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Beyond Anesthesia Toxicity: Anesthetic Considerations to Lessen the Risk of Neonatal Neurological Injury

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Abstract

Infants who undergo surgical procedures in the first few months of life are at a higher risk of death or subsequent neurodevelopmental abnormalities. Although the pathogenesis of these outcomes is multifactorial, an understanding of the nature and pathogenesis of brain injury in these infants may assist the anesthesiologist in consideration of their day-to-day practice to minimize such risks. This review will summarize the main types of brain injury in preterm and term infants and their key pathways. In addition, the review will address key potential pathogenic pathways that may be modifiable including intraoperative hypotension, hypocapnia, hyperoxia or hypoxia, hypoglycemia, and hyperthermia. Each of these conditions may increase the risk of perioperative neurological injury, but their long-term ramifications are unclear.

Considerable information has been published about the neurotoxicity of common anesthetic agents to the neonatal brain, including studies in nonhuman primates. Repeated anesthetic exposures and longer durations of anesthesia may exacerbate the risks of neurological injury.[1] While preclinical studies show an association between brain injury markers after neonatal anesthesia, including neuroapoptosis and altered synaptogenesis, the translation of these

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findings to clinically significant neurodevelopmental impairments in humans has proven elusive.[2–4] However, other perioperative clinical factors may affect the risk of neonatal neurological injury.[5,6]

To explore the risk of perioperative harm further, it is necessary to understand the major types of brain injury in the preterm and term-born infant highlighting the nature of the regional vulnerability of the brain. It is also important to consider the key pathways related to neonatal brain injury and how anesthetic care can influence these pathways. Although postnatal physiological changes and injuries occur along a continuum, it is helpful to divide neonates into 3 groups because of differing anesthetic concerns. Infants born before 37 weeks postmenstrual age are premature or preterm; born between 37 and 42 postmenstrual weeks are term; and infants who have reached >37 weeks postmenstrual age but were born preterm are considered ex-premature or ex-preterm. Premature infants can be further classified as very preterm if they were born before 32 weeks postmenstrual age. These infants are sometimes classified by their birth weight: infants ≤1500 g are considered very low birth weight (VLBW) and infants ≤1000 g are considered extremely low birth weight (ELBW).

BRAIN INJURY IN THE PRETERM AND TERM INFANT

Preterm Infant Brain Injury

Neurological injury in the preterm includes germinal matrix–intraventricular hemorrhage (IVH), hemorrhagic parenchymal infarction, periventricular leukomalacia (PVL), and post–hemorrhagic ventricular dilation.

IVH and its most severe form, parenchymal hemorrhagic infarction, are directly correlated with birth weight and gestation. Cranial ultrasound is readily available and reliable, and its use has shown some decrease in the incidence of IVH over the past 3 decades.[7] The pathogenesis of IVH appears related to cerebral ischemia–reperfusion as shown in Figure 1. PVL is the term that has historically been used to describe cerebral white matter injury (WMI). The incidence of ultrasound-detected PVL among very preterm infants by literature report is approximately 10%, but ultrasound imaging is unreliable.[11,12] Magnetic resonance imaging (MRI) technology has revealed that the majority of very preterm infants will develop some degree of WMI, both cystic and diffuse.[13,14] Cystic PVL occurs deep within the brain white matter of the cerebrum with localized areas of brain necrosis leading to cyst formation and eventually white matter scar tissue. Diffuse PVL is a less severe and more widespread injury that is thought to be more specific to oligodendroglial precursor cells. The pathogenesis of PVL can be simplified to several major interacting factors:

- Cerebral vascular, anatomical, and physiological factors
- Oligodendroglial precursor cell maturation–dependent vulnerability
- The inflammatory response and oxidative stress
- Infection

The arterial vascular supply to the brain consists of short and deep penetrating arteries. Focal PVL takes place in the end zones of the deep penetrating arteries that are incompletely developed in the preterm brain (Figure 2). Diffuse PVL occurs where the border zones of the deep penetrating arteries and end zones of the short penetrating arteries overlap.

In addition to these anatomical factors, cerebral blood flow (CBF) regulation in the preterm neonate increases the risk of neurological injury. Positron emission tomography studies show very low CBF in the white matter (<5 mL/100 g/min) of preterms compared to 50 mL/100 g/min in the adult brain.[16,17] Thus, premature infants have a narrower safety margin for CBF than do adults and children. This safety margin is further decreased by the fact that many preterm infants have dysfunctional cerebrovascular autoregulation and a potentially narrower blood pressure range of cerebral pressure autoregulation than adults and children. Using near-infrared spectroscopy (NIRS), Tsuji et al[18] established that preterm infants with a pressure passive circulation had a 4-fold increased risk of PVL or severe IVH. The cerebral artery and arteriole muscularis layers that are required for autoregulatory vasoreactivity probably develop during the third trimester.[8] Transcranial Doppler measurements of CBF velocity in premature neonates indicate that CBF-pressure reactivity to systolic and mean arterial blood pressure develops between the 23rd and 33rd gestational weeks, whereas blood flow during diastole remains pressure-passive until 33 weeks gestation. Infants born earlier than 26 weeks gestation may have largely pressure-passive CBF that renders them vulnerable to neurological injury with low and high blood pressure.[19]

We must note that there is a difference between CBF velocity measured by transcranial Doppler and actual CBF. Because vessel diameter is not measured by transcranial Doppler, the CBF cannot be technically calculated. However, transcranial Doppler velocity is generally considered to be an acceptable bedside measure to estimate CBF.[20] We further discuss the relationship between flow and velocity below in the Blood Pressure and Cerebral Autoregulation section.

The concept of “maturation-dependent vulnerability” of oligodendrocyte (OL) precursor cells is now central to our understanding of the pathophysiology of PVL.[21] Volpe[21] demonstrated that OL is “susceptible to injury” by oxygen-free radicals produced during ischemia and reperfusion. When OL cell death occurs, the mode of OL cell death includes both necrotic and apoptotic pathways. They demonstrated that immature OL cells were vulnerable, but mature OL cells were resistant to oxidative damage by using a cysteine deprivation model. Cysteine is used by cells to manufacture the antioxidant glutathione. Immature cells are deficient in the antioxidant enzymes glutathione peroxidase and catalase, which allows hydrogen peroxide to accumulate within the cells. With iron as a catalyst, the Fenton reaction creates the hydroxyl radical and cell death. The iron-chelating agent desferrioxamine is protective. Inder et al[22] demonstrated that infants with MRI-documented WMI had elevated levels of free radical products in the cerebrospinal fluid (CSF) compared to infants without WMI. Altogether, these findings suggest that hyperoxia could promote oxidative stress and WMI in preterm neonates. Based on this evidence, anesthesiologists should consider avoiding hyperoxia in the perioperative period given the risk of very low CBF (with potential tissue ischemia) and dysfunctional autoregulation (with potential hypoperfusion and hyperperfusion from pressure-passive CBF) in premature neonates.

