Effects of surfactant distribution and ventilation strategies on efficacy of exogenous surfactant

CAROLYN L. KERR,1 YUSHI ITO,2 STUART E. E. MANWELL,2 RUUD A. W.VELDHUIZEN,1,2,3 LI-JUAN YAO,3 LYNDA A. MCCAI,G3 AND JAMES F. LEWIS1,3

Departments of 1Physiology and 3Medicine, 2Lawson Research Institute, St. Joseph’s Health Centre, The University of Western Ontario, London, Ontario, Canada N6A 4V2

Kerr, Carolyn L., Yushi Ito, Stuart E. E. Manwell, Ruud A. W. Veldhuizen, Li-Juan Yao, Lynda A. McCaig, and James F. Lewis. Effects of surfactant distribution and ventilation strategies on efficacy of exogenous surfactant. J. Appl. Physiol. 85(2): 676–684, 1998.—The effects of both surfactant distribution patterns and ventilation strategies utilized after surfactant administration were assessed in lung-injured adult rabbits. Animals received 50 mg/kg surfactant via intratracheal instillation in volumes of either 4 or 2 ml/kg. A subset of animals from each treatment group was euthanized for evaluation of the exogenous surfactant distribution. The remaining animals were randomized into one of three ventilatory groups: group 1 (tidal volume (VT) of 10 ml/kg with 5 cmH2O positive end-expiratory pressure (PEEP)); group 2 (VT of 5 ml/kg with 5 cmH2O PEEP); or group 3 (VT of 5 ml/kg with 9 cmH2O PEEP). Animals were ventilated and monitored for 3 h. Distribution of the surfactant was more uniform when it was delivered in the 4 ml/kg volume. When the distribution of surfactant was less uniform, arterial PO2 values were greater in groups 2 and 3 compared with group 1. Oxygenation differences among the different ventilation strategies were less marked in animals with the more uniform distribution pattern of surfactant (4 ml/kg). In both surfactant treatment groups, a high mortality was observed with the ventilation strategy used for group 3. We conclude that the distribution of exogenous surfactant affects the response to different ventilatory strategies in this model of acute lung injury.

acute respiratory distress syndrome; exogenous surfactant therapy; mechanical ventilation; tidal volume; positive end-expiratory pressure

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is an acute lung injury defined by its clinical characteristics. These include the presence of hypoxemia and reduced pulmonary compliance, as well as diffuse pulmonary infiltrates on chest radiograph (2). Mechanical ventilation is the primary supportive therapy for patients with ARDS and, despite advances in the technology of ventilatory support, the mortality of these patients remains above 50% (2).

Abnormal surfactant function has been regarded as a potential contributor to the progressive deterioration in lung function observed in these patients (20). This observation, together with the knowledge that exogenous surfactant administration has greatly decreased the morbidity and mortality of premature infants born deficient in pulmonary surfactant (15), has led to the testing of this treatment strategy in patients with ARDS (11). Although physiological responses to exogenous surfactant have been impressive in several different animal models of lung injury (3, 12, 18, 24, 30, 31), the response to this treatment strategy in patients with severe ARDS has been variable (1, 10, 26, 29, 31). It is possible that the distribution of the exogenously administered surfactant was suboptimal in some patients, thereby mitigating subsequent physiological responses. Indeed, in animals with lung injury, responses to surfactant were shown to be inferior when surfactant distribution was less uniform throughout the lung (21, 27, 32). Although relatively uniform distribution patterns of exogenous surfactant may be achieved in fluid-filled fetal lungs (32), this is more difficult in larger patients with severe ARDS. This is due, in part, to the present methods used to administer the surfactant, as well as to differences in the underlying patterns of lung injury at the time of administration (1, 8, 10, 21).

The mode of ventilation utilized after surfactant administration has also been shown to impact the host’s response to exogenous surfactant (7, 13, 17). This observation, together with the potential for nonuniform distribution patterns of exogenous surfactant, may result in poor outcomes due to regional differences in ventilation and consequently overdistention of some alveoli (19). This phenomenon represents a mechanism that may account for some of the variability in physiological responses observed with different ventilation strategies after exogenous surfactant administration.

