies for $PbrO_2$ monitoring (*ie*, colorimetric systems) became available.[99] All systems display numeric values, expressing the oxygen tension in millimeters of mercury. Normal values in the brains of various species, including humans, are > 20 mm Hg. Prolonged and profound reductions below this value have proven to be an independent predictor of unfavorable outcome and death.[100]

Hemphill et al[101] showed a linear relation between $PbrO_2$ and CBF with changes in end-tidal CO_2 and further confirmed a linear relation between $PbrO_2$ and end-tidal CO_2 levels over ranges between 20 and 60 mm Hg. Various other experimental studies[102–104] have shown a decrease in $PbrO_2$ following hyperventilation. In a study on 16 swine, Manley et al[103] showed a 40% decrease in mean ($\pm$ SD) $PbrO_2$ level from 36 ± 11 to 20 ± 9 mm Hg after hyperventilation. The deleterious effect of hyperventilation on $PbrO_2$ has been confirmed in many clinical studies.[91,105–111] In two studies,[112,113] however, the decrease in $PbrO_2$ was not significant, and some studies[108,110,111] have even reported an increase in $PbrO_2$ in some cases. These seemingly conflicting results may be explained by differences in pathophysiology between individual patients and would seem to favor the optimized hyperventilation approach advocated by Cruz et al.[98] In patients with raised ICP that is due mainly to cerebral vasodilation (hyperemia), hyperventilation may restore blood flow within damaged regions. This is also illustrated by different responses on SjO_2 monitoring compared to brain tissue oxygenation when $PbrO_2$ catheters are placed near the penumbra of focal lesions.[113]

The effect of hyperventilation on $PbrO_2$ seems to be time-dependent. Initially, van Santbrink et al[105] showed in 1996 that the tissue oxygen response to changes in $PaCO_2$ was most marked on day 5 after trauma. In a follow-up study in 2000, Carmona Suazo et al[109] showed increasing tissue oxygen response to hyperventilation over time, and found a significant relation between increased tissue oxygen response on day 5 and poorer outcome. Similar observations have been reported by others.[107,114] The observation that the deleterious effect of hyperventilation on $PbrO_2$ increases over time is intriguing. Until now, the greatest clinical concern for the risk of ischemia following hyperventilation has been within the first 24 h after injury as low CBF frequently occurs in this time period. It may, however, be argued that within this time frame of 24 h a general state of vascular narrowing exists and that further effects of hyperventilation may not have serious adverse consequences. The increasing tissue oxygen response over time may indicate an increased risk of ischemia, particularly at later time points. However, further research is necessary to confirm these results.

Hyperventilation, Neurochemical Monitoring, and Metabolism

Information on the metabolic status of the brain can be obtained from chemical monitoring in the jugular venous blood, from microdialysis studies, from PET scan studies, or from MRI spectroscopy. After severe head injury, elevated levels of lactate in the CSF have been frequently shown.[115–119]

Based on the results of lactate determinations in jugular venous blood, various authors[116,120,121] have shown the increased cerebral formation of lactate. In the study by Robertson et al,[120] lactate levels increased in proportion to the severity of cerebral trauma experienced during the first 2 days after injury. Murr et al,[122] in a study of 21 patients with severe TBI, showed that in patients with intracranial hypertension the cerebral lactate level difference remained significantly increased from the first to the fifth day after injury, but normalized over this period in the group with normal or minimally elevated ICP

values. Averaged over the short-term course, patients with increased ICP had significantly higher mean lactate level differences, and a significant correlation of increased mean cerebral lactate difference to poor outcome was noted.

Cerebral microdialysis is a relatively new technique for measuring metabolic parameters in the extracellular fluid and is being increasingly used in the monitoring of TBI patients, particularly in the research setting. Artificial CSF is injected into, and recovered from, a probe inserted in the cerebral cortex. The fluid equilibrates with the extracellular concentration of various metabolites, depending on the permeability of the microdialysis membrane, the length of the probe, and the velocity of injection. Microdialysis allows the long-term measurement of extracellular fluid energy-related metabolites (*eg*, glucose, lactate, and pyruvate) and amino acids in the cerebral cortex.[123] Goodman et al[45] measured lactate and glucose levels in 126 patients with head injuries. They found an initial increase in lactate level, perhaps indicating the presence of compensated hyperglycolysis, which gradually decreased during the first 24 to 48 h. Correlations have been demonstrated between low brain tissue oxygen levels and increased lactate levels.[124,125] Reinert et al[126] further demonstrated that increases in potassium levels were correlated with lactate accumulation, and were associated with increased ICP and poorer outcome. In contrast to other studies,[126] however, some episodes of high lactate levels were not associated with low brain tissue oxygen levels. The specific effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local CBF in patients with TBIs were reported by Marion et al.[127] Hyperventilation studies, lowering arterial P_{CO_2} by 8 to 12 mm Hg, were conducted 24 to 36 h after injury and again at 3 to 4 days after injury. At 24 to 36 h after TBI, hyperventilation led to a significant increase in lactate levels and in the lactate/pyruvate ratio. At 3 to 4 days after TBI, hyperventilation also led to a significant increase in lactate levels, but the differences in the lactate/pyruvate ratio were not significant. The authors concluded that hyperventilation-induced changes are more pronounced during the first 24 to 36 h after TBI than at 3 to 4 days after TBI.