Inflammation, and in particular, the systemic inflammatory response to fetomaternal and neonatal sepsis, is another critical component in the pathogenesis of PVL. Inflammation is the body's response to damaging occurrences such as infection, ischemia, or trauma (including surgery). Necrotizing enterocolitis (NEC) is one of the most common neonatal emergencies that the pediatric anesthesiologist will encounter, and the inflammatory response is a critical mediator of neurological injury. The inflammatory response can spiral out of control and develop into the systemic inflammatory response syndrome (SIRS). The results of long-term neurodevelopmental outcome studies of infants who developed NEC are conflicting. A comprehensive meta-analysis on this topic included 7843 VLBW infants in the analysis, 821 of whom had NEC.[23] Overall, 45% of infants with NEC had neurodevelopmental impairment at follow-up compared to 35% of those who did not have NEC (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.25–1.99). These data support the theory that the inflammatory response with NEC is harmful to the immature brain. However, the burden of adverse outcome was greatest among those infants who had either the most severe form of the disease (evidence of peritonitis or bowel perforation) or who underwent surgery. When medically treated infants with NEC were compared to infants without NEC, the differences in neurodevelopmental outcome were not significant (OR, 1.02; 95% CI, 0.73–1.44). Surgically treated infants had worse disease, so it is difficult to separate the effects of disease severity from the impact of surgery and anesthesia.

BRAIN INJURY IN THE TERM-BORN INFANT

The major causes of neurological injury in the term-born infant include hypoxia, ischemia, and subsequent increased perfusion.

The common etiologies of hypoxia include (1) hypoxia–ischemia from intrauterine disruption of oxygenation and failure to establish independent respiration at birth, including birth asphyxia; (2) postnatal respiratory inadequacy from respiratory disorders or problems with respiratory management; and (3) major right-to-left shunts from cardiac disease or persistent fetal circulation.[24] The chief sources of serious ischemia are intrauterine and birth asphyxia, postnatal cardiac failure, and postnatal circulatory failure from cardiovascular collapse from sepsis or patent ductus arteriosus with "ductal steal."[24] Ductal steal occurs when there is shunting from the systemic to pulmonary circulation which can lead to systemic hypoperfusion that results in a decrease in cerebral circulation and oxygenation.

Term newborns often have greater cortical and deep gray matter injury than premature neonates.[25,26] Common patterns of brain injury include selective neuronal injuries, parasagittal cerebral injury, WMI, and multifocal and focal ischemic brain necrosis. The selective vulnerability of specific neuronal populations, which may be related to high neuronal energy demand and glutamate distribution,[27] often manifests as widespread injury in the cerebral cortex, basal ganglia, thalamus, hippocampus, brainstem, and cerebellum. In a brain injury study after perinatal sentinel events, 13 infants with uterine rupture (n = 9), maternal collapse (n = 2), and umbilical cord separation (n = 2) were reported among 48 term infants. These infants all had thalamic and basal ganglia injury, 50% had cortical and brainstem injury, and 25% had hippocampal injury.[28] Parasagittal areas of the perirolandic cortex, subcortical white matter, putamen, and ventrolateral thalamus are injured in more

than one-third of term infants after hypoxia-ischemia.[29,30] Watershed regions are particularly vulnerable. The anesthesiologist must minimize the risk of exacerbating any evolving “postnatal” brain injury.

FACTORS ASSOCIATED WITH ADVERSE PATHOPHYSIOLOGY FOR THE PRETERM AND TERM INFANT BRAIN

We will discuss 3 modifiable factors that may influence neonatal neurological injury during the perioperative period. First, altered cerebral perfusion can occur from systemic hypotension or hypertension and high intracranial pressure; obstructed cerebral venous drainage from high intrathoracic pressure or head position; and hypo- or hypercapnia which, respectively, cause cerebral vasoconstriction or vasodilation. Second, “metabolic cellular sufficiency” from inadequate metabolic fuel (hypoglycemia or hypoxia) or high and unmet metabolic demand (pain, stress, fever, or seizures) may promote neural cell death. Finally, the “production of neurotoxic mediators” from hypoxia, ischemia, and reperfusion as well as free radicals from hyperoxia promote brain injury.

DEFINITION OF HYPOTENSION

Normal blood pressure values depend on chronological and postmenstrual age (Figure 3). Blood pressure is normally at its lowest in the first 24 hours of life in preterm and term infants as they transition from fetal to extrauterine circulation. For a term baby, the normal expected systolic blood pressure is approximately 63 mm Hg, which is almost identical to the Pediatric Advanced Life Support definition of neonatal hypotension.[32] Blood pressure rises during the first week of life, reaching an average blood pressure in term infants of 71.8/50.5 mm Hg for girls and 72.7/51.1 mm Hg for boys on day 7. Between day 8 and week 4, the average blood pressure rises another 14% for both sexes.[33] The ideal perioperative blood pressure targets for neonates are not well delineated.