The purpose of the present study was to evaluate the effects of utilizing different modes of mechanical ventilation in lung-injured animals that had either a uniform or nonuniform distribution pattern of exogenously administered surfactant. Specifically, we studied the effects of varying tidal volume (VT) and positive end-expiratory pressure (PEEP) levels on physiological outcomes of animals with different distribution patterns of exogenous surfactant.

METHODS

Animal Preparation and Induction of Lung Injury

Adult New Zealand White rabbits, weighing 2.7 ± 0.1 kg, were initially anesthetized with ketamine hydrochloride (100 mg/kg) intramuscularly, and lidocaine (1 mg/kg) was administered locally for all surgical procedures. An endotracheal tube (4.0 mm) with an injection side-port adapter was placed through a tracheotomy in the midcervical region, and arterial cannulation of the carotid artery was performed for arterial blood-gas (ABG) sampling and measurement of mean arterial blood pressure (MABP). Mechanical ventilation was then initiated with a pressure-limited infant ventilator (model IV-100B, Sechrist, Anaheim, CA) by using an inspired O2 fraction of 1.0, a fresh gas flow of 10 l/min, an inspiratory-to-expiratory ratio of 1:1, a respiratory rate of 30 breaths/min,
and a PEEP level of 5 cmH₂O. VT was measured by using a pneumotachometer (Hans Rudolph, Kansas City, MO) placed between the endotracheal tube and inspiratory limb of the ventilator circuit, and peak inspiratory pressure (PIP) was adjusted to maintain a VT of 10 ml/kg body weight. Throughout the experimental protocol, anesthesia and muscle paralysis were maintained by using intermittent infusions of 0.2% thiopental and 0.5% pancuronium bromide, respectively.

After initial measurements of MABP, VT, and PIP and collection of samples for ABG analysis, repetitive saline whole lung lavage was performed as previously described (12). Briefly, animals were placed in the prone position, disconnected from the ventilator circuit, and 25–30 ml/kg of warmed (37°C) 0.15 M NaCl was instilled via the endotracheal tube into the lungs by using a syringe. The infused volume was recovered by using gentle suction on the infusion syringe. Reinfusion of the saline and subsequent recovery was repeated two more times before the reinstitution of mechanical ventilation. This whole lung lavage procedure was repeated a minimum of three times, with additional lavages being performed every 10 min as required to achieve an arterial Po₂ (PaO₂) value below 120 Torr while maintaining the ventilatory settings previously established. After the final lung lavage procedure was completed, animals were ventilated for 3 h before being randomly assigned to an experimental group. Monitoring of ABG, MABP, VT, and PIP was performed throughout this 3-h period of ventilation. At the end of this ventilatory period, only animals with a PaO₂ value above 50 Torr and less than 120 Torr fulfilled entry criteria for randomization into one of the subsequent experimental groups. It has previously been shown that 3 h of mechanical ventilation by using this ventilatory pattern after the induction of a surfactant-deficient state resulted in a lung injury characterized by neutrophil infiltration and hyaline membrane formation (12). The morphological changes observed in these animals were comparable to those observed in patients with severe ARDS (5).

Surfactant Administration

Bovine lipid extract surfactant (BLES Biochemicals, London, ON), supplied at a concentration of 25 mg phospholipid/ml, was used for these experiments. Stock solutions of dipalmitoylphosphatidylcholine (DPPC)-radiolabeled bovine lipid extract surfactant were combined with unlabeled material before instillation for surfactant recovery and distribution analyses. After the lung injury was established, animals were randomized to receive a total dose of 50 mg lipid/kg (0.7 ± 0.1 µCi/animal) of the exogenous surfactant in either 2 ml/kg (25 mg lipid/ml concentration) or 4 ml/kg (12.5 mg lipid/ml concentration) volumes. When the latter volume was administered, saline was used to dilute the surfactant to the appropriate concentration. Surfactant was administered as a bolus dose over several breaths during the inspiratory phase of ventilation through a side-port adapter of the endotracheal tube. The animal was held in an upright position during surfactant administration to prevent reflux of the material up the endotracheal tube. The time at completion of surfactant administration was designated as time 0. During surfactant instillation, PIP was increased by 3 cmH₂O to maintain VT. After surfactant instillation, PIP was increased by 3 cmH₂O to maintain VT.

