Cerebral Autoregulation in Sick Infants

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Cerebral Autoregulation in Sick Infants: Current Insights

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KEYWORDS

• Cerebral autoregulation • Cerebral hemodynamics • Preterm infant
• Fetal growth restriction • Hypoxic-ischemic encephalopathy
• Congenital heart disease • Neonatal surgery

KEY POINTS

- Assessing cerebral autoregulation in sick infants is feasible but not yet standard care.
- Infants born preterm, after fetal growth restriction, with congenital heart disease or hypoxic–ischemic encephalopathy are at risk for impaired cerebral autoregulation.
- Awareness of risk factors for impaired cerebral autoregulation and individualizing hemodynamic care accordingly may in time decrease cerebral injury in sick infants.
- Determining the individual limits of blood pressure at which cerebral autoregulation works best may improve the outcome of these infants and needs further investigation.

INTRODUCTION

The brain is important for our survival and identity. It has high metabolic demands and is therefore particularly vulnerable to hypoxia and hypoglycemia. To prevent injury and safeguard proper function, the brain's vasculature has developed the ability to maintain a stable cerebral blood flow (CBF) regardless of a broad range of cerebral perfusion pressures (CPP) (**Fig. 1**). This ability is called cerebral or cerebrovascular autoregulation (CAR), which is a primitive reflex known to exist in mammals as part of an "enigmatic reflex to preserve life."[1]

Although complex and not yet fully understood, CAR is largely effected through myogenic mechanisms mediated by smooth muscle cells lining the cerebral arteries. It involves a response to increased intraluminal pressure, which causes depolarization of smooth muscle cell membranes and calcium-dependent vasoconstriction, thereby preventing hyperperfusion.[2] The opposite occurs at low intraluminal pressure, resulting in vasodilation and increased CBF. Both the range of pressures, wherein cerebral

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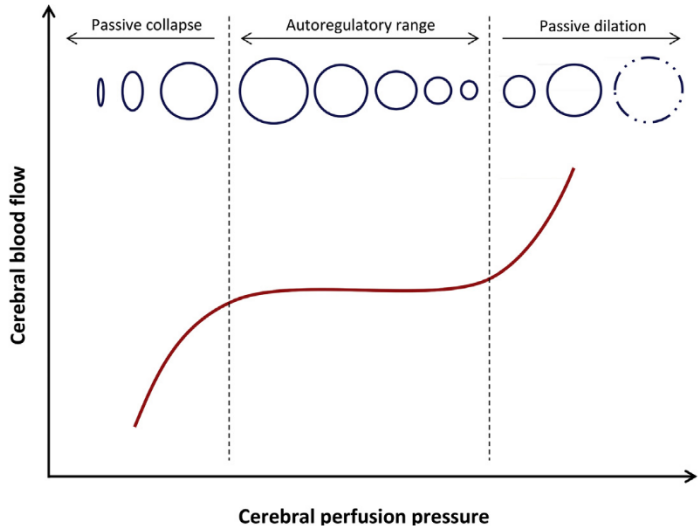

Fig. 1. The cerebral autoregulatory curve. Circles represent the schematic arterial diameter. Active vasoconstriction or vasodilation are only possible within a certain autoregulatory range, ensuring a constant CBF. The lower and the upper pressure-dependent limit of this range are depicted by vertical dotted lines. If CPP falls below the lower limit of autoregulatory capacity, arteries collapse and CBF ceases. If pressure rises above the upper limit of autoregulatory capacity, arteries dilate by force and may snap, causing hemorrhage.

autoregulation is effective and CBF remains constant, and the level of CBF within that range can be affected by several biochemical and autonomic factors. First, arterial oxygen and carbon dioxide partial pressure may alter cerebrovascular tone.[3] Although hypoxia and hypercapnia induce cerebral vasodilation, hypocapnia has shown to cause cerebral vasoconstriction.[4,5] Both arterial oxygen and carbon dioxide partial pressure affect the CPP range and the CBF level at which the autoregulatory system effectively works.[5] Second, the cerebral vasculature is rich in α_1-adrenergic receptors and thereby a target of the autonomic nervous system, although autonomic control seems to play only a modest, frequency-dependent role in basal CAR.[6,7] Furthermore, it seems that, in newborn infants, hypoglycemia also induces cerebral capillary recruitment, increasing CBF.[8,9] Last but not least, neuronal activity may alter basal arterial tone and thus CBF according to regional metabolic demands known as neurovascular coupling or functional hyperemia. It involves neuronal glutamate signaling, the release of neuronal and glial vasoactive substances, and subsequent relaxation of vascular smooth muscle.[2,7] All these factors need to be taken into account when understanding and assessing the dynamic and integrative mechanisms of CAR.

