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MULTI-FREQUENCY 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. We hypothesized that oscillating a premature lung with multiple frequencies simultaneously would improve gas exchange compared to traditional single-frequency oscillatory ventilation (SFOV). The goal of this study was to develop a novel method for HFOV, termed

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DISCLOSURES

The other authors declare no competing interests.

‘multi-frequency 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 randomized to either SFOV or MFOV for 1 hour, followed by crossover to the alternative regimen for 1 hour. The SFOV waveform consisted of a pure sinusoidal flow at 5 Hz, while 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_{ao}) and inspired O_2 fraction were adjusted as needed, and root mean square of the delivered oscillatory volume waveform (V_{rms}) was adjusted 15-minute intervals. A ventilatory cost function for SFOV and MFOV was defined as $V_C = (V_{rms}^2 P_a CO_2) Wt^{-1}$, 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 mL² mmHg kg⁻¹) and P_{ao} (12.8 ± 0.3 vs. 14.1 ± 0.5 cmH₂O) compared to SFOV, suggesting more efficient gas exchange and enhanced lung recruitment at lower mean airway pressures.

Conclusions—Oscillation with simultaneous multiple frequencies may be a more efficient ventilator modality in premature lungs compared to traditional single-frequency HFOV.

Keywords

high frequency oscillatory ventilation; electrical impedance tomography; gas exchange; ventilation distribution; premature lung

INTRODUCTION

Preterm infants are prone to respiratory failure due to structural immaturity and surfactant deficiency, and often require mechanical ventilatory support with increased oxygen concentrations.¹ Protective ventilation strategies limit cyclic end-expiratory derecruitment via appropriate positive end-expiratory pressure (PEEP),² and end-inspiratory overdistension with low tidal volumes (V_T).^{3–5} 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 overdistension. Despite the potential benefit of 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} Non-superiority 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 (VILI).^{15–17} Since premature lungs are mechanically heterogeneous,¹⁸ the most effective ventilation frequency for gas exchange may vary substantially across different lung regions.¹⁵ 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 frequency,²² and may cause sizable portions of a heterogeneous lung to be

simultaneously underventilated 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 to single-frequency oscillatory ventilation (SFOV), as this would distribute ventilation more evenly to different lung regions according to their respective local mechanical properties. 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 ‘Multi-Frequency Oscillatory Ventilation’ (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.

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, to ensure human 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 gestation, term 150 days) weighing 3.15 ± 0.39 kg were delivered via Cesarean section from anaesthetized ewes. Ewes had received 150 mg medroxyprogesterone intramuscularly at 100 days gestation, and 0.15 mg kg⁻¹ betamethasone 72 and 48 hours prior to 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 (ETT) 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 G needle electrodes were placed subcutaneously at equidistant locations around the chest ~3 cm above the xiphisternum. The electrodes were secured using a 5-cm wide self-adherent bandage (Coban; 3M, ST. Paul, MN).^{24,25} After cutting the umbilical cord, the lamb was weighed, placed prone in a radiant warmer, given two recruitment maneuvers of 30 cmH₂O of 10 second duration. The lamb was then stabilized for 30 minutes on CMV at a rate of 50 min⁻¹, V_T of 7 mL kg⁻¹, PEEP of 6 cmH₂O, and F_iO_2 of 30% (Fabian, ACUTRONIC Medical Systems AG, Switzerland). General anesthesia and suppression of spontaneous breathing efforts was maintained using continuous intravenous infusions of propofol (1 to 2 mg kg⁻¹min⁻¹) and remifentanyl (0.5 to 1.0 µg kg⁻¹min⁻¹). Heart rate, arterial blood pressure, rectal temperature, and pre-ductal oxygen saturation (S_pO_2 , as measured at the right ear) were monitored continuously (HP48S; Hewlett Packard, Andover, MA). Airway pressure (P_{ao}) and flow (V) 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 (V) was determined using trapezoidal integration of the sampled V signal.²⁶