Evaluation of Ventilation Strategies

By using identical techniques of animal preparation, induction of lung injury, and inclusion criteria, separate animals received the same dose of exogenous surfactant in either the 2 or 4 ml/kg volumes by using the method of instillation previously described. Immediately after the collection of the t₁₀₅₀ min blood-gas sample, however, these animals were then randomized into one of three different ventilatory groups: group 1 [VT = 10 ml/kg, breathing frequency (f) = 30 breaths/min, and PEEP = 5 cmH₂O]; group 2 [VT = 5 ml/kg, f = 60 breaths/min and PEEP = 10 cmH₂O]; and group 3 [VT = 5 ml/kg, f = 60 breaths/min, and PEEP = 9 cmH₂O]. Animals were subsequently monitored for a total of 3 h after instillation of the exogenous surfactant, with ABG sampling and MABP and PIP measurements recorded at 20, 30, 45, 60, 90, 120, 150, and 180 min after treatment. VT was measured and corrected to the appropriate volume via PIP adjustment after each blood-gas measurement. At the end of the ventilation period (t₁₈₀₅₀ₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕₕ₅
component of the material (4). The radioactivity of CAW, LH, and input samples was determined by liquid scintillation counting. The percent recovery of the exogenous surfactant relative to the total amount administered was calculated by dividing the sum of the radioactivity in the CAW and the LH by the total amount of radioactivity in the administered input dose of surfactant. Percent tissue association was calculated by dividing the radioactivity in the LH by the total amount of radioactivity in the CAW and LH. The total protein in the CAW was determined by the method of Lowry and colleagues (22) by using bovine serum albumin as the standard.

Statistical Analysis

Surfactant distribution. To compare the distribution patterns between the two surfactant treatment groups (2 and 4 ml/kg), an unpaired t-test was performed. Comparisons were made between surfactant treatment groups on the sum of the percentage of lung pieces included in the <0.1 and >1.9 distribution intervals. Comparisons between surfactant treatment groups at the lobar level were also performed by performing unpaired t-tests on the percentage of lung pieces within each lobe. Probability values are reported, and values <0.05 were considered significant.

Ventilatory strategies. Statistical analysis of the physiological data measured over time among groups was performed by using analysis of variance for repeated measures with treatment and time as the main effects and Tukey’s honestly significant difference (HSD) test as a post hoc test (P < 0.05). In those analyses that demonstrated a significant interaction between the main effects, analysis of variance with Tukey’s HSD post hoc test was used at each time period (P < 0.05). Comparisons at each time period after manipulation of ventilatory values (t<sub>10min</sub>) within each group were performed by using a paired t-test (P < 0.05). For single comparison of means among groups, analysis of variance with Tukey’s HSD post hoc test was utilized (P < 0.05).