Under healthy conditions, CAR develops and matures with arterial muscularization starting before midpregnancy.[10,11] In utero, minor changes in fetal CPP are usually endured, because ample—and with progression of pregnancy continuously increasing—placenta perfusion ensures a stable fetal perfusion.[12] After term birth, CAR has developed to be functional for the small blood pressure (BP) changes that occur during the day. However, if a child is born preterm, after fetal growth restriction (FGR), or with congenital heart disease (CHD) or perinatal asphyxia, the risk for a lower CPP and larger fluctuations in CPP after birth is increased. Especially in the preterm infant, an immature and inadequate CAR in combination with hemodynamic instability

and immature fragile cerebral blood vessels may cause periventricular hemorrhage or intraventricular hemorrhage (IVH).[13,14] Moreover, hypoperfusion of the developing white matter, which is highly susceptible to hypoxia[15] and hypoglycemia, imposes the serious threat of white matter injury on this infants brain.[16] This injury can have lifelong consequences, including cognitive problems, motor dysfunction, and/or behavioral disorders. Similarly, in term born infants with hypoxic–ischemic encephalopathy (HIE) receiving therapeutic hypothermia, pressure-passive changes in cerebral metabolism have been associated with poorer neurodevelopment.[17]

This review therefore aims to summarize current knowledge on how CAR is measured, interpreted, and affected in the susceptible neonate.

HOW CAN CEREBROVASCULAR AUTOREGULATION BE ASSESSED IN THE NEONATE?

To measure CAR, one needs to assess the potential relation between CPP and CBF. When both change correspondingly, implying a pressure-passive CBF, autoregulation is absent. Several difficulties are encountered when trying to measure these parameters in the infant, and even more so when trying to measure for prolonged time periods.

First, particularly in preterm born infants during transition, CPP is not identical to BP for several reasons.[18] Invasive BP measurements are usually performed by a catheter inserted into the small arteries of either one of the extremities or into the aorta via the umbilical artery. However, except for the right arm, postductal BP hardly represents BP in the carotid arteries as blood tends to shunt away from the aorta into the pulmonary arteries through the patent ductus arteriosus (PDA). Moreover, during the transitional period, the presence of intracardiac and extracardiac shunts may vary and will affect BP differently at various anatomic locations. For technical and safety reasons, it is not feasible to invasively measure carotid BP in these small infants. Still, systemic BP is probably the closest we have to CPP. Because preterm or FGR born infants are less able to increase cardiac output to increase BP, but more able to increase heart rate (HR), HR may be a considerable alternative for BP to represent CPP.[19]

Second, CBF can be intermittently estimated using cranial Doppler sonography.[20] Alternatively, near-infrared spectroscopy (NIRS) has been introduced for a continuous and noninvasive assessment of cerebral oxygenation as a surrogate for cerebral perfusion.[21] Assuming a stable cerebral metabolism, changes in cerebral tissue oxygen saturation as measured by NIRS will likely result from changes in CBF. NIRS, however, has its limitations, because it is based on several assumptions, such as a stable hemoglobin level and a fixed arterial–venous volume ratio. This factor has led to the use of a diversity of algorithms within the various devices and sensors available, hampering the comparison of measurements performed.[22] Also, repeatability and precision are imperfect, with variations within and between infants of 5% to 7%.[23] Nevertheless, the precision of the mean tissue oxygen saturation using NIRS is probably comparable with that of pulse oximetry.[23] Longitudinal NIRS assessment can reliably demonstrate clinically relevant changes in cerebral oxygenation and perfusion.

Having encountered these difficulties, increasing research on the assessment of autoregulation in preterm born infants is being done, mainly using BP as a surrogate for CPP and Doppler or NIRS to determine CBF. Interpretation of the results of this research needs to be done with caution, given the considerations as just presented.

