Recognizing and Treating Ischemic Insults to the Brain: The Role of Brain Tissue Oxygen Monitoring

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Insults to the brain from trauma or subarachnoid hemorrhage (SAH) produce changes in structure, pressure dynamics, chemical balance, and blood flow. Ultimately, the delivery of oxygen to the cranial vault may become compromised. The devastating primary insult creates structural damage to neurons, vessels, and cranial nerves as well as compression of the brain and vasculature. The resulting edema and pathophysiologic processes further compromise the delivery of blood flow and oxygen to the brain. Patients who sustain severe traumatic brain injury (TBI) or SAH are vulnerable to secondary brain insults that can worsen their outcome [1–6]. Cerebral ischemia results from impaired autoregulation, systemic hypotension, hypoxia, hypocapnia, increased intracranial pressure (ICP), or vasospasm and leads to cerebral hypoxia [1–6]. Andrews [7] stated “it is believed that the final common pathway in all acute brain injury is the failure of oxygen delivery (ischemia).” Detecting low oxygen states in the brain is vital to reducing secondary brain damage. Emerging technology, such as brain tissue oxygen monitoring by way of probes placed in the brain parenchyma, allows for the regional measurement of dissolved cerebral oxygen, and reflects the balance between oxygen delivery and consumption [1,4,6]. Use of this technology in the ICU assists practitioners in making decisions on interventions to reduce secondary brain injury. This article describes the potential application of the partial pressure of brain tissue oxygen (PbtO2) monitoring technology in the care of patients who have sustained TBI or SAH. To accomplish this objective, a review of the intracranial dynamics that are created by primary and secondary brain injury and the challenges of optimizing oxygen delivery to the injured brain are presented. Furthermore, interventions that facilitate cerebral oxygen supply and reduce oxygen consumption are identified. Finally, application of this technology is highlighted by using case vignettes of patients who have experienced TBI or SAH.

The brain under assault: impact of traumatic brain injury and subarachnoid hemorrhage

Severe TBI and SAH are different mechanisms that produce similar pathophysiologic changes that can lead to neuronal injury and death. To understand how each impacts the brain, a brief overview of their pathophysiology is presented.

Traumatic brain injury: the dynamics of primary and secondary injury

In TBI, a mechanism produces a primary injury to the cranial vault. This primary injury occurs at the time of the event and the damage caused cannot be altered [2,8]. There is structural damage to the neurons and disruption in neurochemical processes [9]. Various types of injuries are produced, including shearing of the neurons and injury to the vessels of the brain [8]. These insults result in hemorrhages, brain tissue edema, and compression of the brain and its structures [8]. Because the brain and its contents, including blood and cerebrospinal fluid (CSF), normally occupy and share space inside the cranial
that lead to axonal swelling [9]. The edema can lead to cytoskeletal function, and axon transport mechanisms [8,9]. Cerebral edema is a direct result of damage to impaired autoregulation, and chemical derangements of cerebral blood flow (CBF) and metabolic rate, primary insult, and those that are caused by extracerebral events.

The processes that arise from the initial injury include development of cerebral edema, alteration of cerebral blood flow (CBF) and metabolic rate, impaired autoregulation, and chemical derangements [8,9]. Cerebral edema is a direct result of damage to neurons and the disruption of membrane stability, cytoskeletal function, and axon transport mechanisms that lead to axonal swelling [9]. The edema can lead to an increase in the tissue volume in the cranial vault. If significant, it can produce mass effect and increase ICP.

Following the primary injury, additional processes produce secondary insult to the brain [2]. This type of injury occurs at a cellular level and has many causes [2]. Chesnut [8] divided these two processes into those that arise from the traumatic event or changes to the brain and vasculature that occur following the primary insult, and those that are caused by extracerebral events.

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Following TBI, there is an alteration in CBF or cerebral metabolic rate of oxygen [10]. Martin and colleagues’ [11] study on CBF after TBI revealed three distinct patterns of flow. First, there is a state of hypoperfusion and a decrease in CBF in the first 24 hours after injury (day 0). Earlier studies confirm this finding [12,13]. The cause of the decrease in CBF may be an increase in distal microcirculatory resistance as well as intravascular clot formation [10,11]. After the first 24 hours, CBF increases. This occurs from days 1 through 5 and exceeds the cerebral metabolic demand for oxygen [11]. This phenomenon could lead to impairment in metabolic coupling that cause vascular engorgement, swelling, and increased ICP [14]. In the third phase, CBF is altered beginning somewhere on days 4 or 5 and continues through day 14. This phase is characterized by slow flow from vasospasm. Autoregulation is another important factor that alters CBF. Pressure autoregulation is the ability of the brain to maintain a constant CBF in the face of changing blood pressure (BP) or cerebral perfusion pressure (CPP) [15]. In patients who have sustained TBI, CPP is measured when an ICP monitor is placed. CPP is equal to the mean arterial pressure (MAP) minus the ICP. Optimal CPP levels differ in patients, probably as a result of whether pressure autoregulation is intact or impaired. The impairment of autoregulation can contribute to cerebral ischemia, and thus, reduced CBF and oxygen delivery [5,15].

