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“The Immature Brain in Complicated Transition: Risks and Anticipatory Management” The critical role of the central autonomic nervous system in fetal-neonatal transition

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Abstract

Objective: The objective of this article is to understand the complex role of the central autonomic nervous system in normal and complicated fetal-neonatal transition and how autonomic nervous system dysfunction can lead to brain injury.

Findings: The central autonomic nervous system supports coordinated fetal transitional cardiovascular, respiratory, and endocrine responses to provide safe transition of the fetus at delivery. Fetal and maternal medical and environmental exposures can disrupt normal maturation of the autonomic nervous system in utero, cause dysfunction, and complicate fetal-neonatal transition. Brain injury may both be caused by autonomic nervous system failure and contribute directly to autonomic nervous system dysfunction in the fetus and newborn.

Conclusion: The central autonomic nervous system has multiple roles in supporting transition of the fetus. Future studies should aim to improve real-time monitoring of fetal autonomic nervous system function and in supporting typical autonomic nervous system development even under complicated conditions.

Introduction

Transition from a fetal to neonatal physiology is not only the most complex and profound event before death, it is also the first major challenge of postnatal life. The central autonomic nervous system (ANS) centers in the brain stem play a critical role in the cardiovascular and respiratory adaptations required for successful fetal-neonatal transition. At birth, the ANS

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centers in the brain stem, both sympathetic and parasympathetic divisions, exert coordinated control over the infant's cardiovascular and respiratory systems. These neural systems are supported by major endocrine changes, including a powerful surge of catecholamine levels at birth which provides more sustained support to the sympathetic nervous system. Together these processes enable both brisk and sustained responses by which the cardiovascular system adapts to postnatal life.¹ Prenatal maternal and fetal conditions may impair these physiological adaptive systems of the ANS in the transitioning fetus and necessitate the use of medical interventions and devices to support the neonate at transition and in the early days after birth. In addition, recent data support an important role for the mature ANS in critical higher order cortical functions involving behavior, affect/mood, and adaptive responses to stress; dysfunction in these domains may significantly impact long-term health and psychological well-being of the individual.² Evidence is emerging that adverse early exposures, even prior to birth and in the neonatal period, can impact ANS maturation and function and that this can lead to infant mortality,^{3,4} psychological and mood disorders,^{2,5} and cardiovascular disease into adulthood.⁶

In spite of our growing understanding of the mature ANS, our understanding of normal ANS maturation, at both the brain stem and cerebral levels, as well as factors that disrupt normal ANS development and create additional challenge for the fetus at transition, remains limited. In this article we review the anatomy of the central ANS, review what is known about ANS maturation and development during fetal life, and how ANS function can be noninvasively measured. We then explore how the central ANS supports normal and complicated fetal-neonatal transition and discuss how ANS failure or dysfunction may lead to brain injury (or brain injury lead to ANS dysfunction). Finally, we address future areas for research and clinical advancements for the field.

Anatomy and function of the developing central ANS

The central ANS has two major branches, the sympathetic nervous system, responsible for the well-known "fight-or-flight" response and the parasympathetic nervous system, responsible for relaxation and moderating control over the active sympathetic system. This is a rather simplified view of the competing roles of these systems, as in reality they are considerably complex. It is the coordinated and in some ways opposing activities of these systems that maintains the body endogenous systems in balance, despite fluctuating external conditions. These two systems do not act independently, but interact at multiple levels to allow appropriate ANS responsiveness.⁷ The nucleus tractus solitarius (NTS) and the paraventricular hypothalamic nucleus are principal regulators of sympathetic and parasympathetic ANS activity.⁷ Within the brain stem, the key autonomic centers, including the primary sensory center, the NTS, and such efferent nuclei as the dorsal motor nucleus of the vagus and the nucleus ambiguus, exert control over the ANS to regulate heart rate, respiration, digestive, and other critical body functions (Figure 1, A-B). Important areas of the central nervous system known to innervate all levels of sympathetic preganglionic outflow include the 1) paraventricular hypothalamic nucleus, 2) A5 noradrenergic cell group (superior olivary complex in the pontine tegmentum), 3) caudal raphe region, 4) ventrolateral medulla, and 5) ventromedial medulla.⁸⁻¹⁰ The medulla in particular is an important area of sympathetic outflow. Animals subjected to transection of the rostral pons

at delivery fail to increase their heart rate, arterial blood pressure, and renal sympathetic nerve activity as normally at birth as in intact animals.¹ The medulla's NTS responds to input from baroreceptor afferents in the carotid bodies and aortic arch, during changing arterial blood pressure, to adjust sympathetic and parasympathetic tone.¹⁰ The NTS sends inputs to other centers, like the ventrolateral medulla, parabrachial nucleus, and the paraventricular nucleus of the hypothalamus, which then directly signal the sympathetic and parasympathetic preganglionic neurons.⁷

