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The Role of Systemic Hemodynamic Disturbances in Prematurity-Related Brain Injury

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Abstract

Premature infants who experience cerebrovascular injury frequently suffer acute and long-term neurologic complications. In this paper, we explore the relationship between systemic hemodynamic insults and brain injury in this patient population and the mechanisms that might be at play.

Cerebrovascular injury is a major cause of acute and long-term neurologic complications in the premature infant.^{1,2} Systemic hemodynamic instability is commonly diagnosed in the premature infant and has been implicated in both hemorrhagic and hypoxic-ischemic forms of cerebrovascular injury in this population.^{3–6} Both “unstable” systemic hemodynamics and cerebrovascular injury are related inversely to gestational age at birth, and consequently immaturity of systemic hemodynamic control has been invoked as an important mediator of prematurity-related brain injury. However, the role of systemic hemodynamic insults in the development of prematurity-related brain injury in the newborn period, and their contribution to the high prevalence of neurodevelopmental sequelae in survivors of prematurity, are far from established. Our ongoing inability to establish and characterize a precise link between systemic circulatory factors and prematurity-related brain injury has generated a growing skepticism about its importance. Importantly, it has precluded the development of rational and effective interventions. We explore the available, often scant, evidence for such a relationship, as well potential reasons for the ongoing controversy in this area.

Cerebrovascular Injury in Premature Infants: Prevalence and Potential Mechanisms

Early autopsy studies demonstrated the vulnerability of the premature cerebral white matter to injury, particularly in the periventricular regions.^{7,8} With the advent of cranial ultrasound, this predilection to white matter injury was described in living premature infants.^{9,10} Typically, the cranial ultrasound features were those of a focal echogenic lesion often evolving into a cystic lesion. However, cranial ultrasound is relatively insensitive to the noncystic form of periventricular white matter injury.¹¹ In fact, the magnitude of this problem was not appreciated until recent magnetic resonance imaging (MRI) studies¹² suggested that white matter injury may be present in more than half of very premature infants.^{13,14} Various mechanisms unique to the premature brain have been proposed to underlie this vulnerability. First, arterial ingrowth into the developing brain is incomplete in prematurely born infants, leaving undervascularized end-zones in the cerebral white matter.^{10,15–20} Whereas cerebral blood flow in the mature brain exceeds the ischemic

threshold injury by 5-fold,²¹ in the premature infant both global^{22–30} and regional cerebral blood flow (especially in the white matter)^{31,32} are significantly lower, suggesting a limited margin of safety for cerebral perfusion.³³ Lastly, at a cellular level there is a rapidly growing body of data (discussed elsewhere in this journal) supporting the notion of increased susceptibility of the immature oligodendrocyte^{34,35} to insults, including hypoxia-ischemia.

Intracranial hemorrhage, especially germinal matrix-intraventricular hemorrhage (GM-IVH), is a common complication of prematurity. The germinal matrices are predominantly situated in the periventricular regions of the developing brain and are supported by a profuse but transient and fragile vascular system.^{36–42} These regions are vulnerable to ischemic insults during periods of hypoperfusion and rupture during fluctuations (“water-hammer” effect) in perfusion pressure.^{36–38,43–45} Although the incidence has decreased in recent decades,^{46–51} GM-IVH continues to affect 15% to 20%^{52–56} of premature infants born below 1500 grams, and almost half of those born <750 grams.⁵⁷ This translates into a large absolute number of affected infants at increased risk for the long-term consequences of GM-IVH. The magnitude of this problem is further highlighted by the fact that both the incidence and severity of GM-IVH is highest in the smallest sickest infants (ie, the population with the most rapid recent increases in survival).

