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Running Title: Neonatal cerebrovascular autoregulation

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Abstract:

Cerebrovascular pressure autoregulation is the physiologic mechanism that holds cerebral blood flow (CBF) relatively constant across changes in cerebral perfusion pressure (CPP). Cerebral vasoreactivity refers to the vasoconstriction and vasodilation that occur during fluctuations in arterial blood pressure (ABP) to maintain autoregulation. These are vital protective mechanisms of the brain. Impairments in pressure autoregulation increase the risk of brain injury and persistent neurologic disability. Autoregulation may be impaired during various neonatal disease states including prematurity, hypoxic-ischemic encephalopathy (HIE), intraventricular hemorrhage, congenital cardiac disease, and infants requiring extracorporeal membrane oxygenation (ECMO). Because infants are exquisitely sensitive to changes in cerebral blood flow (CBF), both hypoperfusion or hyperperfusion can cause significant neurologic injury. We will review neonatal pressure autoregulation and autoregulation monitoring techniques with a focus on brain protection. Current clinical therapies have failed to fully prevent permanent brain injuries in neonates. Adjuvant treatments that support and optimize autoregulation may improve neurologic outcomes.

Unique features of infant cerebral physiology

CBF regulation in the premature and term infant's brain is distinct from that of the fully matured brain. Term infants have functional autoregulation and vasoreactivity. Preterm infants, especially those born at the limits of viability, have anatomically incomplete and underdeveloped cerebral vasculature that cannot yet autoregulate fully. Studies in preterm lambs suggest that the cerebral artery and arteriole muscularis layers develop after 13 weeks' gestation, which is equivalent to approximately 25 weeks' of human gestation. Autoregulation is functional by 19 weeks' gestation in lambs, which is approximately 36 weeks' of human gestation.[1] In clinical studies of premature neonates, autoregulatory function progressively improves between 23 and 33 weeks gestation.[2] Therefore, the vasoreactive mechanisms that support autoregulation develop during the third trimester, which has implications for many infants who are born prematurely.

In addition to the on-going vascular development, anatomical features of the premature cerebral vasculature may place the premature infant at-risk for injury. Preterm neonates have fragile periventricular vascular overgrowth in the germinal matrix that is prone to hemorrhage. White matter vascularization from penetrating pial arterial growth and collateral vascularization are also incomplete. Moreover, the newborn's subarachnoid space contains a network of thin-walled vessels. These fragile and under-developed vascular networks place these infants at high risk of germinal matrix and subarachnoid hemorrhages, periventricular leukomalacia, leukoencephalopathy, corpus callosum gliosis and multi-cystic encephalopathy.[3]

These unique aspects of preterm cerebral vasculature and anatomy are accompanied by gross differences in CBF between preterm and term neonates. CBF increases progressively during fetal life and infancy, peaking in the pre-teen years and then declines steadily into adulthood. The infant brain

consumes 17% of cardiac output and accounts for 17% of the body mass. In comparison, the adult brain comprises just over 2% of total body mass but utilizes 25% of the cardiac output. Low placental vascular resistance and low arterial oxygen content of fetal blood both influence fetal CBF. After birth, CBF increases during the first day of life due to decreasing cerebrovascular resistance and then CBF continues to gradually increase over the first week of life.[4] However, CBF in many infants hovers near the ischemic threshold of 20 cc/100g/min. In healthy term and pre-term infants without respiratory distress syndrome, CBF at birth is roughly one-third of adult values.[5-8] Rapid postnatal brain development then causes cerebral glucose consumption and blood flow to rapidly increase after birth and peak at approximately 5 years of age.[9,10]

Finally, the preterm neonate with hypotension can have CBF that is more influenced by cardiac cycle changes than term neonates. Premature neonates have very low blood pressure compared to term neonates. During diastole in a hypotensive preterm neonate, CBF is passive to diastolic blood pressure, and often absent entirely. CBF autoregulation, when it occurs in this population, is most robust and present during the systolic phase cardiac cycle compared to CBF autoregulation of the mean and diastolic phases of the cardiac cycle. Further, pressure reactivity and autoregulation to systolic and mean ABP is not observed until 26 to 28 weeks' gestation.[2]

Neonatal arterial blood pressure management

Hypotension with low CBF and post-ischemia reperfusion contribute to the pathogenesis of brain injury in human prematurity,[11-14] HIE, and experimental animal models.[15-20] Hypoperfusion, reperfusion and hyperemia may promote neural injury through a variety of mechanisms that include oxygen-glucose deprivation, endoplasmic reticulum stress, disruptions in proteostasis, glutamate excitotoxicity, oxidative

stress, inflammation and ultimately activation of cell death pathways in gray and white matter.[21-27] Ensuring appropriate CBF to the injured neonatal brain could block these injurious mechanisms and minimize secondary brain injury.