Cardiac ganglia are innervated by vagal preganglionic neuron cell bodies from the nucleus ambiguus within the ventrolateral medulla and also from the dorsal motor nucleus of the vagus (and the area in between) to regulate cardiovascular function (Figure 1A).¹⁰ Each of these cell groups (nucleus ambiguus and dorsal motor nucleus of the vagus) may have different effects on cardiovascular control. Cardiac preganglionic vagal neurons fire along with the cardiac cycle due to excitation from the baroreceptors via the NTS.¹⁰ Respiratory control is performed by ANS centers in the brain stem (Figure 1B). The major central pattern generators consist of neuron groups such as the pontine respiratory group, Bötzing complex (expiratory rhythm generator), pre-Bötzing complex (inspiratory rhythm generator), retrotrapezoid nucleus, the rostral ventral respiratory group, and the caudal ventral respiratory group.¹¹ The NTS, in the dorsal medulla, receives input from peripheral chemoreceptors and pulmonary mechanoreceptors to then modulate respiratory rhythmogenesis in the central pattern generators (Figure 1B).¹¹ Angiotensin receptors located throughout the brain and in ANS areas, including the NTS are involved in blood pressure regulation.¹⁰ There is a high density of angiotensin receptors in the rostral ventrolateral medulla associated with sympathetic premotor neurons.¹⁰ Activation of angiotensin receptors leads to increased blood pressure and sympathetic vasomotor activity essential for successful fetal-neonatal transition.

The central ANS also has a function in intrinsic cerebral autoregulation. Briefly, cerebral perfusion is maintained by a background perfusion pressure within the cerebral vasculature provided by the cardiovascular system and modulated by complex intrinsic autoregulatory mechanisms involving stimulation of alpha- and beta-adrenoceptors by norepinephrine (sympathetic nervous system) to cause vasoconstriction and vasodilation, respectively, of cerebral vessels. In animal studies, the sympathetic nervous system has a greater influence on cerebral blood flow maintenance and autoregulation during fetal and perinatal periods than at older ages.¹² In a postmortem human neonate study, neonatal cerebral arteries had higher sympathetic nerve density compared to adult cerebral arteries.¹³ Although cerebral pressure-flow autoregulation is well-characterized in children and adults, this is not the case for the fetus and newborn.¹⁴ Cerebral autoregulatory capacity is under-developed at mid-gestation, but undergoes significant maturation by term gestation.¹⁵ With decreasing gestational age, the autoregulatory plateau is much narrower and lower^{16,17} and normal resting blood pressure (for gestational age) is closer to the lower threshold of autoregulation.¹⁸

Supra-tentorial ANS centers include the anterior thalamus, anterior cingulate gyrus, and the amygdala which integrate the more primitive functions of the brain stem ANS with higher cortical autonomic centers that mediate adaptive responses to stress and mood, a major

evolutionary advantage for humans. Sympathetic outflow is also strongly influenced by the hypothalamus,¹ especially the paraventricular nucleus of the hypothalamus, where lesions in a near-term fetal sheep model stunts the normal sympathetic surge at birth.¹⁹ Conversely, electrical stimulation of the hypothalamus in a fetal sheep model increases heart rate and blood pressure, a response which is blocked by an alpha-adrenoceptor antagonist.²⁰ Stimulation of the medial prefrontal cortex (in animal model), which has connections with the amygdala, hippocampus, thalamus, hypothalamus, parabrachial nucleus, and the NTS, induces bradycardia and hypotension and modulates gastric secretion.⁹ Activation of the insula, an important visceral sensorimotor area, induces hypertension, tachycardia, piloerection, pupillary dilation, salivation, and alters gastrointestinal function.⁹ Clearly there are complex connections between the central ANS centers with multiple pathways for exerting ANS control. The role of higher brain structures in normal fetal to neonatal transition, and the effect of pre- and perinatal brain injury, remains poorly understood.

