Multifrequency Oscillatory Ventilation in the Premature Lung

Effects on Gas Exchange, Mechanics, and Ventilation Distribution

David W. Kaczka, M.D., Ph.D., Jacob Herrmann, M.S., C. Elroy Zonneveld, M.Sc., David G. Tingay, M.B.B.S., Ph.D., Anna Lavizzari, M.D., Peter B. Noble, Ph.D., J. Jane Pillow, M.B.B.S., Ph.D.

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 ($\bar{P}_{ao}$) 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 $V_C = \left(V_{rms}^2 \; PaCO_2\right) Wt^{-1}$, 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 ml^2 mmHg kg^{-1}) and $\bar{P}_{ao}$ (12.8 ± 0.3 *vs.* 14.1 ± 0.5 cm H_2O) 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.[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 overdistention. Despite the potential benefits of

What We Already Know about This Topic

- High-frequency oscillatory ventilation (using a set frequency) is an important technique for mechanical ventilation during lung injury although trials have not confirmed "outcome" advantages. However, injured lungs are characterized by heterogenous regional mechanics.

What This Article Tells Us That Is New

- In preterm lambs, high-frequency oscillatory ventilation using simultaneous multiple oscillatory frequencies improved gas exchange and lung recruitment at lower distending pressures; thus, future trials of high-frequency oscillatory ventilation might incorporate this approach.

Portions of this work have been presented in abstract form at the American Thoracic Society International Conference on May 19, 2014, in San Diego, California.

Submitted for publication February 17, 2015. Accepted for publication August 18, 2015. From the Departments of Anesthesia, Biomedical Engineering, and Radiology (D.W.K.) and Department of Biomedical Engineering (J.H.), University of Iowa, Iowa City, Iowa; Neonatal Research, Murdoch Childrens Research Group, Melbourne, Victoria, Australia (C.E.Z.); Department of Paediatrics, University of Melbourne, and Neonatal Research, Murdoch Childrens Research Institute, and Department of Neonatology, Royal Children's Hospital, Melbourne, Victoria, Australia (D.G.T.); Neonatal Research, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia, and NICU, Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (A.L.); School of Anatomy, Physiology, and Human Biology, and Centre for Neonatal Research and Education, School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia (P.B.N.); and School of Anatomy, Physiology, and Human Biology and Centre for Neonatal Research and Education, School of Paediatrics and Child Health, University of Western Australia, and Neonatal Clinical Care Unit, Women and Newborn Health Service, Perth, Western Australia, Australia (J.J.P.).

 Anesthesiology 2015; 123:1394-403

HFOV on gas distribution, volume recruitment, and ventilation-to-perfusion ($\dot{V}/\dot{Q}$) 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.[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 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 H_2O of 10-s duration. Then, the lamb was stabilized for 30 min on CMV at a rate of 50 min^{-1}, V_T of 7 ml/kg, PEEP of 6 cm H_2O, and F_{IO_2} 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 (Spo_2, as measured at the right ear) were monitored continuously (HP48S; Hewlett Packard, USA). Airway pressure (P_{ao}) and flow ($\dot{V}$) 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 $\dot{V}$ signal.[26]

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 (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 nonzero mean of the volume signal ($\bar{V}$), the root mean square of the discretized volume (V_{rms}) was determined as follows:

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

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 (E_{dyn}) at 5 Hz was computed from 2-min samples of P_{ao} and $\dot{V}$ 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, $Paco_2$, and Pao_2 were obtained every 15 min throughout the entire protocol. During SFOV and MFOV,

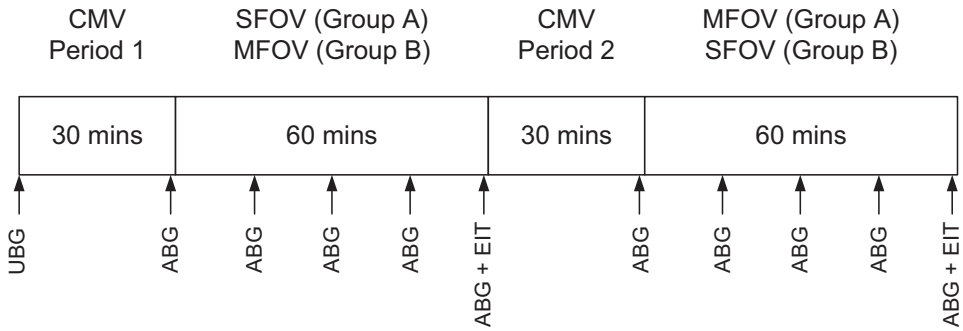

Fig. 1. Overview of experimental protocol. ABG = arterial blood gas; CMV = conventional mechanical ventilation; EIT = electrical impedance tomography; MFOV = multifrequency oscillatory ventilation; SFOV = single-frequency oscillatory ventilation; UBG = umbilical cord blood gas.