ABP is the most frequently monitored parameter to assess hemodynamic status in infants. However, ABP does not correlate to systemic blood flow as shock can occur during normotension.[28,29] While the goal of neonatal ABP management is to adequately perfuse the brain and other vital organs, evidence-based ABP thresholds that define hypotension with cerebral hypoperfusion do not exist. Moreover, we do not know whether we should support ABP with vasopressors, inotropes, or fluid resuscitation and when to initiate these treatments. Defining optimal neonatal ABP management to support cerebral and other vital organ perfusion would significantly advance clinical care.[30-34]

Multiple observational cohort studies report "normative" ABP ranges based on birth weight, gestational age (GA), and postnatal age.[35-40] Many neonatologists define hypotension on the first day of life as mean ABP less than or equal to the GA in weeks.[41] However, outcomes are similar between neonates with mean ABP less than GA and those with normal blood pressure when perfusion is clinically adequate.[42,43] The paucity of evidence showing improved outcomes after raising ABP to a "normal range" has prevented neonatologists from defining hypotension and setting ABP treatment thresholds. In fact, treating hypotension may be deleterious and could increase the risk of intraventricular hemorrhage.[42,44]

Cerebrovascular pressure autoregulation curves vary among individual neonates

Cerebrovascular pressure autoregulation protects the brain from deleterious CBF fluctuations in the face of changing CPP. The classic mechanistic depiction is a sigmoidal curve with stable CBF across a range of CPP and pressure passive CBF outside this range. (Figure 1) The range of functional

autoregulation, which is called the autoregulatory plateau, is bounded by the upper limit of autoregulation (ULA) and the lower limit of autoregulation (LLA). Cerebral vasoreactivity functions only when CPP is along this plateau. Above the ULA and below the LLA, CBF is passive to blood pressure due to impaired vasoreactivity and the brain is at risk of hyperemic or hypoperfusion injury.

The optimal ABP and CPP are conceptually located in the center of the autoregulatory plateau and represent the pressures at which vasoreactive responses are most robust. Optimizing ABP and CPP to maximize vasoreactivity may reduce the risk of secondary brain injury. Because neonatal intracranial pressure (ICP) monitoring is generally not feasible, neonatologists must rely upon ABP management to support autoregulation.

Pressure autoregulation is one of many cerebral servomechanisms that regulate CBF. Other mechanisms include neurovascular coupling; the systemic vasoconstrictive response to shock with activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and vasopression release; and cerebral vasoreactivity to carbon dioxide, oxygen, and glucose. [45-49] Pressure autoregulation can be measured independent of these other CBF regulators by collecting ABP and cerebral waveform data at the frequency of 0.004-0.05 Hz (20-250 seconds). This frequency is where slow wave changes in CBV occur during pressure autoregulatory vasoreactivity.[50]

Autoregulation can be characterized by static, or dynamic metrics. Static autoregulation describes the steady state changes of cerebrovascular resistance when ABP varies, and dynamic autoregulation metrics describe changes in cerebrovascular resistance and flow in a faster time course. The results of these methods are related, but not necessarily interchangeable, and there is no gold standard measure of autoregulation. Autoregulation metrics must capture a change in ABP alongside a synchronous measurement of CBF, cerebral blood volume (CBV), or cerebral oxygenation. The relationship between

the change in ABP and change in CBF, CBV, or oxygenation is mathematically estimated to provide an index of autoregulatory function. Vasoreactivity is measured by changes in CBV. Autoregulation is measured by changes in CBF or oxygenation.

Pressure autoregulation monitoring can define an individual patient's unique cerebral autoregulation and vasoreactivity physiology to determine the optimal ABP with most functional autoregulation in addition to the ULA and LLA. This could enable patient-oriented, neonatal precision medicine that is superior to generalized ABP goals based on gestational age or body weight.

An individual infant's LLA, optimal ABP, ULA, and autoregulatory plateau may shift during evolving brain injury and treatment. In a piglet model of hydrocephalus, the LLA shifted to a higher CPP during progressive intracranial hypertension from artificial cerebrospinal fluid infusion or from cephalic venous outflow obstruction with intracranial venous congestion.[51,52] Additional analysis from the piglet hydrocephalus data showed that optimal ABP increases with rising ICP. Intracranial hypertension can also move the ULA to a lower CPP.[53] The combination of an increased LLA (rightward shift) and a decreased ULA (leftward shift) causes the autoregulatory plateau to narrow. Whole-body hypothermia after neonatal brain hypoxia acutely decreases the LLA, although this LLA shift was not sustained with longer durations of hypothermia.[54,55] Further, autoregulatory responses to different vasopressors may vary by sex and age after brain injury.[33,56-59] Milrinone may significantly decrease blood pressure to below optimal ABP in girls.[33] Common neonatal clinical situations with the potential physiologic changes outlined above include progressive intracranial hypertension with hydrocephalus, cerebral venous outflow impediments with cavo-pulmonary shunts for cardiac anomalies, high ventilator airway pressures, therapeutic hypothermia for HIE, extracorporeal membrane oxygenation (ECMO), and vasopressor and afterload reduction therapies.

