High-frequency oscillatory ventilation: Learning which way to turn the dials*

High-frequency oscillatory ventilation (HFOV) is rapidly becoming a standard mode of ventilatory support in the pediatric intensive care unit (1, 2). To date, just two randomized trials of HFOV in pediatric patients have been published (3, 4). Despite the paucity of clinical trial data, there has been movement from use of HFOV as a salvage therapy after failed trials of conventional modalities to earlier institution of HFOV as a primary lung-protective ventilatory modality. Given the absence of robust clinical trial data, what do we know about the use of HFOV in acute lung injury and acute respiratory distress syndrome (ARDS)? One potential advantage of HFOV as a lung-protective strategy is that adequate ventilation may occur with lower peak-to-trough pressure amplitudes. Typically during mechanical ventilation, the pressure amplitude is assessed at the airway opening, but this is not a valid way to quantify peak-to-trough pressure amplitudes in the alveoli during HFOV. To that end, it has been shown in small animal models that there is tremendous regional heterogeneity regarding the relationship between proximal pressures and pressure amplitude measured in the alveolus. In particular, inspiratory time and frequency profoundly influence the relationship between proximal and distal pressures. For example, increasing the inspiratory/expiratory ratio from 1:2 to 1:1 can, in some lung regions, lead to significant increases in the distal/proximal pressure ratio. Furthermore, at higher frequencies, the filtering effect of the endotracheal tube and airways is amplified. This has been demonstrated in animal models (5–8) as well as in critically ill adults (9). Allen et al (7) have also demonstrated substantial asynchrony of alveolar filling during HFOV, suggesting interregional gas transport as an important contributor to gas mixing during HFOV. What has yet to be systematically studied is the effect of bias flow on these observations.

In clinical trials, it has been demonstrated that HFOV causes rapid improvement in oxygenation and is well tolerated (3, 10). In a population of pediatric patients with acute lung injury and airleak, HFOV was associated with an increased arterial to alveolar oxygenation (PaO₂/PaO₂) ratio and a decreased oxygenation index (mean airway pressure × FiO₂ ÷ 100/PaO₂) (3). The patients treated with HFOV had a lower incidence of barotrauma, defined by any use of supplemental oxygen at 30 days, compared with the patients managed with conventional mechanical ventilation (CMV). In terms of other clinically relevant outcomes, there were no differences between the groups in duration of mechanical ventilation, frequency of airleak, or 30-day survival rates (3). Samransruekkit et al (4) reported 16 pediatric patients (≥1 month and <15 yrs of age) diagnosed with ARDS, who were randomized to receive either HFOV or CMV. The patients in the HFOV group had a better chance of survival compared to the controls (71% vs. 31.5%), but the difference was not statistically significant (p = .2).

Clinical trial experience in adult populations has not shown convincing superiority of HFOV (11, 12). In the largest published randomized control trial of HFOV in adults, Derdak et al (10) demonstrated a rapid increase in the PaO₂/FiO₂ ratio in the HFOV group as well as a significant relationship between oxygenation index and mortality over the first 3 days of enrollment. There was no difference in adverse events between the groups, and there was a trend toward a lower 30-day mortality rate in the HFOV group compared to that in the group receiving CMV. The mortality differences were not statistically significant and the trial was closed once equivalence with conventional ventilation was demonstrated, since the trial had been designed as a device-approval study (10). In a follow-up trial in adults with acute lung injury conducted in Europe, HFOV was not associated with decreased mortality or other improved outcomes (13).

The Oscillation for ARDS Treated Early (OSCILLATE) Trial Pilot Study has recently completed initial pilot enrollment with the goal of assessing whether HFOV will reduce the relative risk of dying from ARDS in patients treated within 72 hrs of the diagnosis of ARDS. There are, as of yet, no reports of data analysis from this trial (14).

A recently published meta-analysis of eight randomized control trials in both adults and children from 1994 to 2007 has suggested that HFOV may decrease mortality, has a lower incidence of treatment failure, and is unlikely to cause harm (15). On balance, the clinical trial data are intriguing but not compelling. The critical care community (neonatal, pediatric, and adult) has divided itself into the land of the believers and the nonbelievers. The upcoming analysis of the OSCILLATE Trial may add relevant data to the dialogue. For the moment, it is the task of the believers to objectively describe safe practice using HFOV and delineate physiology-based management approaches in relevant patient populations.

