Multifrequency Oscillatory Ventilation in the Premature Lung

Effects on Gas Exchange, Mechanics, and Ventilation Distribution

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ABSTRACT

Background: Despite the theoretical benefits of high-frequency oscillatory ventilation (HFOV) in preterm infants, systematic reviews of randomized clinical trials do not confirm improved outcomes. The authors hypothesized that oscillating a premature lung with multiple frequencies simultaneously would improve gas exchange compared with traditional single-frequency oscillatory ventilation (SFOV). The goal of this study was to develop a novel method for HFOV, termed “multifrequency oscillatory ventilation” (MFOV), which relies on a broadband flow waveform more suitable for the heterogeneous mechanics of the immature lung.

Methods: Thirteen intubated preterm lambs were randomly assigned to either SFOV or MFOV for 1 h, followed by crossover to the alternative regimen for 1 h. The SFOV waveform consisted of a pure sinusoidal flow at 5 Hz, whereas the customized MFOV waveform consisted of a 5-Hz fundamental with additional energy at 10 and 15 Hz. Per standardized protocol, mean pressure at airway opening ($P_{aw}$) and inspired oxygen fraction were adjusted as needed, and root mean square of the delivered oscillatory volume waveform ($V_{rms}$) was adjusted at 15-min intervals. A ventilatory cost function for SFOV and MFOV was defined as $V_C = (V_{rms}^2 \times \text{PaCO}_2) / \text{Wt}^{3/5}$, where Wt denotes body weight.

Results: Averaged over all time points, MFOV resulted in significantly lower $V_C$ (246.9 ± 6.0 vs. 363.5 ± 15.9 ml$^2$ mmHg kg$^{-1}$) and $P_{aw}$ (12.8 ± 0.3 vs. 14.1 ± 0.5 cm H$_2$O) compared with SFOV, suggesting more efficient gas exchange and enhanced lung recruitment at lower mean airway pressures.

Conclusion: Oscillation with simultaneous multiple frequencies may be a more efficient ventilator modality in premature lungs compared with traditional single-frequency HFOV. (Anesthesiology 2015; 123:1394-403)

PRETERM infants are prone to respiratory failure due to structural immaturity and surfactant deficiency and often require mechanical ventilatory support with increased oxygen concentrations. Protectiv ventilation strategies limit cyclic end-expiratory derecruitment via appropriate positive end-expiratory pressure (PEEP) and end-inspiratory overdentension with low tidal volumes ($V_t$). High-frequency oscillatory ventilation (HFOV) is an alternative form of mechanical ventilation that incorporates the goals of a lung-protective strategy: high mean airway pressures to sustain alveolar recruitment, with small $V_t$ to avoid end-inspiratory overdentension. Despite the potential benefits of such ventilation approaches, multiple randomized clinical trials have failed to confirm improved outcomes in preterm infants. The authors hypothesized that oscillating with multiple frequencies simultaneously may be a more efficient ventilator modality in premature lungs compared with traditional single-frequency HFOV. (Anesthesiology 2015; 123:1394-403)
HFOV on gas distribution, volume recruitment, and ventilation-to-perfusion (V/Q) matching.6–10 Systematic reviews of clinical trials do not confirm superior outcomes of HFOV over conventional mechanical ventilation (CMV) in preterm infants.11–14 Nonsuperiority of HFOV over CMV may be due to the variable and poorly understood regional effects of frequency, amplitude, and mean airway pressure when oscillating a heterogeneously injured lung, each of which may contribute to worsening ventilator-induced lung injury.15–17 Because premature lungs are mechanically heterogeneous,18 the most effective ventilation frequency for gas exchange may vary substantially across different lung regions.19 Regional mechanical heterogeneity causes local ventilation distribution to become highly frequency dependent.19–21 Thus, the most effective frequency for effective flow penetration into the periphery, and optimal gas exchange, will vary from region to region.15,16 Conventional HFOV is delivered at only a single high frequency22 and may cause sizable portions of a heterogeneous lung to be simultaneously under-ventilated or overventilated, with corresponding decrements in gas exchange and exacerbation of injury.16,23