RESULTS

Characteristics of Animals

There were no significant differences in the mean body weights of animals (2.7 ± 0.1 kg) among groups or in the number of lavages (5.0 ± 0.6 lavages) required to obtain PaO<sub>2</sub> values <120 Torr. There were no significant differences in the mean arterial P<sub>CO<sub>2</sub></sub>, pH, PIP, and MABP values among groups of animals subsequently receiving surfactant at 3 h after the final lavage before treatment (time 0) or at 10 min after surfactant treatment (i.e., t<sub>10min</sub>; data not shown). Mean PaO<sub>2</sub> values for animals in the 2 and 4 ml/kg-volume surfactant treatment groups were 74.0 ± 4.0 and 64.0 ± 2.0 Torr, respectively, at time 0 and 344.4 ± 18.2 and 349.3 ± 14.7 Torr, respectively, at t<sub>10min</sub>. Of the 72 animals that were ventilated for 3 h after the initial lung lavage procedure, 5 animals were excluded before surfactant treatment and 8 animals were excluded 10 min after treatment for not meeting the established inclusion criteria noted previously. Of the eight animals not meeting posttreatment criteria, five were in the 2 ml/kg treatment group and three were in the 4 ml/kg treatment group. Forty-three of the remaining 59 animals were assigned to the 6 groups that were subsequently evaluated for their response to the different ventilatory strategies over time. The remaining 16 animals represented the 8 animals in each surfactant treatment group (2 and 4 ml/kg) that were evaluated for surfactant distribution analysis. As noted, these animals were not subsequently randomized to different ventilation strategies.

Exogenous Surfactant Distribution

The mean number of pieces per lung that were processed for surfactant distribution analysis was similar in each surfactant treatment group (147.3 ± 4.6 pieces/lung) as was the total percent recovery of the administered radiolabeled surfactant in each group at the t<sub>10min</sub> after treatment (data not shown).

Figure 1 shows the normalized distribution histograms for animals receiving surfactant in volumes of either 2 ml/kg (Fig. 1A) or 4 ml/kg (Fig. 1B). Animals receiving surfactant in the lower volume had a significantly greater percentage of lung pieces at the ex-
tremes of the distribution intervals with 31.8 ± 6.1 (SE) % of the pieces falling in the <0.1 or >1.9 intervals compared with 16.6 ± 2.4% of the pieces falling in these intervals for the animals given surfactant in the higher volume (P = 0.03). When the lobar distribution patterns were assessed, animals receiving surfactant in the 2 ml/kg volume had significantly more surfactant deposited in the cardiac lobe (P = 0.007) and significantly less in the left upper lobe (P = 0.04) compared with animals receiving surfactant in the 4 ml/kg volume (Fig. 2). For both of these lobes, surfactant recovery in the 4 ml/kg treatment group was relatively closer to the normalized distribution value of 1.0 compared with the 2 ml/kg group.

Physiological Data After Ventilatory Adjustment

Mean PaO₂ values in the three ventilatory groups for animals receiving surfactant in the 2 ml/kg volume are shown in Fig. 3A. Comparisons over time within each group showed that animals in group 1 had a significant decrease in PaO₂ values at 60–180 min after treatment compared with their respective t₁₀min values (P < 0.05). Although less marked, group 2 also had a significant decrease in PaO₂ values at 20–120 min after treatment relative to t₁₀min values (P < 0.05). In contrast, group 3 had no significant change in PaO₂ values over time. Comparisons among groups revealed that group 3 had significantly greater PaO₂ values compared with both groups 1 and 2 at 30 min, and, compared with group 1, throughout the remainder of the ventilatory period (P < 0.05). Group 2 had significantly greater PaO₂ values compared with group 1 at 120–180 min posttreatment (P < 0.05).

Mean PaO₂ values for the three ventilatory groups receiving surfactant in the 4 ml/kg volume are shown in Fig. 3B. Similar to the 2 ml/kg volume group, group 1 animals had a significant decrease in PaO₂ values at 30–150 min posttreatment compared with their respective t₁₀min values (P < 0.05). Animals in group 2 also had a significant decrease in PaO₂ values at 20–90 min relative to their respective t₁₀min value (P < 0.05). Group 3 animals showed no significant changes in PaO₂ values over time relative to their t₁₀min values. Comparisons among groups showed that PaO₂ values in group 2