A third challenge to discuss when assessing CAR using BP and cerebral tissue oxygen saturation is how to mathematically proof any relation between both parameters.[24] A rough correlation may fail to detect brief episodes of altered CAR or a potential delay in cerebrovascular response. Also, because both BP and cerebral tissue oxygen saturation by nature tend to oscillate at a high frequency (Mayer waves),

which is partially linked to sympathetic nervous activity,[25] it is necessary to focus on waves of certain lower frequencies, at which myogenic CAR may operate,[26] to ensure a causal relationship. Several studies have been performed to identify the optimal frequency range for the assessment of CAR.[27] Also, the optimal method to assess the correlation between the 2 parameters has been investigated. Relating the parameter in the time domain by (partial) correlation between input (BP) and output (cerebral tissue oxygen saturation) signal or in the frequency domain by determining gain (the difference between amplitudes of input and output oscillations; ie, the dampening potential of CAR), phase shift (the time difference in oscillations; ie, a potential delay of CAR), or (partial) coherence (the strength of linear correlation between oscillations) have been presented.[24,26] In general, most report CAR as either a "moving" correlation or coherence coefficient (0–1), with 0 representing no pressure dependency (intact CAR) and 1 representing full pressure dependency (absent CAR). Cut-off values of 0.3 to 0.5 for impaired CAR have been suggested.[24] By relating the 2 parameters for a certain time window and then gradually moving to the next with a certain overlap (ie, moving window), a continuous assessment of CAR can be quantified. Mathematical nonlinear approaches have also been suggested, to take into account the nonstatic behavior of BP.[28,29] Currently, software to detect CAR at the cot site is being developed, which will hopefully help the clinician to recognize an infant with pressure-passive CBF at risk for cerebral injury.[30,31] Also, individualizing care by finding each infant's own optimal BP range potentially decreases cerebral harm.[32,33]

CEREBROVASCULAR AUTOREGULATION IN THE PRETERM INFANT

CAR is frequently disturbed in preterm infants.[27] This is in part due to an immature cardiovascular and cerebrovascular control.[34] Verma and colleagues[35] showed in 62 preterm and term neonates that a higher gestational age (GA) was related to a quicker return of CBF velocity to normal after a change in arterial BP. This finding was supported by Rhee and colleagues,[36] who found mostly pressure-passive CBF velocity in preterm infants between 23 and 33 weeks GA. Moreover, the correlation between systolic (and less so diastolic) BP and CBF velocity decreased with increasing GA, suggesting increased efficacy of CAR with advancing GA. Similarly, Vesoulis and colleagues[37] showed that although more mature infants (GA of 26–28 weeks) display increased cerebral oxygen extraction at low BPs (implying low CBF), more preterm infants (GA of 23–25 weeks) show a paradoxic decrease in cerebral oxygen extraction, suggesting maturation of the metabolically driven autoregulatory response with GA.

Illness Severity

Several studies have evaluated the effect of illness on CAR in preterm neonates. An Australian study demonstrated an association between the Clinical Risk Index for Babies, an increased coherence between mean arterial BP (MABP), NIRS-derived CBF measures, and HR/BP variability at the low frequency range, suggesting impaired CAR by reduced cardiac baroreflex sensitivity.[38] Accordingly, Wong and colleagues[39] found increased BP variability to be associated with an increased coherence between MABP and cerebral oxygenation, which in critically ill preterm infants seems to be already apparent at relatively low BP variability. Schat and colleagues[40] studied CAR in 15 preterm infants with necrotizing enterocolitis (NEC) for 48 hours after the onset of symptoms and in 13 control infants. Although a statistically insignificant difference, they found a pressure-passive cerebral fractional tissue oxygen extraction (being inversely related to CBF assuming stable cerebral metabolism) in 60% of

infants with and 38% of infants without NEC. Because infants with NEC also had a higher $Paco_2$, were more hypotensive, and had more signs of inflammation, these factors may have mediated impaired CAR in infants with NEC. Hahn and colleagues[41] evaluated whether signs of inflammation (ie, placental signs of fetal vasculitis or increased postnatal IL-6 levels) are associated with impairment of CAR using transfer function analysis between MABP and cerebral oxygenation. They found no direct association between inflammation and CAR. However, postnatal inflammation at 18 hours after birth was associated with hypotension and the more hypotensive an infant was, the more impaired was CAR.