Cerebral metabolism is altered severely by the loss or decrease in blood flow that shifts the metabolism of oxygen from aerobic to anaerobic [9]. It also is impacted by depressed cerebral activity, inflammatory response, mitochondrial dysfunction, and the uncoupling of autoregulation [2,9,10]. Finally, chemical derangements, including calcium-induced cellular damage, glutamate excitotoxicity, and free radical formation, lead to cell damage and death [9]. Research continues in an effort to understand these intense cellular and chemical derangements and to find drugs that might ameliorate the changes.

Extracerebral causes of secondary brain injury include hypoxia, hypotension, hypocapnia, impaired autoregulation, acidosis, and hyperglycemia [1,2,4,5,8,16,17]. Each factor produces a reduction in oxygen delivery or blood flow (hypoxia, hypotension, hypocapnia, or anemia) or an alteration in biochemical processes (acidosis and hyperglycemia). Appreciation of each of these factors is imperative for the reduction of secondary brain injury.

The two most commonly linked causes, hypoxia and hypotension, are seen in patients who have sustained TBI. This is especially true in the presence of multisystem trauma. In numerous studies hypoxia was identified as increasing the morbidity and mortality of patients who had a severe TBI [18–21]. Gracias and colleagues’ [16] pilot study used brain tissue oxygen measurements and reported that episodes of cerebral hypoxia—defined as a partial pressure of brain tissue oxygen (PbtO2) of less than 20 mm Hg—are associated with a significantly lower mean PaO2. Two recent studies that examined hypoxia and hypotension in severe TBI found that hypotension was associated significantly with worsening outcomes, whereas hypoxia did not impact mortality significantly [22,23]. Strong evidence in the literature demonstrates that one or more episodes of hypotension experienced in the prehospital or in-hospital setting correlated with increased morbidity and mortality [2,18,19,21–25].

Hypocapnia, a reduction of the PaCO2, causes vasoconstriction of cerebral blood vessels and leads to a reduction in CBF [26]. This reduction decreases oxygen delivery to the brain, as represented by decreases in Pbto2, and may produce cerebral ischemia [1,27–29].

Acidosis was identified as a secondary brain injury factor in Jeremitsky and colleagues’ [2] study. They found that a base deficit of greater than −4 correlated
with a longer stay in the ICU. Mulvey and colleagues [9] reported that an increase in lactate concentration and low tissue pH correlated with poor outcome in animal and human studies. Hyperglycemia—blood glucose levels greater than 200 mg/dL—correlated with an increase in worst neurologic outcomes [30–32]. Jeremitsky and colleagues [2] found that hyperglycemia was associated with increased mortality and longer hospital stays. The exact mechanism may be related to an increase in production of lactate, which creates neuronal injury [30].

Aneurysmal subarachnoid hemorrhage

Aneurysmal SAH carries a high mortality and morbidity because of devastating primary and secondary insults. The primary hemorrhage—from blood rapidly escaping a ruptured aneurysm into the subarachnoid space, brain parenchyma, or ventricles—creates compression of structures and increased ICP. Secondary insults can occur, including impaired autoregulation, hypotension, hypoxia, hydrocephalus, cardiac complications, hypovolemia, vasospasm, and increased metabolism from seizures and pyrexia [6,33,34]. Impaired autoregulation, hypotension, and hypoxia were alluded to in the previous section. Hydrocephalus—a build-up of CSF in the ventricles—causes increased ICP because of an increase in CSF volume. Cardiac complications and hypovolemia may impair the delivery of blood to the brain, which leads to inadequate delivery of oxygen. Vasospasm—arterial narrowing of the proximal intracranial vessels—may occur in 60% to 70% of all patients who have an aneurysmal SAH [3]. Thirty percent will suffer a delayed ischemic neurologic deficit from the reduction in CBF to the vascular territory [3]. Lastly, seizures and fever increase the use of oxygen by the brain and should be avoided to prevent further injury [33].

Significant factors contribute to secondary brain injury in severe TBI and SAH. Detecting these events requires intense vigilance by practitioners. Traditionally, hemodynamic and ICP monitors are used as a primary means to guide therapies to keep brain pressure within normal limits and to optimize CPP. These monitors are limited in their ability to detect changes in cerebral oxygenation or blood flow. New technologies are emerging in the ICU setting to monitor other variables. One of the technologies, brain tissue oxygen monitoring, has undergone intense study and is being used in many neuro-ICU centers in Europe and the United States. The advantages of monitoring brain oxygen tension continuously are that it brings practitioners closer to identifying ischemic episodes and ensures adequate oxygen delivery to the injured brain through various interventions.

Monitoring brain tissue oxygen

The measurement of PbtO₂ is accomplished by placing a small, oxygen-sensitive probe into the brain tissue. Measuring PbtO₂ in this manner reflects local or regional oxygen tension. Debate exists over whether to place the specific catheter on the injured side of the brain or in the contralateral side of the brain. Haitsma and Maas [35] suggested that placing the catheter near the injury reflects local brain oxygen levels, whereas placing it in the normal or undamaged brain reflects global cerebral oxygenation (Fig. 1). In patients who have an aneurysmal SAH, the catheter’s most desirable placement is in the arterial zone of probable vasospasm. The resulting measurements of PbtO₂ are reflective of the balance between the supply of oxygen and the demand for oxygen in the brain tissue [35].

Types of brain tissue oxygen monitors

Two brain oxygen monitoring systems are available commercially. The origin of both systems is a Clark-type electrode that measures oxygen tension polarographically in blood or tissue [35].