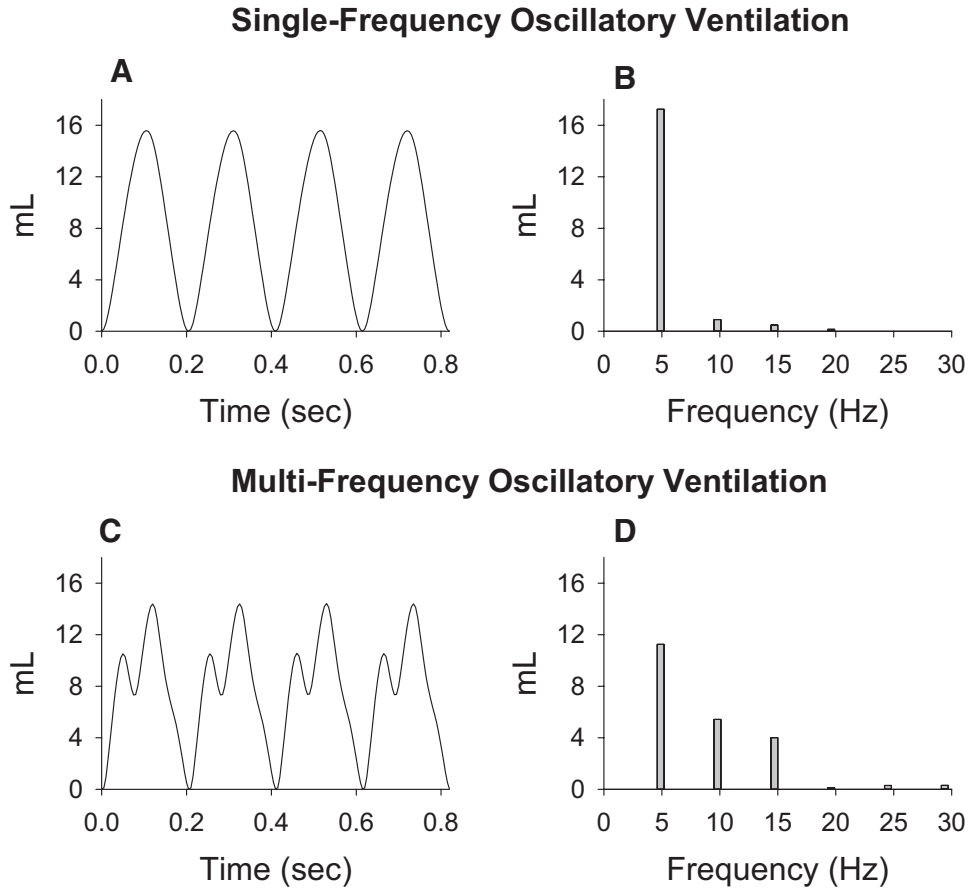

Fig. 2. Representative examples of time domain tracings (*A* and *C*) and magnitude spectra (*B* and *D*) for single-frequency oscillatory ventilation and multifrequency oscillatory ventilation volume waveforms, as generated by the Acutronic Fabian oscillator (Acutronic Medical Systems AG, Switzerland).

mean airway pressure ($\bar{P}_{ao}$) 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[28]:

$$OI = \frac{F_{IO_2} \quad \bar{P}_{ao}}{Pa_{O_2}}. \tag{2}$$

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 Pa_{CO_2} range of 45 to 55 mmHg. Since carbon dioxide 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:

$$V_C = \left(V_{rms}^2 \; Pa_{CO_2}\right) Wt^{-1}, \tag{3}$$

where Wt denotes body weight in kilogram. Thus for a given value of Pa_{CO_2}, lower values of V_C indicate more efficient ventilation.