A study of hemodynamically stable, extremely low gestational age neonates (mean estimated gestational age [EGA] at birth, 25.7 weeks) found that mean blood pressure in the first few hours of life was 33 mm Hg with an increase to 36 mm Hg by 72 hours.[34] In 292 premature and 81 term infants who were hemodynamically stable and without ventilator support, the mean blood pressure at 24 hours of life ranged from 32 ± 3 mm Hg for infants ≤28 weeks EGA to 48 ± 4 mm Hg for term infants.[35] A study of 45 healthy preterm infants born at a mean postmenstrual age of 31 weeks reported that the average blood pressure at 10 weeks of age was 90.8/55.3 mm Hg, which is higher than expected for term infants at 41 weeks postmenstrual age (PMA). The etiology for higher blood pressures in older preterm infants compared to that of term infants is unknown, but this finding may be related to inflammation with secondary high systemic vascular resistance in preterm infants.[36,37]

A consensus statement to pediatricians published in 1992 defined hypotension in the first 48 hours of life as the mean arterial blood pressure below the infant’s gestational age in weeks. This guideline is still used today as a general rule in neonatal intensive care units (NICUs) because this number generally corresponds to the tenth percentile of normative values for the first 48–72 hours of life.[38] After this time, however, blood pressures rapidly rise in preterm

infants and rules based on gestational age may no longer apply. For example, infants born at 28 weeks EGA may have blood pressures at 14 days of life that are similar to that of term infants[39] There is also evidence that premature infants with sustained periods of mean blood pressure <30 mm Hg have a higher incidence of IVH. This had led many neonatologists to consider a mean arterial pressure <30 mm Hg to be in the hypotensive range, even for neonates of extremely low gestational age.[40]

The optimal treatment of hypotension for neonates is currently being evaluated, and there are few available evidence-based recommendations. Because infants are most susceptible to IVH during the first 3 days of life, increasing the blood pressure by either fluids or inotropes could lead to reperfusion injury and IVH.[41] The European Management of Hypotension In the Preterm Extremely Low Gestational Age Newborn (HIP) trial (www.hip-trial.com) is currently enrolling preterm infants with an EGA 23–28 weeks who are randomly assigned to either dopamine treatment or permissive hypotension.

The maximal safe allowable decrease in blood pressure from baseline for young infants during anesthesia is unknown. Babies <3 months of age may have decreases in both cerebral perfusion and oxygenation when blood pressure decreases by >20% from baseline.[42,43] Blood pressure measurements are an inexact proxy for brain perfusion because intracranial pressure cannot be routinely measured and the cerebral perfusion pressure cannot be calculated. Moreover, continuously measuring CBF, such as with transcranial Doppler, is not routine in most operating rooms.

BLOOD PRESSURE AND CEREBRAL AUTOREGULATION

Cerebral blood pressure autoregulation maintains relatively constant CBF across changes in systemic blood pressure. When perfusion pressure is on the autoregulatory plateau, cerebral vessels dilate with decreasing blood pressure and constrict with increasing blood pressure to maintain steady CBF (Figure 4). There are no absolute values for the upper and lower limits of the autoregulatory plateau because these limits are dynamic.[45] Neonatal and pediatric swine models demonstrate that the autoregulation curve may shift with hypercarbia, intracranial hypertension, or obstructions in cephalic venous flow.[46–49] Importantly, the neonate’s open fontanelles do not necessarily provide protection against intracranial hypertension, and they should not be considered a safeguard against cerebral hypoperfusion[50] because the dura does not stretch. Blood pressure that is maintained within the range that optimizes autoregulation in neonates with hypoxic brain injuries may decrease the risk of brain injury as assessed by early MRI imaging and neurodevelopmental testing at 2 years of age.[51,52]

The blood pressure autoregulation curve can be identified during pediatric anesthesia even though volatile agents uncouple CBF and metabolic demand.[53,54] One study identified similar lower limits of autoregulation among patients ranging from 6 months to 14 years. Because baseline blood pressure is lower in young children than in older children and therefore closer to the lower limit of autoregulation, young children have less autoregulatory reserve.[55] A separate study examined autoregulation in infants <6 months of age who received sevoflurane anesthesia and caudal epidural ropivacaine. CBF decreased once the

mean blood pressure decreased by 20% from baseline, implying that the lower limit of autoregulation was approximately 20% below the baseline.[42] Additional studies are needed to clarify the limits of autoregulation during pediatric anesthesia and the potential effects of age, disease including those with elevations in intracranial pressure, and blood gas physiology on these limits.[46,47]

Few studies have correlated blood pressure during anesthesia to postoperative neurological outcomes in neonates. A small case series described 6 infants <3 months of age who underwent sevoflurane anesthesia and later developed postoperative seizures and watershed cerebral ischemic injuries on neuroimaging. In these babies, the mean arterial blood pressures were <35 mm Hg during the surgical procedures, which lasted >2 hours.[56]

In summary, neonates have low cerebral autoregulatory reserve and are vulnerable to inadequate cerebral perfusion from low blood pressure during anesthesia. Because the highest risk period for hypotension is during anesthesia induction and before incision,[57] hemodynamic instability must be avoided during induction, and surgical start times cannot be delayed.

Very little research exists on identifying safe upper limits of blood pressure or the upper limit of autoregulation during neonatal anesthesia. A study of unanesthetized neonates showed that the upper limit of autoregulation rises with age. The authors used transcranial Doppler to measure CBF velocity during bottle feeding, and they identified mean blood pressure upper limits of autoregulation between 45 and 60 mm Hg in infants of postconceptual age 33–35 weeks.[58]

Ideally, intraoperative hemodynamic goals would be guided by real-time measures of brain perfusion. CBF velocity can be measured by transcranial Doppler although Doppler monitoring is difficult to maintain for long periods. The measure of flow is basically derived from the relationship between velocity (distance traveled over time) and the vessel's diameter. Physiological parameters that change vessel size, such as hyper- or hypocarbia, should be constant to use Doppler velocity as a surrogate measure of CBF. An alternative method is cerebral NIRS, which measures regional oxygenated and deoxygenated hemoglobin saturations in the cortex. Some studies have used NIRS oxyhemoglobin level as a surrogate measure of CBF. This assumption requires physiological parameters that affect cerebral oxygen supply to remain constant, including temperature, anesthetic depth, hemoglobin level, and oxygen supply. The metabolic demand for oxygen must also remain constant, so the patient must not have pain or seizures.