The distribution and intensity of the uptake of positron-emitting radiotracers in the tissue is an indicator of metabolism. PET scanning is a technique that allows the precise measurement of biomolecules such as glucose or oxygen in a living organ, such as the brain. A short-lived radioisotope is synthetically bound to the molecule of interest to form a positron-emitting radiotracer, which can be detected and quantitatively measured by PET scanning.[128]

The effect of hyperventilation on the cerebral oxygen metabolism has been studied by Diringer et al[129] with PET scan studies. Nine patients with severe TBIs were moderately hyperventilated, and four more patients were intensely hyperventilated to a mean Pa_{CO_2} of 25 ± 2 mm Hg. Although this study demonstrated a significant decrease in CBF and an increase in oxygen extraction fraction following hyperventilation, CMR_{O_2} remained unchanged. It was concluded that brief hyperventilation may produce large reductions in CBF but does not lead to energy failure, and the authors considered that the observed reductions in CBF are therefore unlikely to cause further brain injury. Some serious limitations of this study were that only a few patients were studied, and that the duration of hyperventilation was relatively short and was maintained only for the duration of the actual PET scan study.

Coles et al[94] have shown in studies by conducted by PET scanning (see next section) that hyperventilation increases the volume of severely hypoperfused tissue within the injured brain, despite improvements in CPP and ICP. The same group has suggested more recently[130] that the injured brain may be less capable of increasing oxygen extraction in response to hypoperfusion, so that shortly after injury the brain could be more vulnerable to the CBF reduction induced by hyperventilation.

Hyperventilation and Clinical Outcome

Despite the wide use of hyperventilation in the treatment of raised ICP after TBI and the large body of evidence indicating the possible deleterious effects of hyperventilation on CBF levels, oxygenation, and metabolism, only one prospective randomized clinical trial has been reported concerning the effect of hyperventilation on clinical outcome. Muizelaar et al[131] compared the outcomes of patients who were hyperventilated to a Pa_{CO_2} of 25 mm Hg for 5 days to patients in whom the Pa_{CO_2} was kept at 35 mm Hg. At both 3 and 6 months after injury, patients with an initial Glasgow coma scale motor score of 4 or 5 had a significantly better outcome when they were not hyperventilated. This study formed the basis for the recommendation at the level of a standard (class I evidence) in the guidelines for the management of TBI stating the following: ". . . in the absence of increased ICP, prolonged hyperventilation therapy ($Pa_{CO_2} \leq 25$ mm Hg) should be avoided." In addition, the guidelines state that "the use of prophylactic hyperventilation ($Pa_{CO_2} < 35$

mm Hg) should be avoided during the first 24 h after severe TBI because it can compromise cerebral perfusion during a time when CBF is reduced." However, at the level of an option, it is recognized that hyperventilation therapy may be necessary for brief periods when there has been acute neurologic deterioration or for longer periods if intracranial hypertension is refractory to other therapy.

We consider the class I evidence underlying the standard of these guidelines debatable and open to criticism. First, the control group was in fact mildly hyperventilated with a $PaCO_2$ of 31 to 32 mm Hg. Second, the subgroup of patients with a Glasgow coma score motor score of 4 to 5 was not prespecified, and numbers were small (control group, 21 patients; hyperventilation group, 17 patients). Third, the study was confined to patients without raised ICP. Fourth, the best outcome was achieved by a third group of TBI patients, included in the study but neglected in further discussions, who had been hyperventilated and had received tromethamine (TRAM).

Synthesis and Conclusions

The use of hyperventilation in the treatment of patients with TBI remains controversial. Studies reporting beneficial and potentially adverse effects of hyperventilation on cerebral parameters are summarized in Table 2. The controversy has been illustrated by various editorials and comments in the literature.[111,132–135] The proponents of hyperventilation claim that it is effective in reducing ICP and that, despite a concomitant reduction in CBF levels, there is no evidence that this results in further metabolic derangement, and from this they conclude that the risk of ischemia is a nonissue. Adversaries of hyperventilation focus on the deleterious effects on CBF level, cerebral oxygenation, and neurochemical parameters obtained in microdialysis studies. Further, the lack of evidence of a beneficial effect on clinical outcome has been emphasized.[136]

How can these two widely different points of view and approaches be reconciled? The answer to this question touches on the general discussion on standardized management vs more individually targeted approach. As Chesnut[132] summarizes in the following way: "It is unclear why the various treatment modalities are felt to be mutually exclusive and all encompassing in the area of neurotrauma management." Even the greatest proponent of hyperventilation[88] has emphasized the need for "optimized hyperventilation" aiming at correcting the mismatch between flow and oxygen metabolism, to which purpose multimodality monitoring including jugular oximetry is required. The adversaries of hyperventilation, who usually belong to the school advocating CPP therapy, will have to admit that the inadvertent use of therapy with vasopressors and hypervolemia also carries risks concerning a prolonged course of raised ICP, fluid overload, and an increased risk of ARDS.[137] We submit that both approaches may be appropriate under specifically defined circumstances, targeting the therapy to the individual requirements of patients. The standard, as contained in the international guidelines[14] on hyperventilation, stating that prolonged hyperventilation in TBI patients without raised ICP should be avoided, must be put into the appropriate perspective. It may be argued that in patients without raised ICP there is no indication for hyperventilation. To date, there is no evidence in the literature unequivocally demonstrating that hyperventilation for the treatment of raised ICP in patients with TBI is related to poorer outcome, and there is also no evidence showing beneficial effects on overall outcome. When considering a therapy without proven clinical efficacy, a careful analysis of risks and benefits is required, considering the indication for and the duration of treatment. Risks concern systemic and cerebral complications. Systemic risks would appear to be greater, particularly in patients with preexistent cardiac disease and in patients with absolute or relative hypovolemia. In this regard, it should be noted that inadvertent hyperventilation is frequent in the prehospital setting at a time when optimal volume resuscitation has not yet been accomplished. Thomas et al[138] reported an incidence of low end-tidal CO_2 in 70% of patients with TBI who were undergoing helicopter transport to an urban level 1 trauma center.