Following the initial 30 minute period of CMV, each lamb was randomized to receive either SFOV or MFOV for 60 minutes, followed by a 30 minute CMV washout period and crossover to the alternative regimen for 60 minutes (Figure 1). The SFOV waveform consisted of a pure sinusoidal volume waveform at 5 Hz (Fabian, ACUTRONIC AG), while the customized MFOV waveform consisted of a 5 Hz fundamental with additional energy at 10 Hz and 15 Hz (Figure 2). The MFOV waveform was generated by custom-modification of the Fabian firmware. Peak-to-peak volume excursions (V_{pp}) were determined for both SFOV and MFOV as the difference between the maximum and minimum of the volume signal. After subtraction of the non-zero mean of the volume signal ($\bar{V}$), the root mean square of the discretized volume (V_{rms}) was determined as:

$$V_{rms} = \sqrt{\frac{1}{N} \sum_{n=1}^N (V_n - \bar{V})^2} \quad (1)$$

where V_n denotes the discretized volume waveform and N is the number of data points per each 0.2 second period of the SFOV or MFOV waveform. Dynamic respiratory system elastance (E_{dyn}) at 5 Hz was computed from 2 minute samples of P_{ao} and V waveforms at 15 minute intervals during SFOV and MFOV, using a periodogram technique with a 1-second rectangular window and 80 % overlap.²⁷

Arterial pH, carbon dioxide tension (P_aCO_2), and oxygen tension (P_aO_2) were obtained every 15 minutes throughout the entire protocol. During SFOV and MFOV, mean airway pressure (P_{ao}) and % inspired O_2 fraction (F_iO_2) were adjusted as needed according to the algorithm shown in Figure 3. The oxygenation index (OI) was calculated as:²⁸

$$OI = \frac{F_iO_2 \bar{P}_{ao}}{P_aO_2} \quad (2)$$

The V_{rms} was increased or decreased by 0.01 mL kg⁻¹ at 15 minute intervals, for every 1 mmHg above or below our target P_aCO_2 range of 45 to 55 mmHg. Since CO_2 elimination during HFOV is roughly proportional to V_T^2 ,²⁹ we defined a ventilatory cost function (V_C) to compare the efficiency of gas exchange for SFOV and MFOV:

$$V_C = (V_{rms}^2 P_aCO_2) W_t^{-1} \quad (3)$$

where W_t denotes body weight in kg. 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 (EIT)

Electrical Impedance Tomographic (EIT) measurements were analyzed at the end of each 60 minute SFOV and MFOV period (i.e., at $t = 90$ and 180 minutes of the protocol) for both crossover groups, using the Goe-MF II system with Thorascan software (CareFusion, Höchberg, Germany). The EIT data were acquired at a resolution of 32×32 pixels and a

frame rate of 44 Hz. The EIT images were reconstructed using the GREIT image reconstruction algorithm³⁰ with anatomic boundary shapes based on a transverse CT-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 was filtered using a 5th order digital Butterworth high-pass filter with 2 Hz cut-off frequency. From these filtered images, functional EIT (fEIT) images of ventilation generated from the standard deviation of the time course of the impedance value within each pixel.^{25,31,32} From the fEIT 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 left hemithorax.

Statistical Analysis

Birth weights and umbilical cord blood gas values at delivery were compared between the two groups of lambs using Student's *t*-tests. Lambs in Group A were randomized to receive SFOV first followed by MFOV, while those in Group B received MFOV first followed by SFOV. At the end of the initial and washout 30 minute CMV periods, gas exchange and mechanics data for the two groups were compared using a two-way analysis of variance (ANOVA), with group (A vs. B) and period (initial vs. washout) as variable components. During the 60 minute SFOV and MFOV periods, gas exchange and mechanics data were analyzed via two-way repeated measures ANOVA, with treatment mode (SFOV vs. MFOV) and time (from 15 to 60 minutes after the start of oscillation, in 15 minute 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 minutes), and hemithorax (left vs. right) as the variable components. If significance was obtained with ANOVA, *post hoc* comparisons were performed using the Tukey HSD (honest significant difference) criterion. Unless otherwise specified, all data are expressed as mean $\pm$ S.D., and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SigmaPlot (version 12.3, Systat Software, Inc., San Jose, CA), and all comparisons were assumed to be two-tailed.