Normal development of the central ANS: Current understanding

The ANS matures during development of the central nervous system in the fetal period and continues to mature after birth.^{21,22} A number of studies have demonstrated the non-synchronous maturation of the sympathetic and parasympathetic systems. The unmyelinated and more primitive, dorsal motor nucleus of the vagus (parasympathetic) is the first to structurally appear, however is slow and not very responsive to the demands of the fetus/newborn.²³ Onset of sympathetic development is next and begins earlier than that of the myelinated parasympathetic division. The maturation of the sympathetic division occurs steadily throughout gestation. Parasympathetic activity from the nucleus ambiguus and its myelinated vagal fibers, shows accelerated maturation between 25 and 32 weeks gestation, a time period when premature newborns may be undergoing fetal-neonatal transition.^{23–25} A further steep increase in vagal tone occurs around 37 to 38 weeks gestation, as evidenced by increased high-frequency heart rate variability (HRV; see section below).^{26,27} Prior to term, basal fetal cardiovascular function is predominantly influenced by the sympathetic nervous system; there is progressive parasympathetic influence on resting heart rate with increasing postnatal age.¹ Natural variability in sympathetic tone thus plays an important role in heart rate and blood pressure variability during fetal life and in prematurely born newborns since parasympathetic tone is underdeveloped.¹ Therefore at birth, especially for the preterm infant, the ANS is immature and is predominantly influenced by the sympathetic nervous system.²⁸ Over the first few months after birth, the parasympathetic nervous system exerts an increasing influence on HRV, visceral regulation, social, and stress responses of the infant.^{23,29}

Another important feature of ANS development is its incorporation into fetal behaviors and sleep states. In the third trimester there is increased correlation between heart rate accelerations and fetal movements.²⁷ In a study of maternal-fetal daily rhythmicity, fetal movements as early as 16 to 20 weeks of gestation were associated with increases in fetal heart rate and HRV.³⁰ During hours of maternal quiet state (sleep), fetal activity was often increased showing that maternal and fetal quiet and active states may occur during different hours of the day.³⁰

Current techniques for assessing the ANS

Fetal heart rate is the only reliable continuous physiologic signal that is readily accessible from the fetus. Within the fetal electrocardiogram (EKG) signal is embedded information regarding the ANS functional status and maturation level. Although Doppler-based measures of fetal heart rate do not have the resolution required for quantitative measures of ANS function, a number of devices have been developed capable of acquiring high-quality fetal EKG signals from the mother's abdomen (e.g. Monica AN24, Monica Healthcare Ltd, Nottingham, UK, Meridian M110, MindChild Medical, Inc., North Andover, MA, USA, and NEMO system, NEMO Healthcare BV, the Netherlands). The performance of these devices is dependent on their capability to filter background artifacts (i.e. maternal heart rate and fetal movements) and to amplify the low voltage fetal heart signal.^{31–33} The fetal EKG signal provides high-resolution measures of HRV, measured as the fluctuation in the length of time between heart beats (R-R intervals), which in turn allows assessment of underlying sympathetic and parasympathetic tone and its maturation.^{21,34} Measurements of ANS function may also be a biomarker for long term neurodevelopmental outcome.^{35–37} Fetal magnetocardiography is another method to detect fetal EKG but requires a specialized superconducting quantum interference device that uses a micromagnetic field (10^{-12} tesla) to detect fetal heart signals, making it costly and non-portable to the bedside or clinic.^{38,39}

Both frequency-domain and time-domain approaches have been applied to derive HRV metrics. High-frequency (0.4 to 1.5 Hz) HRV is mediated by the parasympathetic nervous system and is influenced by the respiratory rate (respiratory sinus arrhythmia). Low-frequency (0.04 to 0.15 Hz) HRV reflects baroreflex function and is mediated by both sympathetic and parasympathetic inputs.⁴⁰ The low frequency-to-high frequency ratio provides a measure of sympatho-vagal balance. With maturation of the ANS (as discussed above) there is an absolute and relative increase in parasympathetic function, with greater high-frequency HRV, increase in HRV indices overall, and lower heart rate.^{32,41,42} Time-domain analysis of HRV evaluates both short- and long-term variability in the heart rate. Long-term variability is influenced by both the sympathetic and parasympathetic nervous systems, while short-term variability is influenced by the parasympathetic nervous system based on rapid ANS needs.²⁹ Resting heart rate decreases as infants mature from term gestation to a few months of age, due to higher influence (and development) of the parasympathetic nervous system after birth.²⁹