Cerebral complications particularly relate to the risk of ischemia. Considering the risk-benefit relation, it would appear to be clear that the possibility of instituting hyperventilation therapy should be considered only in patients with raised ICP. No benefit may be expected in the absence of raised ICP. Theoretically, the benefit of hyperventilation may be more particularly expected in patients in whom raised ICP is considered mainly due to increased cerebral blood volume due to vasodilation. In the opinion of the authors, this would preferentially be the pediatric and young adult population. In clinical practice, however, it may be very difficult, if not impossible, to differentiate between the contribution of edema and cerebral blood volume to traumatic brain swelling following TBI, without facilities for PET scanning or MRI diffusion-weighted imaging. Marmarou et al[139] showed in a study of 31 patients with TBI that brain swelling due to cerebral blood volume averaged 2.94% compared with an average of 9.1% for brain swelling due to edema. In this group

Table 2—*Effect of Hyperventilation on Cerebral Parameters

Study/Year	No. Patients	Duration of hyperventilation	ICP	CBF	TCD	SJO_2	$PbrO_2$	Comments and Remarks
Ausina et al[142]/1998	33	4 h	⇓	⇓				Maximum effect at 30 min; mild tendency to return at 2 h; on average, no change in $AVDO_2$, but dangerous increase in 1 patient
Berré et al[143]/1998	36	20 min	⇓	⇓	⇓	⇓		$CMRO_2$: no change
Carmona Suazo et al[109]/2000	90	15 min					⇓	Absent or low effect on day 1, increasing to day 5
Cold et al[81]/1989	27	10 min	⇓	⇓				Increase of regional oligemia of 5–16%
Coles et al[94]/2002	33	10 min	⇓	⇓				PET studies shows an increase in the volume of critically perfused brain tissue at $PaCO_2$ values < 34 mm Hg
Dings et al[114]/1996	17	10 min			⇓		⇓	Absent or low CO_2 reactivity on day 1; highest reactivity on day 5
Diringer et al[129]/2002	9	30 min		⇓				$CMRO_2$, no change; OEF, ⇑; CvO_2, ⇓; CBV ⇓
Fandino et al[107]/1999	9	10 min			⇓	⇓	⇓	Higher CO_2 reactivity day 5–7
Fortune et al[67]/1995	22	20 min	⇓			⇓		
Gupta et al[113]/1999	13	15 min				⇓	⇓	Decrease in $PbrO_2$ most marked in areas of focal pathology. Local changes not detected bo SJO_2
Imberti et al[111]/2002	36	20 min	⇓			⇓	⇓	Critical decrease of $PbrO_2$ or increase of SjO_2 in 7 patients
Lee et al[144]/2001	20	10 min			⇓			Mean CO_2 reactivity, 3.3 ± 1.6% Vmca/mm Hg; tendency to higher values on days 5–13
Marion and Bouma[145]/1991	17	20 min		⇓				CO_2 responsivity ranges from 1.3–8.5%/mm Hg PcO_2; regional differences of ≥ 50% compared to global values in 16 patients
Marion et al[127]/2002	20	30 min		⇓				Decrease in pericontusional CBF more pronounced 24–36 h after trauma; microdialysis studies demonstrate increase in glutamate and lactate following hyperventilation
McLaughin and Marion[86]/1996	10	20 min		⇓				Large variations in vasoresponsitivity to hyperventilation in and around contusions
Minassian et al[150]/1998	12	10–15 min	⇓		⇓			$AVDO_2$; higher reactivity on days 4–6 is related to better outcome
Newell et al[152]/1996	10	10 min	⇓		⇓			Mild hyperventilation may improve vascular tone and autoregulation
Obrist et al[68]/1984	31	Short duration	⇓	⇓				Higher reactivity in patients with hyperaemia
Oertel et al[146]/2002	33	15 min	⇓		⇓	⇓		Greater effect at higher baseline $PaCO_2$
Oertel et al[147]/2002	20	?			?			Normal ICP, hyperventilation increases pulsatility index ICP, > 30: hyperventilation decreases pulsatility index The authors suggested that hyperventilation may improve cerebral microcirculation in the setting of raised ICP
Schneider et al[112]/1998	15	10 min	⇓				⇓	Hyperventilation challenge stopped in 1 patient because of a critical decrease in $PbrO_2$
Skippen et al[83]/1997	23	15 min		⇓				Pediatric population; mean CO_2 reactivity 2.7%/mm Hg (range, 7.1–2.3%/mm Hg)
Thiagarajan et al[151]/1998	18	30 min				⇓		Decrease in SjO_2 following hyperventilation may be offset by increasing PAO_2
Vigue et al[141]/2000	20	20 min	⇓	⇓		⇓	⇓	Changes in ICP and Vmca following hypothermia can be explained by changes in temperature-corrected $PaCO_2$

*⇓ = decrease; ⇑ = increase; CvO_2 = venous oxygen content; Vmca = velocity in the middle cerebral artery change for every mm Hg; ? = unknown.

of patients, cerebral blood volume was increased in only five patients compared to the levels obtained in seven volunteers. However, no mention was made on the time period within which these studies were performed.

