Preemie Brains Don't Like Mechanical Ventilation!

Over the last 50 years, invasive mechanical ventilation via endotracheal intubation has become a mainstay of neonatal intensive care unit (NICU) respiratory care. This has been the inevitable consequence of managing extremely preterm infants in whom immature respiratory control is superimposed on underdeveloped lungs.[1] Prolonged mechanical ventilation is clearly associated with bronchopulmonary dysplasia (BPD), and the association between BPD and impaired neurodevelopmental outcomes is well documented.[2] Thus, there are intimate (albeit poorly studied) interconnections between the maturing lungs and brain that can potentially be adversely impacted by life-saving therapeutic interventions in the NICU.

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The last decade has seen a strong worldwide push toward various noninvasive modes of assisted ventilation that avoid the need for endotracheal intubation. This has been aided by the acceptance of delivery room continuous positive airway pressure (CPAP), avoidance of prophylactic surfactant, use of less invasive routes of surfactant delivery, and early caffeine administration. Nonetheless, initial and prolonged invasive mechanical ventilation in the NICU setting is still widespread, as recently reported in the Prematurity and Respiratory Outcomes Program cohort.[3,4] Increasing sophistication in ventilators needs to be complemented by studies addressing any adverse consequences.

In this volume of *The Journal*, investigators from Canada and Switzerland have made 2 important interrelated observations in 2 prospectively collected cohorts of preterm infants born at <30 weeks of gestation and receiving invasive mechanical ventilation. The duration of mechanical ventilation, especially if prolonged, was associated with smaller brainstem volumes at term equivalent age, and this in turn predicted adverse motor outcomes at age 4.5 years.[5] Although the authors acknowledge that mechanical ventilation is a known risk factor for adverse neurorespiratory outcomes, previous studies might not have expanded the investigation to preschoolers.

The authors propose an interesting calculation in which each 10 days of mechanical ventilation is associated with a 4.6-point decline in motor performance score (Movement Assessment Battery for Children, second edition) at age 4.5 years. Of note, the adverse effects appear to be focused on motor outcomes rather than cognitive outcomes; IQ was not significantly impacted by the duration of mechanical ventilation. In that context, it is interesting that the longer-term benefits of neonatal caffeine therapy, including decreased ventilator and positive pressure needs 1 week earlier compared with placebo,[6] were also focused in the motor area of development.[7]

From a historical perspective, neonatal brain imaging, initially via ultrasound, has been available only since the late 1970s and has focused mostly on cerebral structures. The current investigators are focusing primarily on the brainstem via magnetic resonance imaging (MRI) at 32 weeks postmenstrual age and again at term. This is quite novel. Via state-of-the-art imaging, they have documented that smaller pons and medulla volumes at term equivalent age were associated with a greater duration (in days) of mechanical ventilation. Although the focus was on brainstem changes, the changes were associated with widespread abnormalities in white matter maturation. How are we to interpret these findings?

These clinical and imaging findings raise many mechanistic questions. The authors propose several biological pathways with direct injurious effects on brainstem volume., including abnormal myelination implicating oligodendroglia, degeneration of descending white matter tracts, and focal necrotic changes within the brainstem structures. These could arise from a wide variety of injurious perinatal events that were more prevalent in the prolonged ventilation group. Was mechanical ventilation confounded by indication in the sickest neonates? Respiratory control is based in the pons and medulla, and an adverse hit in this region from any of the aforementioned mechanisms might necessitate increased ventilator support if respiratory drive is impaired.

There is increasing interest in the adverse effects of intermittent hypoxic episodes on negative respiratory and adverse neurodevelopmental outcomes.[8,9] Such episodes may be a consequence of an underdeveloped brainstem and contribute to the motor deficits at preschool age. Interestingly, intermittent hypoxic episodes are most frequent in preterm infants receiving mechanical ventilation beyond the first weeks of life.[10] Finally, prolonged ventilation may be associated with various forms of sedation, and such pharmacotherapy may have its own confounding neural consequences.[11,12]

Clearly, the development of the preterm brain, maturation of breathing, need for invasive ventilation, and longer-term neurocognitive outcomes are interrelated (**Figure**). Does mechanical ventilation impair brainstem maturation, or does brainstem insult and maldevelopment prolong the need for mechanical ventilation in the high-risk neonate? Multicenter collaborations are currently working to identify the characteristics and exposures preterm patients experience in