Accordingly, we hypothesized that oscillation of a heterogeneous, preterm lung with several frequencies simultaneously would improve gas exchange compared with single-frequency oscillatory ventilation (SFOV), as this would distribute ventilation more evenly to different lung regions according to their respective local mechanical properties. Multifrequency oscillatory ventilation (MFOV) allows the local impedances of the injured parenchyma to selectively filter out flows of “less-desirable” frequencies and allows flows at frequencies more “optimal” for a particular region to participate in gas exchange. The overall goal of this study was to develop a novel method for HFOV, termed MFOV, which relies on a broadband flow waveform more appropriate for heterogeneous parenchymal mechanics. The aims of this study were to determine the effects of MFOV on gas exchange, lung mechanics, and the spatial distribution of ventilation as assessed with electrical impedance tomography (EIT) in preterm lambs.

Materials and Methods

Animal Preparation and Measurements

The protocol for our study was approved by the Animal Care and Use Committee at the University of Western Australia, Perth, Western Australia, Australia, to ensure humane treatment of animals. Sample size for the study was estimated based on our previous experience with measurements of gas exchange and lung mechanics in preterm lambs.24,25 Thirteen preterm lambs (128 to 130 days of gestation, term 150 days) weighing 3.15 ± 0.39 kg were delivered via cesarean section from anesthetized ewes. Ewes had intramuscularly received 150 mg medroxyprogesterone at 100 days of gestation and 0.15 mg/kg betamethasone 72 and 48 h before delivery. After delivery of the fetal head, the carotid and external jugular vessels were catheterized. Each lamb was intubated with a 4.5-mm cuffed endotracheal tube via direct laryngoscopy. Lung liquid was manually aspirated using a 50-ml syringe. The fetal thorax was then exteriorized from the uterus and dried. In preparation for the EIT measurements, 16 custom-built 23-gauge needle electrodes were placed subcutaneously at equidistant locations around the chest approximately 3 cm above the xiphisternum. The electrodes were secured using a 5-cm-wide self-adherent bandage (Coban; 3M, USA).24,25 After cutting the umbilical cord, the lamb was weighed, placed prone in a radiant warmer, and given two recruitment maneuvers of 30 cm H2O of 10-s duration. Then, the lamb was stabilized for 30 min on CMV at a rate of 50 min−1, V̇e of 7 ml/kg, PEEP of 6 cm H2O, and FiO2 of 30% (Fabian; Acutronic Medical Systems AG, Switzerland). General anesthesia and suppression of spontaneous breathing efforts were maintained using continuous intravenous infusions of propofol (1 to 2 mg kg−1 min−1) and remifentanil (0.5 to 1.0 μg kg−1 min−1). Heart rate, arterial blood pressure, rectal temperature, and preductal oxygen saturation (SpO2, as measured at the right ear) were monitored continuously (HP48S; Hewlett Packard, USA). Airway pressure (Paw) and flow (V̇e) were sampled at 200 Hz by the ventilator using a hot-wire anemometer and pressure port at the proximal end of the endotracheal tube. Volume delivered at the airway opening (V̇e) was determined using trapezoidal integration of the sampled V̇e signal.

After the initial 30-min period of CMV, each lamb was randomly assigned to receive either SFOV or MFOV for 60 min, followed by a 30-min CMV washout period and crossover to the alternative regimen for 60 min (fig. 1). The SFOV waveform consisted of a pure sinusoidal volume waveform at 5 Hz (Fabian; Acutronic AG), whereas the customized MFOV waveform consisted of a 5-Hz fundamental with additional energy at 10 and 15 Hz (fig. 2). The MFOV waveform was generated by custom modification of the Fabian firmware. Peak-to-peak volume excursions (Vpp) were determined for both SFOV and MFOV as the difference between the maximum and minimum of the volume signal. After subtraction of the nonzero mean of the volume signal (V̄), the root mean square of the discretized volume (V̇ rms) was determined as follows:

\[ V_{\text{rms}} = \sqrt{\frac{1}{N} \sum_{n=1}^{N} (V_n - \bar{V})^2}, \]

where \( V_n \) denotes the discretized volume waveform and \( N \) is the number of data points per 0.2-s period of the SFOV or MFOV waveform. Dynamic respiratory system elastance (Ers) at 5 Hz was computed from 2-min samples of Paw and V̇e waveforms at 15-min intervals during SFOV and MFOV, using a periodogram technique with a 1-s rectangular window and 80% overlap.27