It has been argued that the main risk of ischemia due to hyperventilation will be present within the first 24 h after injury, as this is the period in which low CBF levels occur. We think that this generally accepted opinion may be challenged. If indeed this acute phase is characterized by a generalized state of vascular narrowing, the additional effect of hyperventilation may be expected to be low, and this has indeed been demonstrated in various studies.[109] Therefore, it may be tentatively concluded that the institution of hyperventilation therapy may be more appropriate during the relative hyperemic phases of days 2 and 3 after TBI. Nevertheless, the risk of ischemic complications cannot be excluded, and the careful monitoring of cerebral oxygenation is required.

Current evidence would favor a relatively short duration of hyperventilation therapy. The general consensus is not to hyperventilate TBI patients below a $Paco_2$ of 30 mm Hg. In exceptional circumstances, more intense hyperventilation may, however, be considered under careful monitoring.

Jugular oximetry permits the monitoring of global cerebral oxygen extraction, and local brain tissue Po_2 monitoring may yield additional information in the penumbra around contusions. McLaughlin and Marion[86] have reported increased vasoreactivity in the penumbra zones around the contusions up to nearly three times normal, suggesting the hypersensitivity of this region to hyperventilation therapy. Metabolic studies with MRI spectroscopy or PET scanning may be required before the possibility of local adverse effects of hyperventilation can be fully evaluated.

When considering the appropriate depth of hyperventilation, two specific circumstances need to be recognized. First, at higher altitudes normal $Paco_2$ levels may be well below the generally accepted levels of 35 to 45 mm Hg that were determined at sea level. A correction for the influence of altitude is therefore required. Second, the influence of temperature, particularly when hypothermia therapy is used, should be considered. In the laboratory, blood gas measurements are generally performed at 37°C, and the results are not corrected for body core temperature. The validity for performing temperature corrections has been argued.[140] In a more recent article, Vigue et al[141] showed that the institution of hypothermia leads to a decrease in end-tidal CO_2 and $Paco_2$ due to a systemic and cerebral reduction of metabolism. In fact, these authors argued that the reduction of ICP following hypothermia may be fully explained by the concomitant decrease of $Paco_2$.

In conclusion, controversy exists, as exemplified in Table 2, and conflicting data may support a range of therapeutic options, from the enthusiastic overuse of hyperventilation to the avoidance of hyperventilation. It is our opinion that the careful use of hypocapnia for the short-term control of raised ICP remains a useful therapeutic tool. Multimodality monitoring is required in order to safely target hyperventilation therapy to specific patients who may benefit from it.

References

1 Rossanda M, Vecchi G. Determination of cerebral autoregulatory status and Pco_2 responsiveness. Int Anesthesiol Clin 1979; 17:425–438
2 Raichle ME, Plum F. Hyperventilation and cerebral blood flow. Stroke 1972; 3:566–575
3 Davis H, Wallace WM. Factors affecting changes produced in electroencephalogram by standardized hyperventilation. Arch Neurol Psychiat 1942; 47:606–625
4 The Brain Trauma Foundation. The American Association of Neurological Surgeons: the Joint Section on Neurotrauma and Critical Care; guidelines for cerebral perfusion pressure. J Neurotrauma 2000; 17:507–511
5 Brian JE Jr. Carbon dioxide and the cerebral circulation. Anesthesiology 1998; 88:1365–1386
6 Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Acta Neurochir Suppl (Wien) 1990; 49:1–64
7 Obrist WD, Marion DW. Xenon techniques for CBF measurement in clinical head injury. In: Narayan RK, Wilberger J, Povlishock JT, eds. New York, NY: McGraw-Hill, 1996; 471–485
8 Go KG. Cerebral pathophysiology. Amsterdam, the Netherlands: Elsevier, 1991
9 Giller CA, Bowman G, Dyer H, et al. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. Neurosurgery 1993; 32:737–741
10 Zonta M, Angulo MC, Gobbo S, et al. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci 2003; 6:43–50
11 Kontos HA, Raper AJ, Patterson JL. Analysis of vasoactivity of local pH, Pco_2 and bicarbonate on pial vessels. Stroke 1977; 8:358–360
12 Muizelaar JP, van der Poel HG, Li ZC, et al. Pial arteriolar vessel diameter and CO_2 reactivity during prolonged hyperventilation in the rabbit. J Neurosurg 1988; 69:923–927
13 Marion DW, Firlik A, McLaughlin MR. Hyperventilation therapy for severe traumatic brain injury. New Horiz 1995; 3:439–447
14 Bullock MR, Chesnut R, Clifton G, et al. Hyperventilation. J Neurotrauma 2000; 17:513–520
15 Chesnut RM. Hyperventilation in traumatic brain injury: friend or foe? Crit Care Med 1997; 25:1275–1278
16 Vender JR. Hyperventilation in severe brain injury revisited. Crit Care Med 2000; 28:3361–3362
17 Dexter F. Research synthesis of controlled studies evaluating the effect of hypocapnia and airway protection on cerebral outcome. J Neurosurg Anesthesiol 1997; 9:217–222