The Paratrend system (Diametrics Medical, High Wycombe, U.K.) originally was designed to be used in the intravascular measurement of oxygen, carbon dioxide, pH, and temperature [36]. Three sensors were placed over a 4-cm long probe that was 0.5 mm in diameter. The Paratrend system was altered in 1999 to incorporate fluorescent technology, but its measuring length was shortened to 2 cm [36]. The new catheter was called the Neurotrend (Codman, Raynam, Massachusetts). The oxygen-sensing section of the probe was reduced to 1.4 mm. Because of the limited area of oxygen sensing, there seemed to be more variability in the PbtO₂ measurements compared with the other systems with larger monitoring area [36].

The LICOX brain oxygen monitoring system (Integra Neurosciences, Plainsboro, New Jersey) uses the Clark electrode, which is 0.5 mm in diameter and has a 5-mm long oxygen-sensing area [35,37]. The original LICOX system has two separate small probes (0.8 mm in size) that are placed down separate channels into an introducer (Fig. 2A) [37]. The oxygen and temperature probes are passed approximately 25 to 35 mm into the white matter of the brain, usually in the frontal lobe (see Fig. 1).
The catheters measure oxygen and brain temperature separately. The oxygen measurement requires temperature to give accurate PbtO$_2$ levels. In the past year, the LICOX catheter has been altered; the oxygen and temperature sensors have been placed on one catheter (Fig. 2B). The PMO catheter has a sampling surface area of 18 mm$^2$ with an oxygen-sensing length of 7 mm [38]. The temperature sensing area is 4.5 mm in length. The PMO catheter has a slightly larger diameter (0.65 mm). The overall length of the catheter is 460 mm. This catheter can be placed through a bolt system or tunneled into the parenchyma, which is especially useful in infants and toddlers with thin skulls. Once in place, the catheter(s) requires a “settling in” period from 10 to 120 minutes because of potential local tissue trauma during placement [37].

The oxygen probe must be placed in “viable tissue,” not in contused or infarcted brain. The position of the catheter should be assessed by CT of the brain [35]. A catheter response test can be performed by increasing the fraction of inspired oxygen (FIO$_2$) to 100% for 2 minutes. Appropriately placed catheters respond with a significant increase in the PbtO$_2$ while the FIO$_2$ is increased [35].

Several studies have been undertaken to determine the safety and reliability of the oxygen probes/systems. Nine studies demonstrated no infectious complications [1,17,29,39–44]. A study by Dings and colleagues [43] reported two small intraparenchymal hematomas in 118 patients. Clinical experience at Mission Hospital, with 200 catheters placed in the last 4 years, produced no infections and two small hematomas around the catheter site.

*Measured values of partial pressure of brain tissue oxygen*

After the catheters are placed and verified to be in correct position, the measurements (in mm Hg) will be displayed. Because of the different oxygen-sensing areas on the two different systems, studies found different ranges of normal and abnormal [35,36]. In an attempt to test the two different probes in a zero-oxygen solution, Valadka and colleagues [45] found that the Paratrend probes gave an average reading of 7.0 mm Hg compared with 0.3 mm Hg for the LICOX probes. The investigators stated the Paratrend “overestimated P$_{O_2}$ when values were near zero.” The Paratrend/Neurotrend catheter has been examined in a limited number of human studies. Nemani and Manley [36] cited ethical constraints as limiting the pursuit of validating “normal brain oxygen levels” in noninjured humans. One study of patients who underwent neurosurgery revealed a normal average of 37 mm Hg in patients with intact circulation in noncompromised brain and an average of 10 mm Hg in regions with compromised circulation [46]. Zauner and colleagues [47] studied patients who had sustained head injuries. The average PbtO$_2$ was 39 mm Hg in patients who had a good outcome, whereas patients whose levels were less than 31 mm Hg sustained moderate to severe dis-
ability. Patients who died or were in a persistent vegetative state had an average value of 19 mm Hg [47]. Doppenberg and colleagues [48] studied 25 patients who had a severe TBI; 4 patients with PbtO$_2$ values of less than 18 mm Hg died.

Using the LICOX system, Maas and colleagues [49] found PbtO$_2$ levels of 25 to 30 mm Hg in uninjured white matter of frontal lobes. Sarrafzadeh and colleagues [44] determined that uninjured areas of brain tissue had PbtO$_2$ values of 20 to 35 mm Hg. Meixensberger and colleagues [50] placed surface probes in normal brain of patients who underwent craniotomy, and reported a mean PbtO$_2$ of 47.9 mm Hg. Because of the lack of studies in normal brains, it has been difficult to identify true normal values.

Hlatky and colleagues [51] estimated normal values of PbtO$_2$ to be between 20 and 40 mm Hg. This range gave a target PbtO$_2$ with the understanding that true “normals” have not been validated and that various intracranial pathologies may cause different CBF and oxygen states.