RESULTS

Of the thirteen lambs studied, seven were randomized to receive SFOV first followed by MFOV (Group A), and six were randomized to receive MFOV first followed by SFOV (Group B). There were no significant differences in birth weights or umbilical cord pH, $P_a\text{CO}_2$, and $P_a\text{O}_2$ values between the two groups (Table 1). Table 2 shows V_T normalized by weight, $F_i\text{O}_2$, PEEP, P_{ao} , peak inspiratory pressure (PIP), arterial pH, $P_a\text{CO}_2$, and $P_a\text{O}_2$ at the end of each 30 minute CMV period for Groups A and B, just prior to receiving 60 minutes 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 $F_i\text{O}_2$ ($P = 0.015$) and PIP ($P < 0.001$).

Figure 4 shows a summary of the gas exchange and mechanics data at 15 minute 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 effect of modality or time on arterial pH, $P_a\text{CO}_2$, $P_a\text{O}_2$, or normalized V_{pp} . Normalized V_{rms} was significantly effected by oscillatory modality ($P < 0.001$), as well as the interaction between modality and time ($P < 0.001$). *Post hoc* analysis demonstrated that normalized V_{rms} was significantly higher for SFOV compared to MFOV for all time points after 15 minutes. Normalized V_{rms} ranged from 1.3 ± 0.1 and $1.3 \pm 0.2 \text{ mL kg}^{-1}$ for MFOV and SFOV, respectively, at 15 mins to 1.2 ± 0.2 and $1.5 \pm 0.1 \text{ mL kg}^{-1}$ at 60 mins. A significant effect of oscillatory modality, with MFOV lower than SFOV in all cases, was observed for V_C (MFOV: 246.9 ± 6.0 , SFOV: $363.5 \pm 15.9 \text{ mL}^2 \text{ mmHg kg}^{-1}$; $P < 0.001$), P_{ao} (MFOV: 12.8 ± 0.3 , SFOV: $14.1 \pm 0.5 \text{ cmH}_2\text{O}$; $P = 0.007$), OI (MFOV: 5.3 ± 0.1 , SFOV: $6.4 \pm 0.2 \text{ \% cmH}_2\text{O mmHg}^{-1}$; $P = 0.011$), and E_{dyn} (MFOV: 1.02 ± 0.02 , SFOV: $1.26 \pm 0.05 \text{ cmH}_2\text{O mL}^{-1}$; $P < 0.001$), when averaged over all time points. However, no significant effect of time or the interaction between modality and time was observed for these variables (see Table 3).

Figure 5 shows the spatial distribution of ventilation at the end of each 60 minute SFOV and MFOV periods (i.e., at 90 and 180 minutes 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, $P = 0.225$).

DISCUSSION

Premature lungs exhibit mechanical and spatial heterogeneity due to structural immaturity and surfactant deficiency.¹⁸ Conventional mechanical ventilation (CMV) in preterm infants may inadvertently worsen existing lung injury due to repeated alveolar overdistention and opening / closing of airways.¹ By contrast, high frequency oscillatory ventilation (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 ARDS have shown that HFOV does not reduce mortality, despite physiological evidence of enhanced gas distribution, volume recruitment, and $V/\dot{Q}$ matching.^{6–10} 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 end points, 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.^{15–17} There is no doubt that the mechanical complexity of the heterogeneous lung is fundamental to the distribution of ventilation^{15,16,19–21,23}.

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 $V/\dot{Q}$ matching by distributing

ventilation more evenly to different regions, according to their respective local mechanical properties. The mechanism for such improvements may be 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.¹⁶ Since local ventilation distribution becomes highly frequency-dependent in the presence of regional mechanical heterogeneity,^{19–21} the most effective frequency for optimal gas exchange will vary from region to region.^{15,16} 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.^{16,23} Such ventilation heterogeneity within the lung may result not only in decrements of gas exchange, but also worsening 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.^{15,16} Thus the application of multiple, simultaneous frequencies may be better suited to complement the heterogeneous mechanics 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 (Figure 6).