Several studies in anesthetized infants have shown decreases in cerebral oxygen levels by >20% from baseline.[59–62] The rates of cerebral deoxygenation varied widely in these studies and occurred between 2% and 18% of the time. Identified risk factors for cerebral desaturations were decreases in systolic blood pressure by >20%, systemic oxygen desaturations, and decreases in mean arterial blood pressure. Care must be taken when trying to extrapolate CBF information from NIRS oxyhemoglobin data because the NIRS oxyhemoglobin saturation levels change with factors that are independent of CBF, including regional changes in oxygen supply and demand. Advanced signals processing improves the

ability to use NIRS data to study autoregulation. Indices that measure autoregulation as blood pressure changes in real time are currently being tested during pediatric anesthesia and in neonates.[51,63–66]

CBF CRITICAL CLOSING PRESSURE

Premature neonates are vulnerable to cerebral hypoperfusion during episodes of low blood pressure. The cerebral perfusion pressure, which is calculated as the mean arterial blood pressure minus the intracranial pressure, drives CBF. The critical closing pressure is the arterial blood pressure where vessels begin to collapse and CBF stops. A study of 179 premature infants with gestational age 23–31 weeks identified a mean critical closing pressure of approximately 19 mm Hg at 23 weeks gestation. The mean critical closing pressure increased with gestational age to reach 31 mm Hg at 31 weeks gestation.[66] These low critical closing pressures may permit cerebral perfusion at very low blood pressures in some neonates. However, those with diastolic blood pressure below these thresholds are at high risk of cerebral hypoperfusion and ischemic injury during the diastolic portion of the cardiac cycle.

HYPOCAPNIA

The tissue partial pressure of arterial carbon dioxide ($tPco_2$) and CBF as estimated by the tissue oxygen index (TOI) are approximately linearly related over a large range in neonates (Figure 5). Vanderhaegen et al[67] calculated the TOI as the oxyhemoglobin concentration divided by the sum of the oxygenated and deoxygenated hemoglobin concentration detected by cerebral NIRS. It is estimated that CBF in children decreases by 3% for each 1 mm Hg decrease in partial pressure of carbon dioxide ($Paco_2$), which translates to a 33% decrease in CBF when the $Paco_2$ decreases from 40 to 29 mm Hg.[68] In infants and young children with bacterial meningitis who had preserved cerebral blood pressure autoregulation, hypocapnia independently decreased cerebral perfusion to ischemic ranges.[68] Hypocapnia has also been implicated in neuronal apoptosis in the newborn brain.[69]

Many neonatology studies have shown an association between hypocapnia in brain-injured neonates and poor neurocognitive outcomes.[70–73] A prospective, randomized trial of therapeutic hypothermia for infants with neonatal encephalopathy found that both the minimum $Paco_2$ value and the cumulative exposure to $Paco_2$ <35 mm Hg were risk factors for death and disability.[71] A retrospective, single-center review of neonates with VLBW reported a 38% incidence of severe IVH in infants with $Paco_2$ >60 mm Hg or <39 mm Hg compared to 3% incidence in those without hyper- or hypocapnia.[74] $Paco_2$ <35 mm Hg is also a risk factor for PVL in preterm infants.[75,76] Altogether, these studies demonstrate that even modest decreases in $Paco_2$ could exacerbate pre-operative neurological injury or increase the risk of a primary brain injury.

HYPERCAPNIA

The era of permissive hypercapnia for premature infants requiring ventilatory support was heralded in 1999 with a randomized trial of 49 VLBW neonates treated with normocapnic

respiratory support versus mild hypercapnic (45–55 mm Hg) respiratory support.[77] This study found a 75% reduction in total ventilator days for the hypercapnic group compared with the normocapnic group. The mortality of patients with congenital diaphragmatic hernia decreased with the use of permissive hypercapnia with 1 center reporting an increase in survival from 55% to 85% after permissive hypercapnia was utilized.[78] Moderate hypercapnia ($Paco_2 \geq 55$ mm Hg) has not found to have advantages over mild hypercapnia in low birth weight preterm infants.[79–81]

In addition, preclinical studies suggest that hypercarbia may increase the CBF lower limit of autoregulation. In piglets, increases in $Paco_2$ were directly related to a higher lower limit of autoregulation. This occurred over a range of $Paco_2$ from approximately 30 mm Hg to >100 mm Hg.[46] We are not aware of pediatric clinical studies that have examined hypercarbia and the limits of autoregulation. Nonetheless, it would be reasonable to avoid low blood pressure particularly in neonates with hypercarbia.

Unfortunately, end-tidal capnography ($Etco_2$) has limited accuracy in some infants, especially in VLBW infants or those with severe lung disease. In these infants, the difference between $Etco_2$ and arterially measured $PaCO_2$ can be as high as 17.8 ± 6.7 mm Hg.[82–84] Generally, the bias is toward a lower value for the end-tidal measurement than for the $Paco_2$ value, but this is not consistent for every case. There is good correlation between transcutaneous CO_2 (TC CO_2) monitoring and arterial blood gas $Paco_2$ (BG CO_2) in neonatal intensive care studies, but in a small study of 25 neonates found that there poor correlation between trancutaneous and arterial blood gas values of CO_2 when used in the operating room setting.[85–87] Capillary or arterial gas measurements of $Paco_2$ should be obtained in high-risk infants to correlate with the $Etco_2$ values and guide the anesthesiologist in identifying ventilator parameters that avoid hypo- or hypercapnia.[82–84,88]

HYPEROXIA OR HYPOXIA

Oxygen therapy has clear benefits for critically ill neonates, but prolonged or hyperoxic exposure carries significant risks. Pulse oximetry saturation levels above 94% increase the risk of retinopathy of prematurity, chronic lung disease, and brain injury in premature infants.[89–91] A large prospective study comparing general anesthesia with spinal anesthesia found that infants exposed to general anesthesia were at greater risk for both hyper- and hypoxia during general anesthesia.[92]

Hyperoxia from excess oxygen supply or from reperfusion after hypoxia generates free radicals that can cause oxidative stress that induces deoxyribonucleic acid (DNA), protein, and cell membrane damage. This damage can trigger neuronal, OL, and astrocyte cell death if the oxidative stress is not resolved. Scavenging systems that detoxify reactive oxygen species are poorly developed in healthy and ill neonates.[93] Oxidative stress markers are significantly higher in infants and mothers who receive 40% inhaled oxygen compared to room air during cesarean delivery with regional anesthesia.[93–95]

The optimal target for oxygen saturation in preterm infants is generally 90%–94%, which decreases the risk of retinopathy of prematurity without increasing mortality.[96,97] The

optimal target for term infants is similar. Because the risks of serious oxygen toxicity from high oxygen saturations are less in healthy term infants, many practitioners permit a saturation level of >95%.

