Unsolved Mysteries: High-Frequency Jet Ventilation in the Neonatal ICU

Premature neonates born prior to 28 weeks of gestation have a mortality rate 183 times greater than those born at full-term, and nearly two thirds of infant deaths in the United States are those born before 37 weeks gestational age.[1] Premature neonates also carry an increased risk of hypoglycemia, temperature instability, feeding difficulties, and respiratory distress.[2] Premature neonates often need increased respiratory support (eg, CPAP, supplemental oxygen, invasive ventilation) during their first days of life due to surfactant deficiency, underdeveloped airway structures, and diaphragm weakness. A recent study reported that 35% of premature neonates developed respiratory distress syndrome (RDS), and the rate for those born ≤ 28 weeks gestational age was 55%.[3] Current management strategies suggest avoidance of invasive mechanical ventilation because time on mechanical ventilation is associated with an increased risk of developing bronchopulmonary dysplasia, neurological dysfunction, and worse overall neurodevelopment.[4] Infants with lower gestational age are more likely to require surfactant administration and invasive mechanical ventilation.[3]

The challenge of mechanical ventilation in premature infants, as in other patient populations, is balancing the risk of ventilator-induced lung injury while providing adequate gas exchange. Most premature children can be supported with conventional mechanical ventilation, but more severe cases may be placed on high-frequency oscillatory ventilation or high-frequency jet ventilation (HFJV). A Cochrane review evaluating elective high-frequency oscillatory ventilation compared to conventional ventilation found no mortality benefit and a small reduction in chronic lung disease in those treated with high-frequency oscillatory ventilation.[5] The Cochrane group was unable to perform a meta-analysis on elective HFJV due to a lack of randomized clinical trials[6] and were also unable to make a determination on the use of HFJV as a rescue therapy due to low-quality data.[7]

Despite the lack of high-quality, high-level supporting data, HFJV is widely used in neonatal ICUs as a rescue mode and as an elective mode intended to reduce bronchopulmonary dysplasia and chronic lung disease. In this issue of RESPIRATORY CARE, Wheeler et al[8] reported on risk factors for mortality in 53 premature neonates treated with rescue HFJV in their quaternary neonatal ICU. The overall survival rate was 74%, and univariate analysis revealed gender, gestational age,

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postmentrual age at HFJV initiation, born < 28 weeks gestational age, weight, length of stay, arterial access, inhaled nitric oxide, patent ductus arteriosus, F_{IO_2}, peak inspiratory pressure at 1 h after HFJV initiation, and oxygen saturation index at 4 h after HFJV were all statistically different between survivors and non-survivors. After HFJV initiation, univariate analysis revealed differences in HFJV peak inspiratory pressure at 1 h after initiation, and F_{IO_2} was significantly different 4 h later. In multivariable analysis, the authors report that gender (female vs male), patent ductus arteriosus, and oxygen saturation index > 5.5 at 4 h after HFJV initiation were associated with increased mortality. They developed a risk score based on these 3 factors and noted that a score ≥ 2 had a sensitivity of 79% and specificity of 78% for mortality.

As with their prior publication on HFJV,[9] Wheeler et al[8] should be applauded for their efforts to expand the evidence on HFJV in the neonatal ICU. Important unanswered questions on the use of HFJV are: who benefits and when should HFJV be initiated? The survivors in this study were younger and smaller, and had lower F_{IO_2} and higher PEEP at HFJV initiation. In addition, non-survivors had lower pH with lower capillary P_{CO_2}, which may be indicative of mixed respiratory and metabolic acidosis. They also had higher peak inspiratory pressure, tidal volume, and driving pressure, although these did not reach statistical significance. HFJV was associated with significant decreases in capillary P_{CO_2} but no difference in oxygen saturation index, with no observed differences between survivors and non-survivors 12 h after HFJV initiation. While driving pressure has not been specifically studied in premature neonates, both adult and pediatric data suggest driving pressure is highly associated with mortality in patients with ARDS.[10,11] Thus, the addition of a driving pressure threshold to help guide decision-making on when to initiate HFJV and evaluation of its utility as a risk factor for mortality require investigation. Importantly, this study did not report the cause of death, which could be related to neonatal sepsis, genetic disorders, intraventricular hemorrhage, and not related to refractory respiratory failure.

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As discussed by the authors, their study is limited by the small sample size, selection bias, and lack of a control group that did not receive HFJV. Importantly, the small sample size greatly limits the number of variables that can be included in their multivariable model. The authors did not include the number of nonsignificant variables, and the variables chosen may have affected the results. Certain factors that are known to be associated with mortality (eg, gestational age and birthweight) are important risk factors that should be included in all models, regardless of their significance in the univariate analysis. Finally, survival is an important outcome, but in the future we should consider including a composite outcome, such as survival without significant morbidity, in premature neonates because many survivors carry significant morbidities such as cerebral palsy, bronchopulmonary dysplasia, developmental delay, increased hospitalizations, and other long-term health sequelae.[12]

The renewed interest in HFJV in the neonatal ICU has illustrated the need for randomized controlled trials investigating HFJV as both a rescue mode like in the study by Wheeler et al[8] and as an elective strategy to prevent bronchopulmonary dysplasia. Given the relative rarity of HFJV use and logistical challenges associated with a randomized controlled trial, it is likely that observational data will be our best source of evidence for now. Having investigators share data in a multicenter collaborative to increase sample size and increase the generalizability of HFJV studies may be a strategy to help guide HFJV use. With larger sample sizes, advanced statistical techniques can be used to more rigorously evaluate outcomes from observational data. This potential collaborative could be modeled after the Pediatric Acute and Critical Care Medicine Asian Network collaboration, which recently investigated high-frequency oscillatory ventilation in pediatric subjects with ARDS in Singapore.[13]

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