One of the recurring frustrations among clinicians using HFOV is the inability to reliably provide enough bias flow to meet the peak inspiratory flow needs of pediatric and adult populations (16). This drawback of the current device configuration requires transition to a conventional ventilator before successful weaning and separation from a ventilator, and may possibly prolong total duration of mechanical ventilation. Complicating the issue are anecdotal reports that high

*See also p. e108.

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bias flow rates may increase work of breathing and compromise CO\textsubscript{2} elimination (17, 18).

In this issue of Pediatric Critical Care Medicine, Turner and colleagues (19) directly address this issue in an animal model of acute lung injury. This study was designed to systematically explore the relationship between bias flow and CO\textsubscript{2} elimination in an effort to answer whether increasing bias flow to support spontaneous breathing on HFOV would compromise alveolar ventilation. Sixteen juvenile swine with saline lavage-induced lung injury were transitioned from CMV to HFOV. Each animal was ventilated with bias flows of 10, 20, 30, and 40 L/min. For ten animals, power was set at a constant level to maintain PaCO\textsubscript{2} 50–60 mm Hg, and amplitude was allowed to vary. For the remaining six animals, amplitude was set to maintain PaCO\textsubscript{2} 50–60 mm Hg, with power adjusted as needed with changes in bias flow. For each animal, bias flow rates of 10, 20, 30, and 40 L/min were provided in random order and maintained at each flow rate for 15 mins. PaCO\textsubscript{2}, PaO\textsubscript{2}/FIO\textsubscript{2} (P/F) ratio, cardiac output, arterial pH, hemoglobin, bicarbonate, and HFOV settings (mean airway pressure, amplitude, and power) were all recorded at 15-min intervals.

The primary outcome measure of this study was to assess whether ventilation was adversely affected by changes in bias flow. In a linear regression analysis controlling for both power and amplitude, there was no statistically significant change in PaCO\textsubscript{2} as bias flow varied from 10 to 40 L/min. This finding is important since it is reassuring that bias flow may be increased without detrimental effects on ventilation, making it more practical to pilot this approach in a clinical study. Cardiac output and pH also did not change significantly with variation in bias flow. This supports the idea that manipulating bias flow in patients should be safe from a hemodynamic standpoint.

The troublesome finding in this study is that the P/F ratio decreased as bias flow was increased from 10 to 40 L/min \( (p = 0.03) \) despite no change in proximally measured mean airway pressure. On regression analysis, a decrease of 5 in the P/F ratio was seen for each 1 L/min increase in bias flow (95% confidence interval; \(-9.5, -0.04\)). The fact that increasing bias flow may have detrimental effects on oxygenation is concerning, since HFOV has historically been used as a rescue therapy for acute, hypoxicemic respiratory failure (2). The degree to which the P/F ratio changed was relatively small, but in a hypoxicemic patient population it is difficult to predict whether or not this would be clinically relevant. Furthermore, worsening oxygenation may necessitate an increase in mean airway pressure, which may have detrimental hemodynamic effects and reduce the lung-protective effects of the modality. The authors do not provide insight regarding mechanisms explaining this alteration in oxygenation; invariably, this observation must relate to the effects of bias flow on the relationship between distal (alveolar) pressure and proximal (airway opening) pressure, with increased bias flow producing a decreased distal/proximal airway pressure ratio.

As with all scientific investigation, this preclinical trial in an animal model of lung injury was not perfect. Following lung injury, the animals were placed on HFOV at different bias flow rates for 15 mins. It may well be that this is an inadequate equilibration period, which may have altered the study conclusions despite randomization of bias flow order. The rationale for undertaking this animal study was to determine the effects of increased bias flow on alveolar ventilation to provide insight regarding the upper limits of safe bias flow rates on patients allowed to breathe spontaneously during HFOV. Unfortunately, all animals in this trial were anesthetized and paralyzed for the duration of the protocol, leaving the critical clinical question unanswered. While increased bias flow rates did not adversely affect alveolar ventilation, this study is unable to comment on the reducing the need for use of muscle relaxants or the efficacy of ventilation with high bias flows during spontaneous ventilation. This is an intriguing idea for a follow-up study, since any modification of the current HFOV-CMV transition that allows spontaneous ventilation on a high-frequency device may significantly decrease duration of mechanical ventilation and limit associated morbidity.

