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Better Survival with Less Morbidity in Extremely Preterm Infants
Attacking the Heart of the Matter

Advances in perinatal care of extremely low gestational age newborns (ELGANs) have led to dramatic improvements in the survival of extremely preterm infants, even those born at the limits of viability of 22–23 weeks. However, considerable intercenter variations in outcomes exist (1), and, with the increased survival of ELGANs, concerns persist regarding the need for novel strategies to optimize the overall quality of survival, especially regarding brain injury due to severe intraventricular hemorrhage (IVH) and long-term sequelae of impaired neurocognitive development and cerebral palsy (2).

The etiology of IVH is multifactorial, and its severity is dependent on interactions between the fragile developing germinal matrix vasculature, with striking fluctuations in cerebral blood flow due to cardiorespiratory and hemodynamic instability during early postnatal life (2). IVH is strongly associated with marked swings in systemic hemodynamics during the transition at birth that are due to rapid changes in cardiac performance and pulmonary vascular tone, resulting in intermittent or sustained hypotension with low cardiac output. These dynamics are critically modulated by "hemodynamically significant" changes in the degree of shunting of blood flow across the patent ductus arteriosus (PDA) (3, 4). Adverse hemodynamic effects on IVH pathogenesis persist despite the common use of antenatal corticosteroids, delayed cord clamping, and indomethacin prophylaxis, which have each been shown to partly reduce the risk of IVH (5). Whether aggregate strategies that achieve greater hemodynamic stability in preterm infants by addressing specific physiologic targets can reduce the risk of severe IVH and other outcomes of prematurity has been uncertain.

Many challenges and controversies persist on how to best define and manage systemic and pulmonary hemodynamics in preterm infants after birth. There has been an increasing recognition among neonatologists that traditional assessment of cardiovascular stability based solely on bedside monitoring of blood pressure, heart rate, and perfusion has been overly simplistic and ineffective. During the past decade, medical centers throughout the world have been actively working to develop essential skills and expertise in the application of targeted neonatal echocardiography (TnECHO; also termed functional echocardiography) to tackle the challenge of providing comprehensive evaluations of cardiac function, ductal flow, and pulmonary hemodynamics with the overall goal of providing individualized, physiology-driven approaches to cardiovascular management in sick newborns (6–10). Past studies have provided insights into the integration of cardiovascular and pulmonary physiology for patient care, but data are limited regarding the impact of TnECHO strategies on such critical outcomes as survival and IVH, as well as key morbidities such as necrotizing enterocolitis and bronchopulmonary dysplasia.

In a study published in this issue of the *Journal*, Giesinger and colleagues (pp. 290–300) examined the effects of applying early hemodynamic screening (HS) with TnECHO on mortality and IVH as primary endpoints (11). After first developing a uniform approach to the care of ELGANs, standardized TnECHO protocols for HS were applied in the neonatal ICU. This highly skilled team studied the impact of HS by performing echocardiography at 12–18 hours of age in ELGANs between 22 and 27 weeks' gestation. Care was based on physiology-guided therapies that were based on specific echocardiographic assessments of systemic hemodynamics, right and left ventricular function, the presence of a hemodynamically significant PDA, and pulmonary hypertension. Outcomes achieved after the early HS program had been established (the "HS epoch"; 2018–2022) were compared with a historical control cohort of babies born before the program was launched (2010–2017). Babies in the HS cohort received a comprehensive TnECHO assessment using a predefined protocol performed by a small group of specialists with extensive experience and expertise in neonatal echocardiography and hemodynamics. Cardiovascular support was provided in a standardized manner according to physiological phenotype based on comprehensive baseline and serial echocardiographic examinations. The principal components of management were early targeted closure of a moderate- to high-volume ductal shunt (defined by using a PDA scoring system), treatment of acute pulmonary hypertension

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with inhaled nitric oxide, and early inotropic support for ventricular dysfunction with dobutamine.

The remarkable finding of the study was a nearly 50% reduction in the primary outcome of death or severe IVH associated with early HS and standardized care. These findings are especially striking considering that infants in the HS cohort were far more likely to be born at 22–23 weeks than in the historical control group. After adjustment, the odds ratio for survival without severe IVH was 2.09 (95% CI, 1.19–3.66), with a corresponding reduction in the individual components.

In this study, the authors employed a "before-and-after" study design to compare babies cared for during the HS epoch versus a historical control cohort. This design carries the limitation that changes in practice over time lead to interval improvement in aggregate neonatal care unrelated to TnECHO *per se*, and that this could account for a significant portion of the clinical benefit observed. However, the authors acknowledge and account for this limitation by demonstrating that the significant associations between epoch effect and clinical outcomes persist even when accounting for year of birth as a continuous variable.

How might HS have impacted survival and severe IVH in this study? Those advocating HS point to the potential benefits and rationale of physiology-driven, individualized cardiovascular management (9, 11). Early identification of, and targeted therapy for, conditions such as hemodynamically significant ductal shunting, ventricular dysfunction, and acute pulmonary hypertension are likely to be preferable to unfocused symptom-based treatment of hypotension or hypoxemic respiratory failure. Interestingly, despite an association between early screening and lower mortality rates, recent randomized controlled trials lacking such precision strategies have failed to demonstrate clinical benefit (12, 13).

Overall, these exciting findings support the need for a more precise definition of physiologic phenotypes to better target selective strategies that can reduce mortality or modulate the development of such critical morbidities as IVH, necrotizing enterocolitis, and bronchopulmonary dysplasia. Given the striking findings of this study, it seems imperative to further consider training and workforce implications for any service intending to implement early HS in their neonatal ICU. The success of this hemodynamic model is linked with the performance of high-quality, well-standardized, and extensive echocardiographic studies by well-trained experts in TnECHO, beyond simple point-of-care ultrasound evaluations, which can be limited and nonstructured. In addition to clinical care, this study also has important implications regarding clinical research, suggesting that a failure to define subgroups of preterm infants more precisely before enrollment may mask the benefits or adverse effects of given interventions within subgroups of patients. In this era of precision medicine, TnECHO is likely a vital tool to better characterize subjects for greater success with randomized trials and related studies. ■

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