In this study we demonstrated the feasibility of maintaining and improving gas exchange with ‘Multi-Frequency Oscillatory Ventilation’ (MFOV) in preterm lambs, using a commercially available hybrid ventilator-oscillator with custom-written firmware. Our data suggests that MFOV results in more uniform distribution of ventilation to the alveoli compared to 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 (Figure 4). Our ventilatory cost function (V_C) is defined as the product of ventilatory ‘power’ (V_{rms}^2) multiplied by arterial CO_2 tension ($P_a\text{CO}_2$). This index is justified by empiric evidence that CO_2 elimination is roughly proportional to the square of tidal volume during HFOV.²⁹ Our V_C index was significantly lower during MFOV compared to SFOV, consistent with more efficient CO_2 elimination. More efficient CO_2 elimination in MFOV was due largely to the increased V_{rms} required of the SFOV modality compared to MFOV in order to maintain $P_a\text{CO}_2$ within our desired target range of 45 to 55 mm Hg; there were no significant differences in the peak-to-peak volume excursions or $P_a\text{CO}_2$ between SFOV and MFOV.

The OI and $\bar{P}_{ao}$ were significantly lower at all time points during MFOV compared to SFOV, with no significant differences in $P_a\text{O}_2$. These findings indicate that MFOV facilitates more efficient oxygenation at lower distending pressures. The E_{dyn} was also significantly reduced during MFOV, although we cannot be certain whether lower E_{dyn} was the result of enhanced lung recruitment or reduced parenchymal strain-stiffening.³³ The

lower E_{dyn} suggests that the enhanced spectral content of the MFOV waveforms may prevent time-dependent derecruitment of lung units,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 via a variable stretch mechanism, similar to that observed with biologically variable ventilation.^{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, since 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.³⁷ Despite its utility as a potential bedside tool for rapid, noninvasive quantification of regional aeration,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 dynamic volumetric computed tomography during Xenon washout,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,^{22,40} although there is no evidence to suggest that these arbitrary ‘broadband’ ventilator patterns influence clinical efficacy.⁴¹ There have also been attempts to superimpose HFOV on CMV, such as during high-frequency percussive ventilation (HFPV).^{8,42–45} In some situations, this hybrid mode of ventilation may improve oxygenation and V/Q matching compared to either CMV or HFOV alone.⁴⁶ However HFPV has not been studied systematically, nor been shown to reduce mortality associated with ARDS.^{42,45} This lack of improved mortality may also be related to the reliance on large tidal volumes at lower frequencies.

While these experimental results are certainly compelling, our pilot study was limited by: 1) its small sample size; 2) a MFOV waveform consisting of only three frequencies that were not optimized for the heterogeneous lung; and 3) minimal information on the mechanical properties of these preterm lungs. Despite these deficiencies, our data indicate that MFOV may have distinct advantages as a ventilator modality in preterm lungs compared to traditional HFOV, and maintains lung recruitment at lower mean airway pressures. While 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 pathophysiologies such as the acute respiratory distress syndrome (ARDS). Since 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. There remain fundamental questions regarding the convective mechanisms by which this oscillatory modality improves gas exchange. While our crossover study did not examine outcomes associated with VILI, 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 may be useful in the ventilator management in other diseases that affect the lungs in a heterogeneous manner, such as asthma, COPD, 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.⁴⁷ However in certain pathological conditions, the presence severe expiratory flow-limitation due to dynamic airway compression may require additional modification or enhancement of the MFOV waveform,⁴⁸ since 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 to SFOV, and 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 to more conventional ventilation and oscillation strategies. MFOV thus has the potential to significantly change the care of critically-ill, ventilated patients.

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Dr. Kaczka and Mr. Herrmann are listed as co-inventors on a United States Provisional Patent on the MFOV concept.