Critical Closing Pressure

The critical closing pressure (CrCP) is a crucial component of neonatal cerebrovascular physiology that remains relatively understudied. The CrCP is the ABP at which CBF ceases due to vascular collapse. It is posited to be the sum of vascular wall tension and ICP.[60] CrCP normalizes the ABP to an "effective CPP" or "closing margin" where the effective CPP = ABP – CrCP.[61,62] In premature neonates, low diastolic blood pressures can approach or reach the CrCP with little evident CBF.[2,63] The CrCP in HIE and other neonatal neurologic diseases deserves further study. CrCP is distinct from and lower than the autoregulatory plateau. When ABP is below the lower limit of autoregulation, CBF is passive to ABP. When ABP is below the CrCP, CBF ceases altogether. The low diastolic blood pressure of the preterm neonate results in a CBF pattern that can occur only during systole as ABP cycles above and below CrCP with each cardiac cycle. Intuitively, one might hypothesize that this state is a vulnerability to ischemia and white matter injury, but these associations have not yet been studied as the tools to measure CrCP are relatively new.

The CrCP increases gradually from 23 to 31 weeks' gestation at a rate of 1.4 mm Hg per week and is approximately 22-33 mm Hg in premature and term infants.[63-65] Intersubject variability in the CrCP was high in that study, suggesting that CrCP cannot be estimated by age, but requires direct measurement (Figure 2). The time courses of CrCP changes during transition to extrauterine life, and during common comorbid conditions have not yet been elucidated. Small variances in CrCP cause large variances in effective CPP in preterm infants. For example, a 10 mm Hg increase in CrCP from 20 to 30 mm Hg would profoundly decrease CBF in a preterm infant with a mean ABP of 30 mm Hg because the effective CPP would change from 10 mm Hg to zero. An identical 10 mm Hg CrCP increase would have trivial effect on CBF in an adult with a mean ABP of 70 mm Hg.

The proximity of ABP to CrCP in preterm infants may make CrCP an effective cerebral perfusion metric in this population. Simply stated, the ABP and CrCP-derived effective CPP may be more relevant to define brain perfusion in preterm neonates than ABP alone. Therefore, autoregulation monitoring in these infants should take into account CrCP and the effective CPP. Further, in very preterm neonates who may lack autoregulatory capacity entirely, the CrCP measurement may provide an alternate therapeutic target to manage cerebral hemodynamics in an "adequate but not hyperemic" range that has yet to be elucidated by wider study of this parameter in this population.

Non-invasive autoregulation and vasoreactivity monitoring in neonates

ICP monitoring is frequently used to measure changes in CBV during cerebral vasoreactivity in adults and children. Because invasive cranial monitors are not routinely used in neonatal clinical practice, non-invasive autoregulation metrics have been developed and applied to neonates. All non-invasive autoregulation metrics are limited by anatomic region. For instance, dysfunctional autoregulation in cerebellum will not be detected by measures in the frontal cortex or in a single cortical cerebral artery.[1]

Historically, neonatal cerebral autoregulation has been monitored most frequently with transcranial Doppler (TCD) ultrasound to measure CBF-velocity in a target artery, such as the middle or anterior cerebral artery.[2,66-70] Prior to this technique, measurement of CBF in human subjects relied on indicator-dilution techniques. TCD allows for non-invasive estimates of CBF velocity and can easily be performed at the bedside. However, TCD has its limitations. It is only capable of measuring velocity and not flow, and there are technical challenges of obtaining a stable long-term signal in very preterm infants.