Hypotension

Low BPs are common in the preterm infant and this factor may cause impaired CAR because it causes the CPP to drop below the lower limit of autoregulation. A small British study found similar but possibly slightly increased MABP-CBF reactivity and lower pCO_2–CBF reactivity in hypotensive versus normotensive ventilated neonates, using the 133Xe technique to measure CBF.[42] However, infants experiencing hypotension, defined as a BP below the 10th percentile of Watkins reference values,[43] were also of lower postnatal age. However, a study by Gilmore and colleagues[44] supported the finding that low BP was related to impaired autoregulation. Moreover, their findings demonstrated that impaired CAR was unlikely to occur at hypertensive BP ranges. Fyfe and colleagues[34] suggested that this finding may indicate that in general in these infants, the baseline MABP may lie closer to the lower pressure limit of the autoregulatory range. Accordingly, changes in the MABP during and after volume expansion with saline do not seem to affect cerebral oxygen extraction, indicating an adequate CAR.[45] Da Costa and colleagues[46] evaluated whether it is possible to determine the individual optimal MABP ($MABP_{OPT}$) at which CAR is most effective in infants of a median GA of 26 weeks. Measuring the moving correlation coefficient between the cerebral tissue oxygenation index and HR, they were able to determine the $MABP_{OPT}$ in 82% of 60 preterm infants. The mean $MABP_{OPT}$ was 35 ± 6.4 mm Hg and increased with GA. Moreover, they demonstrated that deviation of MABP by 4 mm Hg or more below $MABP_{OPT}$ was associated with higher mortality, whereas deviation by 4 mm Hg or more above $MABP_{OPT}$ was associated with more severe IVH.

Cord Clamping

Until lung inflation and properly lowered pulmonary vascular resistance, preterm infants may struggle with inadequate preload during transition. Delayed cord clamping (DCC) has been shown to improve preload and cardiac output by increasing circulating volume and decreasing the risk of IVH.[47,48] Vesoulis and colleagues[49] studied the effect of DCC on the transfer function gain coefficient between MABP and cerebral tissue oxygen saturation within the first 72 hours after preterm birth. It was lower in infants with DCC than in infants with immediate cord clamping, implying an improved dampening function of CAR. Moreover, better CAR was associated with less IVH in these infants. They, therefore, hypothesized that increased intravascular volume associated with DCC improves the arterial baroreceptor sensitivity and reflex, which keeps BP and CPP within a more adequate range for CAR to be effective.

Dopamine

Eriksen and colleagues[50] studied whether dopamine use in hypotensive preterm newborns may affect CAR. They found a higher correlation between MABP and cerebral tissue oxygen saturation in those with than those without dopamine treatment. They therefore suggested that dopamine might cause a right shift and/or steeper slope of

the CAR curve by α-adrenergic vasoconstriction. They subsequently studied the effect of dopamine on induced BP fluctuations during 2 phases of either stepwise increase or decrease of MABP through aortic balloon catheter deflation and inflation in newborn piglets.[51] The order of the 2 phases, the phase during which dopamine was given, and the rate of dopamine infusion were randomized. They found that dopamine did not disturb CAR, but rather tended to improve CAR efficacy at low MABP, shifting the lower MABP limit of CAR capacity to the left rather than the right, depending on dopamine infusion rate. Because they did not detect simultaneous increases in CBF or cerebral tissue oxygen saturation, they concluded that this may not relate to vasodilatory effects of low-dose dopamine, but decreased vasoparalysis at low MABP instead. Later the same group demonstrated that dopamine plasma clearance is increased in piglets compared with neonates during continuous dopamine infusion, which may have affected the effects on CAR.[52] Preliminary unpublished data from the HIP ("Hypotension in Preterm Infants") trial[53] also suggest no negative effect of dopamine on CAR capacity in hypotensive preterm.

Patent Ductus Arteriosus

The presence of a PDA in preterm infants is common and may affect CBF. Chock and colleagues[54] therefore studied CAR in a small sample of preterm infants with and without a hemodynamically significant PDA. Although statistically insignificant, infants without a hemodynamically significant PDA had less pressure-passive cerebral tissue oxygen saturation than infants with a hemodynamically significant PDA. Moreover, infants undergoing surgical ligation as PDA treatment had a transient increase in pressure passivity for up to 6 hours after surgical intervention compared with infants with conservative or medical treatment for the PDA. They proposed that, in combination with a sudden increase in CBF after ductal closure, impaired CAR after surgical ligation may transiently predispose to the development of IVH. Although a left-to-right shunting PDA is primarily associated with decreased diastolic BP, little is known about the effect of the diastolic phase of BP on CBF and CAR,[55] and how this relates to cerebral hypoxia.