GLOSSARY OF NOMENCLATURE

ABG	Arterial blood gas
ARDS	Acute respiratory distress syndrome

CMV	Conventional mechanical ventilation
E_{dyn}	Dynamic respiratory system elastance ($\text{cmH}_2\text{O mL}^{-1}$)
EIT	Electrical impedance tomography
$F_{\text{I}}\text{O}_2$	Fraction of inspired oxygen concentration (%)
MFOV	Multi-frequency oscillatory ventilation
OI	Oxygenation index ($\% \text{ cmH}_2\text{O mmHg}^{-1}$)
P_{ao}	Pressure at the airway opening (cmH_2O)
$\bar{P}_{\text{ao}}$	Mean pressure at the airway opening (cmH_2O)
$P_{\text{a}}\text{CO}_2$	Partial pressure of arterial carbon dioxide (mmHg)
$P_{\text{a}}\text{O}_2$	Partial pressure of arterial oxygen (mmHg)
PEEP	Positive end-expiratory pressure (cmH_2O)
pH	Negative base-10 logarithm of hydrogen ion concentration
PIP	Peak inspiratory pressure (cmH_2O)
SFOV	Single frequency oscillatory ventilation
$S_{\text{p}}\text{O}_2$	Arterial oxygen saturation based on pulse oximetry (%)
UBG	Umbilical cord blood gas
V_{C}	Ventilatory cost function ($\text{mL}^2 \text{ mmHg kg}^{-1}$)
VILI	Ventilator-induced lung injury
V_n	Discretized volume waveform (mL)
V_{pp}	Peak-to-peak volume amplitude (mL)
V_{rms}	Root mean square of volume (mL)
$\bar{V}$	Mean of volume waveform
V_{T}	Tidal volume (mL)
$\dot{V}$	Airway flow
$V/\dot{Q}$	Ventilation-to-perfusion ratio
Wt	Weight (kg)

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Figure 1.

Overview of experimental protocol. CMV: conventional mechanical ventilation; SFOV: single frequency oscillatory ventilation; MFOV: multi-frequency oscillatory ventilation; UBG: umbilical cord blood gas; ABG: arterial blood gas; EIT: electrical impedance tomography

Single-Frequency Oscillatory Ventilation

Multi-Frequency Oscillatory Ventilation

Figure 2.

Representative examples of time-domain tracings (left panels **A** and **C**) and magnitude spectra (right panels **B** and **D**) for SFOV and MFOV volume waveforms, as generated by the ACUTRONIC Fabian oscillator.

Figure 3. Algorithm for adjusting mean airway pressure ($\bar{P}_{ao}$) and fraction of inspired oxygen concentration (F_iO_2) based on arterial oxygen saturation (S_pO_2), as needed.

Figure 4.

Summary of (A) arterial pH, (B) arterial CO₂ tension ($P_a\text{CO}_2$) (C) arterial O₂ tension ($P_a\text{O}_2$), (D) peak-to-peak tidal volume normalized by weight, ($V_{pp}\text{Wt}^{-1}$), (E) root mean square volume normalized by weight ($V_{rms}\text{Wt}^{-1}$), (F) ventilatory cost function (V_c), (G) mean airway pressure (P_{ao}), (H) oxygenation index (OI), and (I) dynamic respiratory system elastance (E_{dyn}) versus time during single-frequency oscillatory ventilation (SFOV, closed symbols) and multi-frequency oscillatory ventilation (MFOV, opened symbols). *Significant difference between SFOV and MFOV modalities, using two-way repeated measures ANOVA with Tukey HSD criterion. †Significant interaction between

SFOV and MFOV modality and time, based on Tukey HSD criterion. All data are expressed as mean $\pm$ S.E.

Figure 5.

Summary of the fractional distribution of ventilation within 32 slices of the left (gray bars) and right (white bars) hemithoraces following one hour of SFOV and MFOV modalities (i.e., at 90 and 180 minutes of the protocol) for Groups A (n = 6) and B (n = 6). Direction from dependent to nondependent slices is indicated by vertical arrow. Data are expressed as mean $\pm$ S.D. of functional EIT values. Anatomic directions are denoted as: R: right; L: left; V: ventral; D: dorsal

Figure 6.

Schematic of the concept of Multi-Frequency Oscillatory Ventilation (MFOV), illustrating how lung units with varying mechanical properties selectively 'filter' the spectral content of a broadband flow excitation presented to the airway opening.

Table 1

Birth weights and umbilical cord blood gas data for the thirteen lambs at time of delivery, separated into Groups A and B.

	Group A (n = 7)	Group B (n = 6)	Significance
Wt (kg)	3.18 ± 0.41	3.11 ± 0.39	0.77
pH	7.33 ± 0.06	7.33 ± 0.20	0.39
P_aCO₂(mm Hg)	57.0 ± 3.7	61.6 ± 6.2	0.15
P_aO₂(mm Hg)	31.9 ± 2.6	27.7 ± 8.9	0.29

Data are expressed as mean ± S.D. Significance level assessed using two-tailed Student's t-test, with the exception of pH which was assessed by Wilcoxon Rank Sum Test.