18 Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. Cochrane Database Syst Rev (database online). Issue 2, 2000
19 Pinsky MR. Cardiovascular effects of ventilatory support and withdrawal. Anesth Analg 1994; 79:567–576
20 Takata M, Robotham JL. Effects of inspiratory diaphragmatic descent on inferior vena caval venous return. J Appl Physiol 1992; 72:597–607
21 Citerio G, Vascotto E, Villa F, et al. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. Crit Care Med 2001; 29:1466–1471
22 Imai T, Uchiyama M, Maruyama N, et al. Influence of constant sustained positive airway pressure on right ventricular performance. Intensive Care Med 1993; 19:8–12
23 Jardin F, Farcot JC, Gueret P, et al. Echocardiographic evaluation of ventricles during continuous positive airway pressure breathing. J Appl Physiol 1984; 56:619–627
24 Janicki JS, Weber KT. The pericardium and ventricular interaction, distensibility, and function. Am J Physiol 1980; 238:H494–H503
25 Butler J. The heart is in good hands. Circulation 1983; 67:1163–1168
26 Wallis TW, Robotham JL, Compean R, et al. Mechanical heart-lung interaction with positive end-expiratory pressure. J Appl Physiol 1983; 54:1039–1047
27 Qvist J, Pontoppidan H, Wilson RS, et al. Hemodynamic responses to mechanical ventilation with PEEP: the effect of hypervolemia. Anesthesiology 1975; 42:45–55
28 Pinsky MR, Summer WR. Cardiac augmentation by phasic high intrathoracic pressure support in man. Chest 1983; 84:370–375
29 Rose BD, Post WT. Clinical physiology of acid-base and electrolyte disorders. 5th ed. New York, NY: McGraw Hill, 2001
30 Nunn JF. Applied respiratory physiology. 3rd ed. Cambridge, UK: Butterworth & Co, 1987
31 Dempsey JA, Forster HV. Mediation of ventilatory adaptations. Physiol Rev 1982; 62:262–346
32 Kuschinsky W. Role of hydrogen ions in regulation of cerebral blood flow and other regional flows. Adv Microcirc 1982; 11:1–19
33 Ui M. A role of phosphofructokinase in pH-dependent regulation of glycolysis. Biochim Biophys Acta 1966; 124: 310–322
34 Trivedi B, Danforth WH. Effect of pH on the kinetics of frog muscle phosphofructokinase. J Biol Chem 1966; 241: 4110–4112
35 Kjallquist A, Nardini M, Siesjo BK. The regulation of extra- and intracellular acid-base parameters in the rat brain during hyper- and hypocapnia. Acta Physiol Scand 1969; 76:485–494
36 Depre C, Ponchaut S, Deprez J, et al. Cyclic AMP suppresses the inhibition of glycolysis by alternative oxidizable substrates in the heart. J Clin Invest 1998; 101:390–397
37 Jundi K, Barrington KJ, Henderson C, et al. The hemodynamic effects of prolonged respiratory alkalosis in anesthetized newborn piglets. Intensive Care Med 2000; 26:449–456
38 Fanconi A, Rose GA. The ionized, complexed, and protein-bound fractions of calcium in plasma; an investigation of patients with various diseases which affect calcium metabolism, with an additional study of the role of calcium ions in the prevention of tetany. Q J Med 1958; 27:463–494
39 Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med 1992; 20:251–262
40 Polderman KH, Bloemers FW, Peerdeman SM, et al. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. Crit Care Med 2000; 28:2022–2025
41 Wasserman K. Coupling of external to cellular respiration during exercise: the wisdom of the body revisited. Am J Physiol 1994; 266:E519–539
42 Gotoh F, Meyer JS, Takagi Y. Cerebral effects of hyperventilation in man. Arch Neurol 1965; 12:410–423
43 Cruz J, Gennarelli TA, Hoffstad OJ. Lack of relevance of the Bohr effect in optimally ventilated patients with acute brain trauma. J Trauma 1992; 33:304–310
44 Kazmaier S, Weyland A, Buhre W, et al. Effects of respiratory alkalosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. Anesthesiology 1998; 89:831–837
45 Goodman JC, Valadka AB, Gopinath SP, et al. Extracellular lactate and glucose alterations in the brain after head injury measured by microdialysis. Crit Care Med 1999; 27:1965–1973
46 Fujita Y, Sakai T, Ohsumi A, et al. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. Anesth Analg 1989; 69:152–157
47 Gustafsson U, Sjoberg F, Lewis DH, et al. The effect of hypocapnia on skeletal muscle microcirculatory blood flow, oxygenation and pH. Int J Microcirc Clin Exp 1993; 12:131–141
48 Barker SJ, Hyatt J, Clarke C, et al. Hyperventilation reduces transcutaneous oxygen tension and skin blood flow. Anesthesiology 1991; 75:619–624
49 Hirano Y, Ozasa Y, Yamamoto T, et al. Hyperventilation and cold-pressor stress echocardiography for noninvasive diagnosis of coronary artery spasm. J Am Soc Echocardiogr 2001; 14:626–633
50 Krapf R, Beeler I, Hertner D, et al. Chronic respiratory alkalosis: the effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 1991; 324:1394–1401
51 Eiam-ong S, Laski ME, Kurtzman NA, et al. Effect of respiratory acidosis and respiratory alkalosis on renal transport enzymes. Am J Physiol 1994; 267:F390–F399
52 Domino KB, Swenson ER, Hlastala MP. Hypocapnia-induced ventilation/perfusion mismatch: a direct CO2 or pH-mediated effect? Am J Respir Crit Care Med 1995; 152:1534–1539
53 Traystman RJ, Batra GK, Menkes HA. Local regulation of collateral ventilation by oxygen and carbon dioxide. J Appl Physiol 1976; 40:819–823
54 Traystman RJ, Terry PB, Menkes HA. Carbon dioxide: a major determinant of collateral ventilation. J Appl Physiol 1978; 45:69–74
55 Domino KB, Lu Y, Eisenstein BL, et al. Hypocapnia worsens arterial blood oxygenation and increases VA/Q heterogeneity in canine pulmonary edema. Anesthesiology 1993; 78:91–99
56 Turner E, Hilfiker O, Braun U, et al. Metabolic and hemodynamic response to hyperventilation in patients with head injuries. Intensive Care Med 1984; 10:127–132
57 Reynolds AM, Zadow SP, Scicchitano R, et al. Airway hypocapnia increases microvascular leakage in the guinea pig trachea. Am Rev Respir Dis 1992; 145:80–84
58 Oyarzun MJ, Donoso P, Quijada D. Role of hypocapnia in the alveolar surfactant increase induced by free fatty acid intravenous infusion in the rabbit. Respiration 1986; 49:187–194
59 Cutillo A, Omboni E, Perondi R, et al. Effect of hypocapnia on pulmonary mechanics in normal subjects and in patients