Near-infrared spectroscopy (NIRS) has been widely used to study neonatal cerebral hemodynamics and oxygenation; NIRS takes advantage of the relative transparency of biological tissue to

near-infrared light (700-1000 nm) and the wavelength dependent absorption characteristics of hemoglobin, which varies with oxygenation. As well as changes in oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb), changes in the sum of HbO_2 and HHb can be calculated as a surrogate measure of CBV during autoregulatory vasoreactivity. Fluctuations in ICP and CBV during vasoreactive responses correlate to fluctuations in the NIRS relative total tissue hemoglobin.[50] While absolute quantitative measurements of CBF and CBV can be made, they rely on manipulation of FiO_2 or injection of an optical tracer and provide only a static measurement.[71] The difference between oxygenated hemoglobin and deoxyhemoglobin (HbD) has also been shown to reflect changes in CBF.[72,73] More recently, NIRS-based metrics including oxyhemoglobin optical density have been used to estimate CBF.[74] The regional oxyhemoglobin saturation (rSO_2) is primarily a venous-weighted signal and reflects the hemoglobin bound oxygen that remains after tissues have taken what they need. In other words, rSO_2 demonstrates changes in oxygen supply and demand and thus is affected by factors independent of pressure autoregulation, including hemoglobin level, inspired oxygen, seizures, sedation and temperature. rSO_2 may be a better surrogate of CBF in the premature infant because of the low and constant cerebral metabolic rate of oxygen in this population.

Calculating vasoreactivity indices: slow wave pressure monitoring

Pressure autoregulation monitoring can identify the optimal ABP with most robust vasoreactivity in individual patients after pediatric and adult traumatic brain injury, during cardiopulmonary bypass, after pediatric cardiac arrest and in neonatal HIE.[75-77] The ability to accurately monitor pressure autoregulation depends on analyzing spontaneous and repetitive slow CBV and ICP waves. Lundgren first categorized these slow waves as "B waves" which occur with a period between 20 and 200 seconds.[78]

These slow waves are generated from the cerebral autoregulatory vasodilation and vasoconstriction that occur with fluctuations in CPP. As the vessels dilate, the CBV increases and the ICP correspondingly increases. When the vessels constrict, the CBV decreases and the ICP decreases. Autoregulatory vasoreactivity can then be measured by synchronously measuring ABP at the same frequency to analyze the relationship between the ABP and intracranial waveforms.

Multiple mathematical algorithms have been used to describe the relationship between ABP and CBV, ICP or CBF to estimate autoregulation. These include simple correlation, and in the frequency domain, cross-correlation functions of coherence, phase, and gain have all been used. When vasoreactivity is impaired, CBF, CBV and ICP are passive to ABP, and each of these functions quantifies passivity in a different way. The interchangeability of these myriad metrics is not known and this proliferation of methods with minimal validation is a major limitation of the current literature of autoregulation. From controlled animal models with known states of intact and impaired autoregulation, it has been shown that fluctuations in ABP cause coherent and in-phase fluctuations in CBV and ICP when autoregulation is absent. This is equivalent to a positive correlation. When autoregulatory vasoreactivity is functional, CBV is pressure-reactive and the CBV and ICP waveforms are coherent with ABP but have a 180° phase shift. This is equivalent to a negative correlation. (Figure 3)

Continuous measurement of correlation between ABP and CBV or ICP can identify the optimal ABP with most functional vasoreactivity. The optimal ABP found at the nadir of the plot with correlation coefficients on the y-axis and ABP on the x-axis. (Figure 4) A criticism of this technique is that optimal ABP is not identifiable in patients without a U-shaped curve and apparent nadir. Maintaining blood pressure within optimal ABP is associated with less brain injury on MRI and improved 2-year neurodevelopmental outcomes in neonatal HIE.[79-83] Traumatic brain injury and preterm neonate studies also support using optimal MAP as a hemodynamic goal.

Spontaneous slow wave activity can have variable periodicity and amplitude which generates imprecision in autoregulation monitoring. In order to minimize this effect, filters can be applied to the data to eliminate time epochs with inadequate slow wave power and multiple measurements at the same ABP are commonly averaged together to mitigate noise in the measurements. This important limitation of continuous autoregulation monitoring is the subject of ongoing studies using advanced signal processing techniques. Limiting noise from this effect would result in a faster and more reliable determinant of optimal ABP for autoregulation.

Methods to measure neonatal autoregulation

The above concepts have been applied to near-infrared measurements of HbD or rSO_2 to estimate CBF autoregulation in neonates. Although slow waves of ABP are erratic and introduce noise in autoregulation measurements, they occur naturally and are therefore the safest way to measure autoregulation.[84] In contrast, traditional autoregulation monitoring techniques that intentionally change the ABP with thigh cuff deflation, or vasoconstrictor injections are not generally suitable for critically ill neonates.[85]

Time-domain analysis (correlation) has been used with filters to limit the analysis to the specific frequency range of slow waves. This method detected the LLA with high sensitivity and specificity in animal models.[50,54,55,74] Maintaining the blood pressure within the optimal ABP from this method is associated with survival and neurologic recovery in large adult studies of traumatic brain injury [50,75,86,87] and in single-center studies of neonatal HIE, pediatric cardiac arrest, and pediatric traumatic brain injury.[79-81,83,88,89] Blood pressure deviation from optimal ABP delineated in this way may also be associated with cardiopulmonary and renal injury in neonatal HIE and renal injury after

cardiopulmonary bypass.[32-34]