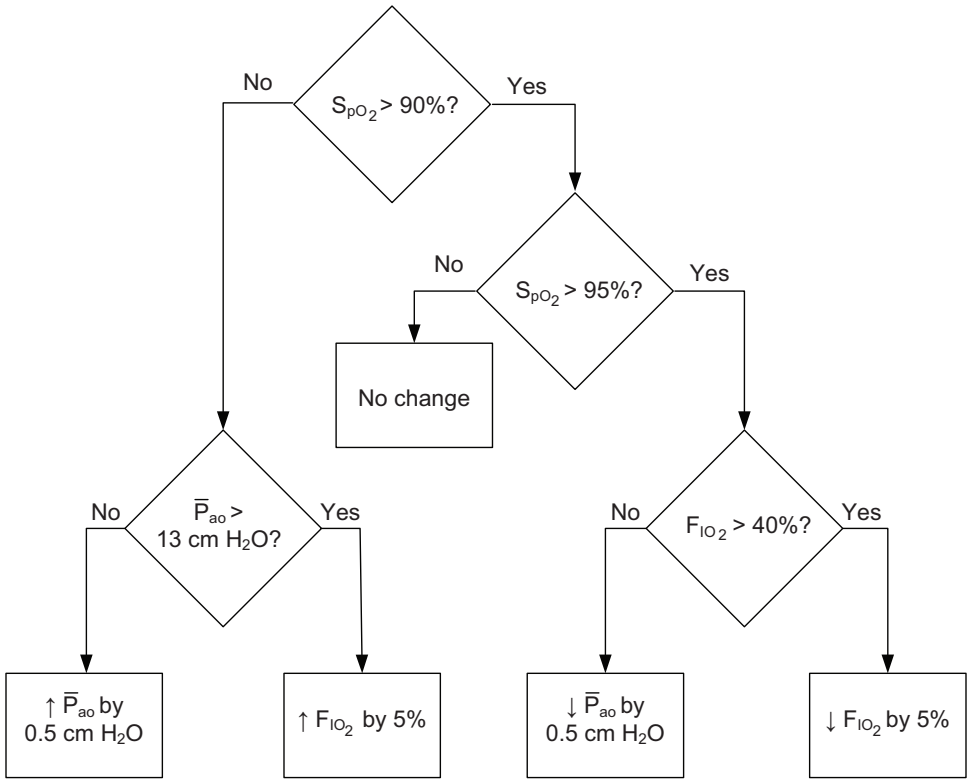

Fig. 3. Algorithm for adjusting mean airway pressure ($\bar{P}_{ao}$) and fraction of inspired oxygen concentration (F_{IO_2}) based on arterial oxygen saturation (Spo_2), as needed.

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 32×32 pixels and a frame rate of 44 Hz. The EIT images were reconstructed using the GREIT image reconstruction algorithm[30] 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.[25,31,32] 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 treatment mode (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.

Table 1. Birth Weights and Umbilical Cord Blood Gas Data for the 13 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
$Paco_2$ (mmHg)	57.0 ± 3.7	61.6 ± 6.2	0.15
Pao_2 (mmHg)	31.9 ± 2.6	27.7 ± 8.9	0.29

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.

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, $Paco_2$, and Pao_2 values between the two groups (table 1). Table 2 shows V_T normalized by weight, FIO_2, PEEP, $\bar{P}_{ao}$, peak inspiratory pressure, arterial pH, $Paco_2$, and Pao_2 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 FIO_2 ($P = 0.015$) 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 effect of modality or time on arterial pH, $Paco_2$, Pao_2, or normalized V_{pp}. Normalized V_{rms} was significantly affected 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 with that for MFOV for all time points after 15 min. Normalized V_{rms} 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 V_C (MFOV: 246.9 ± 6.0, SFOV: 363.5 ± 15.9 ml^2 mmHg kg^{-1}; $P < 0.001$), $\bar{P}_{ao}$ (MFOV: 12.8 ± 0.3, SFOV: 14.1 ± 0.5 cm H_2O; $P = 0.007$), OI (MFOV: 5.3 ± 0.1, SFOV: 6.4 ± 0.2% cm H_2O/mmHg; $P = 0.011$), and E_{dyn} (MFOV: 1.02 ± 0.02, SFOV: 1.26 ± 0.05 cm H_2O/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; $P = 0.225$).

