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Injury and repair in perinatal brain injury: Insights from non-invasive MR perfusion imaging



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ABSTRACT

Injury to the developing brain remains an important complication in critically ill newborns, placing them at risk for future neurodevelopment impairments. Abnormal brain perfusion is often a key mechanism underlying neonatal brain injury. A better understanding of how alternations in brain perfusion can affect normal brain development will permit the development of therapeutic strategies that prevent and/or minimize brain injury and improve the neurodevelopmental outcome of these high-risk newborns. Recently, non-invasive MR perfusion imaging of the brain has been successfully applied to the neonatal brain, which is known to be smaller and have lower brain perfusion compared to older children and adults. This article will present an overview of the potential role of non-invasive perfusion imaging by MRI to study maturation, injury, and repair in perinatal brain injury and demonstrate why this perfusion sequence is an important addition to current neonatal imaging protocols, which already include different sequences to assess the anatomy and metabolism of the neonatal brain.

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Critically ill newborns are at risk for developing brain injury and subsequent neurodevelopmental impairments, since the injury happens at a time when the brain is actively maturing. Research is ongoing to better understand how these brain injuries develop and how early-life injury impacts brain development, with a long-term goal being prevention and/or repair. Among the technologies used to study maturational, destructive, and repair processes in the neonatal brain, magnetic resonance imaging (MRI) has enabled the study of perinatal brain injury *in vivo*. Different MRI sequences—such as diffusion-weighted imaging, diffusion-tensor imaging, and spectroscopy (described elsewhere in this Seminar Series)—have been

developed to assess the anatomy, micro-organization, and metabolism of the neonatal brain in normal conditions, as well as at different times following injury. More recently, a specific MRI sequence has been adjusted for the neonatal brain to non-invasively assess brain perfusion and might be an interesting addition to the current neonatal imaging protocols. Thus, this review illustrates the potential role of non-invasive perfusion imaging by MRI to study maturation, injury, and repair in perinatal brain injury. In addition, this article includes a brief overview of why assessing brain perfusion in newborns is of utmost importance and summarizes the current limitations of non-invasive perfusion imaging by MRI.

Abbreviations: ASL, arterial spin labeling; MRI, magnetic resonance imaging; PASL, pulsed arterial spin labeling; pCASL, pseudo-continuous arterial spin labeling; SNR, signal-to-noise ratio

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Importance of assessing brain perfusion in newborns

Abnormal brain perfusion is a key underlying mechanism in acquired neonatal brain injury. For example, brain injury following birth asphyxia or perinatal stroke is known to follow an evolving process initiated by an insult that leads to decreased blood flow to the brain and necrosis (primary lesions), followed by the restoration of blood flow in the injured brain and an initiation of a cascade of pathways. The biochemical cascade that accompanies the restoration of brain perfusion (so-called “reperfusion injury”) includes an accumulation of extracellular glutamate with an excessive activation of glutamate receptors, calcium influx, and a generation of reactive oxygen and nitrogen species, which lead to delayed cell death and brain injuries (secondary lesions).¹ Periventricular white matter injury in premature newborns and in newborns with congenital heart disease is also known to involve complex mechanisms that include hypoxia-ischemia, hypotension, and hypocapnia in the context of an immature cerebrovascular autoregulation.^{2–5} Assessing brain perfusion and its regulation in these critically ill newborns may thus enhance our understanding of how abnormal brain perfusion contributes to the development of brain injury, which may enable us to develop more targeted neuroprotective and neurorestorative therapies.

