

A Comparison of High-Frequency Oscillation Superimposed onto Backup Mechanical Ventilation and Conventional Mechanical Ventilation on the Distribution of Exogenous Surfactant in Premature Lambs¹

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ABSTRACT. Twenty-six premature lambs were treated by tracheal instillation of [¹⁴C]labeled natural sheep surfactant before the onset of breathing or after the establishment of respiratory distress syndrome 30 min after birth. Half of both groups were subsequently ventilated for 3 h with 100% O₂ by conventional mechanical ventilation (CMV) and half by high frequency oscillation superimposed onto backup mechanical ventilation (HFOV). Mean airway pressure, arterial blood pressures, and heart rate were recorded continuously. Arterial blood gases and pH were obtained every 15 min. After sacrifice, the distribution of radiolabeled surfactant was quantified and alveolar expansion was evaluated by morphometrics. At comparable oxygenation, mean airway pressures were significantly lower in the lambs treated with surfactant at birth (groups CMV-B and HFOV-B) than in lambs on CMV and treated with surfactant during RDS (group CMV-R). Mean airway pressures in both groups of lambs on HFOV (groups HFOV-B and HFOV-R) were comparable at values lower than in group CMV-R and higher than in group CMV-B. The distribution of radiolabeled surfactant was more homogeneous in lambs treated at birth and not different for both types of ventilatory assistance. Morphometrics demonstrated significantly better expansion of the alveoli of lambs ventilated with HFOV than of those on CMV, irrespective of the timing of surfactant administration. These results indicate that prophylactic surfactant administration at birth leads to a better distribution of surfactant than rescue treatment with surfactant after the establishment of respiratory distress syndrome and is not affected by a subsequent type of ventilatory assistance. Rescue treatment with surfactant and subsequent HFOV leads to better oxygenation and alveolar expansion at comparable mean airway pressures than rescue treatment followed by CMV. (*Pediatr Res* 22: 725-729, 1987)

MAP, mean airway pressure
PaO₂, partial arterial oxygen pressure
PaCO₂, partial arterial carbon dioxide pressure
PEEP, positive end-expiratory pressure
RDS, respiratory distress syndrome
VI, ventilatory index
VT, tidal volume

Tracheal instillation of exogenous surfactant into premature animals and infants with RDS induces a rapid improvement of pulmonary function. Giving surfactant at birth takes advantage of the lungs being filled with fluid. It allows for the mixing of surfactant with lung fluid and leads to an even distribution of surfactant as the lung fluid recedes (1). After birth, lung fluids diminish quickly and the distribution of exogenous surfactant after air breathing will be more uneven (1). This is in line with the observation that injecting surfactant into the fluid-filled airways of animals and infants before the initiation of breathing leads to a clinical response of longer duration than administration of a surfactant suspension after a period of air breathing (2-4).

However, the distribution of exogenous surfactant may not only depend on the timing of its instillation, but also on the type of ventilatory assistance used thereafter. Data on the influence of different modes of assisted ventilation on the ultimate distribution of exogenous surfactant in infants with respiratory distress syndrome are lacking. Several studies in adult rabbits with surfactant deficient lungs (6-8) indicate that HFOV may be superior to CMV due to the absence of swings in end-tidal lung volume. We compared the effects of HFOV and CMV on the distribution of exogenous surfactant in premature lambs treated with radiolabeled surfactant before the onset of breathing or after a period of CMV because of RDS.

Abbreviations

CMV, conventional mechanical ventilation
HFOV, high frequency oscillation ventilation

METHODS

Mechanical ventilation. HFOV was delivered at a frequency of 15 Hz and a tidal volume of 2 ml/kg using a HFOV-CMV system (8, 9). HFOV was generated by an electric piston pump with a volume adjustable between 1 and 50 ml and frequencies between 1 and 30 Hz. The piston was connected with the upper part of the endotracheal tube by means of a noncompliant tube. It oscillated the gas flowing through the ventilator circuit without

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adding new gas. The oscillations were added on the CMV waveforms. CMV was administered with a constant-flow, time-cycled, pressure-limited ventilator (Amsterdam Infant Ventilator, MK 2, Hoek and Loos, Amsterdam, The Netherlands) delivering humidified and warmed oxygen. Ventilator settings were as follows: an initial peak inspiratory pressure of 25 cm H₂O, a PEEP of 3 cm H₂O, a rate of 40 breaths/min, an inspiratory time of 0.75 s, and a FiO₂ of 1.0. Subsequently, only peak inspiratory pressures were changed in an attempt to normalize PaCO₂.