Discussion

Premature lungs exhibit mechanical and spatial heterogeneity due to structural immaturity and surfactant deficiency.[18] CMV in preterm infants may inadvertently worsen existing lung injury due to repeated alveolar overdistention and opening/closing of airways.[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 $\dot{V}/\dot{Q}$ 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

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

	After Initial CMV Period		After Washout CMV Period		ANOVA Significance Level		
	Group A	Group B	Group A	Group B	Group	Period	Group × Period
V_T Wt^{-1} (ml/kg)	7.37 ± 0.65	7.10 ± 0.39	7.32 ± 0.81	6.97 ± 0.33	0.201	0.709	0.861
FIO_2 (%)	30.9 ± 7.1	30.3 ± 9.1	23.6 ± 5.3	23.3 ± 5.7	0.889	**0.015**	0.958
PEEP (cm H_2O)	6.5 ± 0.5	6.4 ± 0.6	5.7 ± 0.8	6.2 ± 0.6	0.557	0.054	0.251
PIP (cm H_2O)	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
$Paco_2$ (mmHg)	58.5 ± 13.4	53.8 ± 11.2	59.6 ± 23.0	53.4 ± 4.4	0.374	0.946	0.887
Pao_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 ± 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; FIO_2 = 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; V_T = tidal volume.

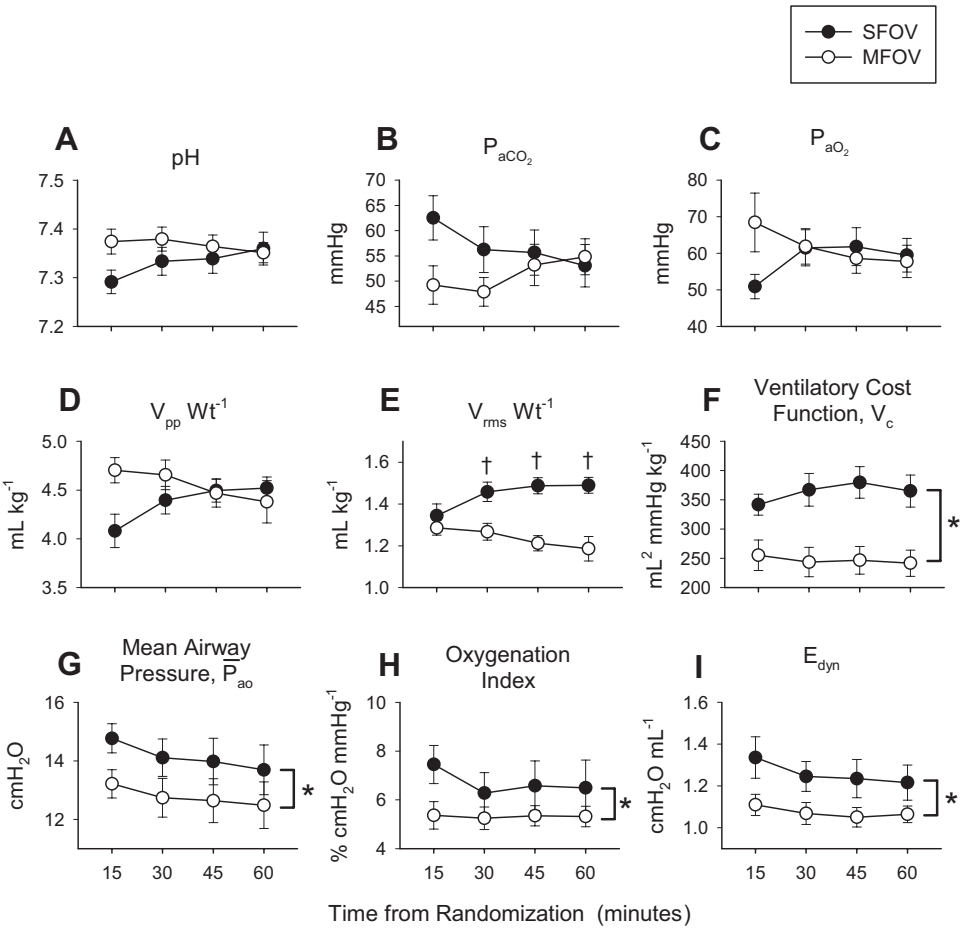

Fig. 4. Summary of (*A*) arterial pH, (*B*) $Paco_2$, (*C*) Pao_2, (*D*) peak-to-peak tidal volume normalized by weight, (V_{pp} Wt^{-1}), (*E*) root mean square volume normalized by weight (V_{rms} Wt^{-1}), (*F*) ventilatory cost function (V_C), (*G*) mean airway pressure ($\bar{P}_{ao}$), (*H*) oxygenation index, and (*I*) dynamic respiratory system elastance (E_{dyn}) *versus* time *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.