Several studies have provided insight into “critical” or abnormal levels of PbtO$_2$ using the LICOX monitor. van den Brink and colleagues [17] studied 101 comatose patients who had TBIs and found that the duration of time and depth of local tissue hypoxia correlated with outcomes at 6 months. The survivors had significantly higher PbtO$_2$ levels during the monitoring period than did the patients who died. Lower PbtO$_2$ levels were related to a greater risk for reducing ischemic insults to the brain.
death [17]. The investigators found that a PbtO₂ of less than 15 mm Hg for longer than 30 minutes or less than 10 mm Hg for 10 minutes correlated with a statistically significant risk for death. In one study of 39 patients, the investigators found that a PbtO₂ of less than 15 mm Hg correlated with a greater chance of death. A value of less than 6 mm Hg at any time was associated with a greater risk for dying [45]. In a study 35 patients who had TBI, Bardt and colleagues [52] found that episodes of a PbtO₂ of less than 10 mm Hg for more than 30 minutes correlated with a poor neurologic outcome; this occurred in 23 of the patients. At 6 months 55.6% had died, 22.2% were severely disabled or in a persistent vegetative state, and 22.2% had a favorable outcome. van Santbrink and colleagues [41] studied 22 patients who had TBI, and reported that 4 of 5 patients with a PbtO₂ of less than 5 mm Hg died. The only survivor had a cerebral contusion in the location of the probe, which may have confounded the accuracy of the readings. Palmer and Bader [53] reported that 11 of 72 patients who had varying neurologic diagnoses and LICOX catheters in place experienced brain death. All 11 patients had their PbtO₂ decrease to 0 mm Hg, whereas none of the remaining patients 61 had PbtO₂ levels of 0 mm Hg.

It is apparent that the type of oxygen system that is used to measure PbtO₂ impacts the range of normal and abnormal levels. Although more research is needed to validate “normal” PbtO₂ levels, most practitioners recognize that lower levels of PbtO₂ tend to correlate with poorer neurologic outcomes. It is prudent to consider the PbtO₂ value in relation to pulmonary/cerebrovascular physiology, as well as pulmonary, hemodynamic, and cerebral variables. Practitioners must be knowledgeable in both of these areas.

**Pulmonary/cerebrovascular physiology**

Fundamental to understanding the use of PbtO₂ monitoring is the team’s ability to relate concepts of systemic oxygenation to oxygen delivery to the brain. The functions of the lungs are to ventilate the alveoli, diffuse gases into and out of blood, and bring blood flow to the lungs to transport blood rich in oxygen (O₂) and low in carbon dioxide (CO₂) to the body [54]. O₂ is transported in the blood bound to hemoglobin (SaO₂) or dissolved in the plasma of arterial blood (PaO₂). Approximately 20 mL of O₂ is carried per 100 mL of blood; most O₂ is carried by hemoglobin but a small amount is dissolved in plasma. Less hemoglobin in the blood results in a lower oxygen-carrying capacity. O₂ quickly binds to hemoglobin as it crosses from the lungs to the vasculature. It stays bound until it is released at the tissue level. The oxyhemoglobin curve is an S-shaped curve, which illustrates the concepts of the relationship between PO₂ and SaO₂. Varying clinical situations impact the affinity of O₂ to stay bound to hemoglobin versus oxygen’s ability to dissociate from hemoglobin at the tissue level. A right shift correlates with hemoglobin giving up its bound O₂ to the tissues. Acidosis, high CO₂, increased temperature, and high levels of 2-3 diphosphoglycerate (DPG) tend to increase the dissociation of O₂ from hemoglobin [54]. A shift to the left correlates with the affinity for O₂ to stay bound to hemoglobin instead of unloading at the tissue level. Alkalosis, hypocapnia, decreased temperature, and low levels of 2-3 DPG tend to decrease the release of O₂ to the tissues [54]. The delivery of O₂ to the tissues of the brain is dependent on the vasculature.

The cerebrovasculature must deliver the O₂ and other nutrients to the brain on a continuous basis. Approximately 15% of the cardiac output is directed to the brain [36]. Generally, when practitioners describe oxygen delivery to the body, the cardiac output is used as a major factor in calculating the delivery. When describing oxygen delivery to the brain, CBF must be factored into the equation. CBF is the CPP divided by the cerebrovascular resistance. CBF is influenced by influx/efflux pressure, vascular radius, and blood viscosity [56]. CPP, pressure autoregulation, flow–metabolism coupling, and metabolic chemicals impact CBF [56]. CPP and pressure autoregulation were alluded to in a previous section. Flow–metabolism coupling reflects the concept that CBF changes to meet the demand for oxygen or metabolism. Therefore, as cerebral metabolism increases, CBF increases. Conversely, as cerebral metabolism decreases, CBF decreases [56]. The metabolic impact on CBF is related to changes in PaO₂, PaCO₂, and acid–base balance. Vasoconstriction occurs at hyperbaric levels of PaO₂ and decreased levels of PaCO₂ [56]. Johnston and colleagues [57] noted that the ability of the cerebral vessels to constrict to high PaO₂ probably is limited. CBF is more responsive to changes in PaCO₂ than PaO₂ [57]. For every 1 mm Hg decrease in PaCO₂, there is a 2% to 3% reduction in CBF between PaCO₂ levels of 20 and 80 mm Hg. The reverse principle holds true for increases in PaCO₂ [56]. When PaO₂ is less than 60 mm Hg, the cerebral vessels vasodilate [57]. PaO₂ levels of 25 mm Hg double the CBF [57]. The pH of the blood impacts CBF; acidosis causes vasodilation and alkalosis causes vasoconstriction [56]. All of these
factors play an integral part in the delivery of oxygenated blood to the brain. After blood is delivered, oxygen normally is consumed in higher amounts than in other living tissues.