GLUCOSE HOMEOSTASIS

Energy requirements for neonates are roughly 3–6 times greater per body weight than they are for adults.[98] Plasma glucose concentrations normally decrease to approximately 55–60 mg/dL during the first few hours after birth and before the first feeding with 5% of normal newborns having a glucose concentration of ≤28 mg/dL.[99] This nadir can be lower in neonates with peripartum stress related to fetal and birth asphyxia and low Apgar scores. Then, the glucose level typically increases over the next few hours to the range 70–100 mg/dL. The definitions of mild, moderate, and severe hypoglycemia are not well delineated in the literature. Many institutions caring for young preterm and term neonates after the first day of life consider severe hypoglycemia to be serum glucose of <35 mg/dL, moderate hypoglycemia to be a serum glucose between 35 and 47 mg/dL, and mild hypoglycemia to be a serum glucose between 47 and 70 mg/dL. The threshold between mild and moderate hypoglycemia is derived from a study in 1988 found that infants who had a measured glucose level <47 mg/dL for 5 or more days had a 3.5 times greater incidence of cerebral palsy.[100] Subsequent studies have shown that for most infants, mild hypoglycemia or even transient moderate hypoglycemia is not a risk factor for later neurocognitive difficulties.[101–103] However, untreated hypoglycemia may have severe consequences, including neurocognitive impairments. Most clinical signs of mild neonatal hypoglycemia, such as jitteriness, irritability, or poor feeding, may be missed in the perioperative period because these signs are not detectable during anesthesia and are common postoperatively. Moderate-to-severe neonatal hypoglycemia is often heralded by seizure activity. Infants who are small for gestational age, preterm infants who do not have adequate depots of body fat and glycogen, babies born to diabetic mothers, and males are at high risk for perinatal hypoglycemia.[104] Because the gluconeogenic and ketogenic pathways are not mature at birth, full-term infants who are fasted can become hypoglycemic. It is unknown whether the severity, duration, or number of hypoglycemic episodes is most important in causing perinatal brain injury.[105–107] Even mild hypoglycemia is deleterious when paired with mild hypotension in infant nonhuman primates.[108]

During surgical trauma, infants mount endocrine and stress responses that begin with a catecholamine surge followed by sustained elevations in cortisol and glucagon with insulin suppression. This insulin suppression can cause perioperative hyperglycemia, particularly in preterm infants. In 34 neonates (median, 3–4 days of age; mean gestational age, 37 weeks) undergoing tracheoesophageal fistula repair, intravenous fluids containing dextrose 2%–4% maintained metabolic stability.[109] Thus, glucose monitoring and provision of a glucose-containing intravenous solution, when necessary, are essential components of providing a safe anesthetic to neonates.

TEMPERATURE

Continuous core temperature monitoring is critical in the operating room. Infants can rapidly become hypothermic in the operating room given their greater surface-to-body mass/proportion, low subcutaneous fat and keratin content, limited glycogen and brown adipose tissue stores, and immature thermoregulatory mechanisms. Radiant and conductive heat loss predominate in infants for the above reasons, but evaporative losses occur during ventilation and convective heat losses due to draughts are possible. This risk is accentuated in premature infants due to significant heat loss through evaporation from their immature skin during the first 10 days of life.[110] An ancillary analysis of data collected by the Collaborative Pediatric Critical Care Research Network found that therapeutic hypothermia as a neuroprotective strategy in infants undergoing extracorporeal membrane oxygenation was associated with a more than doubling the incidence of intracranial hemorrhage (40.0% vs 15.8%; $P = .012$).[111] A recent, multicenter, prospective cohort study from Brazil of almost 2000 premature infants found that 51% of them were hypothermic at the time of admission to the NICU, and this increased the risk of early neonatal death by a factor of 1.64.[112]

Risk factors for hypothermia in the operating room for infants include low initial core temperature, major surgery, and an operating room temperature of ≤23°C. A quality improvement project designed to better the postoperative temperature of infants returning to the NICU, maintaining the room temperature at 29.4°C at procedure onset and when the drapes were removed after surgery; using warmed fluids, warming blankets, and/or thermal mattresses; and ensuring that the transport incubator was warmed decreased the incidence of NICU admission hypothermia almost 4-fold.[113] As part of this project, surgeons used cooling vests to help them tolerate high environmental operating room temperatures.

The use of forced hot air heating devices as a sole heating device has been successful using a dual air nozzle system which allows better distribution of warm air and increased airflow. In a prospective study of neonates and infants with a mean weight of 4.1 kg and a range between 0.7 and 9.8 kg, the infants core temperature rose from 36.5°C at the onset of the procedure to 37.8°C at the conclusion.[114] There is the risk of inadvertent skin burns from the use of forced air heating devices, especially in infants with compromised circulation or with prolonged use at the highest temperature setting of 43°C.[115]

For infants at very high risk of neurological deficits, such as patients undergoing congenital cardiac surgery, hypothermia plays an important role in decreasing metabolic rate and possibly decreasing the inflammatory responses that can exacerbate previous neurological injuries. However, hypothermia can be associated with bradycardia and an increased need for vasopressor medications. For noncardiac procedures in neonates not known to have neonatal hypoxic–ischemic encephalopathy, it is best to strive for normothermia because hypothermia and hyperthermia are associated with medical risks.

Most centers use a combination of modalities to ensure normothermia in neonates. Forced air heating devices have proven to be the most effective but also need to be monitored extremely carefully because inadvertent disconnects and prolonged use can lead to burns. It is prudent to make sure that all fluids used during procedures (infusions, irrigants, and

preparation solutions) are at 37°C and that breathing devices are humidified. Other active devices such as heated gel mattress pads and warming lights are helpful, especially during induction when the patient is not draped. Passive warming devices (blankets, respiratory exchangers, caps, and polyurethane bags) are useful at maintaining temperatures in a very warm room but will not prevent hypothermia if the room temperature is below 26°C.[116,117]

POSITIONING

The importance of positioning may be an underappreciated aspect of neonatal care during anesthesia. During normal fetal development, the uterus in part acts as a both an enveloping "nest" and an environment which allows the fetus to move. Ideal position for fetuses and newborns is physiological flexion with the head in a neutral position without extension. Positioning devices are commercially available that allow infant movement but then recoil back to put the infant into a flexed body position. These devices may improve symmetry in reflexes and motor responses in very young infants that ultimately may lead to better developmental outcomes.[118] By necessity, neonates are positioned supine with their limbs extended to facilitate intravenous line management and operative access in most surgical cases. Positioning the head in a lateral flexed position in the supine position is not recommended; the endotracheal tube should be secured with the head and neck in neutral positions. Positioning for neurosurgery, including ventricular shunts, should take into account the infant's head position relative to the rest of the body.