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
NICU	Neonatal intensive care unit

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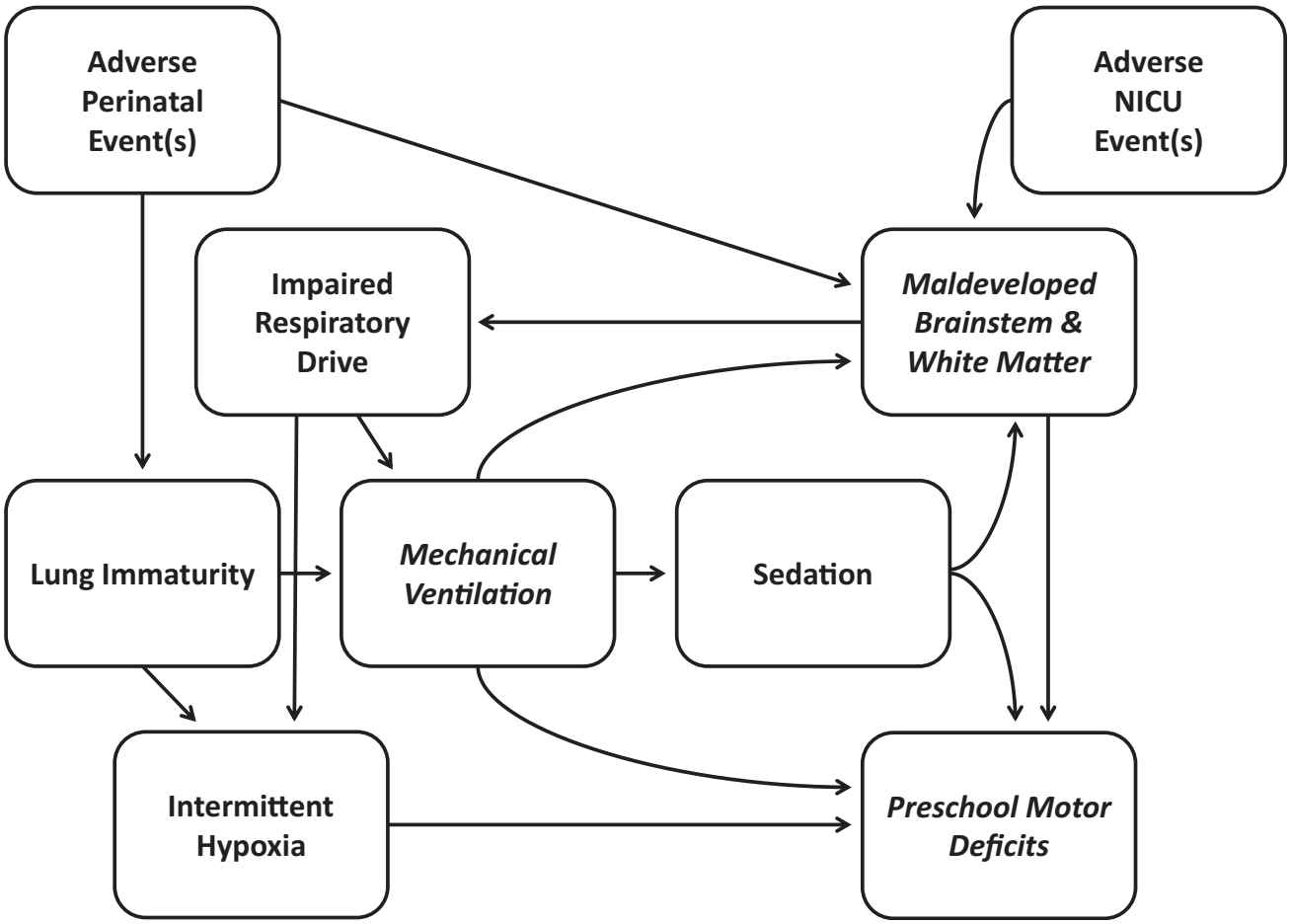

Figure. Potential relationships between mechanical ventilation, brainstem and white matter development, and motor outcomes in the preterm neonate. Shown are proposed interconnected associations of the lung and brain on outcomes; the italicized boxes relate to the primary themes of the Guillot et al study.