Heart rate variability is also influenced by the sleep *state*, with higher sympathetic tone (low-frequency variability) in active sleep than in quiet sleep.²¹ Since active (rapid eye movement [REM]) sleep is the major sleep state in premature ('extra-uterine fetus') and term newborn infants, occupying greater than 50% of sleep time, HRV should be evaluated in the context of sleep state.³⁵ Sleep *position* may also affect ANS regulatory control on heart rate. In a study of term infants during active sleep, infants sleeping in the supine position had higher HRV parameters compared to infants sleeping in the prone position.²⁹ However, breech or cephalic fetal position does not seem to alter ANS maturation or function based on a fetal HRV study.⁴³

Current understanding of the ANS in normal transition

Intact ANS function, especially in the sympathetic nervous system, is critical during birth and transition. Sympathetic outflow from the brain stem and from higher brain centers, including the hypothalamus and forebrain, surges at birth,¹⁹ to support successful transition of the fetus to neonatal life.¹ Cortisol and catecholamine levels in the fetus increase significantly after the 30th week of gestation, and play a critical role during transition of the fetus to the extra-uterine environment by priming the fetal nervous system.²⁹ Fetal cortisol levels are relatively low until about 30 weeks gestation, when they begin to rise steadily until term.⁴⁴ During labor at term, cortisol levels increase about five-fold.⁴⁴ This high cortisol level supports the multiple necessary physiologic elements of transition including cardiovascular, endocrine, and thermoregulatory responses.⁴⁴ Cortisol also promotes respiratory transition by decreasing fetal lung fluid.⁴⁴ Other vasoactive substances, such as renin and angiotensin II, increase after birth and help support transition of the cardiovascular and respiratory systems.⁴⁴ Prior to birth these vasoactive substances are also important for the developing ANS and regulation of normal fetal and maternal blood pressure. Low fetal and maternal angiotensin levels are risk factors for preterm birth.⁴⁵ In a genome-wide association study of pregnant women, AGR2 variants encoding angiotensin II receptor type 2 were associated with gestational duration.⁴⁶ With non-labored birth, e.g., some cases of prematurity or elective caesarian section delivery, cortisol levels may be lower than needed for optimal transition.⁴⁴ In a primate model of extreme prematurity, low urinary cortisol levels on the first day of life were associated with cardiovascular dysfunction.⁴⁷ In the premature infant, adrenal immaturity results in an attenuated rise in cortisol at birth, further compromising transition.⁴⁸ Clinically, the premature newborn can have hypotension which responds to cortisol treatment.⁴⁹

Like cortisol, catecholamines (norepinephrine, epinephrine, and dopamine) are critical for successful transition of the fetus. Within minutes of birth and cord clamping, epinephrine and norepinephrine levels increase.⁵⁰ This increase is heightened in premature newborns, although the rise occurs more slowly, likely due to lower organ system responsiveness resulting from overall system immaturity.⁴⁴ The catecholamine surge at birth drives fetal adaptation by supporting blood pressure, energy metabolism, and thermogenesis.⁴⁴ This catecholamine production and response may, however, be decreased in extremely premature newborns.⁵¹

Respiratory function is coordinated by both peripheral and central chemoreceptors that send afferent signals to the NTS that modulates sympathetic tone, thereby adjusting heart rate, respiratory rate, and other homeostatic functions.^{25,52} Responses to changing blood oxygen levels are primarily from carotid body chemoreceptors. Afferent signals from the carotid sinus nerve, a branch of the glossopharyngeal nerve, project to the NTS and other brain stem areas involved in respiratory regulation.¹¹ Denervation of the carotid body at birth results in apnea, hypoxemia, and abnormal respiratory patterns, which highlights the importance of this system for infant survival at transition.¹¹ Central chemoreceptors, found in multiple sites throughout the brain stem, as well as peripheral chemoreceptors respond to changes in blood CO₂/H⁺ levels.¹¹ The retrotrapezoid nucleus in the brain stem has a key role in central O₂ and CO₂ chemosensitivity receiving ascending input directly from the carotid body

chemoreceptors and descending modulation from the hypothalamus.⁵³ This is exemplified well in the case of congenital central hypoventilation syndrome, in which infants with a mutation in the PHOX2B gene responsible for normal development of the retrotrapezoid nucleus have hypoventilation despite high CO₂ levels.^{54,55} Medullary raphe nuclei are also important CO₂ chemosensors and have projections throughout the medulla including the Bötzinger complex, NTS, the hypoglossal nerve, and affect cardiovascular and ANS control.¹¹ CO₂ responsiveness also varies by gestational and postnatal age, with younger premature infants showing less response to elevated CO₂.⁵⁶ This may be due to immaturity of the central chemoreceptors, fewer synaptic connections, or immature neurotransmitter systems.⁵⁶