Surfactant. Natural surfactant was recovered by a series of centrifugation steps from the lung lavage of healthy adult sheep. The isolation procedure, phospholipid composition, protein content, and clinical activity of this surfactant have been reported (10). Uniformly labeled [1-¹⁴C]palmitate dipalmitoylphosphatidylcholine (117 mCi/mmol) was purchased from Amersham International (Buckinghamshire, England). The ¹⁴C solution was dried under N₂, suspended in distilled water by sonication (11) and added to the natural surfactant to a final concentration of 1 μCi of [1-¹⁴C]palmitate dipalmitoylphosphatidylcholine and 180 mg of natural sheep surfactant lipid in 10 ml of natural surfactant. Each lamb received 60 mg of natural sheep surfactant lipid and 0.33 μCi of [1-¹⁴C]palmitate dipalmitoylphosphatidylcholine per kg body weight.

Lambs. All premature lambs were delivered at 126–132 days of gestation by cesarean section under general anesthesia of date-mated Texel breed ewes carrying twins or triplets. The head and neck of each lamb was mobilized, and the midanterior neck exposed through a uterine incision. An uncuffed endotracheal tube (internal diameter 4 mm) was inserted and tied into the trachea. A 10-ml sample of fetal lung fluid was aspirated for phospholipid analysis. The endotracheal tube was occluded to prevent entrance of air to the lungs. A 5 Fr. polyethylene catheter was placed in a carotid artery and a 3.5 Fr. polyethylene catheter was placed into a jugular vein. An umbilical arterial blood sample was obtained for pH and blood gas analysis, the lamb was delivered, weighed, and mechanical ventilation was started. The lambs were paralyzed with 0.1 mg/kg of pancuronium bromide and received 10 mg/kg of phenobarbital sodium intravenously. The lambs were dried and placed on a heating mattress under an infant radiant heater and supplemental heat lamps. Rectal temperature was monitored and body temperature was maintained at 38–39° C. Arterial blood gases and pH were sampled every 15 min and measured with an AVL-940 blood gas instrument. MAP was measured through a saline-filled polyethylene catheter with an internal diameter of 1 mm, which was not connected to the endotracheal tube. It extended 2 cm beyond the distal tip of the endotracheal tube and had, in addition to the central lumen, two intramural lumens close to its tip. The airway catheter was connected to a pressure transducer (Gould Inc., Oxnard, CA). The signal was amplified and displayed continuously on an eight-channel Schwarzer polygraph calibrated to the high range using a mercury manometer and zeroed to atmospheric pressure. Heart rate and arterial blood pressures were recorded continuously on the polygraph. Each lamb received 10% dextrose through the venous catheter at a rate of 100 ml/kg/24 h.

Thirteen lambs received radiolabeled surfactant by tracheal instillation at birth. Six lambs (group CMV-B) were subsequently ventilated with CMV and seven (group HFOV-B) with HFOV. Thirteen lambs were supported on CMV and did not receive radiolabeled surfactant until 30 min after birth. At treatment these lambs were all in respiratory failure as defined by elevated PaCO₂ levels and low pH values on at least two blood gas samples. Seven of these lambs (group CMV-R) were continued on CMV and six (group HFOV-R) were switched over to the HFOV after instillation of surfactant. This led to the formation of four study groups. HFOV and CMV were alternately assigned to the first, second, or third born lamb of each twin or triplet. Three h after the tracheal instillation of radiolabeled surfactant, all lambs were sacrificed by a lethal pentobarbital overdose and

subsequent exsanguination. A few minutes before sacrifice inadvertent PEEP was determined in the lambs on HFOV by clamping the endotracheal tube at end-expiration for 5 s. This clamping procedure was repeated three times and the values were averaged to estimate inadvertent PEEP.