Arterial pH, PaCO₂, and PaO₂ were obtained every 15 min throughout the entire protocol. During SFOV and MFOV,
mean airway pressure ($P_{aw}$) and % inspired oxygen fraction ($F_{iO_2}$) were adjusted as needed according to the algorithm shown in figure 3. The oxygenation index (OI) was calculated as follows:

$$OI = \frac{F_{iO_2}}{\overline{P_{aw}}}. \quad (2)$$

The $V_{rms}$ was increased or decreased by 0.01 ml/kg at 15-min intervals, for every 1 mmHg above or below our target $P_{aco_2}$ range of 45 to 55 mmHg. Since carbon dioxide elimination during HFOV is roughly proportional to $V_c$,

we defined a ventilatory cost function ($V_c$) to compare the efficiency of gas exchange for SFOV and MFOV:

$$V_c = \left(\overline{V_{rms}} \cdot P_{aco_2}\right)Wt^{-1}, \quad (3)$$

where Wt denotes body weight in kilogram. Thus for a given value of $P_{aco_2}$, lower values of $V_c$ indicate more efficient ventilation.
At the conclusion of the experimental protocol, each lamb was humanely euthanized using an overdose of intravenous pentobarbital.

**Electrical Impedance Tomography**

Electrical impedance tomographic measurements were analyzed at the end of each 60-min SFOV and MFOV period (i.e., at \( t = 90 \) and 180 min of the protocol) for both crossover groups, using the Goe-MF II system with Thorascan software (CareFusion, Germany). The EIT data were acquired at a resolution of \( 32 \times 32 \) pixels and a frame rate of 44 Hz. The EIT images were reconstructed using the GREIT image reconstruction algorithm with anatomic boundary shapes based on a transverse computed tomographic scan of the chest of a lamb at the same height. Thirty seconds of artifact-free representative data were chosen for analysis. To minimize cardiogenic disturbances, the EIT data were filtered using a fifth-order digital Butterworth high-pass filter with a 2-Hz cutoff frequency. From these filtered images, functional EIT images of ventilation were generated from the SD of the time course of the impedance value within each pixel. From the functional EIT images, the spatial distribution of ventilation within each of the 32 equally sized right-to-left and anterior-to-posterior slices could be determined. The percentage of fractional ventilation was determined, defined as the percentage of the total ventilation captured in each slice, for either the right or the left hemithorax.

**Statistical Analysis**

Birth weights and umbilical cord blood gas values at delivery were compared between the two groups of lambs by using Student \( t \) tests. Lambs in group A were randomly assigned to receive SFOV first followed by MFOV, whereas those in group B received MFOV first followed by SFOV. At the end of the initial and washout 30-min CMV periods, gas exchange and mechanics data for the two groups were compared using a two-way ANOVA, with group (A vs. B) and period (initial vs. washout) as variable components. During the 60-min SFOV and MFOV periods, gas exchange and mechanics data were analyzed via two-way repeated-measures ANOVA, with oscillatory modality (SFOV vs. MFOV) and time (from 15 to 60 min after the start of oscillation vs. in 15-min increments) as the variable components. EIT ventilation distributions were analyzed via three-way ANOVA, with oscillatory modality (SFOV vs. MFOV), measurement time (90 vs. 180 min), and hemithorax (left vs. right) as the variable components. If significance was obtained with ANOVA, post hoc comparisons were performed using the Tukey Honest Significant Difference criterion. Unless otherwise specified, all data are expressed as mean ± SD, and \( P \) value less than 0.05 was considered statistically significant.

