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A “Neurovascular Unit” approach in newborns with HIE: Can we improve outcomes?

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Neonatal encephalopathy resulting from hypoxic-ischemic injury remains a major public health problem that afflicts millions of newborns worldwide and may result in cerebral palsy, mental retardation, learning disabilities, and death.¹ Understanding of the mechanisms that underlie cerebral injury in these asphyxiated infants is urgently needed to help guide future neuroprotective strategies, as 50% of infants continue to have abnormal outcomes despite implementation of hypothermia therapy.^{2,3,4} A conceptual ‘neurovascular unit’ depends on intact neurovascular coupling and includes the vascular endothelial cells, astrocytes, neurons, as well as supporting glial cells, which all contribute to the regulation of cerebrovascular function.^{5,6} This special edition of the journal puts emphasis on the neurovascular unit, with the hopes that such approach can help optimize outcomes of newborns with HIE in the future.

Specific highlights include:

1. The mechanisms of CBF regulation, which relies on the integrity of the neurovascular unit. The acidosis, hypoxia and hypercarbia, which results from HIE can result in varying disturbances of the homeostatic system. Hence, we will summarize a methodological review of NIRS, Doppler and AEEG which could provide useful prognostic information. Significant gaps of knowledge remain with development of tools to quantify the extent of impaired autoregulation, and whether autoregulation modulation can affect outcomes.
2. Development of non-invasive brain imaging techniques to measure neonatal cerebral oxygen metabolism. Because oxidative metabolism is the primary form of energy production in the brain, the cerebral metabolic rate of oxygen (CMRO₂), represents a key marker for tissue viability and brain function. Several promising techniques to quantify neonatal CMRO₂, which had been a challenging task in the past, are summarized.

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3. Clinical implications of monitoring cerebral blood flow and cerebral oxygenation, as it is yet unclear whether these abnormalities contribute to the injury or constitute a compensatory mechanism.
4. Development of serum biomarkers to evaluate the severity scale, timing of injury and real time responses to therapy. Using a panel rather than a single biomarker seems most likely to yield results but is still mostly research based. While GFAP and UCHL1 appear the most promising as brain specific biomarkers, there is no currently available biomarker to be recommended for immediate use in the clinical setting.
5. Optimal target temperature needed to keep the integrity of the neurovascular unit. While advances in uncovering the multiple pathways involved in the pathogenesis of brain injury with HIE have all been well described, we will focus the review on studies uncovering the cerebral vasculature blood brain barrier (BBB) component of brain injury and how it is modulated by temperature.

The fundamental premise of neuroprotection has historically focused on the prevention of neuronal death. However, despite tremendous advances in molecular pathways, hypothermia the only effective neuroprotective therapy to date in newborns with encephalopathy is a broad non selective neuroprotective modality. The concept of the neurovascular unit emphasizes homeostatic signaling among the various neuronal, glial, and vascular compartments, while dysfunctional signaling contributes to disease. Critical knowledge of the functional regulation of the neurovascular unit, which is highlighted in this review, may lead to improved ability to differentiate non responders to hypothermia who could benefit from additional therapies. Future research should focus on refinement and precision of monitoring tools, gaining insight mechanisms in neonatal cerebral autoregulation, and demonstrating clinically improved outcomes.

REFERENCES

1. Levene ML, Kornberg J, Williams TH. The incidence and severity of post-asphyxial encephalopathy in full-term infants. *Early Hum Dev.* 1985 May; 11(1):21–26. [PubMed: 4006822]
2. Azzopardi D, Strohm B, Edwards AD, et al. Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: how cooling is managed in the UK outside a clinical trial. *Arch Dis Child Fetal Neonatal Ed.* 2009 Jul; 94(4):F260–F264. [PubMed: 19060009]
3. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* 2005 Oct 13; 353(15):1574–1584. [PubMed: 16221780]
4. Higgins RD, Raju T, Edwards AD, et al. Hypothermia and Other Treatment Options for Neonatal Encephalopathy: An Executive Summary of the Eunice Kennedy Shriver NICHD Workshop. *J Pediatr.* 2011 Aug 27.
5. del Zoppo GJ. The neurovascular unit in the setting of stroke. *J Intern Med.* 2010 Feb; 267(2):156–171. [PubMed: 20175864]
6. Zonta M, Angulo MC, Gobbo S, et al. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nature neuroscience.* 2003 Jan; 6(1):43–50.