Systemic Hemodynamic Instability in Premature Infants: Prevalence and Potential Mechanisms

Control of cardiac output is dependent on heart rate and myocardial contractility, and is maintained through opposing tonic and reflex input from the sympathetic and parasympathetic nervous systems. Development of the fetal sympathetic nervous system precedes that of the parasympathetic system, which is incompletely developed in the premature infant.⁵⁸ Furthermore, contractility of the immature myocardium is close to maximal, with limited ability to increase stroke volume. Consequently, during periods of low cardiac output the premature infant becomes particularly dependent on heart rate. However, since baseline sympathetic activity is close to maximal, the ability to increase cardiac output by accelerating the heart rate is limited. In addition, baroreflex and chemoreflex systems are underdeveloped in premature infants.^{59,60} Lastly, delayed closure of fetal circulatory channels further compromises efficiency of the cardiovascular system in the premature infant. Together, these factors leave the premature infant poorly equipped to deal with the sudden transition from the low-resistance placental bed to the higher peripheral vascular resistance of extrauterine life. It is therefore not surprising that premature infants may experience periods of low cardiac output during the early postnatal hours.^{61–65}

Systemic and Cerebral Hemodynamic Interactions in Premature Infants

Under normal conditions, tissue perfusion is maintained by a background perfusion pressure provided by the cardiovascular system, which is then “fine-tuned” at the tissue level by intrinsic autoregulatory mechanisms in response to changing tissue substrate demands. Pressure-flow autoregulation acts as a buffer system to maintain a relatively constant cerebral blood flow during periods of fluctuating systemic blood pressure. However, this buffering capability is possible only while systemic blood pressure is maintained within certain bounds, defined as the autoregulatory plateau, outside of which cerebral blood flow becomes pressure passive and the risk of brain injury escalates.

Studies in animal models^{66–81} have explored the role of brain maturation in intrinsic cerebral vasoregulation. Pressure-flow autoregulation emerges during fetal life but is underdeveloped in the immature infant brain. Specifically, with decreasing gestational age the autoregulatory plateau is narrower and lower,^{82,83} with normal resting blood pressure

close to the lower threshold of autoregulation.^{67,71,75} In humans, cerebral pressure-flow autoregulation is well-characterized in children and adults^{84–87} but not in the newborn,⁸⁸ and least of all in the sick premature infant.^{30,89–95} In fact, in the sick premature infant the existence and bounds of the pressure autoregulatory plateau remain controversial.^{89,90,94,109,110,156,166,169} Some studies have suggested a lower limit of the autoregulatory plateau in stable preterm infants is around 25 mmHg to 30 mmHg.^{30,96,97} In large part, these controversies are perpetuated by the lack of reliable techniques for continuous cerebral blood flow measurement during the high-risk period soon after premature birth. Nonetheless, given their predilection to systemic hemodynamic instability, the limited cerebral pressure autoregulation may expose premature infants to cerebrovascular insult during transition from fetal life.⁹⁸

Disturbed Cerebral Hemodynamics and Prematurity-Related Brain Injury: Evidence for an Association

A link between disturbances in cerebral hemodynamic disturbances and injury to the immature brain has been suggested in animal models and several clinical studies.⁹⁹ The changes implicated have included increased, decreased, and fluctuating cerebral perfusion. Early animal studies used a hypoperfusion-reperfusion model in newborn beagle puppies^{100–103} to induce GM-IVH. Other animal models, including fetal sheep^{104–107} and fetal rabbits,⁹⁹ have been used to demonstrate vulnerability of the immature cerebral white matter to hypoperfusion injury.

Understanding of the dynamic relationship between cerebral hemodynamics and brain injury in the premature human has been impeded by a lack of techniques for direct and continuous volumetric cerebral blood flow measurement (see below). Most studies in premature infants to date have used static point measures and/or indirect surrogates for CBF.^{26,108–113} An association has been more frequently reported between cerebral perfusion disturbances and GM-IVH than with PVL (discussed below). Recent studies^{62,63,114–116} have shown that superior vena cava flow, used as a surrogate for cerebral blood flow, may be decreased in the first 24 hours after premature birth, both the nadir and duration of which is associated with severe GM-IVH^{117–119} and later adverse neurologic outcome.^{62,63} In subsequent studies this decrease in superior vena cava flow is associated with lower cerebral hemoglobin oxygen saturation measured by near infrared spectroscopy.¹²⁰ The GM-IVH developing in these infants appears to develop *after* recovery of superior vena cava flow flow, suggesting the hypoperfusion-reperfusion mechanism described in earlier animal models.^{100,121,122} Similar findings have been reported using intermittent near infrared spectroscopy measures of cerebral blood flow.¹²³