All statistical analyses were performed using SigmaPlot (version 12.3; Systat Software, Inc., USA), and all comparisons were assumed to be two tailed.

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**Fig. 3.** Algorithm for adjusting mean airway pressure (\( \bar{P}_{aw} \)) and fraction of inspired oxygen concentration (\( \text{FiO}_2 \)) based on arterial oxygen saturation (\( \text{SpO}_2 \)), as needed.
Results

Of the 13 lambs studied, 7 were randomly assigned to receive SFOV first followed by MFOV (group A), and 6 were randomly assigned to receive MFOV first followed by SFOV (group B). There were no significant differences in birth weights or umbilical cord pH, PaCO₂, and PaO₂ values between the two groups (table 1). Table 2 shows Vₗ normalized by weight, FiO₂, PEEP, Pp, peak inspiratory pressure, arterial pH, PaCO₂, and PaO₂ at the end of each 30-min CMV period for groups A and B, just before receiving 60 min of MFOV or SFOV. Also shown are the significance levels using ANOVA, with group and CMV period as factors, along with their corresponding interaction. We observed no significant effect of group (A vs. B) for any variable. However, we did observe a significant effect of CMV period (initial vs. washout) for FiO₂ (P = 0.015) and peak inspiratory pressure (P < 0.001).

Figure 4 shows a summary of the gas exchange and mechanics data at 15-min intervals for the SFOV and MFOV modalities. Table 3 shows results for the two-way ANOVA based on the data plotted in figure 4, with oscillatory modality, time, and corresponding interaction as factors. We observed no significant differences in ventilation distribution for the main effects of oscillatory modality (SFOV vs. MFOV; P = 1.0), group (A vs. B; P = 1.0), or hemithorax (right vs. left; P = 0.225).

Discussion

Premature lungs exhibit mechanical and spatial heterogeneity due to structural immaturity and surfactant deficiency. CMV in preterm infants may inadvertently worsen existing lung injury due to repeated alveolar overdistention and opening/closing of alveoli.1 By contrast, HFOV achieves effective gas exchange with relatively high mean airway pressures to sustain lung recruitment, with small tidal volumes to prevent end-inspiratory overdistention. However, numerous clinical trials in adults and neonates with acute respiratory distress syndrome (ARDS) have shown that HFOV does not reduce mortality, despite physiological evidence of enhanced gas distribution, volume recruitment, and V̇/Q̇ matching.2-10 Why such a theoretically promising mode of mechanical ventilation has so far failed to prove advantageous in clinical practice may be multifactorial: oscillation strategy, treatment analysis demonstrated that normalized Vₗ was significantly higher for SFOV compared with that for MFOV for all time points after 15 min. Normalized Vₗ ranged from 1.3 ± 0.1 and 1.3 ± 0.2 ml/kg for MFOV and SFOV, respectively, at 15 min to 1.2 ± 0.2 and 1.5 ± 0.1 ml/kg at 60 min. A significant effect of oscillatory modality, with MFOV lower than SFOV in all cases, was observed for Vₗ, Pₐ (MFOV: 246.9 ± 6.5, SFOV: 365.5 ± 15.9 ml H₂O/kg; P < 0.001), Pp (MFOV: 12.8 ± 0.3, SFOV: 14.1 ± 0.5 cm H₂O; P = 0.007), OI (MFOV: 5.3 ± 0.1, SFOV: 6.4 ± 0.2% cm H₂O/mmHg; P = 0.011), and E dyn (MFOV: 1.02 ± 0.02, SFOV: 1.26 ± 0.05 cm H₂O/ml; P < 0.001), when averaged over all time points. However, no significant effect of time or the interaction between modality and time was observed for these variables (table 3).

Figure 5 shows the spatial distribution of ventilation at the end of each 60-min SFOV and MFOV periods (i.e., at 90 and 180 min of the protocol) for groups A and B. Due to an electrode failure, one lamb from group A was omitted from the EIT analysis. We observed no significant differences in ventilation distribution for the main effects of oscillatory modality (SFOV vs. MFOV; P = 1.0), group (A vs. B; P = 1.0), or hemithorax (right vs. left; P = 0.225).