Finally, the lung injury model chosen is a notoriously fickle one (20, 21), and the wide range of P/F ratios and arterial CO\textsubscript{2} tensions at baseline suggest a significant degree of variability in severity of lung injury. This degree of heterogeneity would clearly limit the clarity with which one can evaluate the relationship between bias flow and alveolar elimination. Turner and colleagues have conducted an important study that addresses a vital initial question: can we safely increase bias flow without compromising alveolar ventilation? The answer provided by their data is, we believe, maybe. Further data from spontaneously breathing subjects will be the logical next step. Furthermore, the clear adverse effect on oxygenating efficiency at high bias flow rates must be examined and further elucidated before changes in clinical practice can be safely adopted. The larger question is whether or not the ability to breathe spontaneously on HFOV will have effects on duration of mechanical ventilation and patient outcomes. This study is a valuable first step in describing which way to turn the dial.

Jordan S. Rettig, MD
John H. Arnold, MD
Division of Critical Care Medicine
Department of Anesthesia
Children’s Hospital Boston
Harvard Medical School
Boston, MA

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Antioxidants in pediatric sepsis: Do not put the plough in front of the horses!*  

In recent years, important advances have been made in understanding the pathophysiology and the treatment of sepsis. It is currently a unanimous opinion that sepsis is the result of an uncontrolled inflammatory response with loss of the normal homeostatic balance between systemic inflammatory reaction and anti-inflammatory response (1). The inflammatory response to infection is primed by host recognition of microbial patterns, such as bacterial cell wall components (lipopolysaccharide, peptidoglycans, flagellins), leading to cell activation, initiation of inflammatory cascade, and ultimately pathogen clearance. One consequence of the massive liberation of cytokines is the increased production of reactive oxygen species (ROS) and reactive nitrogen species by circulating and resident immune cells and endothelial cells. These highly reactive species, including superoxide anion (O$_2^-$), hydroxyl radical, hydrogen peroxide (H$_2$O$_2$), oxygen singlet, nitric oxide (NO), nitrogen dioxide radicals, and peroxynitrite anion, can mediate cell damage in several ways, including lipid peroxidation and mitochondrial membrane damage (2, 3). Production of ROS by mitochondria is fundamental for normal cellular function, and the electron transport chain of mitochondria is the major source of intracellular ROS in the cell (4). However, paradoxically, mitochondrion is the major target for ROS-mediated damage. Intramitochondrial ROS production can determine oxidative damage against mitochondrial membranes, proteins, and mitochondrial DNA with the release of cytochrome c into the cytosol and consequent cell apoptosis. The mitochondrial damage and cell damage are now recognized as important trigger, also called alarmins, of subsequent innate immune activation (5). Oxidative-mediated damage to mitochondrial DNA also can lead to a vicious circle in which the perpetual ROS production is facilitated by ROS-induced ROS release. When antioxidant defenses are overwhelmed, such as in sepsis, ROS levels also may have adverse effects on circulating and endothelial cells by altering immune functions, such chemotaxis or phagocytosis. There now exists a considerable body of evidence for redox imbalance and oxidative stress in human sepsis, demonstrating increased markers of oxidative damage, abnormal handling of exogenous antioxidants, and low concentrations of individual endogenous antioxidants (AOX) (6). The predominant hypothesis is that this pathologic condition is a direct consequence of an excessive and sprawl defensive and inflammatory response to infection with massive production of ROS, reactive nitrogen species, and inflammatory mediators, which determine the systemic vascular endothelium damage characteristic of sepsis and multiple organ dysfunction syndrome. Physiologically, a complex system of interacting AOX defenses is able to protect cells from ROS and nitric oxide species and to prevent damage to mitochondria. This system composed of trace element–dependent enzymes, such as superoxide dismutase, catalase, and glutathione (GSH) peroxidase (selenium, zinc, manganese, copper, and iron), thiols donors and their precursors, vitamins A, E, and C, β-carotene, urate, albumin, and hormones, such as melatonin, contribute to AOX endogenous defense (7). In this issue of Pediatric Critical Care Medicine, Dr. Bagci and colleagues (8)...

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