In utero, the fetus alternates between REM (active) and non-REM (quiet) sleep states and is kept in a fairly relaxed state by endogenous prostaglandins.⁴⁴ With clamping of the umbilical cord and an abrupt cessation of exposure to rapidly catabolized prostaglandins, the fetus awakens and initiates spontaneous breathing.⁴⁴ Except under circumstances of severe hypoxia and/or brain stem injury, the newborn will typically initiate breathing without stimulation or medical intervention.^{44,52} Central CO₂ sensing chemoreceptors interact with the ANS, promoting wakefulness and stimulating the heart rate, blood pressure, and respiratory adjustments necessary for cardiorespiratory control at birth.⁵² Catecholamines are also thought to mediate the secretion of surfactant into the fetal lungs during labor to aid respiratory transition.⁴⁴

Challenges to the successful role of the ANS in transition

Success of the fetus at transition relies on ANS support of the cardiovascular, respiratory, and hypothalamic-pituitary-adrenal systems. As discussed above, under normal circumstances there is significant development and maturation of the ANS throughout the second half of pregnancy. However, when this development or maturation is disrupted, the fetal ANS may be significantly compromised going into labor and may not be able to support successful transition. Depending upon the severity of cardiovascular and respiratory perturbations, the ANS may be overwhelmed and not able to maintain systemic homeostasis resulting in compromise of the newborn. Various fetal and maternal conditions can result in the ANS being ill-prepared for transition. Adverse environmental conditions in utero (e.g., placental failure with fetal growth restriction [FGR], fetal hypoxemia from congenital heart disease [CHD], maternal substance abuse) or ex utero (prematurity-related influences) during this critical period may cause significant and sustained disruption on ANS development.

Premature birth unfortunately remains a common circumstance that results in difficult neonatal transition, due in part to immature function of the ANS. The ANS, which has vital roles in the integration and regulation of heart rate, blood pressure, and respiratory function, is unprepared to provide adequate support of the premature newborn's transition and to avoid hemodynamic instability. Neonatal resuscitation is therefore often needed at this time in premature newborns which may include need for invasive respiratory support, surfactant administration, pressor support, and steroids. Impaired transition and circulatory fluctuations can increase risk for brain injury, as discussed below. In a longitudinal study of ANS

maturation in 39 preterm newborns (mean gestational age of 28 weeks), indices of HRV (i.e. ANS maturation) did not significantly increase by term equivalent age, compared to term newborns,⁴² suggesting possible arrest of ANS development during the ex-utero third trimester in premature newborns.⁴²

Fetal environments of restricted oxygen-nutrient availability may also promote impaired ANS maturation prior to birth, leaving the newborn under-prepared for successful transition. Two examples of such unsupportive environments include complex (cyanotic) CHD and FGR with placental insufficiency. Compared to early periods in gestation, the fetal brain in the third trimester is undergoing rapid growth and maturation.⁵⁷ Complex forms of CHD, such as hypoplastic left heart syndrome, are complicated by in utero hypoxemia and cerebral hypoperfusion,⁵⁸ which can affect brain growth and maturation during this demanding period in fetal brain development. Fetuses with hypoplastic left heart syndrome showed lower mean heart rate and reduced HRV compared to healthy control fetuses at similar gestational age, suggesting that ANS maturation is delayed even prior to birth in fetuses with complex CHD.⁵⁹ Similarly, FGR is associated with placental insufficiency/failure, chronic nutrient deprivation, and hypoxemia and a recent study found reduced HRV in fetuses affected by FGR compared to controls.^{60,61} ANS immaturity under these circumstances may make transition difficult and risky, increase the need for pressor support, mechanical ventilation, and may prolong duration of intensive care needed after birth. Of additional concern is that ANS immaturity may affect cardiovascular and hemodynamic responses normally required to protect against ischemic brain injuries seen in sick neonates and those with complex medical conditions such as CHD.

