High-Frequency Oscillatory Ventilation on Shaky Ground
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We thought it was impossible. Physiological principles maintained that ventilation at tidal volumes less than the anatomical deadspace should be ineffective (i.e., inspired air not reaching the alveolae). Data from a 1980 study dispelled that myth, showing unequivocally that ventilation with tidal volumes as small as 20 to 30 ml in dogs, a mere fraction of the anatomical deadspace, could maintain adequate ventilation. These unexplained observations sparked transport and mixing theories predicting that CO₂ removal should vary in direct proportion to breathing frequency (although the relationship with tidal volume is more complex), and these predictions were later confirmed experimentally.

Subsequent studies showed that CO₂ removal eventually reaches a plateau when the airways narrow during expiration, indicating the onset of expiratory-flow limitation. This concept is important, since portions of the lung can become hyperinflated dynamically (i.e., regional air trapping) beyond levels predicted from the applied mean airway pressure.

High-frequency oscillatory ventilation (HFOV), in which small tidal volumes are applied at a high respiratory rate, became a focus of research and clinical practice, but widespread use was limited by the unavailability of commercial equipment. As the technology gradually evolved, the field suffered setbacks when trials showed that HFOV did not provide a benefit and could have induced harm in neonates with the respiratory distress syndrome. Although there have been some small clinical trials, the use of HFOV in adult patients never really caught on. More and better data were needed, and the field evolved as our understanding of the physiology of the acute respiratory distress syndrome (ARDS) improved.

Although mechanical ventilation can clearly be life-sustaining for those who are critically ill, there are now compelling data showing that mechanical ventilation can be damaging to the lung if the ventilator is set inappropriately. Excessive tidal volumes can stretch the lung, leading to overdistention and further lung injury. Inadequate positive end-expiratory pressure (PEEP) can promote repetitive alveolar collapse followed by reopening, which may be injurious to the lung (an injury known as atelectrauma). Lung homogeneity is also thought to be important, since injurious forces can develop at junctions of normal and abnormal lung even when the applied pressures are modest. Thus, in theory, HFOV in a well-recruited, homogeneous lung could avoid these problems if the problems with local airflow velocity could be overcome. If so, HFOV could combine small pressure oscillations to minimize overdistention with high mean airway pressures to prevent atelectrauma.

Two major, multicenter, randomized trials now reported in the Journal show that it is hard to put theory into practice. In the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial, the authors found that an HFOV strategy with high mean airway pressures led to more deaths than did a conventional mechanical-ventilation strategy that used relatively high PEEP levels. Patients in both groups underwent a baseline recruitment maneuver (sustained high-pressure inflation) to promote lung homogeneity. In-hospital mortality was 47% in the HFOV group as compared with 35% in the control group (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; P=0.005), a finding that led to premature termination of the trial. The mechanism underlying the poor HFOV outcomes appears to
have been hemodynamic compromise, since the elevated mean airway pressures with HFOV were associated with increased requirements for pressor medications and probably end-organ failures. Was the disconnect between mean airway pressure and regional lung volume noted above at play here?

In the Oscillation in ARDS (OSCAR) trial,\textsuperscript{15} the authors found no major difference in the outcome between an HFOV strategy and usual care with conventional mechanical ventilation. The rate of death from any cause at 28 days was 41.7% in the HFOV group and 41.1% in the usual-care control group (P = 0.85 by the chi-square test). The hemodynamic compromise associated with HFOV that was induced by high mean airway pressures was minimal in the OSCAR trial as compared with the OSCILLATE trial, perhaps owing to lower applied ventilatory pressures in the OSCAR trial. In accordance with the pragmatic design of the OSCAR trial, there was considerable variance in the management of the disease in the usual-care control group in that trial, perhaps reflecting physician judgment and therapy that was individualized to patient characteristics.\textsuperscript{16} In both the OSCAR and OSCILLATE trials, the patients in the HFOV groups received more sedatives and muscle relaxants than did the patients in the control groups, which perhaps also contributed to the disappointing outcomes. Thus, both trials are helpful in raising caution about widespread routine clinical use of HFOV.

What are the conclusions? First, these data might suggest that HFOV, as applied in these trials, is not an advance. However, one could argue that it is not HFOV itself but the HFOV protocols studied in these trials that were ineffective, and perhaps worse, than usual care. Whether the reduction in preload induced by high mean airway pressures in the OSCILLATE trial could have been mitigated by more aggressive volume resuscitation,\textsuperscript{7} without worsening lung edema, is unclear. Similarly, whether further elevation in mean airway pressures applied to a well-recruited lung may have improved lung protection in the OSCAR trial is also unclear. If iatrogenic injury from heavy sedation or paralysis could be minimized while the comfort of the patient is maintained, perhaps the theoretical benefits of HFOV would be realized.

Second, patient selection may be an important factor. Some patients have recruitable lung (i.e., lung tissue in which alveolar air volume is increased with small increases in airway pressure), whereas others have nonrecruitable lung. Among patients with homogeneous, recruitable lung, increasing mean airway pressure may well be beneficial; however, among patients with heterogeneous and nonrecruitable lung, increasing mean airway pressure may lead to overdistention of some lung regions without increased aeration of collapsed or flooded alveoli. Such in-
dexes of recruitability (which can be assessed, perhaps, with the use of regional imaging or measures of lung or chest-wall mechanics) may help to define which patients may benefit from high mean airway pressures and which patients are likely to suffer deleterious effects without major lung protection. For example, applied ventilatory pressures can affect pleural pressure, which in turn influences hemodynamics, but the interactions are complicated and are dependent on relative lung and chest-wall compliance, left and right ventricular function, volume status, and other factors.

Third, currently recommended strategies that use low tidal volumes may have effectively minimized mechanical stress on the lung,17 and further improvements in outcomes are likely to occur only through improved understanding of the heterogeneous ARDS phenotype and its underlying biologic characteristics. Perhaps patients with ARDS will require individualized therapy that takes into consideration their body habitus, the cause of their disease, and the mechanisms leading to lung injury. Considerable discussion will ensue about which patients should be included and which technologies should be used in the next trial, but for now clinicians should be cautious about applying HFOV routinely in patients with ARDS.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article was published on January 22, 2013, at NEJM.org.


DOI: 10.1056/NEJMoa1300103

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