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.[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 $\dot{V}/\dot{Q}$ matching by distributing ventilation more evenly to different regions, according to their respective local mechanical properties. The mechanism for such improvements may be 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.[16] Because 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 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.[15,16] Thus, the application of multiple, simultaneous frequencies may be better suited to complement the heterogeneous mechanics

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 min) as Factors

	ANOVA *P* Value		
	Oscillatory Modality (SFOV *vs.* MFOV)	Time (15, 30, 45, and 60 min)	Oscillatory Modality × Time
pH	0.056	0.790	0.383
$Paco_2$ (mmHg)	0.052	0.819	0.262
Pao_2 (mmHg)	0.370	0.946	0.154
V_{pp} Wt^{-1} (ml/kg)	0.099	0.843	0.063
V_{rms} Wt^{-1} (ml/kg)	**<0.001**	0.741	**0.032**
V_C (ml^2 mmHg kg^{-1})	**<0.001**	0.947	0.794
$\bar{P}_{ao}$ (cm H_2O)	**0.007**	0.608	0.996
OI (% cm H_2O/mmHg)	**0.011**	0.843	0.896
E_{dyn} (cm H_2O/ml)	**<0.001**	0.610	0.961

P < 0.05 are shown in boldface.

E_{dyn} = dynamic respiratory system elastance; MFOV = multifrequency oscillatory ventilation; OI = oxygenation index; $\bar{P}_{ao}$ = mean pressure at airway opening; pH = negative base-10 logarithm of the hydrogen ion concentration; SFOV = single-frequency oscillatory ventilation; V_C = ventilatory cost function; V_{pp} = peak-to-peak volume amplitude; V_{rms} = root mean square of volume; Wt = weight.

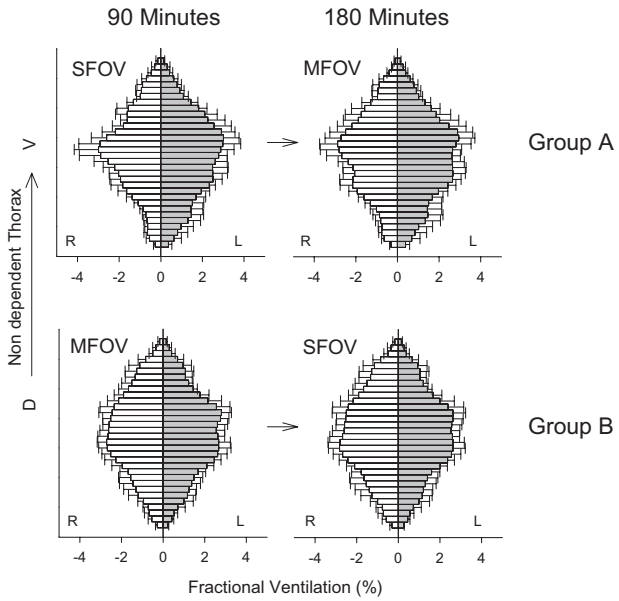

Fig. 5. Summary of the fractional distribution of ventilation within 32 slices of the left (*gray bars*) and right (*white bars*) hemithoraces after 1 h of single-frequency oscillatory ventilation (SFOV) and multifrequency oscillatory ventilation (MFOV) modalities (*i.e.*, at 90 and 180 min of the protocol) 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 ± SD of functional electrical impedance tomography values. Anatomic directions are denoted as follows: D = dorsal; L = left; R = right; V = ventral.

