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Cardiopulmonary Impact of Hypoxic Ischemic Encephalopathy in Newborn Infants

The Emerging Role of Early Hemodynamic Assessment in Determining Adverse Neurological Outcomes

Perinatal hypoxic ischemic insults are frequently accompanied by multiorgan system involvement. Although cerebral injury is the most concerning consequence, myocardial dysfunction may also contribute to postnatal neurological impairment and exacerbate organ damage (1). The cardiovascular determinants of cellular homoeostasis rely on the distinctive interface between myocardial performance, end-organ perfusion, and tissue oxygen delivery and consumption (2). Perturbations to the cardiovascular system in infants with hypoxic ischemic encephalopathy (HIE) can include myocardial damage, right ventricular (RV) dysfunction, and altered transitional circulation (1).

The complexity of the perinatal transition poses a unique challenge for neonates with HIE, particularly when faced with acute cardiopulmonary illness. The increased recognition that cerebral autoregulation can be impaired in this population underpins the need for a comprehensive appraisal of all the determinants of cellular homeostasis. Therefore, a high index of suspicion for cardiopulmonary dysfunction is important in the neonate with clinical and biochemical evidence of a hypoxic ischemic insult (1, 3), but unfortunately, the conventional cardiovascular markers (i.e., blood pressure and heart rate) are recognized as late findings of inadequate myocardial performance to sustain appropriate organ perfusion and tissue oxygenation (2). Along with a lack of clarity regarding thresholds for hemodynamic screening and intervention, traditional parameters make it challenging to delineate the nature of cardiopulmonary instability with precision or to decipher whether compromise is a result of cardiac injury, intra- and extracardiac shunting, alterations in systemic and pulmonary vascular resistance, or a developmentally immature myocardium. Hemodynamic assessment with echocardiography enables enhanced diagnostic precision with a targeted approach to intervention that may complement a clinical examination and more accurately optimize postinsult cerebral blood flow and oxygen delivery. Although echocardiography may offer a blueprint for formulating a diagnostic impression, further investigation is needed to determine the risk/benefit ratio of treatment and the thresholds for initiating treatment (3).

In a study presented in this issue of the *Journal*, Giesinger and colleagues (pp. 1294–1305) used data from a multicenter cohort of neonates with HIE undergoing therapeutic hypothermia (TH), with cerebral hemodynamics assessed by advanced neurophysiological and cardiovascular hemodynamic monitoring systems, to study an association between the severity of cardiopulmonary dysfunction and the composite outcome of death or abnormal magnetic resonance imaging (MRI) (4). This is the largest and most comprehensive evaluation of this high-risk population. They demonstrated that the overall cohort had depressed RV systolic function and increased pulmonary pressures compared with published normative data obtained at 24 hours of age, and that markers of impaired RV performance were independently associated with abnormal basal ganglia and/or watershed injury by MRI. RV systolic parameters and pulmonary pressures normalized on follow-up echocardiography, but evidence of early increased afterload was not discriminatory of neurological outcome. Similarly, left ventricular (LV) systolic and RV and LV diastolic function parameters were also nonpredictive of poor outcome. These findings shed some light on a population of newborns with a high burden of adverse sequelae, and enhance our understanding of additional risk factors and postnatal adaptive processes that may be associated with or predictive of morbidity in infants with HIE. The authors highlight the importance of RV performance for the potential benefit of adapting a rigorous hemodynamics approach to characterize cardiac function in these infants.

This study is timely, as the ability of a cardiac dysfunction to predict the impact of hypoxic insults on neurological outcomes has been elusive, and these results may pave the way for new strategies to address the contribution of RV dysfunction to neurological injury and/or recovery. Recent studies have shown that agents that address RV function may be associated with brain recovery in animal models of HIE (5, 6). So far, two mechanisms of cardiac dysfunction have been described in neonates with a perinatal hypoxic insult: *1*) depressed LV function from the initial insult that is further exacerbated by

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reactive oxygen species (from the reperfusion injury), leading to reduced Q and pulmonary venous hypertension; and *2*) hypoxia vasoconstriction of the pulmonary vascular bed, leading to elevated pulmonary vascular resistance and acute pulmonary hypertension physiology (3). As the pulmonary hypertension worsens (sometimes after initiation of TH), the impairment in oxygenation and pulmonary venous return further compounds the reduced systemic blood flow due to LV dysfunction. In both settings, the right ventricle can be affected by a downstream effect during the initial and reperfusion injury. Giesinger and colleagues suggest that the primary insult to RV performance is most relevant, based on the observation that measures of RV systolic function were decreased in the adverse-outcomes cohort in the setting of preserved LV functional parameters and the normalization of pulmonary hemodynamics. For the first time, these authors describe the impact of TH and rewarming on the relationship between RV performance and cerebral injury. Rewarming hemodynamics and how to actively modify cardiovascular-specific medications throughout this period are areas of ambiguity, but it is possible that the RV dysfunction, which has long been believed to start either on the left side of the heart or in the pulmonary vasculature and progress to the right, may also originate from a primary insult to the right ventricle, with the potential to lead to biventricular enlargement, dilated cardiomyopathy, and further impairment of the systemic circulation and end-organ perfusion (3).

Infants with HIE who are being treated with TH receive extensive laboratory and neurological evaluations, but a complete hemodynamics assessment does not always ensue. Until recently, echocardiography was only considered in the presence of clinical cardiovascular compromise and/or elevation of biomarkers; however, Giesinger and colleagues suggest that advanced hemodynamic assessments should not only be performed early in all infants with HIE treated with a cardiovascular agent, but also in infants with moderate to severe HIE before or at 24 hours after initiation of TH to identify myocardial dysfunction that may not be clinically apparent. Echocardiography assessment coupled with clinical suspicion and biochemical evaluation will offer the clinician the opportunity to tailor therapy to target the predominant component responsible for the myocardial dysfunction, and may result in a significant improvement in restoring cardiovascular stability.

Early evidence of RV dysfunction in newborns with HIE adds to the growing list of complications that occur after a perinatal hypoxic insult and may be a marker for a greater risk of adverse cerebral injury. Giesinger and colleagues demonstrate that the determinants of adverse neurological outcomes are not always limited to the cerebral insult itself, and that RV dysfunction at 24 hours of age is an independent predictor of death or abnormal brain MRI, even after adjusting for the severity of the insult and subsequent disease burden. Future studies should use these predictive hemodynamic risk factors to evaluate targeted management strategies that address the cardiac contribution to neurological injury, the effects of a cardiovascular intervention during the cooling and rewarming phases, and long-term cardiovascular outcomes in relation to neurodevelopmental status. ■

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