Processing of lungs. After sacrifice, the lungs were removed intact and weighed while still attached to the endotracheal tube at 15 cm H₂O distending pressure. The lungs were divided into 65 pieces with a weight of about 200 mg. Sixty biopsies, *i.e.* five superficial and five central biopsies from each of the upper, middle, and lower lobes, were used for estimation of the amount of radiolabeled surfactant. The superior and inferior right middle lobes were counted as one lobe. Five horizontal sections of each of the upper and lower lobes and of one of the right middle lobes were used for morphometrics. The tissue samples for surfactant quantitation were weighed, catalogued as to location, mixed with 0.5 N quaternary ammonium hydroxide in toluene, and placed in a shaking bath at 37° C for 36–48 h to obtain complete solubilization. After addition of Biofluor (DuPont, Boston, MA), the amount of radioactive surfactant was quantified. The biopsies for morphometrics (12) were immediately fixed in a 15:1:4 v/v mixture of alcohol 100%, glacial acetic acid, and formaldehyde 40%, stored overnight at room temperature, routinely paraffine embedded, cut in 4-μm sections, mounted on slides, and stained with hematoxylin and eosin. Each microscopic section was subsequently magnified 250 times under a Zeiss microscope and displayed with a Hitachi FP-10 videocamera on a monitor connected to a digitizer tablet. Using a manually operated cursor and retaining appropriate identification, the outline of each alveolus in a standard surface, encompassing at least 75 alveoli, was entered into a MOP Videoplan computer. Surface calculations (in μm²) for the digitized alveoli were made using methods similar to those of Cook *et al.* (13).

Data analysis and presentation. The number of radioactive counts, corrected for quenching, per piece of lung for each lamb was obtained and corrected for weight (dpm/g wet tissue). The values were then divided by the mean value for the lungs of that lamb to normalize the numbers. These ratios were turned into histograms with interval widths of 10% about the mean value of 1.0. All pieces having a normalized value <0.15 or >1.85 times the mean were grouped at the extremes of the distribution intervals (1).

All values are expressed as mean ± SD unless otherwise indicated. Comparisons between groups were analyzed with Student's two-tailed *t* test or χ² test.

RESULTS

The lambs weighed 3.0 ± 0.8 kg and were delivered at a gestational age of 130.5 ± 1.3 days. Arterial umbilical blood gases for the 26 lambs were pH, 7.29 ± 0.05; PaO₂, 27 ± 8 mm Hg; and PaCO₂, 48 ± 8 mm Hg. Mean wet weight of the lungs was 103 ± 22 g. The lambs in the four groups were similar in terms of weight, gestational age, number of first-, second-, and third-born lambs, arterial umbilical blood gas and pH values, and wet weight of the lungs.

Figure 1 shows the PaO₂, PaCO₂, pH, and MAP values of the lambs treated with radiolabeled surfactant at birth (groups CMV-B and HFOV-B). Figure 2 presents these data for the lambs treated with surfactant after the establishment of RDS at 30 min of age (groups CMV-R and HFOV-R). The mean VI (VI = PaO₂/MAP × FiO₂) of group CMV-B was consistently higher during the experimental period than that of group CMV-R. At the end of the experiment, 3 h after the administration of radiolabeled surfactant, the mean VI was four times higher in the CMV-B group than in the CMV-R group (29.4 ± 21.2 versus 7.5 ± 3.3 mm Hg/cm H₂O, *p* < 0.05), indicating lower MAPs at comparable PaO₂ in the lambs on CMV which were treated at birth. Lambs from group HFOV-B had a higher mean VI than lambs from group CMV-R (14.5 ± 7.9 versus 7.5 ± 3.3 mm Hg/

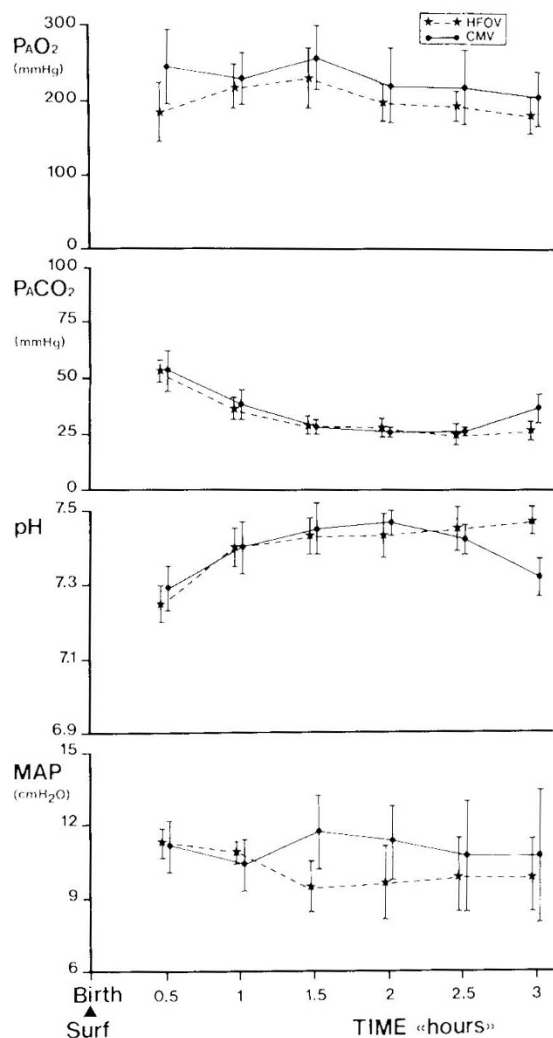


Fig. 1. Mean (\pm SD) values of the PaO₂, PaCO₂, pH, and MAP of the lambs treated with radiolabeled surfactant at birth (groups CMV-B and HFOV-B).