The brain consumes 30% to 40% of the oxygen that is delivered [55]. The consumption of O$_2$ is increased in the presence of severe TBI and with the release of neuroexcitatory chemicals from damaged neurons. It also occurs in hyperthermia and seizures [56].

Adequate oxygenation of the brain is a balance between oxygen supply, oxygen delivery, and oxygen consumption. Measuring oxygen directly in the brain tissue brings practitioners closer to assessing oxygen content and delivery [17]. In addition, it reflects a parameter that is capable of evaluating pulmonary, hemodynamic, and cerebral variables to detect events that lead to oxygen deficits and cerebral ischemia.

**Impact of pulmonary, hemodynamic, and cerebral variables on partial pressure of brain tissue oxygen**

Research has examined the impact of pulmonary, hemodynamic, and cerebral variables on PbtO$_2$ responses. Interventions that are directed at manipulating these variables, and their impact on PbtO$_2$, have been reported in the literature. Translating the outcomes of the research findings and applying them to a patient requires an understanding of the underlying physiology and a coordinated team effort. Specific interventions to increase PbtO$_2$ may impact other systems. The team must be practicing “on the same page” as it strives to maintain adequate cerebral oxygenation while diminishing potential harm to other areas.

**Pulmonary variables, events, and interventions**

Titrating FiO$_2$ and PaCO$_2$ have been investigated in several studies that explored the impact on PbtO$_2$. van Santbrink and colleagues' [41] study of 22 patients who had sustained TBI found that patients who were preoxygenated with 100% FiO$_2$ (hyperoxia) before suctioning had increases in their PbtO$_2$. Decreasing PaCO$_2$ (hyperventilation) decreased PbtO$_2$ [41]. van den Brink and colleagues [29] studied 82 patients who had TBI and noted changes in PbtO$_2$ with various interventions. In a subgroup of 7 patients, the lack of preoxygenation with 100% FiO$_2$ before suctioning led to decreases in PbtO$_2$. In 142 suctioning episodes in which FiO$_2$ was increased to 100% 5 minutes before suction, the PbtO$_2$ increased. Gopinath and colleagues [58] investigated two types of oxygen monitoring systems and the impact episodes of hyperoxia and hyperventilation. The PbtO$_2$ was impacted greatly with increases in PbtO$_2$ during hyperoxia, whereas hyperventilation caused decreases in PbtO$_2$. Menzel and colleagues [59] increased the FiO$_2$ to 100% for 6 hours, and discovered that the PbtO$_2$ increased and improved O$_2$ supply to the brain. Tolias and colleagues [60] studied 52 patients who had TBI and were given 100% FiO$_2$ for the first 24 hours after admission, and compared them with a control group in whom FiO$_2$ was not increased to 100%. They noted that the hyperoxia treatment increased the PbtO$_2$ levels by an average of 36 mm Hg during the 100% FiO$_2$. In addition to studying PbtO$_2$, they measured brain chemicals. In the microdialysis brain fluid, the group that received treatment had reduced glutamate, lactate, lactate/glucose ratios, and lactate/pyruvate ratios that were indicative of improved brain oxidation metabolism. When compared with the control group, the hyperoxia-treated group had significant reductions in ICP during and after the treatment. Reinert and colleagues’ [61] study of 20 patients found similar results, with PbtO$_2$ increasing after hyperoxia. Likewise, the brain microdialysis lactate had decreased. Another study of 8 patients who had TBI revealed similar findings between FiO$_2$, PbtO$_2$, and lactate, except that the other microdialysis substrates did not change [62]. Studies that explored the impact of hyperventilation on PbtO$_2$ found decreases in PbtO$_2$ with corresponding decreases in PaCO$_2$ [1,27,28,63,64].

Critical neurosurgical patients unable to protect their airway because of a decrease in their level of consciousness are intubated with an endotracheal tube and maintained on a ventilator. Support of the airway usually is accomplished by monitoring PaO$_2$ and PaCO$_2$ as well as ventilatory parameters. Many investigators maintain that a PaO$_2$ of 100 mm Hg is adequate, but one must consider that it may or may not ensure adequate PbtO$_2$. The dangers of hypoxia and hypocapnia were alluded to in previous sections on major causes of secondary brain injury. Hyperventilation, once the mainstay of treatment for TBI, has been shown to worsen neurologic outcomes. Studies cited above confirm the impact of decreasing PaCO$_2$ on PbtO$_2$. In patients who have an aneurysmal SAH and who are at risk for cerebral vasoconstriction from vasospasm, decreasing PaCO$_2$ to less than 35 mm Hg may be harmful. Caution must be exercised when titrating PaCO$_2$ in the patient who has a brain injury.

Determining the optimal PaO$_2$ and PaCO$_2$ is accomplished by observing the PbtO$_2$ response and
should be balanced with the condition of the lungs. Continuous monitoring of CO₂ by way of end-tidal capnography is helpful to detect changes that may be harmful to the brain.

Often, patients who have a severe TBI or SAH experience pneumonia as a consequence of their injury and ventilatory management. Some may progress to acute respiratory distress syndrome (ARDS). One study examined using prone positioning in patients who had SAH and ARDS. They found that PaO₂ and PbtO₂ increased significantly when patients were turned from supine to prone. Although the researchers found that the CPP decreased, mainly from an increase in ICP during the proning, the PbtO₂ improved despite these changes [65].