Early exposure to infection and/or inflammation may also affect ANS maturation and affect transition. Among the cohort of premature infants described by Thierez et al., those infants with early-onset sepsis were more likely to have lower ANS tone and abnormal neurologic outcomes.³⁵ Inflammation activates ANS pathways and the hypothalamic-pituitary-adrenal axis to support the early cardiovascular response to infection and sepsis.^{62,63} The parasympathetic nervous system through efferent signaling from the vagal nerve leads to reduced HRV and other characteristics that can be detected through heart rate characteristics monitoring which may indicate impending infection.⁶⁴ Since heart rate changes may precede clinically identifiable infection in neonates, this bedside signal may be used to predict infection and provide earlier antimicrobial therapy.⁶⁵ In addition, the vagal nerve has anti-inflammatory capabilities, i.e., the “cholinergic anti-inflammatory response”, which suppresses activation and release of pro-inflammatory cytokines, and helps regulate the body’s reaction to inflammation and infection.⁶⁶ Immaturity of the ANS, and in particular the parasympathetic nervous system, may affect the robustness of the response to infection in the fetus and neonate. Further study is needed to investigate the effect of gestational age and prematurity on the cholinergic anti-inflammatory response.

Maternal medical conditions, nutrition, and medications can affect the developing fetal ANS and make transition more challenging as well. Developmental plasticity is the mechanism by which early life exposures and events (i.e., health, nutrition, stress, environment, etc., in fetal-neonatal-infancy periods) shape the developmental trajectory of the infant into a sustained change in the way the infant/child interacts with the environment into adulthood.⁶⁷

Gestational diabetes is known to increase perinatal morbidity, contribute to large for gestational age infants, and may affect fetal brain development through changes in fetal programming. During a maternal oral glucose tolerance test, fetuses of pregnancies complicated by gestational diabetes have lower high frequency and low frequency variability compared to fetuses of normoglycemic controls which may be related to effects of maternal metabolic state on fetal ANS function.⁶⁸

Smoking in pregnancy contributes to abnormal ANS maturation likely through a mechanism similar to FGR (i.e., chronic fetal hypoxemia). In a study of autonomic function in premature newborns, those infants whose mothers smoked during pregnancy showed higher sympathetic tone, lower parasympathetic tone, and had less cardiac autonomic adaptability compared to control newborns.⁶⁹ Similarly, among a cohort of 38 premature infants, five women reported smoking during pregnancy and all five of these premature infants had impaired neurological outcomes defined as abnormal neuromotor examination, vision, or hearing impairment at follow-up to five years of age.³⁵ In a study of term infants, even at one year of age, infants exposed to moderate maternal smoking had significant differences in blood pressure response to tilt testing compared to non-exposed infants which suggests long-term abnormal programming in autonomic cardiovascular control.⁷⁰ Fetal exposure to maternal smoking *plus* prematurity and lower birth weight, may thus be an especially risky combination for ANS dysmaturation. Together, these findings support that factors in the intrauterine and early postnatal environment may be the origins of adult diseases (i.e. chronic hypertension) which may take decades to manifest.⁶

Autonomic dysmaturation may also occur through altered fetal programming from maternal stress and illness.⁷¹ Prior to birth, maternal toxic-stress can influence fetal cortisol levels, which may affect the fetal-neonatal transition, the response to stress after birth, and may even result in long-term gray matter volume changes detectable years later.⁷² Mothers with a history of toxic stress are at higher risk for spontaneous preterm labor, and have infants of lower birth weight and of lower gestational age compared to pregnant women without a high stress history.⁷² Maternal stress may therefore be an additional mechanism acting alone or in combination with prematurity and FGR, to lead to *ANS dysmaturation*.

How ANS failure during transition may lead to brain injury

The fetus and transitioning newborn is at risk for brain injury. As described, the ANS is intimately involved in many aspects of successful transition of the newborn including cardiovascular, endocrine, and respiratory functions. These demands on the ANS come at a time when the ANS is still in active development, and therefore at particular risk for developmental derailment. At delivery and especially prior to term, the ANS itself is immature and therefore vulnerable for injury and dysmaturation. In addition, the brain is immature and depending upon the developmental stage of brain development there may be particular areas of vulnerability from poor transition. In the preterm newborn, the periventricular white matter is at particular risk for injury from hypoxemia/ischemia due to immature oligodendrocytes, vascular supply, and immature neurotransmitter systems, with less risk for brain stem injury.⁷³ Hypoxic-ischemic brain injury in the term newborn is more likely to result in injury to the sensory and motor cortex, deep gray matter, and brain stem.⁷³

ANS dysfunction may lead to brain injury for both preterm and term-born infants; however brain injury itself may also lead to ANS dysfunction and failure. Preventing brain injury in the newborn thus requires support of central ANS function.