with chronic obstructive lung disease. Am Rev Respir Dis 1974; 110:25–33
60 Laffey JG, Engelberts D, Kavanagh BP. Injurious effects of hypocapnic alkalosis in the isolated lung. Am J Respir Crit Care Med 2000; 162:399–405
61 Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–354
62 Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999; 282:54–61
63 Garland JS, Buck RK, Allred EN, et al. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 1995; 149:617–622
64 Bratton SL, Davis RL. Acute lung injury in isolated traumatic brain injury. Neurosurgery 1997; 40:707–712
65 Hsieh AH, Bishop MJ, Kubilis PS, et al. Pneumonia following closed head injury. Am Rev Respir Dis 1992; 146:290–294
66 Lundberg N, Kjallquist A, Bien C. Reduction of increased intracranial pressure by hyperventilation: a therapeutic aid in neurological surgery. Acta Psychiatr Scand 1959; 34(suppl):1–64
67 Fortune JB, Feustel PJ, Graca L, et al. Effect of hyperventilation, mannitol, and ventriculostomy drainage on cerebral blood flow after head injury. J Trauma 1995; 39:1091–1097
68 Obrist WD, Langfitt TW, Jaggi JL, et al. Cerebral blood flow and metabolism in comatose patients with acute head injury: relationship to intracranial hypertension. J Neurosurg 1984; 61:241–253
69 Hayes TM, Tindall GT. Effects of altering arterial carbon dioxide pressure on internal carotid blood flow and cerebrospinal fluid pressure in man. Surg Forum 1969; 20:421–424
70 Paul RL, Polanco O, Turney SZ, et al. Intracranial pressure responses to alterations in arterial carbon dioxide pressure in patients with head injuries. J Neurosurg 1972; 36:714–720
71 Reivich M. Arterial P_{CO_2} and cerebral hemodynamics. Am J Physiol 1964; 206:25–35
72 Yoshihara M, Bandoh K, Marmarou A. Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. J Neurosurg 1995; 82:386–393
73 Stocchetti N, Mattioli C, Paparella A, et al. Bedside assessment of CO_2 reactivity in head injury: changes in CBF estimated by changes in ICP and cerebral extraction of oxygen [abstract]. J Neurotrauma 1993; 10(suppl):187
74 Fieschi C, Battistini N, Beduschi A, et al. Regional cerebral blood flow and intraventricular pressure in acute head injuries. J Neurol Neurosurg Psychiatry 1974; 37:1378–1388
75 Bouma GJ, Muizelaar JP, Choi SC, et al. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg 1991; 75:685–693
76 Jaggi JL, Obrist WD, Gennarelli TA, et al. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. J Neurosurg 1990; 72:176–182
77 Bouma GJ, Muizelaar JP, Stringer WA, et al. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992; 77:360–368
78 Drayer BP, Wolfson SK, Reinmuth OM, et al. Xenon enhanced CT for analysis of cerebral integrity, perfusion, and blood flow. Stroke 1978; 9:123–130
79 van Santbrink H, Schouten JW, Steyerberg EW, et al. Serial transcranial Doppler measurements in traumatic brain injury with special focus on the early posttraumatic period. Acta Neurochir (Wien) 2002; 144:1141–1149
80 Raichle ME, Posner JB, Plum F. Cerebral blood flow during and after hyperventilation. Arch Neurol 1970; 23:394–403
81 Cold GE. Does acute hyperventilation provoke cerebral oligaemia in comatose patients after acute head injury? Acta Neurochir (Wien) 1989; 96:100–106
82 Fortune JB, Feustel PJ, deLuna C, et al. Cerebral blood flow and blood volume in response to O_2 and CO_2 changes in normal humans. J Trauma 1995; 39:463–471
83 Skippen P, Seear M, Poskitt K, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. Crit Care Med 1997; 25:1402–1409
84 Dahl B, Bergholt B, Cold GE, et al. CO(2) and indomethacin vasoreactivity in patients with head injury. Acta Neurochir (Wien) 1996; 138:265–273
85 Sioutos PJ, Orozco JA, Carter LP, et al. Continuous regional cerebral cortical blood flow monitoring in head-injured patients. Neurosurgery 1995; 36:943–949
86 McLaughlin MR, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. J Neurosurg 1996; 85:871–876
87 Diringer MN, Yundt K, Videen TO, et al. No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury. J Neurosurg 2000; 92:7–13
88 Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobinsaturation: management strategies and clinical outcome. Crit Care Med 1998; 26:344–351
89 Stocchetti N, Paparella A, Bridelli F, et al. Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins. Neurosurgery 1994; 34:38–43
90 Andrews BT. Management of cerebellar hemorrhage and infarction. Contemp Neurosurg 1991; vol. 13
91 Unterberg AW, Kiening KL, Hartl R, et al. Multimodal monitoring in patients with head injury: evaluation of the effects of treatment on cerebral oxygenation. J Trauma 1997; 42:S32–S37
92 von Helden A, Schneider GH, Unterberg A, et al. Monitoring of jugular venous saturation in comatose patients with subarachnoid haemorrhage and intracerebral haematomas. Acta Neurochir Suppl (Wien) 1993; 59:102–106
93 Oertel M, Kelly DF, Lee JH, et al. Is CPP therapy beneficial for all patients with high ICP? Acta Neurochir Suppl 2002; 81:67–68
94 Coles JP, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 2002; 30:1950–1959
95 Sutton LN, McLaughlin AC, Dante S, et al. Cerebral venous oxygen content as a measure of brain energy metabolism with increased intracranial pressure and hyperventilation. J Neurosurg 1990; 73:927–932
96 Cruz J. Combined continuous monitoring of systemic and cerebral oxygenation in acute brain injury: preliminary observations. Crit Care Med 1993; 21:1225–1232
97 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; 23:1412–1417
98 Cruz J. An additional therapeutic effect of adequate hyperventilation in severe acute brain trauma: normalization of cerebral glucose uptake. J Neurosurg 1995; 82:379–385
99 Hoffmann WE. Measurement of intracerebral oxygen pressure: practicalities and pitfalls. Curr Opin Anaesthesiol 1999; 12:497–502