Table 1. Birth Weights and Umbilical Cord Blood Gas Data for the 13 Lambs at Time of Delivery, Separated into Groups A and B

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 7)</th>
<th>Group B (n = 6)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt (kg)</td>
<td>3.18 ± 0.41</td>
<td>3.11 ± 0.39</td>
<td>0.77</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 ± 0.06</td>
<td>7.33 ± 0.20</td>
<td>0.39</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>57.0 ± 3.7</td>
<td>61.6 ± 6.2</td>
<td>0.15</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>31.9 ± 2.6</td>
<td>27.7 ± 8.9</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. Significance level assessed using two-tailed Student t test, with the exception of pH, which was assessed by Wilcoxon rank sum test.

pH = negative base-10 logarithm of the hydrogen ion concentration; Wt = weight.

Table 2. Gas Exchange and Mechanics Data for Groups A and B, after the 30-min Initial and Washout CMV Periods

<table>
<thead>
<tr>
<th></th>
<th>After Initial CMV Period</th>
<th>After Washout CMV Period</th>
<th>ANOVA Significance Level</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Group</td>
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<td></td>
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<td></td>
<td>Period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group × Period</td>
</tr>
<tr>
<td>Vₗ Wt⁻¹ (ml/kg)</td>
<td>7.37 ± 0.65</td>
<td>7.10 ± 0.39</td>
<td>7.32 ± 0.81</td>
</tr>
<tr>
<td>FiO₂ (%)</td>
<td>30.9 ± 7.1</td>
<td>30.3 ± 9.1</td>
<td>23.6 ± 5.3</td>
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<tr>
<td>PEEP (cm H₂O)</td>
<td>6.5 ± 0.5</td>
<td>6.4 ± 0.6</td>
<td>5.7 ± 0.8</td>
</tr>
<tr>
<td>PIP (cm H₂O)</td>
<td>22.3 ± 2.6</td>
<td>21.7 ± 2.7</td>
<td>13.9 ± 3.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.29 ± 0.07</td>
<td>7.29 ± 0.86</td>
<td>7.34 ± 0.13</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>58.5 ± 13.4</td>
<td>53.8 ± 11.2</td>
<td>59.6 ± 23.0</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>75.4 ± 4.0</td>
<td>68.6 ± 24.6</td>
<td>63.5 ± 22.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. Also shown are the significance levels for the ANOVA, with CMV period (initial vs. washout) and group (A vs. B) as factors, along with their corresponding interaction. P values that are less than 0.05 are shown in boldface.

CMV = conventional mechanical ventilation; FiO₂ = fraction of inspired oxygen concentration; PEEP = positive end-expiratory pressure; pH = negative base-10 logarithm of the hydrogen ion concentration; PIP = peak inspiratory pressure; Wt = weight; Vₗ = tidal volume.
endpoints, and/or operator skills are all potential contributing factors. The lack of improved outcomes with HFOV suggests suboptimal aeration and ventilation of the injured lung, potentially arising from variable regional effects of frequency, amplitude, and mean airway pressure in the setting of heterogeneous disease processes. There is no doubt that the mechanical complexity of the heterogeneous lung is fundamental to the distribution of ventilation. We hypothesized that lung function and gas exchange would improve if volume oscillations were applied at multiple frequencies simultaneously, rather than at a single high frequency. Multiple frequencies may improve oxygenation and $V/Q$ matching by distributing ventilation more evenly to different regions, according to their respective local mechanical properties. The mechanism for such improvements may be the optimization of regional gas distribution, due to the presence of additional frequencies that are more appropriate for the local mechanical properties of the heterogeneous parenchyma. The primary determinant of ventilation distribution in the injured lung is the distribution of regional mechanical properties of the airways and parenchyma, such as resistance, inertance, and elastance. Because local ventilation distribution becomes highly frequency dependent in the presence of regional mechanical heterogeneity, the most effective frequency for optimal gas exchange will vary from region to region. Oscillation at a single high frequency (i.e., standard HFOV) may result in mechanically disparate regions of a heterogeneous lung being underventilated or overventilated, depending on their relative time constants. Such ventilation heterogeneity within the lung may result not only in decrements of gas exchange but also in worsening of injury. Previous simulation studies using computational models indicate that small-amplitude volume oscillation at a single, arbitrary frequency is not suitable for reaching the majority of the gas-exchanging regions in spatially heterogeneous lung. Thus, the application of multiple, simultaneous frequencies may be better suited to complement the heterogeneous mechanics.