Neutral head positioning is recommended by a consensus statement from the Vermont Oxford Network, which is a global consortium of over 700 NICUs that developed "Potentially Best Practice" guidelines for premature newborn care based on evidence-based literature review, benchmarking activities, and expert committee review to decrease the occurrence of IVH and leukomalacia.[119] Although little evidence has been published regarding very premature infants, it is postulated that lateral positioning of the head can occlude or obstruct jugular venous drainage.[120] This in turn could cause cerebral venous congestion and increase the risk of cerebral vessel rupture, IVH, and impaired cephalic drainage with increased intracranial pressure and decreased cerebral perfusion. Several studies have demonstrated a correlation between lateral head rotation and decreased cerebral oxygen index and an increase in cerebral blood volume in neonates, especially those born at <26 weeks postmenstrual age and with VLBWs.[120–122] Accordingly, intracranial pressures were lowest in infants positioned with their heads midline and the head of the bed raised. However, a meta-analysis examining the results of neutral head position with mild head elevation concluded that evidence was insufficient to demonstrate that head positioning and tilting affect the incidence of germinal matrix–IVH, cerebral hemodynamics, and oxygenation in preterm infants.[123] Thus, the anesthesiologist should consider keeping the neonate's head in a neutral and midline position when possible,[124] and further research on this topic is needed.

CONCLUSIONS

The pediatric anesthesiologist must minimize risk factors for perioperative neurological injury in neonates throughout the perioperative period. However, many factors that worsen

neurocognitive outcomes are nonmodifiable, including the deleterious effects of inflammation from disease and the surgery itself as well as the neonate's underlying premorbid state. The task of improving developmental outcomes in young infants requires collaborative efforts among NICU providers, surgeons, and anesthesiologists. While research is underway to identify optimal anesthetic regimens that minimize neurotoxicity, the anesthesiologist must also avoid the numerous additional perioperative risks factors that could increase brain injury. These include avoiding perioperative hypotension and hypertension, hypo- and hypercapnia, hypoglycemia, hyper- and hypoxia, hypothermia and hyperthermia, and malpositioning.

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GLOSSARY

BG CO_2	arterial blood gas $PaCO_2$
CBF	cerebral blood flow
CI	confidence interval
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
EGA	estimated gestational age
ELBW	extremely low birth weight
$Etco_2$	end-tidal capnography
HIP	Management of Hypotension In the Preterm Extremely Low Gestational Age Newborn
IVH	intraventricular hemorrhage
MRI	magnetic resonance imaging
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NIRS	near-infrared spectroscopy
OL	oligodendrocyte
OR	odds ratio
$Paco_2$	partial pressure of carbon dioxide
PMA	postmenstrual age

PVL	periventricular leukomalacia
SIRS	systemic inflammatory response syndrome
TC CO_2	transcutaneous pressure of carbon dioxide
TOI	tissue oxygen index
$tPco_2$	tissue partial pressure of arterial carbon dioxide
VLBW	very low birth weight
WMI	white matter injury

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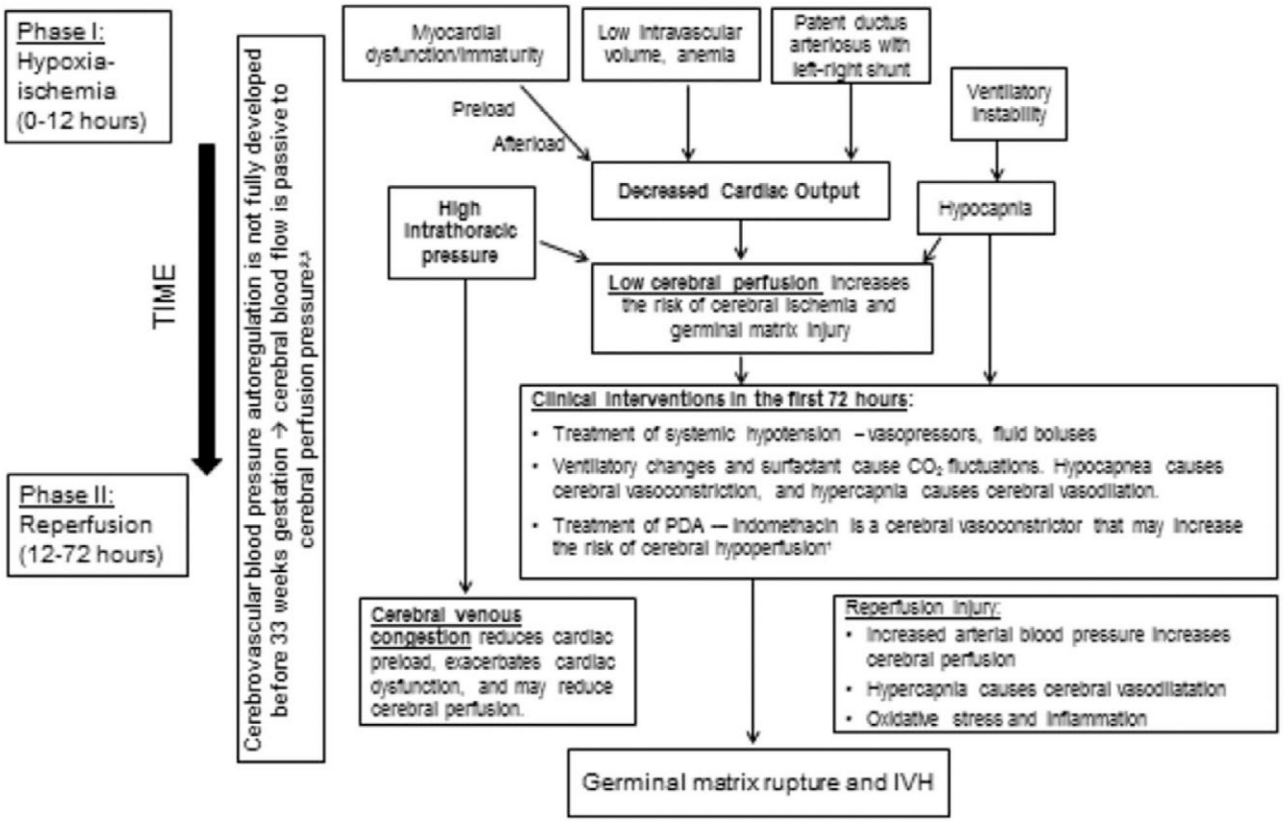

Figure 1.

