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Respiratory Management of Neonatal Acute Respiratory Distress Syndrome

Lucy Loft, MBBS; David G. Tingay, PhD

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High frequency oscillatory ventilation (HFOV) has been used to treat respiratory failure in neonates since the early 1990s.[1] HFOV supports gas exchange by delivering very low tidal volumes at fast rates (>2 Hz). Theoretically, these characteristics of HFOV should result in less lung injury than conventional mechanical respiratory support. Unfortunately, this potential has not been demonstrated in the randomized clinical trial data, with minimal or no difference in key measures of neonatal lung injury, specifically bronchopulmonary dysplasia (BPD).[2] These trials have demonstrated that success, harm, and benefit of any mode of respiratory support, and especially HFOV, depends on how, and to whom, it is applied more than the mode itself.[1,2] Nearly all trials of HFOV in neonates have been limited to first intention (ie, prophylactic) use in preterm infants with acute respiratory distress syndrome (principally related to surfactant deficiency). The clinical use of HFOV has not evolved to reflect the trial populations. Network data has shown that HFOV is used in appropriately 10% to 15% of neonates needing invasive mechanical ventilation, most often when conventional mechanical ventilation (CMV) has failed (ie, rescue use).[3] Thus, HFOV is often used beyond the initial period of surfactant deficiency, when respiratory failure may be multifactorial. This has led to a disconnect between the trial evidence and clinical reality; while we understand how to apply HFOV, there remains substantial knowledge gaps in the clinical setting in whom and when it may be the preferred approach.

In this edition of *JAMA Network Open*, Jie et al[4] have attempted to address this knowledge gap. They report their findings from a single center prospective RCT of preterm neonates born at less than 35 weeks' gestational age and diagnosed with neonatal acute respiratory distress syndrome (NARDS), using the Montreux Definition.[5] Following intubation infants were first stabilized for 2 hours using CMV, and then randomized to receive either HFOV or CMV until first successful extubation. A total of 386 infants were studied (181 HFOV and 205 CMV). The primary end point (intention to treat) was the diagnosis of BPD using the 2001 NICHD definition.[6] The authors found that BPD was 8% less in the HFOV group (RR, 0.92; 95% CI, 0.86-0.99). Among the outcomes reported, the rate of moderate to severe BPD, importantly based on a different (2019) definition, was 17.1% in the HFOV group and 25.4% in the CMV group (RR, 0.68; 95% CI, 0.45-1.00).[7]

This study provides some important context for a relatively new neonatal entity, NARDS, but also illustrates some of challenges in designing and interpreting trials comparing ventilation modalities in neonates. NARDS is a relatively new approach to diagnosing neonatal acute lung disease which brings the benefit of combining a collection of small incidence diagnoses into a single entity based upon a common manifestation of acute respiratory failure without an alternative cause.[5,8] By intent, the current Montreux definition of NARDS shares similarities with ARDS in other populations,[5] including encompasses both direct (eg, aspiration syndromes) and indirect injury (eg, sepsis).[5] NARDS is also divided into infectious and noninfectious, as well as perinatal (less than 72 hours after birth) or late. Importantly, primary RDS is an exclusion factor and lung imaging is required to confirm the diagnosis.[5] In this study, the mean gestational age was 30 weeks' gestational age; NARDS was diagnosed by 48 hours after birth in 99% of infants, and early-onset sepsis (EOS) was the most common precipitant (perinatal indirect NARDS). The overall prevalence of NARDS was 1.5%, with 47.7% of affected infants born at less than 34 weeks' gestational age. Given EOS was the most common precipitant with a higher-than-expected incidence, it would be prudent to define EOS in this cohort. Similarly, details on the overall population screened for NARDS and triggers would aid in determining the study selection. This information is relevant because distinguishing between NARDS

and RDS is very difficult in the early perinatal period, with surfactant response being an unreliable discriminator, especially for indirect NARDS. It is possible, and arguably probable, that some of the included neonates did not have NARDS. Is this a problem? As the entity of NARDS is new, there is a need for high-quality evidence, which requires rigorous population inclusion. A clinician may argue that, irrespective of the diagnostic label, this study is the largest to involve a pragmatic clinical setting, where HFOV is used as a rescue treatment in preterm infants with acute respiratory failure due to multifactorial pathology.