100 van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. Neurosurgery 2000; 46:868–876
101 Hemphill JC 3rd, Knudson MM, Derugin N, et al. Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. Neurosurgery 2001; 48:377–383
102 Zauner A, Bullock R, Di X, et al. Brain oxygen, CO_2, pH, and temperature monitoring: evaluation in the feline brain. Neurosurgery 1995; 37:1168–1176
103 Manley GT, Pitts LH, Morabito D, et al. Brain tissue oxygenation during hemorrhagic shock, resuscitation, and alterations in ventilation. J Trauma 1999; 46:261–267
104 van Hulst RA, Hasan D, Lachmann B. Intracranial pressure, brain PCO2, PO2, and pH during hypo- and hyperventilation at constant mean airway pressure in pigs. Intensive Care Med 2002; 28:68–73
105 van Santbrink H, Maas AI, Avezaat CJ. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. Neurosurgery 1996; 38:21–31
106 Meixensberger J, Jager A, Dings J, et al. Multimodal hemodynamic neuromonitoring: quality and consequences for therapy of severely head injured patients. Acta Neurochir Suppl (Wien) 1998; 71:260–262
107 Fandino J, Stocker R, Prokop S, et al. Correlation between jugular bulb oxygen saturation and partial pressure of brain tissue oxygen during CO_2 and O_2 reactivity tests in severely head-injured patients. Acta Neurochir (Wien) 1999; 141: 825–834
108 Gopinath SP, Valadka AB, Uzura M, et al. Comparison of jugular venous oxygen saturation and brain tissue Po_2 as monitors of cerebral ischemia after head injury. Crit Care Med 1999; 27:2337–2345
109 Carmona Suazo JA, Maas AIR, van den Brink WA. CO_2 reactivity and brain oxygen pressure monitoring in severe head injury. Crit Care Med 2000; 28:3268–3274
110 Imberti R, Ciceri M, Bellinzona G, et al. The use of hyperventilation in the treatment of plateau waves in two patients with severe traumatic brain injury: contrasting effects on cerebral oxygenation. J Neurosurg Anesthesiol 2000; 12:124–127
111 Imberti R, Bellinzona G, Langer M. Cerebral tissue PO_2 and $SjvO_2$ changes during moderate hyperventilation in patients with severe traumatic brain injury. J Neurosurg 2002; 96:97–102
112 Schneider GH, Sarrafzadeh AS, Kiening KL, et al. Influence of hyperventilation on brain tissue: Po_2, Pco_2, and pH in patients with intracranial hypertension. Acta Neurochir Suppl (Wien) 1998; 71:62–65
113 Gupta AK, Hutchinson PJ, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 1999; 88:549–553
114 Dings J, Meixensberger J, Amschler J, et al. Brain tissue Po_2 in relation to cerebral perfusion pressure, TCD findings and TCD-CO2-reactivity after severe head injury. Acta Neurochir (Wien) 1996; 138:425–434
115 Crockard HA, Taylor AR. Serial CSF lactate-pyruvate values as a guide to prognosis in head injury coma. Eur Neurol 1972; 8:151–157
116 DeSalles AA, Kontos HA, Becker DP, et al. Prognostic significance of ventricular CSF lactic acidosis in severe head injury. J Neurosurg 1986; 65:615–624
117 King LR, McLaurin RL, Knowles HC Jr. Acid-base balance and arterial and CSF lactate levels following human head injury. J Neurosurg 1974; 40:617–625
118 Rabow L, DeSalles AF, Becker DP, et al. CSF brain creatine kinase levels and lactic acidosis in severe head injury. J Neurosurg 1986; 65:625–629
119 Sood SC, Gulati SC, Kumar M, et al. Cerebral metabolism following brain injury: II. Lactic acid changes Acta Neurochir (Wien) 1980; 53:47–51
120 Robertson CS, Grossman RG, Goodman JC, et al. The predictive value of cerebral anaerobic metabolism with cerebral infarction after head injury. J Neurosurg 1987; 67:361–368
121 Sahuquillo J, Poca MA, Garnacho A, et al. Early ischaemia after severe head injury: preliminary results in patients with diffuse brain injuries. Acta Neurochir (Wien) 1993; 122: 204–214
122 Murr R, Stummer W, Schurer L, et al. Cerebral lactate production in relation to intracranial pressure, cranial computed tomography findings, and outcome in patients with severe head injury. Acta Neurochir (Wien) 1996; 138:928–937
123 Persson L, Hillered L. Chemical monitoring of neurosurgical intensive care patients using intracerebral microdialysis. J Neurosurg 1992; 76:72–80
124 Robertson CS, Gopinath SP, Uzura M, et al. Metabolic changes in the brain during transient ischemia measured with microdialysis. Neurol Res 1998; 20(suppl):S91–S94
125 Valadka AB, Gopinath SP, Contant CF, et al. Relationship of brain tissue Po_2 to outcome after severe head injury. Crit Care Med 1998; 26:1576–1581
126 Reinert M, Khaldi A, Zauner A, et al. High level of extracellular potassium and its correlates after severe head injury: relationship to high intracranial pressure. J Neurosurg 2000; 93:800–807
127 Marion DW, Puccio A, Wisniewski SR, et al. Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. Crit Care Med 2002; 30:2619–2625
128 American Academy of Neurology. Assessment: positron emission tomography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1991; 41:163–167
129 Diringer MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. J Neurosurg 2002; 96:103–108
130 Menon DK, Coles JP, Gupta AK, et al. Diffusion limited oxygen delivery following head injury. Crit Care Med 2004; 32:1384–1390
131 Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991; 75: 731–739
132 Chesnut RM. Hyperventilation versus cerebral perfusion pressure management: time to change the question. Crit Care Med 1998; 26:210–212
133 Zornow MH, Prough DS. Does acute hyperventilation cause cerebral ischemia in severely head-injured patients? Crit Care Med 2002; 30:2774–2775
134 Spiss CK. Hyperventilation in head injuries: who, when, which. how long. Minerva Anestesiol 1999; 65:697–699
135 Diringer MN, Dacey RG Jr. Traumatic brain injury and hyperventilation. J Neurosurg 2002; 96:155–157
136 Roberts I, Schierhout G, Alderson P. Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review. J Neurol Neurosurg Psychiatry 1998; 65:729–733
137 Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med 1999; 27:2086–2095