Frequency-domain analyses including coherence, phase, and gain of transfer function have also been used to assess autoregulation in the preterm neonate.[84] These analyses include assumptions of linearity and stationarity that are not always present in biologic systems.[90] Limited animal data have validated these frequency domain cross-correlation functions for estimating cerebral autoregulation.[91] Coherence and gain analyses of HbD and mean ABP identified an association between dysfunctional autoregulation and brain injury on MRI or death in neonatal HIE.[73] Limitations include low precision that make monitoring for several hours essential to reliably measure coherence. In some studies coherence is found to be high when blood pressure is either above or below the LLA, and we suggest that coherence may be most useful as a filter to delineate adequate slow wave power to measure autoregulation with either phase or correlation.

Wavelet coherence analysis characterizes continuous or intermittent cross-correlations between two time series at multiple time scales, which makes no assumption about the stationarity of input signals. This technique has been performed in limited studies especially in preterm infants, and it can detect frequencies up to 0.017 Hz due to limitations of instruments and not by the analysis itself.[92] Wavelet coherence analysis of ABP and cerebral oximetry at ultra-low frequencies <0.0002 Hz (80 min time scale) has been associated with neurologic outcome in HIE.[93]

Finally, an alternative assessment of autoregulation uses the relationship between heart rate changes and cerebral oxygenation. The tissue oxygenation heart rate reactivity index (TOHRx), an index of cerebral vascular reactivity, is derived from the correlation coefficient between slow waves of heart rate (HR) and tissue oxygenation index (TOI) measured with NIRS.[94] Higher TOHRx values were observed in infants with worse clinical score of mortality and morbidity (Clinical Risk Index for Babies II).

In addition, increased passivity between TOI and HR was observed with arterial hypotension. These TOHRx findings are unique to the preterm population and may be related to systemic hemodynamic control as cardiac output in preterm infants is mainly regulated by heart rate due to the immature myocardium. In adults, CBF has no correlation with output, however, in preterm infants a positive correlation between CBF and left cardiac output has been described.[95,96] Further, in preterm infants, optimal mean arterial blood pressure has been defined using TOHRx in a cohort of infants born at ≤ 32 weeks gestational age. Absolute deviations away from optimal blood pressure were higher in those infants who died. Infants who developed severe IVH had deviations away from optimal values greater than 4 mmHg. [97]

Limitation of NIRS-based autoregulation monitoring

There are limitations of NIRS autoregulation monitoring. NIRS placed on the forehead or tempero-parietal region of the head measures the frontal lobe and tempero-parietal lobes and cannot capture vasoreactivity in other areas known to be vulnerable in HIE and prematurity, including many white matter regions (such as periventricular white matter), basal ganglia, thalamus, and other cortical regions. Thus, frontal optimal ABP may not reflect that of other anatomic regions. Autoregulation has a prominent macrocirculatory component from involvement of large cerebral arteries and pial arterioles that are upstream from local parenchymal tissue. Autoregulatory vasoreactivity is primarily mediated by intrinsic myogenic responses to changes in transmural pressure. Global cerebral ischemia in HIE and vascular immaturity in preterm neonates would not be expected to cause large regional differences in optimal ABP. It is also likely that prolonged and large deviations in blood pressure from optimal MAP in frontal or tempero-parietal cortex will affect perfusion throughout much of the brain. In the absence of clinically

available autoregulation metrics for regional autoregulatory function, identifying optimal MAP in the frontal lobe is a reasonable first approximation to guide hemodynamic management in critically ill neonates. NIRS also permits continuous monitoring over long periods of time that cannot be easily accomplished with transcranial Doppler.

NIRS autoregulation monitoring in specific neonatal diseases

The purpose of this review of relevant studies was to examine those studies that were associated with specific outcome measures. The studies presented were found through PubMed search using "prematurity" or "premature" or "neonate" and "hypoxic ischemic encephalopathy" or "neonatal encephalopathy" with "autoregulation" and "cerebral blood flow." Studies were then selected that focused on time and frequency domain or wavelet autoregulation methodologies using NIRS in this population.