As acknowledged by the Jie et al,[4] the heterogeneity of NARDS means that the ventilation strategies may interact differently across the population, limiting the ability to attribute outcomes to the modality itself. Important confounders, including gestational age, birth weight, surfactant timing, other concurrent supportive therapies, and clinician dependent ventilator management, may also impact modality success. Therefore, limiting reporting to mean airway pressure alone at NARDS diagnosis constrains interpretation, and inclusion of additional respiratory support parameters would be informative.

HFOV is commonly used in neonates with NARDS.[8] Not all lung diseases are the same, and the modality needs to be clinically and biologically plausible. Interpreting mechanical ventilation trials requires understanding how the modality was applied, as inappropriate use of HFOV or CMV increases the risk of adverse events, such as air leak, neurological injury, and BPD.[1] The HFOV strategy used was consistent with current concepts of lung volume optimization (reversing atelectasis) and lung protection.[1] The CMV strategy allowed clinicians scope to adjust to varying pathological needs using predefined criteria, allowing a range of critical CMV settings, especially positive end-expiratory pressure and tidal volume. Despite this potential risk, if applied correctly, it was broadly consistent with lung protective practices.[1] Importantly for interpretation, clinicians could crossover to the other modality if treatment failure criteria were met (13% HFOV; 10% CMV) and the infant remained in their initially allocated group. This highlights another complexity of respiratory mode trials—how to account for the dynamic and changing nature of critical care in design, analysis and interpretation. The impact of ventilator mode on lung injury and survival never occurs in isolation. The risk of misattributing group allocation to an outcome is greater in preterm infants compared with older critical care populations due to the longer duration of critical care.

BPD is a common primary outcome in neonatal respiratory trials, but justification must always be considered. It is likely Jie et al[4]chose BPD as a meaningful proxy of ventilator induced lung injury, consistent with previous HFOV trials. The risk of BPD is gestation dependent, with very low prevalence after 30 weeks' gestation. A cohort with a mean gestational age of 31 weeks results in nearly half of the study population being unlikely to develop BPD, which the authors acknowledged. Additionally, BPD rates were calculated using the total number of enrolled infants rather than the number of surviving infants, and it remains unclear whether the reported findings would retain statistical significance if reanalyzed using survivors as the denominator. Ideally, gestational age–stratified analysis should be performed to strengthen interpretation whenever BPD is a primary outcome. NARDS is often characterized by inflammatory-mediated lung injury rather than ventilator-induced damage, underscoring the importance of selecting a clinically appropriate primary outcome at the study design stage.

Should HFOV be the modality of choice in early NARDS? NARDS, the complexities of trials in this field, and the study limitations do not allow this conclusion. Rather, this study helps clinicians understand how to consider the use of HFOV as a rescue therapy in preterm infants, especially for the management of NARDS. In both areas, trial evidence has lagged behind clinical need.

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Corresponding Author: David G. Tingay, PhD, Professor, Neonatal Research, Murdoch Children's Research Institute, 50 Flemington Rd, Parkville Victoria 3052, Australia (david.tingay@mcri.edu.au).

Author Affiliations: Neonatal Research, Murdoch Children's Research Institute, Parkville, Australia (Loft, Tingay); Department of Obstetrics, Gynaecology and Newborn Health, University of Melbourne, Parkville, Australia (Loft); Mercy Perinatal, Mercy Hospital for Women, Heidelberg, Melbourne, Australia (Loft); Department of Paediatrics, University of Melbourne, Melbourne, Australia (Tingay); Department of Critical Care, University of Melbourne, Melbourne, Australia (Tingay).

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