cm H₂O), $p < 0.05$). Although the mean VI of the CMV-B group was twice as high as in the HFOV-B group at 2 and 3 h after birth, the difference was not statistically significant. Groups HFOV-B and HFOV-R had about equal VIs throughout the experimental period (14.5 ± 8.0 versus 14.9 ± 10.1 mm Hg/cm H₂O 3 h after surfactant administration). This indicates that MAPs necessary to obtain comparable oxygenation during HFOV were lower than those used for the CMV-R group but equal to or higher than those for the CMV-B group. Minimal MAPs were lower in the HFO-B group than in the HFO-R group (5.92 ± 1.74 versus 8.33 ± 0.72 cm H₂O, $p < 0.02$) and lower in the CMV-B group than in the CMV-R group (6.27 ± 1.39 versus 8.79 ± 0.70 cm H₂O, $p < 0.01$). The differences between the HFO-B and CMV-B and between the HFO-R and CMV-R groups were not statistically significant.

Figure 3 shows the distribution of radioactive labeled surfactant in the four groups. The pieces of lung for the lambs treated after a period of ventilation were distributed in such a way that only 23.8% of the pieces in the HFOV-R group and 28% of the pieces in the CMV-R group received amounts of surfactant per g tissue within $\pm 25\%$ of the mean. Distribution of surfactant in lambs treated at birth was more homogeneous with 45.9% of pieces in the HFOV-B group and 41.3% in the CMV-B group within $\pm 25\%$ of the mean. The differences between the CMV-B and CMV-R groups ($\chi^2 = 12.769$, $p < 0.001$) and between the HFOV-B and HFOV-R groups ($\chi^2 = 34.381$, $p < 0.001$) were statistically significant. In contrast, the differences between the

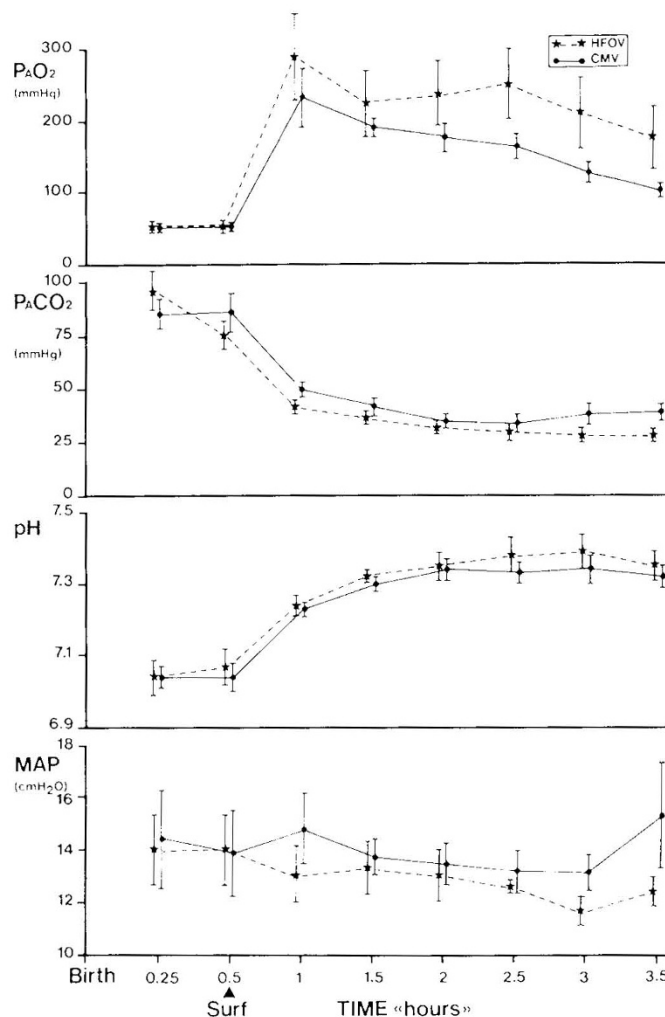


Fig. 2. Mean (\pm SD) values of the PaO₂, PaCO₂, pH, and MAP of the lambs treated with radiolabeled surfactant after 30 min of mechanical ventilation for RDS (groups CMV-R and HFOV-R).