Prematurity/Intraventricular Hemorrhage

Both time domain and frequency domain analyses have been used to measure autoregulation in premature infants. CBF autoregulation to systolic and mean ABP develops between 23 and 33 weeks gestation, and infants younger than 26 weeks GA are at high risk of pressure-passive CBF. However, CBF is overall passive to diastolic ABP before 33 weeks' gestation.[2] Dysfunctional autoregulation is common in premature infants with many demonstrating fluctuating pressure passivity over the first few days of life.[98] In addition, impairments in autoregulation increase the risk of severe intraventricular hemorrhage and death and those infants with IVH often have cerebral hyperperfusion and pressure passive cerebral perfusion with correlation of rSO2 and ABP.[99-103] Further, sick infants are more prone to

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dysautoregulation and have a potentially narrower autoregulatory plateau meaning those infants may be more sensitive to fluctuations in ABP.[104] This is in agreement with our findings that CBF autoregulation to systolic and mean ABP develops between 23 and 33 weeks gestation, and infants younger than 26 weeks GA are at high risk of pressure-passive CBF. Dopamine therapy was associated with dysfunctional autoregulation, but it is unclear whether dopamine impaired autoregulation or if it was an indicator of severe illness.[105] Finally, blood pressure divergence below optimal ABP was associated with death, and deviation above optimal ABP increased the risk of severe intraventricular hemorrhage.[97]

HIE

Frequency, time, and wavelet coherence analyses have been used to study HIE during spontaneous blood pressure fluctuations. Poorer autoregulatory function measured by coherence and gain between HbD and ABP were associated with brain injury on MRI or death.[73] Blood pressure deviation from optimal ABP identified by time domain analysis was associated with greater brain injury on MRI and worse 2-year neurodevelopmental outcomes.[79-83] Finally, in-phase coherence of mean ABP and cerebral oximetry at time scales less than 80 min (< 0.0002 Hz) and anti-phase coherence at time scales of approximately 2.5 h (~ 0.0001 Hz) were reported by wavelet coherence analysis. Both in-phase and anti-phase coherence were related to worse clinical outcomes.[93]

Neonatal cardiac disease and cardiopulmonary bypass

Autoregulation monitoring in neonates with congenital cardiac disease has been conducted in both the frequency and time domains. Hypercarbia and fluctuations in ABP were associated with dysfunctional autoregulation after cardiac surgery.[106] Autoregulatory function worsens at lower blood

pressures during cardiopulmonary bypass, and the LLA can be identified in nearly 80% of patients during bypass.[107] Hypothermia was thought to cause impaired autoregulation in this population, but further study demonstrated that neonates are managed with lower ABP during hypothermia, and the effect of hypothermia cannot be isolated in these data.[108] Finally, term newborns with congenital heart disease displayed associations between abnormal cerebral autoregulation and greater fractional tissue oxygen extraction, lack of sedation, and lower hemoglobin suggesting that impaired oxygen delivery and increased cerebral metabolic demand may overwhelm autoregulatory capacity in these infants.[109]

Extracorporeal Membrane Oxygenation (ECMO)

Wavelet cross correlation was calculated between mean ABP and NIRS oxyhemoglobin saturation in neonates receiving veno-arterial ECMO. NIRS signals were measured in the frontal, parietal and occipital cortices using multi-modal NIRS monitoring and a customized head cap. Decreasing the ECMO flow from 100% to 70% caused dysfunctional autoregulation at lower flow. Right parietal cortex had greater disruptions in autoregulation than the left parietal cortex, which may be related to right-sided cannulation of the common carotid artery and internal jugular vein.[110] Obstructions in cephalic venous drainage may affect autoregulation by increasing the ICP.[51] Further studies are needed on the effects of carotid and jugular ECMO cannulae on cerebrovascular hemodynamics.

Future Directions

The majority of neonatal autoregulation and vasoreactivity studies are limited to small and often single-center studies. Multicenter studies are needed to increase sample size, account for variation in clinical practice, and accommodate the challenges of enrolling neonates, a medically fragile population, in

clinical studies. Moreover, autoregulation monitoring requires an indwelling arterial catheter because non-invasive continuous ABP monitoring techniques, such as photoplethysmography, have not been well established in neonates. The requirement for an arterial catheter and reluctance of some families to enroll their critically ill infants in clinical research limits sample sizes. If large scale observational data support a link between functional autoregulation and improved neurologic outcomes, interventional studies to determine whether identifying and targeting optimal ABP should be considered. Ancillary studies to ongoing neonatal clinical trials, including erythropoietin and other adjuvant therapies, provide additional opportunities to test the effect of drug therapies on cerebral autoregulation.

Neonatal animal models could define the utility and limitations of non-invasive, regional autoregulation monitoring. For instance, regional variation in thalamic and cortical CBF after hypoxia in developing brain could be compared to clinically accessible NIRS and middle or anterior cerebral artery transcranial Doppler.[111] This would require a large animal model that permits synchronized, multi-modal, cerebral measurements, such as piglets. Optimal ABP in discrete anatomic regions, including basal ganglia, thalamus, large white matter tracts, and different cortices could be identified with laser Doppler flowmetry and local brain tissue oxygenation through correlation with ABP. Then, regional optimal ABP could be compared to that of frontal cortex over long monitoring periods to extrapolate information on clinical frontal NIRS autoregulation monitoring.