Wt: weight; pH: negative base-10 logarithm of the hydrogen ion concentration; P_aCO₂: arterial partial pressure of carbon dioxide; P_aO₂: arterial partial pressure of oxygen.

Table 2

Gas exchange and mechanics data for Groups A and B, following the 30-minute initial and washout conventional mechanical ventilation (CMV) periods.

	After Initial CMV Period		After Washout CMV Period		ANOVA Significance Level		
	Group A	Group B	Group A	Group B	Group	Period	Group x Period
V_T Wt ⁻¹ (mL kg ⁻¹)	7.37 ± 0.65	7.10 ± 0.39	7.32 ± 0.81	6.97 ± 0.33	0.201	0.709	0.861
F_iO_2 (%)	30.9 ± 7.1	30.3 ± 9.1	23.6 ± 5.3	23.3 ± 5.7	0.889	0.015	0.958
PEEP (cmH ₂ O)	6.5 ± 0.5	6.4 ± 0.6	5.7 ± 0.8	6.2 ± 0.6	0.557	0.054	0.251
PIP (cmH ₂ O)	22.3 ± 2.6	21.7 ± 2.7	13.9 ± 3.5	16.2 ± 2.2	0.459	<0.001	0.205
pH	7.29 ± 0.07	7.29 ± 0.86	7.34 ± 0.13	7.34 ± 0.03	0.921	0.156	0.853
P_aCO_2 (mmHg)	58.5 ± 13.4	53.8 ± 11.2	59.6 ± 23.0	53.4 ± 4.4	0.374	0.946	0.887
P_aO_2 (mmHg)	75.4 ± 40.9	68.6 ± 24.6	63.5 ± 22.3	55.2 ± 9.6	0.491	0.253	0.946

Data are expressed as mean ± S.D. Also shown are the significance levels for the analysis of variance (ANOVA), with CMV period (initial vs. washout) and group (A vs. B) as factors, along with their corresponding interaction.

V_T : tidal volume; Wt: weight; F_iO_2 : % inspired oxygen concentration; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; pH: negative base-10 logarithm of the hydrogen ion concentration; P_aCO_2 : arterial partial pressure of carbon dioxide; P_aO_2 : arterial partial pressure of oxygen.

P-values that are less than 0.05 are bolded.

Table 3

Significance levels for two-way ANOVA for gas exchange and mechanics data, with oscillatory modality (SFOV vs. MFOV) and time (15, 30, 45, and 60 minutes) as factors.

	ANOVA <i>P</i> -value		
	Oscillatory Modality (SFOV vs MFOV)	Time (15, 30, 45, 60 minutes)	Oscillatory Modality x Time
pH	0.056	0.790	0.383
$P_a\text{CO}_2$ (mmHg)	0.052	0.819	0.262
$P_a\text{O}_2$ (mmHg)	0.370	0.946	0.154
V_{pp} Wt ⁻¹ (mL kg ⁻¹)	0.099	0.843	0.063
V_{rms} Wt ⁻¹ (mL kg ⁻¹)	<0.001	0.741	0.032
V_c (mL ² mmHg kg ⁻¹)	<0.001	0.947	0.794
P_{ao}^- (cmH ₂ O)	0.007	0.608	0.996
OI (% cmH ₂ O mmHg ⁻¹)	0.011	0.843	0.896
E_{dyn} (cmH ₂ O mL ⁻¹)	<0.001	0.610	0.961

pH: negative base-10 logarithm of the hydrogen ion concentration; $P_a\text{CO}_2$: arterial partial pressure of carbon dioxide; $P_a\text{O}_2$: arterial partial pressure of oxygen; V_{pp} : peak-to-peak volume amplitude; V_{rms} : root mean square of volume; Wt: weight; V_c : ventilatory cost function; P_{ao}^- : mean pressure at airway opening; OI: oxygenation index; E_{dyn} : dynamic respiratory system elastance.

P values less than 0.05 are bolded.