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

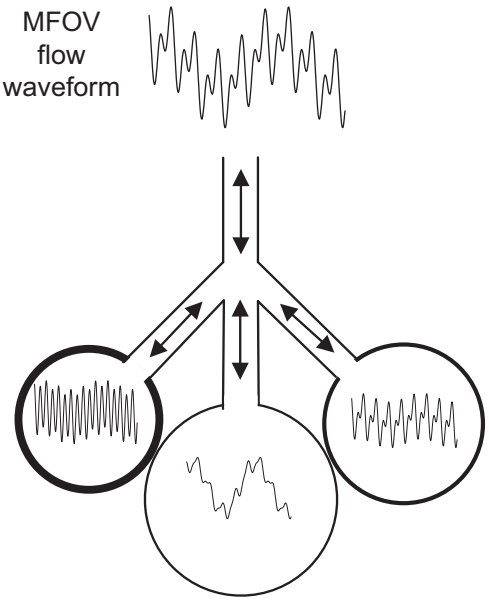

Fig. 6. Schematic of the concept of multifrequency oscillatory ventilation (MFOV), illustrating how lung units with varying mechanical properties selectively "filter" the spectral content of a broadband flow excitation presented to the airway opening.

"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_{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_{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 $\bar{P}_{ao}$ 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_{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 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.[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 as 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 also have been attempts to superimpose HFOV on CMV, such as during high-frequency percussive ventilation.[8,42–45] In some situations, this hybrid mode of ventilation may improve oxygenation and $\dot{V}/\dot{Q}$ matching compared with either CMV or HFOV alone.[46] However, high-frequency percussive ventilation has neither been studied systematically nor been shown to reduce mortality associated with ARDS.[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 pathophysiologies 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 β-agonists, steroids, or even inhaled volatile anesthetics.[47] 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[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.

Acknowledgments

The authors thank Medical Technologies (Osborne Park, Western Australia, Australia) and Acutronic Medical Systems AG (Bubikon, Switzerland) for equipment loans and technical assistance. The authors also thank Monica Hawley, Ph.D., Iowa City, Iowa, for assistance with the statistical analysis of the data and Brett Simon, M.D., Ph.D., Memorial Sloan Kettering Cancer Center, New York, New York, for his helpful suggestions during the preparation of the article.

Support was received from the National Institutes of Health (Bethesda, Maryland; grant no. UM1 HL108724 to Dr. Kaczka and Mr. Herrmann); the National Health and Medical Research Council (Canberra, Australian Capital Territory, Australia; grant no. APP1010575), Women and Infants Research Foundation (Subiaco, Western Australia, Australia), and the Metropolitan Health Research Infrastructure Fund (Perth, Western Australia, Australia) (to Dr. Pillow); National Health and Medical Research Council (Canberra, Australian Capital Territory, Australia; fellowship APP1045824 to Dr. Noble); National Health and Medical Research Council (Canberra, Australian Capital Territory, Australia; fellowship GRP 491286 to Dr. Tingay); and Victorian Government Operational Infrastructure Support Program (Melbourne, Victoria, Australia; to Drs. Tingay and Lavizzari and Mr. Zonneveld).

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.