The ultimate goal of supporting autoregulation is to improve neurologic outcomes, and this can only be accomplished by preventing neural cell death. Animal models can help determine whether functional vasoreactivity blocks neuropathologic processes after hypoxia and reperfusion. These pathways include oxidative and endoplasmic reticulum stress, inflammation, disruptions in proteostasis and synaptogenesis, and activation of cell death pathways in white and gray matter. Premature swine and ovine models could also be used to test interventions aimed at supporting autoregulation.[112,113]

Conclusion

Current clinical practice does not prevent neurologic injuries in critically ill neonates, and generalized blood pressure guidelines are inadequate. Cerebrovascular autoregulation and vasoreactivity monitoring can define the blood pressure range that best supports CBF to the developing brain. In particular, neonates affected by prematurity, hypoxia-ischemia, congenital heart disease or infants requiring ECMO may benefit from autoregulation-directed care. Precision medicine applied to autoregulation and vasoreactivity monitoring can individualize neuroprotective treatments in critically ill neonates.

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Figure Legend

Figure 1. Cerebral blood flow autoregulation curve

Autoregulation is the physiologic mechanism that holds blood flow to the brain constant across a range of blood pressure. The flat area of the curve is a state of pressure reactivity where blood pressure and blood flow go in opposite directions. However, outside the range of autoregulation on the two ends is a state of pressure passivity where blood flow is purely dependent on blood pressure. There is no more reactivity in the vessels.
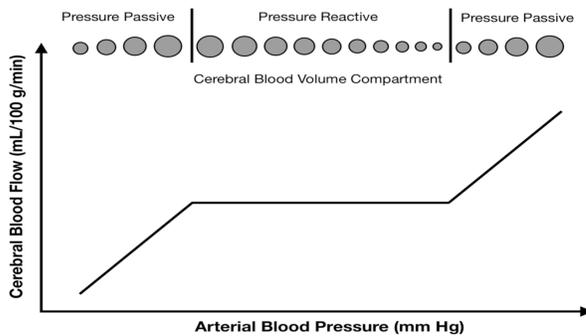

Figure 2. Changes in critical closing pressure across gestational age

Critical closing pressure increases with gestational age at a rate of 1.4 mm Hg per week of gestation (P <

0.0001).

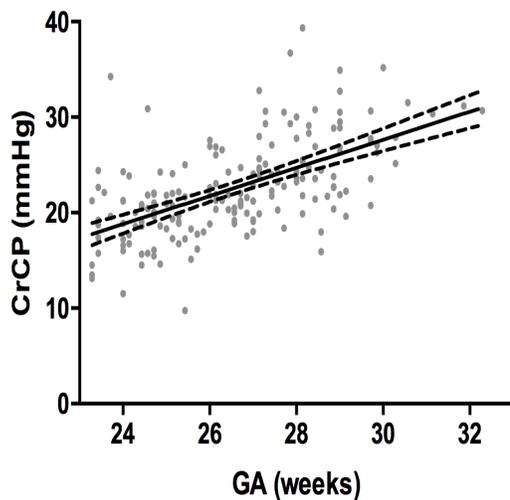From Rhee CJ et al. Pediatr Res. 2015;78(1):71-5.

Figure 3. Graphical explanations of the autoregulation metrics.

(A) Coherence analysis of CBF measured by transcranial Doppler (TCD) ultrasound in preterm neonate. Coherence is high between ABP (red line) and CBF (black line) indicating a state of dysautoregulation at slow wave frequencies. Bottom panel shows coherence as a function of frequency. (B) Waveform 1 (W1, solid line) and waveform 2 (W2, dotted line) are shown for concept. The gain is the damping effect, and the phase shift is the time delay between the two waveforms. Lower gain indicates better autoregulatory function. (C, D) Blood pressure was decreased in a neonatal piglet with continuous mean arterial blood pressure (MAP), intracranial pressure (ICP), cerebral blood volume (CBV) NIRS tissue hemoblobin index, and cerebral blood flow (CBF) laser Doppler flow (LDF) measurements. When MAP exceeds the lower limit of autoregulation and CBF is relatively constant, slow MAP waves are out of phase with the ICP and CBV (red star and box). As MAP decreases below the lower limit of autoregulation and CBF falls, the MAP, ICP and CBV waves are all in phase indicating a state of dysautoregulation (blue cross and box).