HFOV-R and CMV-R and between the HFOV-B and CMV-B groups were only minor. In the CMV-R group more radiolabeled surfactant was found in pieces from the left than from the right lung and more in the upper lobes of each lung than in the lower lobes (Table 1). Left to right lung and upper to lower lobe distribution was comparable for the other three groups of lambs except that the left upper lobes of the lambs in the HFO-B group received more radiolabeled surfactant than the left lower lobes ($p < 0.005$).

Morphometrics (Table 2) demonstrated significantly better expansion of the alveoli of lambs ventilated with HFOV than of those on CMV. This difference was irrespective of the timing of surfactant administration. Hyaline membranes, alveolar edema, and distension of the lymphatic vessels were more often seen in the CMV-R group than in any of the other three groups. Inadvertent PEEP changes were minimal (< 0.5 cm H₂O) in all lambs on HFOV.

DISCUSSION

Although mechanical ventilation has markedly improved outcome in premature infants with RDS, the use of high airway pressures and high oxygen concentrations has also led to the appearance of acute and chronic lung disease (14, 15). High-frequency ventilation has been tried in animals and as a rescue mode for infants in whom lung barotrauma developed or in whom CMV failed because it can provide adequate gas exchange at lower airway pressures than CMV (9, 16, 17). However, it

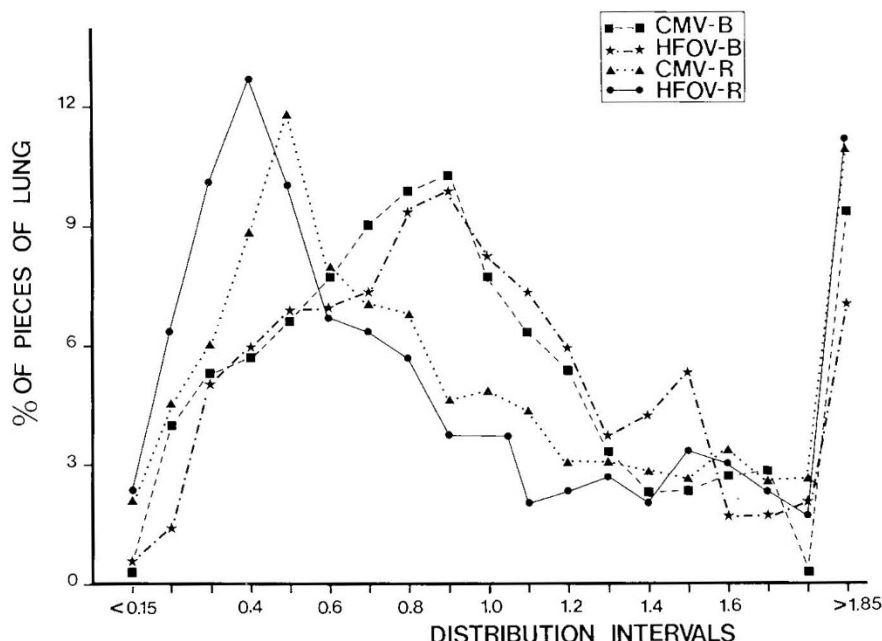


Fig. 3. Distribution of radioactive labeled surfactant in the four groups of lambs.

Table 1. Relative distribution of surfactant by lobes (mean \pm SD)

	CMV-B	HFO-B	CMV-R	HFO-R
Left upper lobe	0.86 \pm 0.51	1.20 \pm 0.53*	1.44 \pm 1.01*	0.99 \pm 1.14
Left middle lobe	0.93 \pm 0.79	1.16 \pm 0.49	1.03 \pm 0.60	0.61 \pm 0.44
Left lower lobe	1.03 \pm 0.77	0.94 \pm 0.49	1.12 \pm 0.61	1.13 \pm 1.26
Right upper lobe	1.19 \pm 1.16	0.95 \pm 0.62	0.95 \pm 0.60*	0.92 \pm 0.96
Right middle lobe	0.98 \pm 0.69	1.02 \pm 0.69	0.79 \pm 0.47	1.12 \pm 0.80
Right lower lobe	0.92 \pm 0.58	0.90 \pm 0.43	0.72 \pm 0.64	1.01 \pm 0.66
Total left lung	0.95 \pm 0.65	1.08 \pm 0.53	1.24 \pm 0.82†	1.00 \pm 1.13
Total right lung	1.03 \pm 0.85	0.96 \pm 0.59	0.79 \pm 0.53	1.02 \pm 0.81

* Upper lobes > lower lobes ($p < 0.05$).