Correspondence

Address correspondence to Dr. Kaczka: Department of Anesthesia, The University of Iowa Hospital and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242. david-kaczka@uiowa.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Chakraborty M, McGreal EP, Kotecha S: Acute lung injury in preterm newborn infants: Mechanisms and management. Paediatr Respir Rev 2010; 11:162–70; quiz 170
2. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–36
3. Amato MB, Barbas CS, Medeiros DM, Schettino Gde P, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Morais C, Fernandes Ede O, Takagaki TY: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995; 152(6 Pt 1):1835–46
4. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–54
5. The ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. New Engl J Med 2000; 342:1301–308
6. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, Granton J; Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial (MOAT) Study Investigators: High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: A randomized, controlled trial. Am J Respir Crit Care Med 2002; 166:801–8
7. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group: High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013; 368:795–805
8. Hurst JM, Branson RD, Davis K Jr, Barrette RR, Adams KS: Comparison of conventional mechanical ventilation and high-frequency ventilation. A prospective, randomized trial in patients with respiratory failure. Ann Surg 1990; 211:486–91
9. Sud S, Sud M, Friedrich JO, Meade MO, Ferguson ND, Wunsch H, Adhikari NK: High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): Systematic review and meta-analysis. BMJ 2010; 340:c2327
10. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH; OSCAR Study Group: High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013; 368:806–13
11. Cools F, Henderson-Smart DJ, Offringa M, Askie LM: Elective high frequency oscillatory ventilation *versus* conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev 2009: CD000104
12. Clark RH, Gerstmann DR, Null DM Jr, deLemos RA: Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992; 89:5–12
13. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Bertrand JM, Battisti O, Langhendries JP, Francois A, Clark RH: The Provo multicenter early high-frequency oscillatory ventilation trial: Improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996; 98(6 Pt 1):1044–57
14. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K, Oguchi K, Togari H, Nishida H, Mishina J: A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. Early Hum Dev 1993; 32:1–10
15. Amini R, Kaczka DW: Impact of ventilation frequency and parenchymal stiffness on flow and pressure distribution in a canine lung model. Ann Biomed Eng 2013; 41:2699–711
16. Colletti AA, Amini R, Kaczka DW: Simulating ventilation distribution in heterogenous lung injury using a binary tree data structure. Comput Biol Med 2011; 41:936–45
17. Luecke T, Herrmann P, Kraincuk P, Pelosi P: Computed tomography scan assessment of lung volume and recruitment during high-frequency oscillatory ventilation. Crit Care Med 2005; 33(3 suppl):S155–62
18. Attar MA, Donn SM: Mechanisms of ventilator-induced lung injury in premature infants. Semin Neonatol 2002; 7:353–60
19. Allen JL, Frantz ID III, Fredberg JJ: Heterogeneity of mean alveolar pressure during high-frequency oscillations. J Appl Physiol (1985) 1987; 62:223–8
20. Allen JL, Fredberg JJ, Keefe DH, Frantz ID III: Alveolar pressure magnitude and asynchrony during high-frequency oscillations of excised rabbit lungs. Am Rev Respir Dis 1985; 132:343–9
21. Fredberg JJ, Keefe DH, Glass GM, Castile RG, Frantz ID III: Alveolar pressure nonhomogeneity during small-amplitude high-frequency oscillation. J Appl Physiol Respir Environ Exerc Physiol 1984; 57:788–800
22. Pillow JJ, Wilkinson MH, Neil HL, Ramsden CA: *In vitro* performance characteristics of high-frequency oscillatory ventilators. Am J Respir Crit Care Med 2001; 164:1019–24
23. Lehr JL, Butler JP, Westerman PA, Zatz SL, Drazen JM: Photographic measurement of pleural surface motion during lung oscillation. J Appl Physiol (1985) 1985; 59:623–33