Several but not all authors have reported a decreased cerebral oxygen saturation during thoracotomy for ductal ligation.[54,56,57] This decrease may in part result from a decreased arterial oxygen saturation from manipulation of the lung, but CAR could be affected as well. However, intraoperative CAR during ligation has not been studied so far. No differences in neurodevelopment impairment were found in preterm infants after percutaneous ductal closure compared with surgical closure.[58]

Respiratory Issues

Lemmers and colleagues[59] found that infants with respiratory distress syndrome (RDS) show a significantly greater correlation between MABP and cerebral oxygenation than infants without RDS. Arterial P_{CO_2} levels were similar in both groups, but infants with RDS were possibly sicker and had significantly lower MABPs.

Li and colleagues[60] recently studied the effect of surfactant (SF) administration randomly using the SF administration through brief intubation (INSURE) and less-invasive SF administration using a thin catheter procedure on the CAR of preterm RDS infants. CAR was more pressure-passive during both procedures than before, with significantly worse CAR during INSURE than during less-invasive SF administration using a thin catheter. In addition, CAR recovered less quickly within the next 10 minutes after INSURE. No significant differences in mean cerebral oxygenation and mean MABP were seen between the groups, suggesting the method of SF administration, rather than the SF itself, was associated with impaired CAR. Whether infants

receiving the INSURE were sedated or received positive pressure ventilation remains unclear. This finding may theoretically have interacted with CAR, regardless of the fact that propofol-induced hypotension during endotracheal intubation has not been associated with impaired CAR in a small cohort of 22 preterm infants.[61] However, other studies have shown a significantly increased CBF velocity during the first 15 minutes after SF administration with intubation.[62] This increase in CBF was highly associated with an increased $Paco_2$ and less with changes in MABP. The same study group demonstrated that increasing $Paco_2$ levels cause progressive impairment of MABP–CBF velocity assessed CAR in ventilated very low birth weight preterm infants during tracheal suctioning.[63] It may be possible that hypercapnia during SF administration may therefore disturb CAR.

Caffeine, in contrast, administered to prevent apnea of prematurity, has shown to decrease the correlation between MABP and the cerebral oxygenation index.[64] This finding may be explained by an increased chemoreceptor reactivity to hypercapnia by caffeine. However, in another study, caffeine was also associated with reduced HR and BP variability, suggesting increased autonomic control.[65]

Surgery

Preterm infants need surgery relatively often, mostly laparotomy for NEC or intestinal perforation, as well as the previously discussed thoracotomy for ductal ligation. Preterm infants needing surgery show an increased risk for impaired neurodevelopment compared with their peers with conservatively managed NEC, even after correction for confounders.[66] Impaired CAR from inflammation or anesthetic drugs has been proposed.[67–69] However, little is known about CAR during surgery in preterm infants. During laparotomy for NEC or intestinal perforation in a small cohort of preterm infants, CAR seemed to be impaired in about one-half of patients, which was in part associated with increased $Paco_2$ values and higher sevoflurane administration.[70] Although the major impairment was shown during surgery, it has already been suggested that NEC itself may lead to absent CAR,[40] possibly owing to neuroinflammation resulting from NEC or owing to unfavorable changes in MABP or $Paco_2$.[71]

CEREBROVASCULAR AUTOREGULATION IN NEONATES BORN AFTER FETAL GROWTH RESTRICTION

Placental insufficiency is the most common cause of FGR.[72] It involves chronic fetal hypoxia, which induces a fetal brain-sparing response with peripheral vasoconstriction, cardiac remodeling toward left ventricular predominance, and cerebral vasodilation.[73,74] This fetal brain-sparing effect has been shown to continue after birth, visible as higher cerebral oxygen saturations for at least 3 days after birth.[75] Moreover, chronic fetal hypoxia has been shown to cause cerebrovascular remodeling, including a decrease in vascular density, endothelial cell proliferation, contractile pericytes lining cerebral capillaries, and perivascular stabilizing astrocytes.[76] In addition, a shift from calcium- and nitric oxide-mediated contractility toward adrenergic pathways of vasoreactivity has been observed.[77] Although an adaptive, possibly energy-saving response to preserve contractile function and adequate CBF in chronic hypoxia, these changes altogether alter the cerebrovascular reactivity and increase the permeability of the blood–brain barrier in these infants. Accordingly, Cohen and colleagues[78] demonstrated that, on day 2 and 3 after birth, preterm neonates with a birth weight below the 10th percentile display impaired CAR (correlation between MABP and cerebral tissue oxygen saturation of >0.5) more often than their appropriate-for-GA peers. This finding supported previous research suggesting low birth weight to be a

risk factor for impaired CAR.[27] Polavarapu and colleagues[79] focused on signs of placental insufficiency and fetal brain sparing and showed that an abnormal umbilical arterial pulsatility index (z-score of >2) and cerebroplacental pulsatility ratio (z-score of <−2) were associated with impaired CAR within the first 4 days after preterm birth. Yet data from our research group[80] also supports a strong association between fetal brain-sparing (cerebroplacental ratio of <1) and impaired CAR within the first 5 days after preterm birth.