The oxygen-carrying capacity of hemoglobin and its influence on PbtO₂ were studied by Smith and colleagues [66]. In 35 patients who required packed red blood cell transfusions, the PbtO₂ increased after the transfusion in 26 patients (CPP and ICP were unchanged before, during, and after the transfusions), and decreased in 9 patients. The age of the transfused blood was 19 ± 10 days and 24 ± 10 days, respectively.

Applying the concepts that are related to pulmonary variables in patients who have TBI or SAH takes communication between disciplines and critical thinking. The following vignettes present the impact that the pulmonary system has on PbtO₂.

Vignette 1: traumatic brain injury

TH, an 18-year-old man, sustained a head injury, pulmonary contusions, bilateral pneumothoraces, lacerated liver, and ruptured spleen in a high-speed rollover car accident. After initial resuscitation in the Emergency Department (ED), an ICP monitor, LICOX monitor, and three chest tubes were placed in the operating room. He also underwent an exploratory laparotomy for repair of his liver and spleen. Because surgeons were unable to close his abdomen, prolene mesh was applied and covered with a black sponge that was cut to fit the wound. A wound Vac was placed and suction was applied. Orders were given to titrate the PaCO₂ and FIO₂ to keep the ICP at less than 20 mm Hg and the PbtO₂ at greater than 20 mm Hg. On day 3, the PbtO₂ decreased suddenly from 21 mm Hg to 12 mm Hg. At the time the ICP was 14 mm Hg and the CPP was 72 mm Hg. An immediate arterial blood gas level was obtained on a FiO₂ of 50%, which revealed an acute decrease in his PaO₂. The PaO₂ had decreased from 180 mm Hg to 71 mm Hg. The PaCO₂ went from 35 mm Hg to 44 mm Hg. The respiratory care practitioner increased the FiO₂ to 100%. Despite increasing the FiO₂, the PbtO₂ hovered around 14 mm Hg. The intensivist performed an emergent bronchoscopy, which showed multiple mucous plugs in the right lung. After the bronchoscopy, the PbtO₂ increased to 38 mm Hg. The FiO₂ was weaned down from 100% to 50% over the next hour. The FiO₂ was reduced to 50% and the PbtO₂ stabilized at 25 mm Hg.

Vignette 2: aneurysm

CA, a 40-year-old man, ruptured a giant cerebral aneurysm on his left anterior cerebral artery. His history included hypertension and a two pack per day smoking habit. He was in a coma and extensor posturing on arrival to the ED. After intubation and lines were placed, CA underwent an emergent cerebral angiogram. Three meters of coils were threaded into the giant aneurysm to occlude it. After the coiling procedure, an ICP, LICOX, and pulmonary artery catheter were placed. CA was admitted to the Neurology ICU. On day 4 when the day shift began, CA’s PbtO₂ was 45 mm Hg, his ICP was 19 mm Hg, his systolic BP was 140 mm Hg, and his O₂ saturation was 100%. He was on 45% FiO₂ with a PaO₂ of 120 mm Hg and a PaCO₂ of 35 mm Hg. Five hours into the shift he developed pulmonary issues. CA’s PbtO₂ decreased to 15 mm Hg and his ICP hovered in the low twenties. His FiO₂ was increased to 100% with little change to the PbtO₂. After checking the chest radiograph, the intensivist performed a bronchoscopy, which revealed a large mucous plug. Believing that the patient would do better on a different ventilator mode, changes were made to the ventilator settings. The positive end-expiratory pressure (PEEP) was increased from 8 mm Hg to 12 mm Hg, the tidal volumes were decreased from 750 mL to 450 mL, and the rate was increased from 14 to 22 breaths per minute. This change improved his PaO₂ to 320 mm Hg, but increased the PaCO₂ from 35 mm Hg to 44 mm Hg. The impact to the cranial vault was dramatic. CA’s ICP increased to 56 mm Hg and his PbtO₂ decreased to 3 mm Hg. After an emergent scan of his brain revealed no intracranial changes, a discussion was held among the team. The different ventilator strategy had increased his PaO₂ but had produced astounding changes to his ICP and PbtO₂. A decision was made to reprogram the ventilator by decreasing the PEEP and rate while increasing the tidal volumes back to 750 mL. The team watched the end tidal CO₂ decrease by 9 mm Hg. Within 1 minute, the ICP decreased to 15 mm Hg and the PbtO₂ decreased to 48 mm Hg. The FiO₂ was weaned back to 50% and CA’s PbtO₂ settled at 35 mm Hg.
In both cases, the lungs and ventilator parameters had an astounding impact on the PbTO₂. The PbTO₂ changed before any other parameters.