24. Tingay DG, Bhatia R, Schmölzer GM, Wallace MJ, Zahra VA, Davis PG: Effect of sustained inflation *vs.* stepwise PEEP strategy at birth on gas exchange and lung mechanics in preterm lambs. Pediatr Res 2014; 75:288–94
25. Tingay DG, Wallace MJ, Bhatia R, Schmölzer GM, Zahra VA, Dolan MJ, Hooper SB, Davis PG: Surfactant before the first inflation at birth improves spatial distribution of ventilation and reduces lung injury in preterm lambs. J Appl Physiol (1985) 2014; 116:251–8
26. Kaczka DW, Barnas GM, Suki B, Lutchen KR: Assessment of time-domain analyses for estimation of low-frequency respiratory mechanical properties and impedance spectra. Ann Biomed Eng 1995; 23:135–51
27. Kaczka DW, Dellacá RL: Oscillation mechanics of the respiratory system: Applications to lung disease. Crit Rev Biomed Eng 2011; 39:337–59
28. Ortiz RM, Cilley RE, Bartlett RH: Extracorporeal membrane oxygenation in pediatric respiratory failure. Pediatr Clin North Am 1987; 34:39–46
29. Venegas JG, Hales CA, Strieder DJ: A general dimensionless equation of gas transport by high-frequency ventilation. J Appl Physiol (1985) 1986; 60:1025–30
30. Adler A, Arnold JH, Bayford R, Borsic A, Brown B, Dixon P, Faes TJ, Frerichs I, Gagnon H, Gärber Y, Grychtol B, Hahn G, Lionheart WR, Malik A, Patterson RP, Stocks J, Tizzard A, Weiler N, Wolf GK: GREIT: A unified approach to 2D linear EIT reconstruction of lung images. Physiol Meas 2009; 30:S35–55
31. Frerichs I: Electrical impedance tomography (EIT) in applications related to lung and ventilation: A review of experimental and clinical activities. Physiol Meas 2000; 21:R1–21
32. Frerichs I, Dargaville PA, van Genderingen H, Morel DR, Rimensberger PC: Lung volume recruitment after surfactant administration modifies spatial distribution of ventilation. Am J Respir Crit Care Med 2006; 174:772–9
33. Kaczka DW, Cao K, Christensen GE, Bates JH, Simon BA: Analysis of regional mechanics in canine lung injury using forced oscillations and 3D image registration. Ann Biomed Eng 2011; 39:1112–24
34. Bates JH, Irvin CG: Time dependence of recruitment and derecruitment in the lung: A theoretical model. J Appl Physiol (1985) 2002; 93:705–13
35. Ruth Graham M, Goertzen AL, Girling LG, Friedman T, Pauls RJ, Dickson T, Espenell AE, Mutch WA: Quantitative computed tomography in porcine lung injury with variable *versus* conventional ventilation: Recruitment and surfactant replacement. Crit Care Med 2011; 39:1721–30
36. Arold SP, Suki B, Alencar AM, Lutchen KR, Ingenito EP: Variable ventilation induces endogenous surfactant release in normal guinea pigs. Am J Physiol Lung Cell Mol Physiol 2003; 285:L370–5
37. Frerichs I, Hahn G, Golisch W, Kurpitz M, Burchardi H, Hellige G: Monitoring perioperative changes in distribution of pulmonary ventilation by functional electrical impedance tomography. Acta Anaesthesiol Scand 1998; 42:721–6
38. Wolf GK, Arnold JH: Noninvasive assessment of lung volume: Respiratory inductance plethysmography and electrical impedance tomography. Crit Care Med 2005; 33(3 suppl):S163–9
39. Mulreany DG, Simon BA, Murphy KJ, Easley RB: Volumetric xenon-CT imaging of conventional and high-frequency oscillatory ventilation. Acad Radiol 2009; 16:718–25
40. Harcourt ER, John J, Dargaville PA, Zannin E, Davis PG, Tingay DG: Pressure and flow waveform characteristics of eight high-frequency oscillators. Pediatr Crit Care Med 2014; 15:e234–40
41. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, Dani C, Durand DJ, Gerstmann DR, Henderson-Smart DJ, Marlow N, Peacock JL, Pillow JJ, Soll RF, Thome UH, Truffert P, Schreiber MD, Van Reempts P, Vendettuoli V, Vento G; PreVILIG Collaboration: Elective high-frequency oscillatory *versus* conventional ventilation in preterm infants: A systematic review and meta-analysis of individual patients' data. Lancet 2010; 375:2082–91
42. Allan PF, Osborn EC, Chung KK, Wanek SM: High-frequency percussive ventilation revisited. J Burn Care Res 2010; 31:510–20
43. Chung KK, Wolf SE, Renz EM, Allan PF, Aden JK, Merrill GA, Shelhamer MC, King BT, White CE, Bell DG, Schwacha MG, Wanek SM, Wade CE, Holcomb JB, Blackbourne LH, Cancio LC: High-frequency percussive ventilation and low tidal volume ventilation in burns: A randomized controlled trial. Crit Care Med 2010; 38:1970–7
44. Cioffi WG, Graves TA, McManus WF, Pruitt BA Jr: High-frequency percussive ventilation in patients with inhalation injury. J Trauma 1989; 29:350–4
45. Salim A, Martin M: High-frequency percussive ventilation. Crit Care Med 2005; 33(3 suppl):S241–5
46. Harf A, Le Gall R, Chang HK: Mechanical ventilation with superimposed high frequency oscillation in the normal rat. Respir Physiol 1983; 54:31–40
47. Mondoñedo JR, McNeil JS, Amin SD, Herrmann J, Simon BA, Kaczka DW: Volatile anesthetics and the treatment of severe bronchoconstriction: A concept of targeted delivery. Drug Discov Today Dis Models 2014; doi: 10.1016/j.ddmod.2014.02.004
48. Kaczka DW, Ingenito EP, Lutchen KR: Technique to determine inspiratory impedance during mechanical ventilation: Implications for flow limited patients. Ann Biomed Eng 1999; 27:340–55