In addition, infants with FGR are frequently exposed to maternal medication, which may further interfere with CAR and CBF after birth. Labetalol, which has adrenergic-receptor blocking properties, has been shown to accumulate in the neonate and impair neurogenic vasoreactivity on the first day after birth.[81,82] Possibly, its effect is amplified by the upregulation of adrenergic vasoreactive mechanisms associated with cerebrovascular remodeling, gaining clinical significance, particularly in those neonates born after severe early-onset FGR. Apart from its neurogenic effect on CAR, labetalol may cause neonatal bradycardia and hypotension.[83] In combination with an impaired CAR—induced by fetal hypoxia, brain sparing, and/or labetalol itself—labetalol may cause hypoperfusion of the brain. Moreover, as discussed elsewhere in this article, hypotension itself may cause ineffective CAR by lowering baroreceptor sensitivity and causing a CPP below the lower limit of CAR, adding to impaired CAR. This factor may also apply to other perinatal medications with antihypertensive properties, such as magnesium sulfate ($MgSO_4$), which is frequently given for maternal or fetal neuroprotection in severe preeclampsia or imminent preterm birth, respectively. Prenatal $MgSO_4$ itself does not seem to impair cerebral autoregulation in preterm infants,[80] decreases hypoxia-induced glutamate excitotoxicity, and possibly lowers cerebral oxygen demands.[84–86] Increased serum levels of magnesium in neonates born to preeclamptic mothers treated with $MgSO_4$, however, are associated with an increased risk of hypotension, which may decrease the CPP in these infants.[87,88] Furthermore and regardless of drug exposure, FGR itself is frequently associated with decreased neonatal cardiac output, greater arterial wall stiffness, preterm birth, and hemodynamic immaturity, which can all contribute to neonatal hypotension and increase the risk of impaired CAR and cerebral hypoperfusion.[89–91]

Mechanisms intrinsic to FGR-related placental insufficiency and medications therefore contribute to an impaired CAR and possibly an increased risk of brain injury in infants with FGR. Although the latter needs confirmation, this finding needs to be taken into account when caring for and treating infants with FGR.

CEREBROVASCULAR AUTOREGULATION AND HYPOXIC–ISCHEMIC ENCEPHALOPATHY

After perinatal distress and cerebral oxygen deprivation (asphyxia), HIE may develop. HIE is estimated to occur in 1.5 per 1000 live births.[92] Therapeutic hypothermia after birth decreases cerebral metabolism and improves energy homeostasis by decreasing cellular energy demand.[93] However, after sustained asphyxia, with hypoxia, hypercapnia, acidosis, and decreased myocardial function, cerebral autoregulation may become exhausted.[94] Three decades ago, Pryds and colleagues[95] demonstrated that perinatal asphyxia was associated with disturbed CAR, which seemed related to severe brain injury, especially if vasoreactivity to both changes in MABP and $Paco_2$ was affected. Impaired CAR in infants with HIE during therapeutic hypothermia, or—to be more specific—a pressure-passive cerebral mitochondrial metabolism as demonstrated by Mitra and colleagues,[17] in turn may contribute to cerebral injury and a poorer outcome.[33,96–99] Several animal studies have demonstrated that the

lower BP limit of effective autoregulation can be individually detected using a combination of MABP and NIRS.[100,101] In infants with HIE, the time spent below their individually defined $MABP_{OPT}$, as detected by the lowest correlation between cerebral oxygen saturation measured by NIRS and MABP, has been associated with more severe cerebral injury.[33] Similarly, a higher detected individual $MABP_{OPT}$ in infants with HIE, has been associated with more cerebral edema. One needs to keep in mind that the severity of HIE may be associated with a lower and less stable BP owing to a more severely harmed cardiovascular system, which may contribute to the established associations.[102,103]

CEREBROVASCULAR AUTOREGULATION IN INFANTS WITH CONGENITAL HEART DISEASE

Only very limited preoperative and perioperative data relating to cerebral autoregulation in infants with CHD are available. Two observational cohort studies mainly included older children, but are also discussed.