Fig. 4. Summary of (A) arterial pH, (B) PaCO₂, (C) PaO₂, (D) peak-to-peak tidal volume normalized by weight, (E) root mean square volume normalized by weight, (F) ventilatory cost function, (G) mean airway pressure, (H) oxygenation index, and (I) dynamic respiratory system elastance versus time during single-frequency oscillatory ventilation (SFOV, closed symbols) and multifrequency oscillatory ventilation (MFOV, open symbols). *Significant difference between SFOV and MFOV modalities, using two-way repeated-measures ANOVA with Tukey Honest Significant Difference criterion. †Significant interaction between SFOV and MFOV modality and time, based on Tukey Honest Significant Difference criterion. All data are expressed as mean ± standard error.
of the immature lung, by allowing the local impedances of the injured parenchyma to selectively filter out flows of "less-desirable" frequencies. As a result, flows at frequencies more "optimal" for a particular region pass through and participate in gas exchange (fig. 6).

In this study, we demonstrated the feasibility of maintaining and improving gas exchange with MFOV in preterm lambs by using a commercially available hybrid ventilator–oscillator with custom-written firmware. Our data suggest that MFOV results in more uniform distribution of ventilation to the alveoli compared with traditional SFOV. We contend that the mechanism for such improved functional outcomes is optimization of regional gas distribution, due to inclusion of frequencies that are more appropriate for the local mechanical properties of the heterogeneous parenchyma.

To assess the efficacy of MFOV, we relied on various indices of gas exchange and mechanics (fig. 4). Our ventilatory cost function ($V_C$) is defined as the product of ventilatory "power" ($V_{\text{rms}}^2$) multiplied by PaCO$_2$. This index is justified by empiric evidence that carbon dioxide elimination is roughly proportional to the square of tidal volume during HFOV.29 Our $V_C$ index was significantly lower during MFOV compared with SFOV, consistent with more efficient carbon dioxide elimination. More efficient carbon dioxide elimination in MFOV was due largely to the increased $V_{\text{rms}}$ required for the SFOV modality compared with MFOV to maintain PaCO$_2$ within our desired target range of 45 to 55 mmHg. There were no significant differences in the peak-to-peak volume excursions or PaCO$_2$ between SFOV and MFOV.

The OI and $P_{\text{ao}}$ were significantly lower at all time points during MFOV compared with SFOV, with no significant differences in PaO$_2$. These findings indicate that MFOV facilitates more efficient oxygenation at lower distending pressures. The $E_{\text{dyn}}$ was also significantly reduced during MFOV.
although we cannot be certain whether lower $E_{\text{dyn}}$ was the result of enhanced lung recruitment or reduced parenchymal strain stiffening.\textsuperscript{33} The lower $E_{\text{dyn}}$ suggests that the enhanced spectral content of the MFOV waveforms may prevent time-dependent derecruitment of lung units,\textsuperscript{34} as the higher frequency components may act as a dithering mechanism to keep lung units opened. Alternatively, it may be that such higher frequencies also increase surfactant production \textit{via} a variable stretch mechanism, similar to that observed with biologically variable ventilation.\textsuperscript{35,36}

Despite the improved metrics of gas exchange and mechanics with MFOV, the ventilation distribution as assessed with EIT did not demonstrate significant differences between the SFOV and MFOV modalities. This may be due to a lack of sensitivity with the technique because EIT provides a low-resolution assessment of ventilation distribution based on changes in electrical impedance and only within a single cross-sectional slice of the thorax.\textsuperscript{37} Despite its utility as a potential bedside tool for rapid, noninvasive quantification of regional aeration,\textsuperscript{38} EIT may not describe ventilation distribution appropriately during HFOV modalities due to its maximum sampling rate of 44 Hz and 16-electrode array. Alternative methods for assessing the spatial distribution of ventilation, such as dynamic volumetric computed tomography during xenon washout,\textsuperscript{39} may be more appropriate for the high temporal variations associated with MFOV.

