High-Frequency Oscillatory Ventilation: The Devil May Be in the Details

The study by Sun et al[1] in this issue of RESPIRATORY CARE, comparing high-frequency oscillatory ventilation (HFOV) and conventional mechanical ventilation, merits close attention because it is one of few studies demonstrating clear benefit from HFOV, relative to conventional mechanical ventilation, in preterm infants. In the study, 336 preterm infants (gestational age $<$ 32 weeks, birth weight $<$ 1,500 g) who developed respiratory distress syndrome and required intubation and ventilator support within the first 24 hours of life were randomized to either HFOV (SLE5000 infant ventilator) or conventional synchronous

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intermittent mandatory ventilation (Maquet Servo-i). The criteria for respiratory distress syndrome included a P_{aO_2}/F_{IO_2} $<$ 200 mm Hg and radiographic evidence of severe respiratory distress syndrome. Two major Chinese neonatal ICUs, at Zhengzhou Children's Hospital and Nanjing Children's Hospital, participated in the study. Randomization was computer-generated and stratified by sex and gestational age ($<$ 28 weeks or $\geq$ 28 weeks). Both conventional mechanical ventilation and HFOV ventilator strategies employed "high lung volume" in conjunction with "lung-protective" approaches. The infants were weaned as tolerated, using their respective ventilator strategies, and crossover was not allowed. Infants managed with HFOV had fewer deaths, a lower incidence of bronchopulmonary dysplasia, shorter duration of ventilation and hospital stay, and better neurological outcomes assessed at 18 months of age. The 2 groups were well matched for baseline characteristics, including sex, gestational age, birth weight, use of antenatal steroids, and maternal risk factors.

The results of this study contradict the conclusions of Cools et al[2] in their meta-analysis of 17 randomized controlled trials of HFOV versus conventional mechanical ventilation in preterm infants. Cools et al found no clear benefit from HFOV. The reason for improved outcomes in the infants ventilated with HFOV in the study by Sun et al,[1] relative to previous studies, is unclear. Differences in gestational age, birth weight, time of enrollment, ventilator strategies, and use or non-use of antenatal steroids and postnatal surfactant make direct comparisons across studies difficult. The study by Sun and colleagues enrolled infants with somewhat higher gestational ages and greater birth weights, relative to the 2 most recent and largest multicenter trials. Courtney et al[3] enrolled only infants 600–1,200 g, and described similar increases in "alive without bronchopulmonary dysplasia" and earlier extubation with HFOV. However, in the same journal a study by Johnson et al[4] enrolled infants with gestational ages 23–28 weeks and found no differences in outcomes. Consistent with that study, but contrary to the HIFI study[5] and the study by Moriette et al,[6] neither study demonstrated adverse effects with HFOV. None of these studies reported long-term neurological outcomes.

What possibly accounts for the improved outcomes with HFOV, compared to conventional mechanical ventilation, in the Sun et al study? The patient populations were well matched, the conventional mechanical ventilation strategy was consistent with current approaches, and the investigators included all relevant outcomes. Nearly all outcomes were improved with HFOV. I think the most likely reasons are Sun et al's approach to optimizing lung volume and avoidance of hypocarbia and/or excessive tidal volumes during HFOV. The initial large randomized controlled HIFI Trial[5] found no benefit from HFOV, but was criticized for taking a "low volume" approach to HFOV, which was purported to inadequately recruit the lung. The meta-analysis by Cools et al[2] suggested that a "high volume" (relative to "low volume") HFOV strategy had superior outcomes, and subsequent investigators have largely adopted the high volume approach. How to operationalize a high volume strategy, however, has never been made adequately explicit. This is particularly problematic in multicenter trials, where multiple institutions and clinicians may differently interpret how to achieve optimal lung volume.

Sun and colleagues describe a practical, objective, and likely reproducible approach to what they term "optimal continuous distending pressure" to recruit and maintain lung volume. They employed a step-wise increase in continuous distending pressure until F_{IO_2} could be decreased to 0.25 (or no further improvement in oxygenation was achieved); this was termed the lung "opening pressure." They then stepped down the distending pressure, by increments of 1–2 cm H_2O, until oxygenation deteriorated; this was termed the lung "closing pressure." Finally, they

then again increased the pressure to the opening pressure to re-recruit the lung, and set the final pressure to 2 cm H_2O above the pressure at which oxygenation had deteriorated (that is, 2 cm H_2O above closing pressure). This they called the optimal continuous distending pressure. As has been the case in other studies, the optimal continuous distending pressure resulted in a mean airway pressure (or continuous distending pressure) generally 2–3 cm H_2O above that of conventional ventilation. The same step-wise approach was repeated if the child subsequently received exogenous surfactant. Sun et al also utilized a unique feature of the SLE5000 ventilator, the "gas-transport coefficient," to adjust the expired tidal volume, to assess changes in lung compliance with changes in continuous distending pressure, and to normalize P_{aCO_2}. This may have prevented the initial hypocarbia that can occur with HFOV, and which has been associated with an increased rate of intracranial hemorrhage.[5] Both aspects are unique to this study.

"Open up the lung and keep the lung open" is a strategy first clearly articulated by Lachmann.[7] In conventional ventilation, opening the lung is achieved with positive inspiratory pressure, and PEEP maintains the lung open during the expiratory phase. The propensity of injured lung to "close" during exhalation can be counteracted by increasing the PEEP, but higher PEEP then necessitates higher inspiratory pressure to achieve adequate ventilation. Repeated opening and closing of lung regions and high peek airway pressure are associated with ventilator-induced lung injury, through atelectrauma and barotrauma. Both are implicated in the development of bronchopulmonary dysplasia. By maintaining the lung at high volume while accomplishing ventilation with small tidal volumes and a rapid respiratory rate, HFOV has the potential to avoid both. Unfortunately, this has not been consistently demonstrated in practice. The approach taken by Sun and colleagues to optimizing lung volume, in conjunction with careful attention to tidal volumes (and resultant P_{aCO_2}), with HFOV may offer a practical and reproducible method to allow uniformity across institutions in multicenter trials. These details may be critical in HFOV studies, particularly when multiple institutions and numerous caregivers are involved, and may partly explain the results obtained by Sun et al.[1]

The study by Sun et al has several limitations. The inconsistent use of surfactant adds an element of uncertainty to the analysis, although substantially more conventional-ventilation babies received surfactant. Sun et al also failed to correct for multiple comparisons in their statistical analysis, likely rendering some of the comparisons not statistically different. Additionally, the 3-times-higher rate of cerebral palsy in the conventional-ventilation group is unexplained in the absence of differences in the rates of intraventricular hemorrhage or periventricular leukomalacia. No plausible biological basis for this difference is discussed. It should be noted, however, that follow-up of infants was performed blinded to the intervention.

On the whole, Sun et al should be congratulated on a well designed and executed study. Given the dramatically different results from previous studies of HFOV versus conventional ventilation, it is likely to be met with skepticism in the neonatal community. There appears to be little enthusiasm for yet another HFOV trial in preterm babies. Perhaps these results will prompt other investigators to reexamine this issue with attention to the important HFOV details that Sun et al controlled in their study.

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The author has disclosed no conflicts of interest.

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