Fetal cardiotocography evaluates baseline fetal heart rate, accelerations, decelerations, and variability. Fetal heart rate is monitored routinely in labor as the main indication of fetal well-being and has the goal of improving neonatal outcome and preventing cerebral palsy. Absent/reduced HRV along with a consideration of the duration may indicate fetal distress, hypoxemia, and acidosis.^{74,75} Reduced/absent variability in fetal heart rate can be seen prior to the onset of labor in cases of in utero hypoxemia and ischemia. HRV is known to increase during fetal life to term with maturation of the ANS and greater parasympathetic influence. With exposure to acute or chronic fetal hypoxemia, ANS function slowly fails. In a study of fetal autonomic response to severe acidemia, fetal HRV indices 30 minutes prior to delivery showed increased normalized low frequency variability (reflecting sympathetic and parasympathetic tone) and reduced normalized high frequency variability (reflecting parasympathetic tone) among infants with cord arterial pH less than 7.05 versus those infants with a cord pH of greater than 7.20.⁷⁶ This difference however was not seen at 2 to 3 hours prior to birth, likely indicating that ANS function declined closer to delivery after a more prolonged period of distress.⁷⁶ At birth, the asphyxiated newborn is typically bradycardic, apneic, and hypotensive reflecting poor ANS function. Consequently, the infant's transition may be dependent on full medical support including mechanical ventilation, pressors and inotropic medications, and corticosteroids.

In acute neonatal hypoxic-ischemic encephalopathy in the term newborn, brain injury severity by MRI is associated with HRV depression at 24 hours of age.⁷⁷ The pattern of hypoxic-ischemic injury in the near-term and term newborn depends on the severity and duration of the insult. The injury pattern from prolonged partial hypoxia-ischemia is in the watershed distribution of the cerebral cortex whereas the injury pattern seen in severe acute hypoxic-ischemic injuries involves the deep gray matter and brain stem structures, in addition to cortical injury.⁷³ Both injury patterns can result in ANS dysfunction. Cortical injury acutely affects ANS function, especially that of the sympathetic nervous system.⁷⁷ In addition, at term age there already appears to be cortical lateralization of the two major ANS systems. In a study of term newborns with global hypoxic-ischemic encephalopathy, infants with injury to the right hemisphere showed reduced HRV, i.e. had lower sympathetic nervous system tone (low frequency variability), while injury to the left hemisphere had no significant effect on HRV.⁷⁸ In another study of term newborns with hypoxic-ischemic encephalopathy, infants with right cortical and/or cerebellar injury had reduced low frequency/high frequency HRV spectral analysis ratio compared to infants with left cortical and/or cerebellar injury in which was seen an increase in the low frequency/high frequency HRV spectral analysis ratio.⁷⁹ In adult brain injury patients, those with right hemisphere injury had less ability to perform under stress compared to patients with left hemisphere injury indicating differences in autonomic reactivity based on injured hemisphere.⁸⁰ Other adult studies also support the role of the cerebral cortex in modulation of the ANS, which receives sympathetic tone predominantly from the right hemisphere and parasympathetic tone from the left hemisphere.^{81,82} The timing of development of cortical lateralization of the ANS in the fetus and premature newborn is, however, not well known, nor is the

developmental importance of this finding for supporting fetal-neonatal transition. Brain stem injury can cause direct injury to ANS centers within the brain stem and may result in significant dysautonomia as well as impaired respiratory function and cardiovascular autonomic regulation.

Immature ANS responses during transition and the perinatal period likely contribute to hemodynamic and cardiovascular instability which itself may result in newborn brain injury.^{24,25} The prevailing paradigm for hemodynamically mediated brain injury in the premature infant is centered on a confluence of insults emanating from the unstable immature cardiovascular system and immature intrinsic cerebral autoregulation acting on the fragile cerebral vasculature. The brain's cellular elements are also vulnerable, in particular immature oligodendrocytes, enhancing risk for brain injury from ANS dysfunction and hemodynamic instability. In premature newborns, HRV changes can be seen preceding the development of intraventricular hemorrhage.^{83,84} Whether ANS dysfunction in these newborns contributes to brain injury or whether ANS dysfunction is a more sensitive clinical early biomarker, is not exactly known.