The role of *fluctuating cerebral perfusion* in prematurity-related brain injury remains controversial. Early Doppler studies suggested a role for fluctuating cerebral blood flow velocity in the development of GM-IVH.^{124–127} However, these findings have not been corroborated in other studies.^{90,128,129}

Systemic Blood Pressure Disturbances and Prematurity-Related Brain Injury: Evidence for an Association

Early animal studies described an association between increased systemic blood pressure and GM-IVH, especially following a period of hypotension.^{74,100,102,103,121,122,130–134} Although sustained hypertension is uncommon in premature humans, an association between hypertension during the first 24 hours of life and the development of GM-IVH has been reported.^{6,135} Overall, the role of systemic *hypotension* in prematurity-related brain injury has been more extensively studied. Findings have not been consistent, with some

studies implicating hypotension in the development of GM-IVH,^{4,5,136–141} but other studies finding no such association.^{90,113,129,142–145} Doppler and functional echocardiography studies have suggested that systemic blood pressure measurements during the early hours after premature birth may fail to identify potentially dangerous low cardiac output states and low cerebral perfusion, and are poorly predictive of GM-IVH and adverse outcome.^{62–65,146}

Fluctuating blood pressure in studies of ventilated premature infants has been associated with GM-IVH, presumably through a “water-hammer” effect on the fragile germinal matrix vessels.^{4,6,93,125,126,137,147–149} However, this is not a consistent finding, and in more recent studies no significant relationship was found between blood pressure variability (in the frequency-domain) and GM-IVH.^{90,129}

Studies in immature animals¹⁰⁵ and preterm infants^{4,5,142,150,151} have implicated systemic hypotension in the development of white matter injury; however, other studies have shown no such relationship.^{135,139,144,152} Potential reasons for these disparities are discussed below.

In summary, the role of systemic blood pressure disturbances and impaired cerebral pressure-flow autoregulation in prematurity-related brain injury, particularly to the parenchyma, remains unresolved.

Impediments to Establishing a Causative Relationship Between Systemic Hemodynamic Disturbances and Prematurity-Related Brain Injury

A number of possible factors underlie this ongoing controversy. Perhaps the most fundamental obstacles have been the lack of reliable techniques for continuous cerebral blood flow measurement, poor understanding of the “insult doses” needed to cause prematurity-related injury, and difficulty diagnosing significant brain injury in close temporal proximity to potential hemodynamic insults.

Quantitative cerebral blood flow measurements are difficult in sick premature infants

During the past 3 decades, a number of studies have measured cerebral blood flow in the premature infant.^{62,63,111,114–116,153–157} The vast majority of these studies have measured intermittent, so-called “static” techniques based on the Fick principle and using tracers ranging from xenon-133^{155–157} to oxyhemoglobin.^{111,153,154} These measures assume steady-state conditions during the measurement period, which may last as long as 15 minutes using the ¹³³Xenon clearance technique; such sustained steady-state conditions are unlikely in the sick premature infant. More recently, intermittent measures of superior vena cava flow using Doppler ultrasound have been used as a surrogate for cerebral blood flow.^{62,63,114–116} These static cerebral blood flow measurements have provided valuable insights into cerebral hemodynamics in the premature infant. However, they are not capable of capturing the dynamic nature of cerebral hemodynamics, particularly during the major physiologic changes associated with transition from fetal to premature postnatal life. In addition, these static measurement techniques allow inferences about global cerebral blood flow but do not address regional blood flow within the brain. This latter limitation may be overcome with techniques such as single photon emission computed tomography¹⁵⁸ and positron emission tomography;^{31,159} however, these techniques are also confined to static, point measurements in time and are not feasible in clinically unstable premature infants.