In a small cohort of preoperative infants with a variety of CHDs, all infants seemed to experience episodes of pressure-passive cerebral oxygenation, with an average of 15.3% ± 12.8% of the time studied.[104] Another cohort of infants less than 14 days of age demonstrated that impaired CAR occurred as frequently in infants with CHD as in healthy term infants (75% vs 68%, respectively). CAR was assessed by inducing a sudden postural change from supine to a sitting position, assuming to rapidly affect BP, and using NIRS to assess subsequent recovery rate of cerebral oxygenation. Impaired CAR was defined as a cerebral tissue oxygen saturation value requiring more than 5 seconds to return to baseline after postural change.[105] The sensitivity for this CAR assessment is questionable, as discussed by the authors.

Several perioperative reports regarding cerebral hemodynamics during cardiac surgery in neonates and infants have been published. In particular in infants less than 6 months of age, clamping and declamping the aorta during coarctation repair resulted in significant changes in CBF velocity, with a maximal decrease of 63% after declamping, occurring with fluctuations in systemic BP. End-tidal (expiratory) CO_2, hematocrit, or isoflurane management contributed only a little to this observation. The authors concluded that young infants with CHD may be at an increased risk of cerebral adverse events during marked decreases in systemic BPs.[106] Apart from hypotensive episodes during cardiac surgery, induced hypothermia for the preservation of cerebral tissue during hypoxic-ischemic incidents, may also affect CAR, and is has been suggested that autoregulatory capacity decreases with decreasing temperatures.[107] Taylor and colleagues[108] therefore studied the association between (nasopharyngeal) temperature and pressure–flow relation (ie, CAR) in 25 neonates and infants undergoing continuous low-flow cardiopulmonary bypass (CPB) at 3 to 210 days after birth. They showed that CAR, based on MABP and Doppler-assessed CBF velocity, is preserved in infants and children during normothermic CPB, begins to be altered during moderate hypothermic (<25°C) CPB, and is abolished during profound hypothermic (<20°C) CPB. Moreover, they demonstrated that CBF decreased in a nonlinear fashion with decreasing CPP (calculated as the difference between MABP and anterior fontanel pressure), with CBF being undetectable at a mean CPP of 9 (± 2 SD) mm Hg, suggesting arterial collapse, but becoming apparent at a CPP of 13 (± 1 SD) mm Hg. However, it is important to realize that BP and temperature tend to be collinear, confounding these observations and warranting a normotensive hypothermic

Table 1
Effect and potential mechanisms of various conditions and circumstances on the CAR in newborns, as suggested by current literature

	CAR Capacity	Possible Mechanisms
Prematurity		
Low GA	Impaired	Immaturity, lower/narrow $MABP_{OPT}$
Higher illness severity score	Impaired	Greater HR/BP variability, less tolerance for HR/BP variability
NEC	Impaired	Hypotension, hypercapnia, neuroinflammation?
Systemic inflammation	Unaffected	If not associated with hypotension
Hypotension	Impaired	CPP below the autoregulatory range
DCC	Improved	Increase in circulating volume, increased baroreceptor sensitivity causing greater MABP stability
Dopamine	Improved	Left shift of lower MABP limit of CAR, which may be beneficial in hypotension
(Surgical ligation of) PDA	Impaired	CPP below the autoregulatory range, surgery-associated interventions
RDS	Impaired	Greater illness severity and more hypotension
SF administration, particularly if performed by intubation	Impaired	Procedure related (hypercapnia? BP changes?)
Propofol-induced hypotension during intubation	Unaffected	
Endotracheal suctioning	Impaired	Hypercapnia (shift of the autoregulatory plateau)
Caffeine (as apnea treatment)	Improved	Increased chemoreceptor sensitivity to $Paco_2$, increased autonomic control (reduced HR/BP variability)
Prenatal $MgSO_4$	Unaffected	
FGR/SGA		
Low birth weight	Impaired	FGR-associated mechanisms?
Fetal hypoxia/brain sparing	Impaired	Cerebrovascular remodeling, ongoing postnatal cerebral vasodilation; an increased risk of hypotension may also contribute

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Table 1
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	CAR Capacity	Possible Mechanisms
Maternal labetalol	Impaired	Impaired neurogenic vasoreactivity, possibly through adrenergic blockade (the effect of which may be increased in FGR by an increase in cerebrovascular adrenergic receptors in fetal hypoxia)
Asphyxia/HIE		
With or without therapeutic hypothermia	Impaired	Impaired reactivity to changes in MABP and $Paco_2$; strong relation with brain injury
CHD		
Preoperative	Unaffected?	
Perioperative	Impaired	Hypotension, hypothermia (<25°C)
Up to 6–20 h postoperative	Impaired	High end-tidal CO_2, high MABP variability