our NICUs and their associated risks of longer-term adverse outcomes[3,13]; however, cause-and-effect interactions may be best investigated in animal models. Guillot et al provide compelling new data describing the relationship between duration of invasive mechanical ventilation and diminished brainstem volume.[5] The most troubling data are those showing that these associations manifest as longer-term motor developmental impairments in childhood. Encouragingly, however, noninvasive positive pressure duration was not associated with the reported adverse brain and motor outcomes in their study. As neonatology strives to diminish cardiopulmonary morbidities through less invasive surfactant delivery and more effective noninvasive respiratory support, we may uncover additional important benefits to the developing preemie brain. ■

Thomas M. Raffay, MD
Richard J. Martin, MD
Division of Neonatology
Department of Pediatrics
UH Rainbow Babies and Children's Hospital
Case Western Reserve University School of Medicine
Cleveland, Ohio

Reprint requests: Richard J. Martin, MD, UH Rainbow Babies and Children's Hospital, 11100 Euclid Ave, RBC 3100, Cleveland, OH 44106. E-mail: rxm6@case.edu

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Is Rapid Exome Sequencing Standard of Care in the Neonatal and Pediatric Intensive Care Units?

In this volume of *The Journal*, Freed et al report the results of a 3-year trial of the clinical utility of rapid exome sequencing in critically ill children in the neonatal, pediatric, and cardiac intensive care units of a tertiary children's hospital.[1] The authors conclude that rapid exome sequencing should be considered standard of care for some such children. For readers who are not—yet—aficionados of rapid genomic medicine, let me provide some context for this provocative statement.

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It is now possible to decode the human genome to clinical standards and make a diagnosis of a genetic disease in 19 hours using rapid whole-genome sequencing.[2] Here, genetic disease refers to single-locus disorders, not complex disorders: It includes both ~7000 Mendelian diseases and ~10 000 diseases associated with structural or chromosomal variants. As the name implies, rapid whole-genome sequencing involves decoding about 90% of a critically ill child's 6.4 billion nucleotide diploid nuclear genome and mitochondrial genome and using the child's clinical presentation to search that DNA sequence for the etiology underlying their presentation. This involves both ruling-in and ruling-out specific genetic differential diagnoses, as well as evaluating all known single-locus diseases. The rapid exome sequencing, used by Freed et al, is used interchangeably with rapid whole-genome sequencing but instead involves decoding only the ~60 million diploid nucleotides that are the ~180 000 exons of genes. Rapid exome sequencing identifies ~85% of the variants that cause genetic disease and costs ~75% that of rapid whole-genome sequencing.[2,3] Rapid genomic medicine (or rapid precision medicine) describes the nascent clinical discipline in which rapid whole-genome sequencing or rapid exome sequencing is used as a first-tier test during an intensive care unit stay, and inpatient management is guided by rapid genome sequence results. The turnaround time for such tests to merit the designation "rapid" is evolving. The mean turnaround time in the cohort described by Freed et al was 9 days. Speed is critically important: 12% of the patients reported by Freed et al died before return of results. However, optimal benefit from rapid whole-genome sequencing or rapid exome sequencing requires minimization of time from onset of symptoms to initiation of effective treatment, rather than just testing.[4]

Freed et al report that 43% of children receiving rapid exome sequencing were diagnosed with a genetic disease. This is consistent with other studies of rapid exome sequencing and rapid whole-genome sequencing (weighted average of 37% across 18 studies). Indeed, we have historically underdiagnosed genetic diseases greatly in infants and children in intensive care units. The current estimate is that the incidence of genetic diseases in infants in regional intensive care units is ~15%.[5] Furthermore, the presentations of children who benefit from rapid exome sequencing and rapid whole-genome sequencing are much broader than suspected. Freed et al found that one-half of cases had congenital anomalies with or without congenital heart defects, respiratory failure, or heart failure. Thus, rapid genomic medicine is poised to impact all pediatric subspecialties, not just medical genetics.

Freed et al report that 52% of children tested by rapid exome sequencing had a consequent change in management. This is somewhat greater than other studies (weighted average of 28% across 17 studies). One reason for this is that Freed et al included the clinical utility of negative results. A hitherto under-recognized value of rapid exome sequencing and rapid whole-genome sequencing is ability

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