More recently, continuous measurements of cerebral hemodynamics have become possible with techniques such as near infrared spectroscopy^{89,90,160,161} and Doppler ultrasound.^{125,162–166} Neither of these continuous approaches measures quantitative volumetric blood flow. Instead, near infrared spectroscopy measures changes in cerebral hemoglobin

oxygenation from which continuous changes in cerebral blood volume and the hemoglobin difference or HbD signal (oxyhemoglobin minus deoxyhemoglobin) can be derived. Likewise, Doppler ultrasound measures cerebral blood flow *velocity* rather than volumetric cerebral blood flow, and assumes a constant diameter of the large insonated cerebral arteries, an assumption that has been challenged.^{25,167,168} Current near infrared spectroscopy and Doppler ultrasound techniques are capable of monitoring global (but not regional) cerebral perfusion over time. Both approaches have provided valuable insights into cerebral pressure-flow autoregulation in premature infants.^{89,90,165,166,169–174}

Characterizing the systemic hemodynamic insult is difficult

Fundamental to the lack of understanding regarding the role of systemic hemodynamic factors in prematurity-related brain injury is the fact that the “dose” of insult required to cause these lesions remains unknown. Normal arterial blood pressure may be defined as the range of pressures required to maintain perfusion appropriate for the functional and structural integrity of the tissues. Normal blood pressure ranges remain unknown for the premature infant,^{175,176} a fact that is reflected by the wide variation with which hypotension is diagnosed and treated in premature infants across major centers.^{177–179} Conversely, sustained hypertension is rarely diagnosed in the premature infant.¹⁷⁹ Population-based studies show that blood pressure increases with gestational age at birth, as well as with postnatal age during the first week (ie, during the highest risk period for brain injury).^{143,176,180–182} Two broad approaches have been used in an attempt to define normal blood pressure in premature infants. Several studies have described the blood pressure ranges in populations of normal premature infants (ie, without evidence of significant brain injury).^{143,176,182,183} Other studies have tested various blood pressure thresholds in infants with and without brain injury in an attempt to define the limits of normal blood pressure.^{5,129,142,151} Both approaches have been compromised by limitations in the diagnosis of a hemodynamic insult and that of a normal/abnormal outcome. These issues are discussed below. In addition, a number of these studies are retrospective, with all the associated limitations.^{5,139,143,151,152}

In theory, hemodynamic insults might injure the premature brain in a variety of ways. However, in practice our understanding of the fundamental relationship between a hemodynamic insult “dose,” and the presence, severity, and topography of injury in the premature brain remains very poor. Specifically, the duration and severity of hemodynamic change required to cause injury remain unknown. Presumably, injury thresholds exist for brief but severe, for mild but prolonged, and for repetitive hemodynamic insults. A better understanding of these issues is beginning to emerge in the full-term infant with perinatal asphyxia,^{184–186} but not in the premature infant. In fact, to date most reported studies have used hemodynamic measures that are hopelessly inadequate for exploring the complexity of hemodynamic changes during the fetal-neonatal circulatory transition. For example, neither studies using the single lowest blood pressure on a single (or more) days, nor those using averaged blood pressure over prolonged periods, will adequately address the potential for injury.^{143,144} This uncertainty is reflected in the different definitions of hypotension used in these studies^{4,5,129,137,138,140,141,187} as well as in the different sampling times and durations.^{113,129,139,142–145} The role of hemodynamic fluctuations in brain injury in this population is further complicated by the fact that such changes have been described in both normal¹⁸⁸ and brain-injured term and premature^{173,189–191} newborns.¹⁹²

Systemic arterial blood pressure is a limited indicator of organ perfusion

In clinical practice, systemic arterial blood pressure is the most widely used indicator of systemic hemodynamic function and organ perfusion, including that of the brain. This reliance on systemic blood pressure is largely due to the fact that it can be easily measured,

unlike systemic blood flow or vascular resistance. However, for several reasons arterial blood pressure alone may be a poor surrogate for tissue, and especially cerebral, perfusion during the premature transitional period.