Abbreviations: CO_2, carbon dioxide; $Paco_2$, arterial carbon dioxide partial pressure; SGA, small-for-gestational age.

model.[109] Furthermore, infants needing deep hypothermic circulatory arrest (22°C) during arterial switch operation for transposition of the great arteries demonstrated decreased cerebral oxygen extraction and concomitantly suppressed amplitude-integrated electroencephalogram patterns, which did not relate to cerebral injury as seen on MRI, suggesting that these changes may represent the intended protective suppression of metabolism.[110]

Brady and colleagues[111] used NIRS in combination with MABP for a continuous perioperative assessment of CAR among 54 infants and children with varying forms of CHD and ages ranging from 0 to 222 months. They found an association between hypotension and impaired CAR. The authors speculated that defining and exceeding individual lower limits of pressure-dependent autoregulation would mitigate CPB-induced autoregulatory cerebral disruption, which needed confirmation by larger trials.[111] A recent study of 57 children (youngest 7 months) supported their findings and speculations, showing that impaired CAR assessed using NIRS, related to elevated glial fibrillary acidic protein levels suggesting possible episodes of brain injury from hypoperfusion.[112]

Transcranial Doppler and NIRS have also been used to determine postoperative CAR in infants with CHD by Bassan and colleagues.[113] They found in 43 infants (0–7 months of age) that CAR was still disturbed at 6 to 20 hours after surgery with CPB. Increased end-tidal CO_2 and high MABP variability increased the risk of impaired CAR at this stage, which may be preventable.[113]

SUMMARY

Although mostly observed in small cohorts, it seems that CAR may be impaired in infants under a variety of circumstances. Prematurity, FGR, HIE, and CHD all

present with cardiovascular instability, which may cause BP and CPP to fall below the lower limit of the autoregulatory plateau, leading to low CBF and cerebral ischemia. Likewise, CPP may rise above the upper limit of autoregulatory capacity, increasing the risk of hyperperfusion and rupture of a yet fragile cerebral vascular network. In addition, maturity or certain biochemical factors, such as the $Paco_2$, may shift the autoregulatory plateau and thus the pressure limits within which CAR effectively works. Beside the cardiovascular instability intrinsic to prematurity and disease, several perinatal iatrogenic interventions, including maternal or neonatal medication, SF administration, ventilation, or surgery, may therefore change cerebral vasoreactivity by affecting BP, $Paco_2$, or neurogenic mechanisms of CAR.

As long as we do not have the opportunity to validly assess real-time CAR at the bedside, we need to be aware of the risk factors for impaired or even absent CAR in newborn infants admitted to the neonatal intensive care unit. Being able to identify an infant with an increased risk for impaired CAR, will help the clinician to guide treatment during fluctuating or relatively low BP. **Table 1** summarizes the factors, that may cause impairment or improvement of neonatal CAR, as evaluated by the clinical studies and techniques discussed in this article.

In the future, bedside CAR assessment in these infants may offer the opportunity to prevent hypoperfusion or hyperperfusion and associated brain injury. Until then, clinicians need to know the populations at risk for and circumstances associated with impaired or absent CAR.

DISCLOSURE

The authors have nothing to disclose.

Best Practices

What is the current practice?

Neonatal CAR

- Continuous real-time assessment of CBF and CAR in the neonatal intensive care unit is currently not possible.
- Conventional methods such as BP monitoring are being used to guide general systemic hemodynamic management of sick newborn infants.
- Systemic BP thresholds have been roughly defined for different patient populations, without evidence for improved organ perfusion.

What changes in current practice are likely to improve outcome?

- Awareness of the circumstances and mechanisms leading to impaired or absent CAR in newborns might improve the interpretation and management of fluctuating or low BP.
- Although the effect of noninvasive continuous bedside assessment of CAR on neonatal outcome needs to be investigated first, in the future it may guide the clinician to optimize CBF in patients prone for cerebral hemorrhage and/or hypoxic-ischemic injury.
- Individualizing care by determining the individual limits of BP at which CAR works best may improve these infants' outcome.

Summary statement

Awareness of patient characteristics and circumstances related to impaired cerebral autoregulation and individualizing hemodynamic treatments—ultimately through a continuous assessment of the cerebral autoregulatory capacity at the bedside—may in time decrease cerebral injury in sick infants.

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