Many approaches have been used to measure brain perfusion in newborns. For example, Doppler sonography has been used in the past, but it provides only indirect measurements of brain perfusion and does not provide measurements in different brain regions.⁶ Positron emission tomography, xenon-enhanced computed tomography, or gadolinium-enhanced perfusion-weighted MRI provide better visualizations of specific regions in the brain, but they require the injection of contrast material and/or an exposure to ionizing radiation.^{7–13} Near-infrared spectroscopy offers easy continuous monitoring at the bedside of regional mixed venous saturation^{14,15}—which represents the balance between the oxygen that is delivered to the brain tissue (i.e., cerebral blood flow or oxygen supply) and the oxygen that is extracted at the brain tissue level (i.e., oxygen demand or utilization)—however, it does not provide direct measurements of the cerebral blood flow.^{14,15} By comparison, arterial spin labeling (ASL) perfusion-weighted MRI is the only approach that enables direct and non-invasive measurements of cerebral blood flow in different brain regions without the need to inject contrast material or expose the newborn to ionizing radiation.^{8,10,16,17} To date, a handful of studies have demonstrated the feasibility of using ASL in newborns.^{18–20} In addition, a few recent studies have demonstrated the benefit of combining timely measurements of cerebral blood flow by ASL-MRI with other modalities, such as near-infrared spectroscopy or MR spectroscopy, to better assess changes in cerebral perfusion, metabolism, and oxygenation in sick newborns.^{18–19,21}

MR perfusion imaging to assess maturation in the newborn brain

Newborns have lower brain perfusion compared to older children and adults. Brain perfusion increases with

postmenstrual age, and these changes in newborns can be measured and monitored non-invasively with ASL.²² Moreover, different brain areas display different brain perfusion values, with higher brain perfusion in the cortex and basal ganglia compared to the white matter,^{20,22} in line with previous measurements in newborns by other approaches.^{7–13} These different areas also show changes of brain perfusion according to postmenstrual age, which has been related to synaptogenesis, myelination, and functional activity.²² More detailed studies of normal brain perfusion in newborns and resulting disturbances in cerebral autoregulation in critically ill newborns are important for better understanding the impact of alterations in brain perfusion on normal brain maturation. In the past, such studies have demonstrated interesting results, but they were limited by their invasive nature and the exposure to radiation or radioisotopes that were required by the techniques used to measure brain perfusion. ASL-MRI offers new opportunities to better assess the normal development of brain perfusion in newborns (described below).

MR perfusion imaging to detect injury in the newborn brain

Until now, a few studies have investigated the potential role of MR perfusion imaging with ASL to evaluate brain perfusion in asphyxiated newborns^{18–20} and in newborns with stroke^{23,24} and have compared their measurements to the values obtained in normal newborns. After birth asphyxia, an initial decrease in cerebral blood flow in the first hours after birth has been described, followed by a relative hyperperfusion (Fig. 1) during the first days of life in the brain areas that subsequently demonstrated injury on conventional MRI.^{19–20} This early hyperperfusion has been shown to correlate with later brain injury²⁰ and also with later adverse neurodevelopmental outcomes.¹⁸ In addition, two studies have evaluated the feasibility of ASL in a small number of newborns following stroke during the first month of life.^{23,24} These studies showed that brain perfusion abnormalities were clearly associated with the infarcted area in the acute to subacute phase.^{23,24} Most often, these brain perfusion abnormalities included hypoperfusion within the stroke area and hyperperfusion (Fig. 2) in the periphery of the stroke area.^{23,24}

Thus, ASL-MRI appears to be useful for identifying a developing brain injury.^{19,20} Hyperperfusion has been related to “luxury perfusion,” which is thought to represent the physiologic transient reperfusion (flow restoration),^{25–27} most often described as exceeding the metabolic demands of the injured brain areas.^{10–18,21} This “neurovascular uncoupling” triggers a complex cascade of interconnected perfusion, metabolic, and molecular disturbances—such as excitotoxicity, proinflammatory cascades, and oxidative injury—which lead to secondary injury.^{1,28,29} Experimental data also have suggested a loss of cerebral autoregulation and have examined the role of nitric oxide, free radicals, adenosine, and prostaglandins in generating this hyperperfusion.¹ These data suggest that this hyperperfusion may be used as an early marker of brain injury. Its value

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