First, recent studies have demonstrated that arterial blood pressure may be a poor indicator of cardiac output in the newborn premature infant. These studies have used functional echocardiography to measure cardiac output and superior vena cava flow, the latter used as a surrogate measure of cerebral blood flow.^{62–65,146,193} These studies have suggested that cardiac output is lowest in most premature infants during the first 12 hours after birth. In fact, during this period more than one-third of very premature infants develop significantly decreased blood flow in both the systemic (cardiac output) and cerebral (superior vena cava) circulations.⁶² Importantly, these low-flow states appear to be poorly associated with arterial blood pressure,¹⁴⁶ do not respond to pressor-inotropes,⁶⁵ and may be associated with a decrease in cerebral intravascular oxygenation.¹²⁰ These authors suggest that cardiac output may be a more relevant measure for cerebral perfusion and oxygenation than blood pressure. Other studies have corroborated the poor relationship between cerebral perfusion and arterial blood pressure in the early premature period.^{90,194}

A second limitation of relying on arterial blood pressure alone to reflect cerebral perfusion is that it is only one determinant of cerebral perfusion pressure, the other being cerebral venous pressure. However, since cerebral venous pressure is difficult to measure safely in clinical practice, particularly in the premature infant, cerebral venous pressure is often assumed to play a relatively minor role in cerebral perfusion pressure changes, and therefore disregarded. However, in the critically ill premature infant this assumption may not hold. Specifically, these infants frequently require positive pressure ventilation given their pulmonary immaturity. The intrathoracic pressure changes accompanying positive pressure ventilation may significantly affect central, and therefore cerebral, venous pressure, particularly in situations where arterial blood pressure is close to the lower threshold of cerebral pressure autoregulation. Therefore, cerebral venous pressure changes may play a more important role in cerebral perfusion in unstable premature infants. This question is in clear need of further investigation.

Identifying meaningful outcome measures for acute hemodynamic “insults” is difficult

A crucial step in determining whether a causative relationship between an insult and injury exists is the ability to establish a biologically plausible temporal relationship between them. For several reasons, this remains a major challenge when exploring the relationship between early neonatal systemic hemodynamic factors and brain injury in the sick premature infant. The ultimate outcome measure after any potential neurologic insult is long-term neuropsychological function. In the case of prematurity survivors, this outcome may become clear only at school-age^{195,196} or later.¹⁹⁷ Perhaps for this reason, there has been a lack of studies examining the direct relationship between early neonatal hemodynamics and long-term outcome.^{63,187} In addition, meaningful outcome measures that reliably predict long-term outcome have been difficult to identify in close proximity to the period of maximal hemodynamic instability immediately after birth. Furthermore, other potentially injurious mechanisms may operate before (eg, fetal inflammation), during (eg, blood gas disturbances), and after (eg, apnea and bradycardia of prematurity) this period of hemodynamic instability. Together, the delayed measures of outcome and the potentially confounding neonatal and subsequent comorbidities experienced by these infants have made it difficult to establish the role of early neonatal hemodynamic changes in subsequent neurologic dysfunction.

Given the difficulties relating very early hemodynamic changes to long-term outcome, investigators have sought more proximate outcome measures, which can be categorized into

3 broad types: (1) structural, (2) functional, and (3) failure of compensatory mechanisms (eg, cerebral pressure autoregulation). Measures of *structural* brain outcome, primarily by cranial ultrasound imaging to date, have been most commonly used (see below). Measures of acute changes in neurologic *function* are difficult in the sick premature infant. Unlike in mature subjects, in whom acute changes in neurologic function (eg, syncope) result during significant hypotension, this is seldom the case in sick premature infants. In fact, in premature infants irreversible, sometimes severe, brain injury may occur in the absence of obvious clinical signs. For this reason, most neonatal units have established surveillance cranial ultrasound protocols to detect structural signs of brain injury. Several studies have described the effect of hypotension on acute electrocortical function in premature infants, measured as changes in the amplitude, frequency, or continuity on the electroencephalogram (EEG).^{26,183,198–200} Previous studies in sick premature infants showed a decrease in EEG amplitude during hypotension.^{198,201} More recently, Victor and colleagues¹⁸³ found that in infants less than 30 weeks' gestation, EEG and cerebral oxygen extraction remained normal despite systemic blood pressure levels as low as 23 mmHg, and suggested that cerebral pressure autoregulation was maintained above this blood pressure level. Although this approach is attractive from a logistical standpoint, particularly the more recently applied limited-lead EEG techniques, the sensitivity of bedside EEG as a meaningful outcome measure for hemodynamic changes in the sick premature infant requires further investigation.