**Hemodynamic variables, events, and interventions**

Maintaining an adequate CPP promotes delivery of blood to the brain. When CPP is inadequate, ICP increases and PbTO₂ may decrease. It is believed that when autoregulation is intact, CBF does not change between CPPs of 60 mm Hg to 140 mm Hg [67]. When CPP decreases to less than a threshold of approximately 60 mm Hg, there is a potential for a decrease in CBF and the development of cerebral ischemia. When autoregulation is impaired, the brain becomes dependent on the MAP/CPP for adequate blood flow and oxygen delivery. As ICP increases, the CPP may decrease unless the MAP is increased. Vespa’s [67] review of several studies—in the search for an optimal CPP threshold in patients who have TBI—found that no correct or optimal CPP threshold can be applied to all patients. He concluded that different areas of the brain may require different CPP levels, and that the CPP threshold may change from day to day. The selection of an adequate CPP must be individualized to each patient. Incorporating other cerebral measures, such as ICP, PbTO₂, jugular venous oximetry, and microdialysis, might assist practitioners in determining the optimal CPP threshold for the patient.

Three early studies on optimal CPP thresholds found that when CPP was less than 60 mm Hg, PbTO₂ decreased [29,39,63]. One of the studies noted that when changing intravenous tubing of vasopressors, the CPP decreased significantly and led to dramatic decreases in the PbTO₂ of 4 patients [29]. Reinert and colleagues’ [61] study on the effects of increasing CPP on PbTO₂ noted that PbTO₂ increased as CPP was increased, up to a CPP level of 78 mm Hg. After that point, further elevations of CPP did not increase the PbTO₂. Meixensberger and colleagues’ [4] study on PbTO₂-guided therapy in patients who had TBI compared two groups of patients. Forty patients were cared for by managing the ICP/CPP only, whereas 53 patients were managed using ICP-, CPP-, and PbTO₂-targeted parameters. The investigators noted that there were several episodes of low PbTO₂ when CPP was decreased. Increasing the CPP resulted in increases in the PbTO₂. There was not a statistical difference in the outcome between the two groups at 6 months, although there was a positive trend in the latter group. Stocchetti and colleagues [68] cautioned that despite normal CPP values in their study of 9 patients, there were episodes of low PbTO₂ values. They found that increasing the CPP to higher levels than normal increased the PbTO₂ [68]. In a study on patients who had aneurysms, investigators found a correlation between MAP and PbTO₂. When MAP was decreased to less than 80 mm Hg there was a progressive decrease in the PbTO₂ levels [6]. Johnston and colleagues [69] pointed out that below the autoregulatory threshold of optimal CPP, the PbTO₂ was dependent on CPP. Increased PbTO₂ resulted from increases in CPP. Determining the correct CPP threshold for patients who had TBI or SAH was studied by Soehle and colleagues [5]. They found that increasing CPP did not increase PbTO₂ when autoregulation was intact. When autoregulation was impaired, increasing CPP caused the PbTO₂ to increase. The researchers also described a phenomenon whereby increasing CPP caused the PbTO₂ to decrease in a patient who had intact autoregulation. They called this an inverse PbTO₂-autoregulation state.

Enhancing the CPP to just above the threshold was shown to be beneficial in patients, recognizing that thresholds will differ between patients. When autoregulation is intact, increasing CPP to greater than 60 mm Hg may not be necessary. If autoregulation is impaired, the optimal CPP threshold needs to be determined based on PbTO₂ and ICP response. To enhance CPP, intravenous fluids are used to ensure euvoelma. Vasopressors are used if further enhancement of CPP is needed once volume loaded.

Vasospasm in patients who have SAH results in vasoconstriction of blood vessels and a decrease in oxygen delivery. One study assessed whether PbTO₂ decreased when vasospasm occurred. There were transient decreases in PbTO₂ with vasospasm in 7 patients who had SAH but the levels never decreased to less than 20 mm Hg [70]. A case study reported a decrease in the PbTO₂ to 2 mm Hg with corresponding angiographic confirmation of 80% stenosis of the left internal carotid artery (ICA). After angioplasty, the PbTO₂ increased from 1.5 mm Hg to 40 mm Hg [71]. Patients who have aneurysmal SAH receive nimodipine to mediate vasospasm. The impact of nimodipine administration on PbTO₂ was studied in 11 patients with SAH. The investigators found that the PbTO₂ decreased significantly in 7 of 11 patients, and it persisted for up to 2 hours [72].

Vasospasm has the potential to impact oxygen delivery to the brain. Optimal management includes volume loading and MAP enhancement with vasopressors Observing for a potential decline in the PbTO₂ may help to identify episodes of ischemia in these patients.
Vignette 3: aneurysm revisited
CA, described in vignette 2, had a precipitous decline in his PbtO₂ on day 10 after his SAH. His PbtO₂ decreased from 24 mm Hg to 16 mm Hg. A transcranial doppler exam was obtained which demonstrated an increase in velocities in the right anterior cerebral artery (ACA) distribution. CA was taken to the angiogram suite where an angiogram confirmed severe vasospasm. As the interventionalist threaded the catheter into the right ICA, the artery clamped down and caused the PbtO₂ to decrease to 1.5 mm Hg. Immediate injection of intra-arterial verapamil caused vasodilatation of the right ICA and ACA distribution. The PbtO₂ increased to 30 mm Hg after the treatment.

Vignette 4: traumatic brain injury
PM, a 21-year-old man, sustained a severe TBI. After placement of an ICP, LICOX, and other hemodynamic lines, PM was admitted to the Neuro-Trauma ICU. After stabilization, PM’s CPP decreased suddenly from 74 mm Hg to 60 mm Hg with an increase in his ICP from 21 mm Hg to 28 mm Hg. The PbtO₂ decreased from 26.5 mm Hg to 15.8 mm Hg. After increasing the MAP with 500 mL of albumin and drainage of CSF, the CPP increased, the ICP decreased, and the PbtO₂ returned to normal (Fig. 3). Optimal CPP in this patient was determined to be approximately 75 mm Hg.