Mechanisms that may contribute to the risk of neonatal IVH. Some of these factors are modifiable during perioperative care. CO_2 indicates carbon dioxide; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus.[8–10] Reprinted from *Clinics in Perinatology*, 26, Nuntnarumit P, Yang W, Bada-Ellzey HS, "Blood Pressure Measurements in the Newborn," 981–996, 1999, with permission from Elsevier.[31]

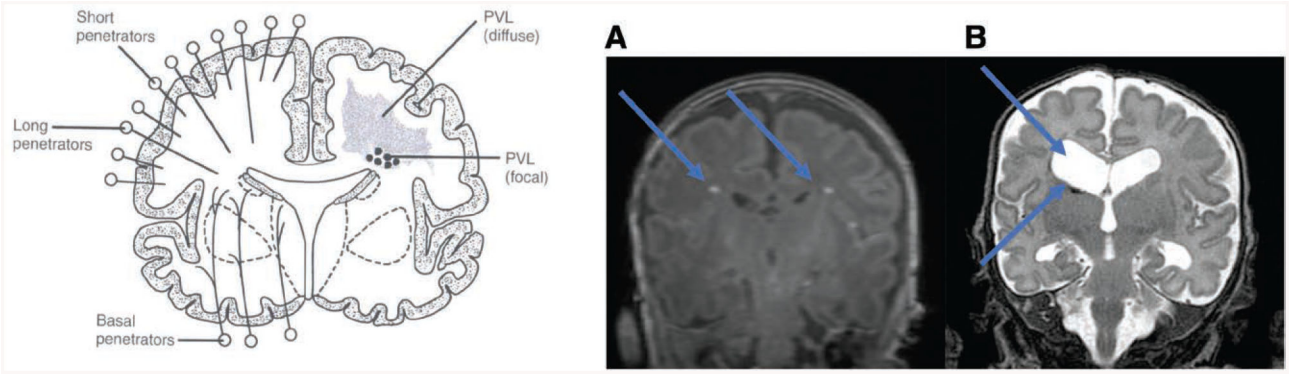

Figure 2.

Illustration of a cerebral coronal section with the vascular anatomy in 1 hemisphere and the 2 components (focal and diffuse) of PVL in the other,[15] with illustrations of (A) focal punctate T1-weighted MRI white matter injury and (b) more diffuse loss of white matter volume with ex vacuo ventriculomegaly. MRI indicates magnetic resonance imaging; PVL, periventricular leukomalacia. Reprinted by permission from Springer Nature, *Journal of Perinatology*, "Definition of Hypotension and Assessment of Hemodynamics in the Preterm Neonate," Cayabyab R, McLean CW, Seri I, 2009;29(suppl 2):S58–S62.[44]

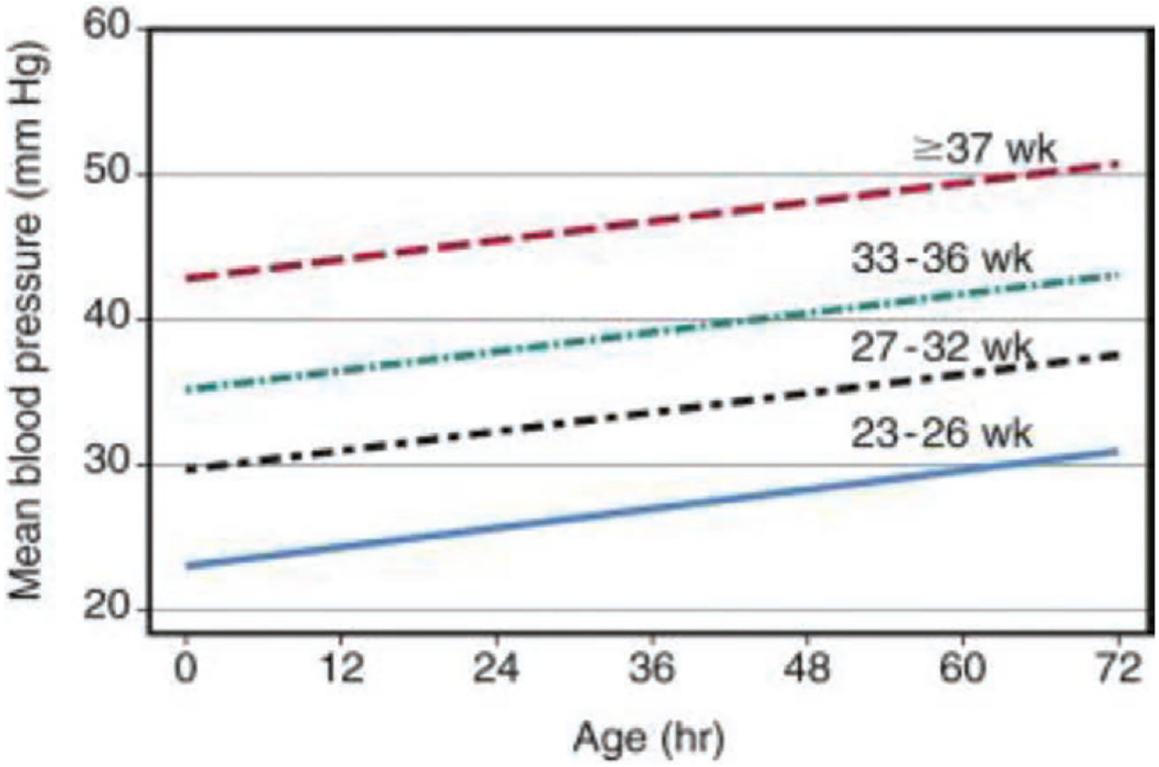

Figure 3.