Although the most commonly used outcome to date, *structural brain imaging* techniques continue to have important limitations as early measures of outcome. Cranial ultrasound has the advantages of being portable to the bedside, relatively unobtrusive, and easily repeatable.^{4,5,129,137–139,143,151,152} In addition, it is sensitive and rapidly detects extravascular blood, making it useful for diagnosing GM-IVH. However, cranial ultrasound not only remains insensitive to but is also delayed in its detection of cerebral ischemic changes. This has been confirmed not only at autopsy^{202,203} but also in several recent MRI studies that indicate that the majority of white matter injury remains undetected by neonatal cranial ultrasound studies.¹² However, MRI studies are difficult to perform safely during the periods of greatest risk for cerebrovascular injury in these infants. Given that, in most studies to date, cranial ultrasound images have been interspersed at relatively long intervals, the temporal association between putative hemodynamic insults and injury has been difficult to define. Furthermore, there has been discrepancy between the frequency and timing of these cranial ultrasound measures across the various studies.^{6,129,135,142,144}

As discussed above, cerebral pressure-flow autoregulation is a compensatory mechanism that fails when systemic blood pressure falls below a critical threshold. Because the onset of cerebral pressure autoregulatory failure heralds an elevated risk for cerebrovascular injury at a point prior to irreversible injury, detection of cerebral pressure-passivity might provide a sensitive cerebrovascular outcome measure to relate to systemic blood pressure changes. The presence and characteristics of pressure autoregulation in the sick premature infant remain controversial.^{91,153,204,205} This is in part due to the intermittent “static” approaches used in previous studies, which precluded monitoring continuous measures of autoregulation over time. Our group has developed a technique for identifying cerebral pressure passivity by analyzing the relationship between continuous time-locked measurements of systemic blood pressure and changes in the near infrared spectroscopy-measured cerebral hemoglobin difference (HbD) signal.^{89,161,206} In earlier animal studies, we demonstrated a strong correlation between changes in cerebral HbD concentration and changes in cerebral blood flow measured by the radioactive microsphere technique.^{89,90} In our studies of premature infants, we use coherence function analysis to identify significant concordance between systemic blood pressure and cerebral HbD changes at different frequencies. Periods of significant coherence between these signals are designated as pressure passive. In this

manner, Tsuji and colleagues⁸⁹ identified a pressure-passive cerebral circulation in more than half of mechanically ventilated premature infants; furthermore, these infants were at significantly increased risk for brain injury by cranial ultrasound.⁸⁹

In a subsequent, larger study⁹⁰ with longer recording periods, we found periods of cerebral pressure passivity in almost all sick premature infants studied. Cerebral pressure passivity was not an all-or-none phenomenon, but fluctuated over time, with the overall group of premature infants spending an average of 20% of the recording period in this state.⁹⁰ Furthermore, the prevalence of cerebral pressure passivity was inversely related to gestational age. There was a significant association between the prevalence of hypotension (diagnosed by widely accepted criteria) and cerebral pressure passivity in these infants; however, cerebral pressure passivity could not be reliably predicted by the presence of hypotension alone, being present at different systemic blood pressure values both between and within infants at different times.⁹⁰ Furthermore, in these preliminary studies, the prevalence of cerebral pressure passivity was not related to cranial ultrasound lesions.⁹⁰ Therefore, the analyses were extended to include a measure of the *magnitude* of cerebral pressure passivity, using the transfer gain between blood pressure and cerebral perfusion. In these preliminary studies we have shown a significant association between high magnitudes of cerebral pressure passivity and GM-IVH by cranial ultrasound.²⁰⁷

Although these preliminary findings suggest the detection of high-magnitude pressure passivity might be used to detect risk for GM-IVH, large prospective validation studies are needed to confirm these findings. Because cerebral pressure passivity may be both a cause and a consequence of cerebrovascular insults,^{72,208–213} such studies will require early and frequently repeated cranial ultrasound.