Neonatal indices of ANS function may predict long term neurodevelopmental outcome.^{35–37} Premature newborns with abnormal neurologic development, especially those with motor disability (i.e. cerebral palsy) have reduced total power and non-harmonic power (autonomic tone) compared to preterm newborns with normal neurologic outcome.³⁵ This finding suggests that part of the long-term impairment in ANS maturation in premature newborns may be due to brain injury itself.³⁵ In a study of premature newborns with and without brain injury, the presence and type of brain injury was associated with HRV and HRV correlated with improved neurologic outcome at one year of age.⁸⁵

ANS dysfunction and changes in ANS maturation may not be amenable to repair or “normal” development after early developmental disturbances,²⁷ and may result in autonomic dysmaturation due to aberrant programming even in the absence of overt brain injury.⁸⁶ Of note, the parasympathetic nervous system is at particular risk, being in a phase of particularly vigorous development at this stage. Resulting ANS dysmaturation increases the risk for neuropsychiatric and mood disorders and reduced cardiovascular health into adulthood.^{67,87,88} These psychological disorders may be as debilitating as structural brain injuries, yet may be overlooked at young ages. Likewise, chronic fetal hypoxemia in FGR and its effects on ANS maturation, may not only have immediate effects in the neonatal period, but can affect neuropsychological and cardiovascular health of the individual into adulthood.^{6,88} Observational studies show that adults born at lower birth weight/size are at increased risk for death in middle age from cardiovascular disease,⁸⁷ and for the development of type II diabetes mellitus.⁸⁹ Low birth weight (i.e., FGR) may also increase the risk for depression and mood disorders,^{90,91} perhaps due to early dysmaturation of the ANS.

Important areas for future focus

Recent technological advancements have enhanced our ability to measure fetal physiology and ANS function using fetal EKG and advanced signal processing. Fetal brain structure can

be quantified through advanced fetal magnetic resonance imaging techniques. These tools are bringing us closer to understanding the complex function of the developing ANS in supporting the fetus at transition. In addition, we are steadily improving our understanding of the multiple maternal and fetal conditions which can adversely affect fetal ANS development and function and lead to complicated neonatal transition. Continued research is needed in the areas of maternal opiate use and neonatal abstinence syndrome, maternal diabetes and effects on the infant ANS, FGR, maternal stress and depression, and prematurity. The next step in this continuum of work is to develop real-time ANS monitoring which can be used at the maternal (fetal) or neonatal bedside in both research and in clinical practice settings to identify a fetus (or newborn) at risk of impaired ANS function/development. HRV analysis methods have already been studied and may predict intraventricular hemorrhage,⁸⁴ brain injury pattern,⁴⁹ developing necrotizing enterocolitis,⁶⁴ and risk for apparent life threatening events.⁴ This technology therefore has the potential to reduce brain injury and adverse neurologic outcomes in high-risk pregnancies and premature or other at-risk newborns. This knowledge can help support safe transition of the at-risk fetus and lead to new methods of care which may better support the developing ANS and hopefully prevent both early and late neuropsychological and other health complications from ANS dysfunction.

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Figure 1. Brain stem cardiovascular (A) and respiratory (B) autonomic nervous system (ANS) centers.

(A) Sympathetic and parasympathetic control centers in the medulla provide ANS mediated control of the cardiovascular system. The nucleus tractus solitarius (NTS) is a key regulator of sympathetic and parasympathetic functions and controls cardiovascular and respiratory system functions. It receives peripheral afferent input from peripheral chemoreceptors and pulmonary mechanoreceptors. The cells of the NTS then modulate sympathetic and parasympathetic tone at the other brain stem centers (rostral ventrolateral medulla, caudal

ventrolateral medulla, nucleus ambiguus, and dorsal motor nucleus of the vagus. (B) In the brain stem is a complex system for respiratory control that is influenced by the ANS. Central pattern generators involved in respiratory function produce rhythmic respiratory motor response based on afferent input. Major central pattern generator neuron groups consists of the pontine respiratory group, Böttinger complex (expiratory rhythm generator), pre-Böttinger complex (inspiratory rhythm generator), retrotrapezoid nucleus, the rostral ventral respiratory group (inspiratory), and the caudal ventral respiratory group (expiratory). The NTS, in the dorsal medulla, receives peripheral input that then modulates respiratory rhythmogenesis in the central pattern generators. The raphe nuclei are serotonergic neurons located within the medulla that project to multiple brain stem respiratory centers including the central pattern generators, Böttinger and pre-Böttinger complexes, as well as the phrenic motor nucleus, hypoglossal nerve, and others.