† Total left lung > total right lung ($p < 0.001$).

Table 2. Alveolar surfaces (in μm^2) obtained by morphometrics (mean \pm SEM)

Groups	Alveolar surface	p
CMV-B	1401 \pm 25	<0.001
HFOV-B	3215 \pm 46	
CMV-R	1985 \pm 35	<0.001
HFOV-R	3443 \pm 56	
CMV-B and CMV-R combined	1643 \pm 21	<0.001
HFOV-B and HFOV-R combined	3318 \pm 42	

remains to be seen whether there is any clinical advantage to this form of mechanical ventilation. In this study, HFOV was delivered with a piston system at a frequency of 15 Hz and a VT of 2 ml/kg. These settings have been shown to be effective in both clinical trials (9, 16, 17) and animal experiments (18, 19). HFOV was superimposed on CMV in order to prevent atelectasis (9). As we had no data on the amount of background ventilation needed, a starting rate of 40/min at the described settings was chosen. The rate could be reduced to a 5–10 breaths/min after confirmation of hyperoxia and normocapnia without detrimental effects.

At comparable PaO_2s , MAPs during CMV were significantly lower in the lambs that received surfactant at birth than in those treated after the establishment of respiratory failure. This indicates that prophylaxis with surfactant leads to lower MAPs than rescue with surfactant followed by CMV. There was no clear difference in mean MAPs between the two HFOV groups, indi-

cating that during HFOV the timing of surfactant instillation was not relevant. Calculation of the VI showed that MAPs during HFOV were significantly lower than in the CMV group rescued after birth with surfactant and equal to or higher than the CMV group treated with surfactant at birth. This positive aspect of HFOV has also been seen in studies in rabbits (8) and premature infants (9, 17).

The distribution of radiolabeled surfactant was independent of the type of ventilation used and clearly related to the timing of its administration. Instillation into the fluid-filled airways before the initiation of breathing at birth appeared to be the optimal time of surfactant administration. This confirms the findings from experiments in premature lambs (2) and rabbits (20). Except in the CMV-R group, we found no difference in left to right lung distribution of radiolabeled surfactant. There was a preference for distribution of exogenous surfactant to the upper lobes of both lungs in the CMV-R group and for the left lung in lambs of the HFO-B group. Preferred distribution of exogenous surfactant to the left lung and to the upper instead of the lower lobes was found by Jobe *et al.* (1) in premature lambs treated with surfactant after a period of mechanical ventilation, but not in lambs treated at birth. The absence of regional maldistribution of surfactant in the HFO-R group is in line with the morphometric findings in both HFOV groups.

The alveoli of both groups of lambs ventilated with HFOV were relatively better expanded than those of the CMV groups. This finding is inconsistent with the physiologic data. If alveolar size were larger one might argue that the "real" VI should also be higher insofar as size reflects volume, whereas we found that

at comparable pressures, alveolar volume was greater. This was not, however, reflected in improved oxygenation as measured by the VI. If the increased alveolar size is a beneficial effect, why is it not reflected in improved oxygenation? Theoretically, the greater alveolar volume may be ascribed to gas trapping (21). The absence of inadvertent PEEP suggests that the effect we observed with HFOV may not be airtrapping but rather more uniform aeration and modification of the "natural" course of RDS by prevention of airway injury, edema, and release of chemical mediators. We expected an independent effect of surfactant administration on alveolar volume as seen in premature rabbits treated with surfactant at birth and ventilated by HFOV (22). This feature did probably not emerge in our study due to surfactant treatment of all lambs, either at birth or after establishment of RDS.

We found surfactant treatment at birth to be the most efficient method of surfactant delivery and HFOV superimposed on CMV to lead to more uniform aeration. Since there were clear differences between the ventilation strategy we chose and that reported by others (using HFOV alone), this may account for the absence of more striking intergroup ventilator-associated differences. As HFOV combined with surfactant administration leads to more uniform aeration and less airway injury of the premature lung, this combination may be advantageous in treatment of severe RDS over either modality alone.

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