![Fig. 2. Lobar distribution of surfactant in rabbits receiving surfactant in 2 or 4 ml/kg volume. Values are means ± SE. Normalized lobar distribution pattern is expressed as normalized radioactivity per gram for right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), cardiac lobe (Card), left upper lobe (LUL), and the left lower lobe (LLL). Animals receiving surfactant in 2 ml/kg volume had a significantly higher normalized radioactivity count per gram of tissue in cardiac lobe and a significantly lower normalized radioactivity count per gram of tissue in left upper lobe compared with animals receiving surfactant in 4 ml/kg volume. dpm, Disintegrations per minute. *P < 0.05.](http://jap.physiology.org/)

![Fig. 3. Effect of different ventilatory strategies on arterial Po₂ (PaO₂) values after surfactant administration (0 min) in animals receiving surfactant in 2 (A) or 4 ml/kg volume (B). Values are means ± SE. *Significantly different from value at 10 min, P < 0.05. *Significantly different from group using tidal volume (VT) = 10 ml/kg and positive end-expiratory pressure (PEEP) = 5 cmH2O (group 1), P < 0.05.](http://jap.physiology.org/)
animals also had significantly lower PaO\textsubscript{2} values than those observed in group 3 at 90 min (P < 0.05). Of note, there were no significant differences among any of the three treatment groups at 180 min after treatment for animals receiving surfactant in the 4 ml/kg volume.

PIP values are shown for the 2 and 4 ml/kg surfactant treatment groups in Fig. 4, A and B, respectively. For animals receiving surfactant in the 2 ml/kg volume, analyses over time within groups showed significant decreases in PIP values for groups 1 and 2 starting at 20 min posttreatment to 180 min relative to their respective t\textsubscript{10min} values (P < 0.05). In group 3, PIP values at 60–180 min after treatment were significantly lower than those observed in group 3 at 90 min (P < 0.05). Comparisons among groups revealed significantly lower PIP values for group 2 relative to group 3 at 20–180 min posttreatment and at 30–180 min posttreatment for group 2 compared with group 1 (P < 0.05). There were no significant differences between groups 1 and 3 at any time point after treatment.

For groups receiving surfactant in the 4 ml/kg volume (Fig. 4B), comparisons over time within each group showed that the mean PIP levels for all three ventilatory groups at 20–180 min were significantly lower than their respective values measured at t\textsubscript{10min} (P < 0.05). Comparisons among groups showed that PIP values for group 2 were significantly lower than those for group 1 at 20 and 30 min posttreatment and significantly lower than those of group 3 at 20–60 min posttreatment (P < 0.05). As in animals given surfactant in the 2 ml/kg volume, there were no significant differences between groups 1 and 3.

For animals receiving surfactant in the 2 ml/kg volume, PaCO\textsubscript{2} values significantly increased over time with all ventilatory strategies compared with t\textsubscript{10min} values (P < 0.05); however, there were no significant differences between the ventilatory groups after treatment (data not shown). For animals receiving surfactant in the 4 ml/kg volume, PaCO\textsubscript{2} values within groups did not significantly change during the ventilatory period after treatment for group 1 or 2, although PaCO\textsubscript{2} levels did increase for group 3 at 20–150 min relative to the t\textsubscript{10min} values (P < 0.05). Comparisons among groups revealed that PaCO\textsubscript{2} values for group 3 were significantly greater than for group 1 at 30 and 90–180 min posttreatment and greater than for group 2 at 120 and 150 min posttreatment (P < 0.05) (data not shown).

pH values within groups for both treatment strategies (2 and 4 ml/kg) were not significantly different over time relative to their respective t\textsubscript{10min} values. Comparison of pH among ventilatory groups also revealed no significant differences among groups at any time point (data not shown).

With the 2 ml/kg surfactant treatment strategy, comparison over time within groups showed that MABP values for group 1 decreased significantly at 90, 150, and 180 min relative to t\textsubscript{10min} values (P < 0.05). Comparison among groups showed that at 150 and 180 min the MABP values for group 1 animals was significantly lower than those recorded for group 2 (P < 0.05) (data not shown). In ventilatory groups given surfactant in the 4 ml/kg volume, no significant differences in MABP values were observed either within groups or among groups after ventilatory adjustment (data not shown).