Nomogram for mean BP in neonates with gestational ages 23–43 wk during the first 72 h of life in 103 infants in the neonatal intensive care unit. These data are derived from continuous arterial BP monitoring. Each line represents the lower limit of the 80% confidence interval (2-tail) of mean BP for the gestational age group. Ninety percent of infants for each gestational age group will be expected to have a mean BP value equal to or above the value indicated by the corresponding line.[31] BP indicates blood pressure. Reprinted from *European Journal of Paediatric Neurology*, 13, Vanderhaegen J, Naulaers G, Vanhole C, et al, "The Effect of Changes in tPCO2 on the Fractional Tissue Oxygen Extraction–as Measured by Near-Infrared Spectroscopy–in Neonates During the First Days of Life," 128–134, 2009, with permission from Elsevier.[67]

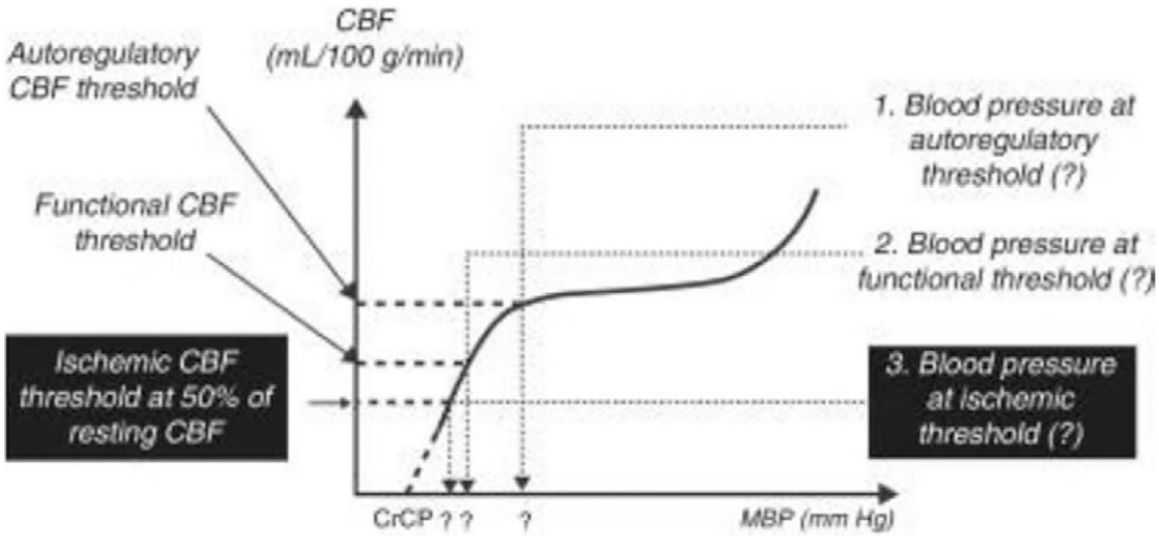

Figure 4.

The CBF–mean arterial pressure relationship with normal cerebral circulation. The flat portion represents the autoregulatory plateau. This figure demonstrates the definition of hypotension by 3 pathophysiology phenomena of increasing severity: the "autoregulatory, functional, and ischemic thresholds" of hypotension.[44] See text for details. CBF indicates cerebral blood flow; CrCP, critical closing pressure; MBP, mean blood pressure. Reprinted by permission from Springer Nature: *Journal of Perinatology*, Cayabyab R, McLean CW, Seri I, "Definition of Hypotension and Assessment of Hemodynamics in the Preterm Neonate," 2009;29(suppl 2):S58–S62.[44]

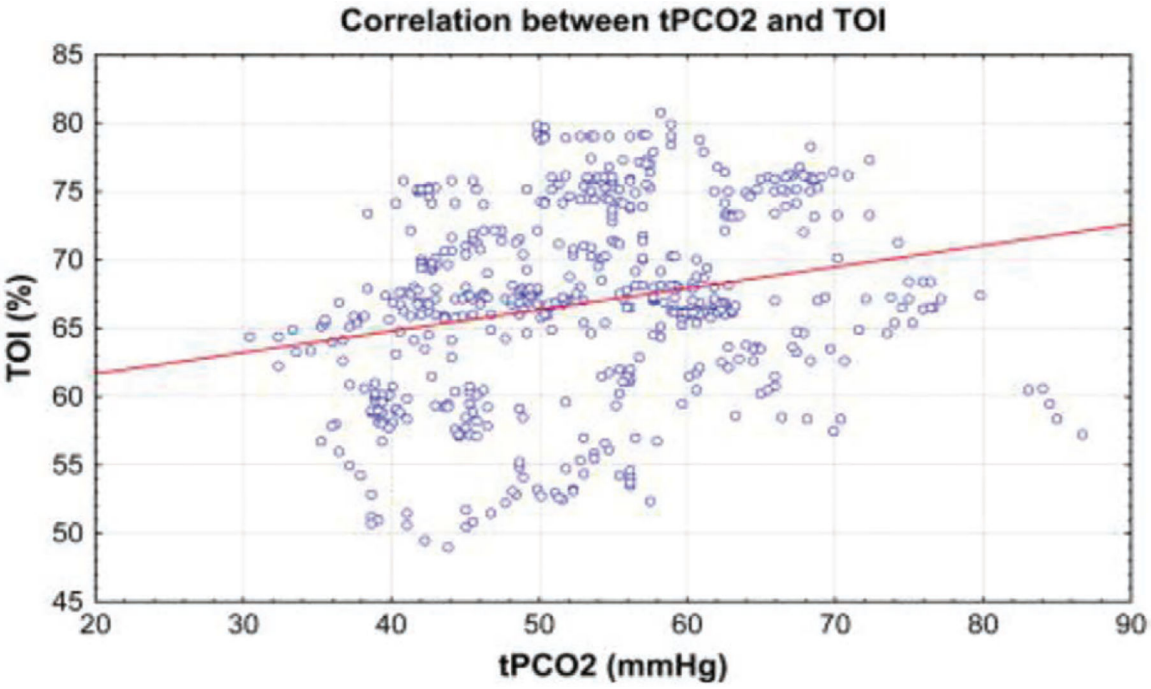

Figure 5.

The correlation between $tPco_2$ (mm Hg) and TOI (%) is plotted in 13 neonates with birth weight <1500 g. The TOI was calculated from the percentage of oxygenated hemoglobin measured by cerebral near-infrared spectroscopy. As carbon dioxide levels increase, cerebral vasodilation causes cerebral blood flow to increase with an increase in the TOI. Decreases in carbon dioxide cause cerebral vasoconstriction, reduced cerebral blood flow, and consequent decrease in TOI.[67] TOI indicates tissue oxygen index; $tPco_2$, tissue partial pressure of arterial carbon dioxide.