Comorbid factors may confound the relationship between systemic hemodynamics and prematurity-related brain injury

In addition to hemodynamic insults, several other mechanisms have been implicated in the development of prematurity-related brain injury. Two of these mechanisms, ie, abnormal carbon dioxide levels and pro-inflammatory cytokines, may exert at least some of their injurious effect by actions in the systemic and cerebral circulations. *Changes in circulating carbon dioxide* have important cerebral vasomotor effects²¹⁴ that have been described in the premature infant.^{215–218} Given their respiratory instability, these infants may experience significant changes in circulating carbon dioxide. Permissive hypercapnea, a strategy used to reduce the pulmonary barotrauma of positive pressure ventilation, has become widely used.²¹⁹ Both hypo- and hypercapnea have been implicated in prematurity-related brain injury.^{220–230} Hypercapneic vasodilation and the resulting hyperemia may lead to hemorrhagic lesions through and engorgement of the microvasculature. Hypercapnea of relatively modest levels has been associated with impaired cerebral pressure autoregulation.²³¹ Hypercapnea during first 3 days of life has been identified as a risk factor for severe GM-IVH.²²¹ Conversely, severe hypocapnea may cause sustained vasoconstriction as well as an increase in oxygen-hemoglobin affinity, thereby limiting cerebral oxygen delivery.^{232,233} Severe hypocapnea decreases cerebral oxygen metabolism^{234,235} and increases cerebral glucose metabolism and cerebrospinal fluid lactate levels,^{236,237} together suggesting anaerobic metabolism. Therefore, hypo- and hypercapnea may mediate brain injury through effects on cerebral perfusion and metabolism. However, this association has been difficult to establish with certainty, because previous studies have not monitored cerebral perfusion and carbon dioxide levels continuously. Furthermore, the temporal relationship between changes in circulating carbon dioxide and cerebral hemodynamics is complex and dynamic.^{238–244} This complex relationship requires further examination.

Infection/inflammation may have deleterious effects directly on the cerebral vasculature, as well as on the systemic vessels with secondary impact on the cerebral circulation. In experimental studies, fetal and neonatal infection as well as exposure to lipopolysaccharide or cytokines may have important systemic hemodynamic effects. In fetal sheep, major impairment in cerebral vasoregulation and oxygen delivery may occur after exposure to lipopolysaccharide²⁴⁵ while other cytokines triggered by infection (especially tumor necrosis factor- α and interleukin-1 β) are known to be vasoactive and may disrupt cerebral vasoregulation.^{246–248} In premature infants, pathological features of chorioamnionitis and elevated blood interleukin-6 levels was associated with decreased mean arterial blood pressure during the early postnatal hours,²⁴⁹ which may persist over the first week of life.²⁵⁰ Although the data for a role of inflammatory mediators in prematurity-related white matter disease has been well described, the role of circulating cytokines in GM-IVH is more controversial.^{251–254}

Conclusion

It has long been accepted that a substantial component of the long-term neurodevelopmental burden in survivors of prematurity originates from neonatal brain injury resulting from systemic hemodynamic insults. However, despite compelling data from animal models, direct evidence of these mechanisms in premature humans remains limited. Both the role of hypotension in prematurity-related brain injury, as well as a role for anti-hypotensive therapies in prevention of such injury, have been difficult to establish. Consequently, there has been growing skepticism in some quarters about the rational basis for current practices, and the suggestion that less-aggressive intervention is warranted for hypotension in premature infants. In this review, we have sought to highlight the fundamental deficiencies in our attempts to establish a relationship between disturbed systemic hemodynamics and brain injury in the premature infant, as well as the major obstacles that need to be overcome if this question is to be resolved satisfactorily. It is also an urgent plea for additional data before radical changes in our approach to hypotension in premature infants are made. The dictum “a lack of evidence for an association is not evidence for the lack of an association” has never been more valid.

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