The total percent recovery of radiolabeled DPPC and the percent tissue association of the radiolabeled DPPC revealed no significant differences among ventilation groups within each surfactant treatment strategy, either when all animals were included in the analysis or when only those animals surviving the 3-h ventilation period were evaluated. The total percent recovery and the percent tissue association of radiolabeled DPPC for all animals were 80.0 ± 3.7 and 24.3 ± 1.4%, respectively. There were also no significant differences in total protein recovery in the CAW samples between ventila-
posttreatment expected to documented on postmortem examination. The results, respectively. Generally, it was observed that ventilation strategies utilizing lower VT and moderate levels of PEEP were superior to those with larger VT, particularly when the distribution of exogenous surfactant was relatively nonuniform. Although responses to these ventilatory strategies were generally superior when surfactant distribution was more uniform (Fig. 3B), the differences between the three ventilatory strategies were less marked compared with animals with the less-uniform surfactant distribution.

The mechanisms by which mechanical ventilation affects physiological responses to exogenous surfactant when the distribution of the surfactant was nonuniform may be similar to the proposed effects of mechanical ventilation in non-surfactant-treated injured lungs (25). In patients with severe ARDS, dependent areas of the lung are frequently atelectatic and edematous relatively early in the course of the injury (6). Significant portions of the VT administered with positive pressure ventilation are directed to the nondependent regions of these lungs (8). Positive pressure ventilation utilizing standard VT (i.e., 10–15 ml/kg) may well promote regional differences in ventilation, with some areas becoming markedly overdistended while other areas of lung remain atelectatic. Although atelectasis has been shown to contribute to ventilation-perfusion mismatching defects within the lung, surfactant inactivation and epithelial damage may also occur in the aerated and overdistended, nondependent alveoli (6, 14, 25). In addition, shear forces may also exist between the atelectic and ventilated lung regions over the course of ventilation, further injuring the lung parenchyma (35). Central to these mechanisms contributing to lung injury specifically induced by mechanical ventilation is the presence of heterogeneity in alveolar ventilation. Because surfactant administration may result in dramatic changes in the lung's mechanical properties (9, 16), a nonuniform distribution of this material may accentuate regional differences in alveolar distention. As with the nontreated lung, overdistended regions of lung may result in a more rapid rate of surfactant inactivation with subsequent epithelial injury and lung dysfunction (14). This regional alveolar overdistension could explain the different outcomes of the groups of animals observed in our study and potentially some of the variability observed in clinical studies evaluating exogenous surfactant administration. On the basis of these results, therefore, we propose that to minimize the potential progression of lung injury and maximize the response to exogenous surfactant therapy in patients with ARDS who require mechanical ventilation, two strategies could be adopted. First, surfactant distribution should be optimized, and, second, the ventilation strategy should be modified to prevent alveolar overdistention.

With respect to the former issue, attempts to optimize surfactant distribution patterns have involved several strategies. Administering exogenous surfactant earlier in the course of lung dysfunction in the surfactant-deficient lungs improved the distribution of the

**DISCUSSION**

In this study, we evaluated the combination of two separate factors that may influence a host's response to exogenous surfactant: the distribution of the surfactant within the lung after administration and the ventilatory strategy utilized after the surfactant was delivered. Our findings suggest that the physiological responses to the various ventilation strategies implemented after the administration of exogenous surfactant may be influenced by the distribution of the surfactant at the onset of ventilation. Generally, it was observed that ventilation strategies utilizing lower VT and moderate levels of PEEP were superior to those with larger VT, particularly when the distribution of exogenous surfactant was relatively nonuniform. Although responses to these ventilatory strategies were generally superior when surfactant distribution was more uniform (Fig. 3B), the differences between the three ventilatory strategies were less marked compared with animals with the less-uniform surfactant distribution.