In both cases, hemodynamic variables were used to optimize PbtO₂. Treating the underlying cause is imperative in determining the optimal CPP.

Cerebral variables, events, and interventions
Normal ICP is 0 to 15 mm Hg. An ICP of greater than 20 mm Hg is considered to be elevated and requires treatment. Increases in ICP reduce blood delivery to the brain. Studies that explored the impact of refractory increased ICP on PbtO₂ showed a decrease in the PbtO₂ when ICP was elevated significantly [52,53,63,73–75]. Strategies to reduce increased ICP include CSF drainage; head of bed elevation; neck position midline; hyperventilation; optimizing CPP; and administering medications, such as Mannitol, hypertonic saline, sedatives, analgesics, neuromuscular blockade, or pentobarbitral [76]. Critical care teams should have an organized plan to reduce ICP. The influence of pentobarbital coma was reported in a case series of three patients; PbtO₂ was increased significantly after the induction of pentobarbital coma [73]. Two papers reported decreases in ICP and increases in PbtO₂ after decompressive craniectomy procedures [74,75].

Interventions to decrease an elevated ICP may help to improve the PbtO₂. In vignette 2, the consequence of a change in ventilator settings on ICP and PbtO₂ illustrated the complexity of the patient’s management. Another example of the ICP–PbtO₂ relationship is presented in the next vignette.

Vignette 5: traumatic brain injury
AB, a 37-year-old man, sustained a severe TBI in a motorcycle accident. Cardiopulmonary resuscitation was started just as the ambulance arrived at the hospital and continued for 4 minutes. Restoration of pulses occurred. The patient was intubated and resuscitated in the ED. He went to the operating room where a large subdural hematoma was evacuated and a torn left ICA was ligated. AB was admitted to the ICU after placement of an ICP, LICOX, and other hemodynamic monitoring lines. He sustained intense periods of increased ICP that correlated with low

Fig. 3. CPP, ICP and PbtO₂ response.
PbtO_2 values. On day 3, AB’s ICP increased to 85 mm Hg and exceeded his MAP. All medical and surgical interventions were used in an attempt to control the ICP. Pentobarbital coma and bilateral craniectomies were performed in an attempt to reduce the ICP. Because all interventions were exhausted, his PbtO_2, which had been declining with the elevated ICP, hit 0 mm Hg (Fig. 4). A bedside nuclear blood flow study was done and confirmed no CBF. The patient was pronounced brain dead. In this case, the patient was refractory to all medical and surgical interventions that were used to reduce the increased ICP. The eventual increase of the ICP, which exceeded the MAP, led to the absence of CBF and neuronal cell death.

Vignette 6: traumatic brain injury

RH, a 39-year-old man, sustained a severe TBI in an automobile accident. He was intubated in the ED and had his intravenous lines, Foley catheter, and
oral gastric tube placed. A scan of the brain showed a large subdural hematoma, intracerebral contusions, a left to right shift of the brain, and cerebral edema. RH underwent surgery for removal of a left subdural hematoma. In the operating room the surgeons placed an ICP, LICOX, and hemodynamic lines. He was admitted to the ICU for care. On the night of day 2, RH’s ICP had become difficult to control, despite CSF drainage, CO₂ titrated to 33 mm Hg, CPP optimized at 80 mm Hg, Mannitol bolus given twice over 2 hours, sedation, and analgesia. His ICP hovered in the middle to high twenties. The neurosurgeon elected to take RH for a decompressive craniectomy. As the neurosurgeon was scrubbing, the operating room nurse turned the patient’s neck 90° lateral to shave and prepare the scalp. Immediately, the ICP increased to 42 mm Hg, MAP/CPP decreased, and PbtO₂ decreased to 9 mm Hg (Fig. 5). The anesthesiologist and ICU nurses tried CSF drainage, increasing the vasopressor, and increasing the propofol to no avail. The neurosurgical clinical nurse specialist came into the room, noted the patient’s position, and instructed the operating room nurse to turn the neck back to the neutral position. Upon the neck’s return to the correct position, the ICP decreased to 25 mm Hg and the PbtO₂ increased to 27 mm Hg. The surgery was performed, and the decompressive craniectomy was effective in reducing the ICP to less than 20 mm Hg while the PbtO₂ maintained in the normal range.

In most clinical situations, interventions to reduce or control elevated ICP are effective. Monitoring the PbtO₂ adds another dimension to consider when planning interventions to control ICP.

Summary

The goal of the critical care team is to detect ischemic insults and to intervene with the most appropriate actions to restore the delivery of oxygen to the brain. The application of brain tissue oxygen monitoring technology gives practitioners another piece of information with which to make decisions when managing patients who have TBI or SAH. Properly placed brain tissue oxygen probes provide continuous data on regional oxygenation. Detecting decreases in the PbtO₂ and identifying the primary cause of the decline provide direction for the critical care team. Altering pulmonary, hemodynamic, and cerebral variables may enhance the delivery of oxygenated blood to the brain, and thus, ameliorate ischemic events.

References