138 Thomas SH, Orf J, Wedel SK, et al. Hyperventilation in traumatic brain injury patients: inconsistency between consensus guidelines and clinical practice. J Trauma 2002; 52:47–52
139 Marmarou A, Fatouros PP, Barzo P, et al. Contribution of edema and cerebral blood volume to traumatic brain swelling in head-injured patients. J Neurosurg 2000; 93:183–193
140 Ream AK, Reitz BA, Silverberg G. Temperature correction of Pco_2 and pH in estimating acid-base status: an example of the emperor's new clothes? Anesthesiology 1982; 56:41–44
141 Vigue B, Ract C, Zlotine N, et al. Relationship between intracranial pressure, mild hypothermia and temperature-corrected $Paco_2$ in patients with traumatic brain injury. Intensive Care Med 2000; 26:722–728
142 Ausina A, Baguena M, Nadal M, et al. Cerebral hemodynamic changes during sustained hypocapnia in severe head injury: can hyperventilation cause cerebral ischemia? Acta Neurochir Suppl (Wien) 1998; 71:1–4
143 Berré J, Moraine JJ, Melot C. Cerebral CO_2 vasoreactivity evaluation with and without changes in intrathoracic pressure in comatose patients. J Neurosurg Anesthesiol 1998; 10:70–79
144 Lee R, Kermani P, Teng KK, et al. Regulation of cell survival by secreted proneurotrophins. Science 2001; 294: 1945–1948
145 Marion DW, Bouma GJ. The use of stable xenon-enhanced computed tomographic studies of cerebral blood flow to define changes in cerebral carbon dioxide vasoresponsivity caused by a severe head injury. Neurosurgery 1991; 29:869–873
146 Oertel M, Kelly DF, Lee JH, et al. Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury. J Neurosurg 2002; 97:1045–1053
147 Oertel M, Kelly DF, Lee JH, et al. Can hyperventilation improve cerebral microcirculation in patients with high ICP? Acta Neurochir Suppl 2002; 81:71–72
148 Miller DJ, Stanek A, Langfitt TW. Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. Prog Brain Res 1972; 31:411–432
149 Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981; 54:773–782
150 ter Minassian A, Melon E, Leguerinel C, et al. Changes in cerebral blood flow during $Paco_2$ variations in patients with severe closed head injury: comparison between the Fick and transcranial Doppler methods. J Neurosurg 1998; 88:996–1001
151 Thiagarajan A, Goverdhan PD, Chari P, et al. The effect of hyperventilation and hyperoxia on cerebral venous oxygen saturation in patients with traumatic brain injury. Anesth Analg 1998; 87:850–853
152 Newell DW, Weber JP, Watson R, et al. Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. Neurosurgery 1996; 39:35–43