Certain commercially available oscillators generate waveforms with higher harmonics above the fundamental frequency\textsuperscript{22,40} although there is no evidence to suggest that these arbitrary “broadband” ventilator patterns influence clinical efficacy.\textsuperscript{41} There also have been attempts to superimpose HFOV on CMV, such as during high-frequency percussive ventilation.\textsuperscript{8,42-45} In some situations, this hybrid mode of ventilation may improve oxygenation and $V/Q$ matching compared with either CMV or HFOV alone.\textsuperscript{46} However, high-frequency percussive ventilation has neither been studied systematically nor been shown to reduce mortality associated with ARDS.\textsuperscript{42,45} This lack of improved mortality also may be related to the reliance on large tidal volumes at lower frequencies.

Although these experimental results are certainly compelling, our pilot study was limited by (1) its small sample size, (2) an MFOV waveform consisting of only three frequencies that were not optimized for the heterogeneous lung, and (3) minimal information on the mechanical properties of the preterm lungs. Despite these deficiencies, our data indicate that MFOV may have distinct advantages as a ventilator modality in preterm lungs compared with traditional HFOV and maintains lung recruitment at lower mean airway pressures. Although MFOV presents a promising and innovative approach to lung-protective ventilation, its clinical use will require considerably more work to extend its application beyond surfactant-deficient preterm lungs to heterogeneous pathophysiology such as ARDS. Because mechanical heterogeneity in the injured lung has important implications for optimal ventilation protocols, an animal model more representative of clinical ARDS would further strengthen the concept of MFOV and establish its eventual use in human clinical trials. Fundamental questions regarding the convective mechanisms by which this oscillatory modality improves gas exchange remain. Although our crossover study did not examine outcomes associated with ventilator-induced lung injury, it may be that MFOV also has potential to improve gas exchange while minimizing the detrimental effects of cyclic alveolar overdistention and derecruitment. This could be accomplished by further adjustment and optimization of oscillatory pressure amplitude and mean airway pressure.

Although our study demonstrates that MFOV results in improved gas exchange at lower distending pressures in an animal model of preterm lung injury, we recognize that MFOV may have more far-reaching implications for both pulmonary medicine and anesthesia. For example, MFOV may not be limited to as a treatment solely for pediatric or adult ARDS, but it may be useful in the ventilator management in other diseases that affect the lungs in a heterogeneous manner, such as asthma, chronic obstructive pulmonary disease, or pneumonia. The possibility that MFOV can more efficiently penetrate “difficult-to-reach” regions of the lung has implications for the optimal delivery of aerosols and drugs, such as $\beta$-agonists, steroids, or even inhaled volatile anesthetics.\textsuperscript{37} However in certain pathological conditions, the presence of severe expiratory flow limitation due to dynamic airway compression may require additional modification or enhancement of the MFOV waveform\textsuperscript{48} because differences between inspiratory and expiratory airway resistances may further enhance the heterogeneity of ventilation distribution.

**Conclusion**

Our data indicate that MFOV is a more efficient ventilatory modality in preterm lungs compared with SFOV, and it maintains lung recruitment at lower mean airway pressures. Future studies will determine whether the spectral content of MFOV waveforms may be further enhanced to improve gas exchange and result in less injurious ventilation compared with more conventional ventilation and oscillation strategies. Thus, MFOV has the potential to significantly change the care of critically ill, ventilated patients.

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Competing Interests
Dr. Kaczka and Mr. Herrmann are listed as coinventors on a U.S. Provisional Patent on the multifrequency oscillatory ventilation concept. The other authors declare no competing interests.

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