Adapted with permission from:

SAGE Publications; van Beek AH, Claasen JA, Rikkert MG, Jansen RW; Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. J Cereb Blood Flow Metab 2008; 28(6):1071-85.

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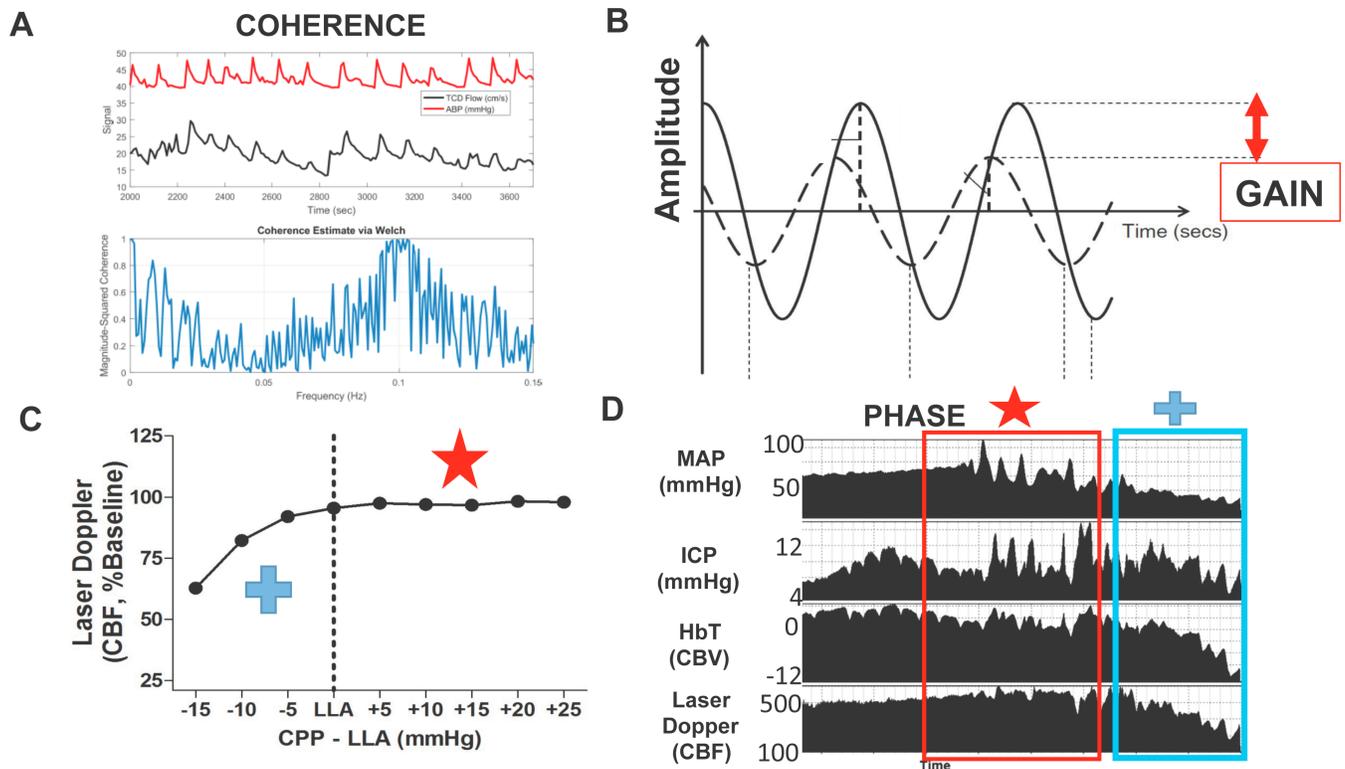
Figure 4. Determining optimal arterial blood pressure

An example of one patient using autoregulation monitoring to determine optimal mean arterial blood pressure (MAP). Slow waves of MAP (top) and cerebral blood volume (CBV, bottom) are depicted (A/C). Autoregulation monitoring during periods of intact and impaired autoregulation in this infant. When autoregulation is intact, MAP waves negatively correlate to changes in NIRS-measured CBV (A/B). The correlation of CBV and MAP is the hemoglobin volume index (HVx). When autoregulation is impaired, MAP and CBV become positively correlated, yielding a positive HVx (C/D). Thus, a more negative HVx indicates functional pressure reactivity and intact autoregulation, and a more positive HVx indicates decreased pressure reactivity and impaired autoregulation. When the measures of HVx are then plotted as a function of MAP and placed in 5 mm Hg bins, optimal MAP is identified as the nadir when the correlation coefficients are plotted against ABP (E). Here for this patient, optimal ABP is 50 mm Hg where autoregulation is intact and most robust.