The mechanisms by which mechanical ventilation affects physiological responses to exogenous surfactant when the distribution of the surfactant was nonuniform may be similar to the proposed effects of mechanical ventilation in non-surfactant-treated injured lungs (25). In patients with severe ARDS, dependent areas of the lung are frequently atelectatic and edematous relatively early in the course of the injury (6). Significant portions of the VT administered with positive pressure ventilation are directed to the nondependent regions of these lungs (8). Positive pressure ventilation utilizing standard VT (i.e., 10–15 ml/kg) may well promote regional differences in ventilation, with some areas becoming markedly overdistended while other areas of lung remain atelectatic. Although atelectasis has been shown to contribute to ventilation-perfusion mismatching defects within the lung, surfactant inactivation and epithelial damage may also occur in the aerated and overdistended, nondependent alveoli (6, 14, 25). In addition, shear forces may also exist between the atelectic and ventilated lung regions over the course of ventilation, further injuring the lung parenchyma (35). Central to these mechanisms contributing to lung injury specifically induced by mechanical ventilation is the presence of heterogeneity in alveolar ventilation. Because surfactant administration may result in dramatic changes in the lung's mechanical properties (9, 16), a nonuniform distribution of this material may accentuate regional differences in alveolar distention. As with the nontreated lung, overdistended regions of lung may result in a more rapid rate of surfactant inactivation with subsequent epithelial injury and lung dysfunction (14). This regional alveolar overdistension could explain the different outcomes of the groups of animals observed in our study and potentially some of the variability observed in clinical studies evaluating exogenous surfactant administration. On the basis of these results, therefore, we propose that to minimize the potential progression of lung injury and maximize the response to exogenous surfactant therapy in patients with ARDS who require mechanical ventilation, two strategies could be adopted. First, surfactant distribution should be optimized, and, second, the ventilation strategy should be modified to prevent alveolar overdistention.

With respect to the former issue, attempts to optimize surfactant distribution patterns have involved several strategies. Administering exogenous surfactant earlier in the course of lung dysfunction in the surfactant-deficient lungs improved the distribution of the

**Table 1. Outcome of animals studied to evaluate ventilatory strategy**

<table>
<thead>
<tr>
<th>Surfactant Treatment Group/ Ventilatory Group</th>
<th>No. of Animal Deaths (% of group)</th>
<th>No. of Animal Deaths With Pneumothorax (% of deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>6</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>8</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>6</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>4 ml/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>9</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>7</td>
<td>1 (14.2%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>7</td>
<td>4 (57.1%)</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of animals. Groups 1, 2, and 3: tidal volume (VT) = 10 ml/kg, positive end-expiratory pressure (PEEP) = 5 cmH2O; VT = 5 ml/kg, PEEP = 5 cmH2O; and VT = 5 ml/kg, PEEP = 9 cmH2O, respectively.
exogenous surfactant, which subsequently resulted in superior lung function. Practically, this involved delivering the surfactant to preterm lungs before the first respiratory effort (16, 28). Unfortunately, patients with ARDS often have regional differences in lung mechanical properties at the time of diagnosis, which is obviously before present treatment strategies involving surfactant administration occur. In this situation, it is difficult to ensure a uniform distribution of exogenous surfactant in these patients. The method of mechanical ventilatory support during surfactant treatment has been shown to impact distribution, with adequate levels of PEEP during instillation recommended (23). Once surfactant was delivered, however, the method of ventilatory support was not shown to alter the pattern of surfactant distribution, suggesting that gross redistribution of surfactant does not occur once the surfactant is instilled (34). Different methods of administering exogenous surfactant have also been evaluated, with the objective of achieving a more uniform surfactant distribution pattern (18, 19, 21, 27). Aerosolization of surfactant has the theoretical advantage of having small particles distributed more evenly throughout the lung over time compared with a liquid bolus of surfactant. However, results of studies testing this delivery technique have been variable (19, 21). Aerosolized surfactant particles were shown to follow the pattern of ventilation so that lungs with a heterogeneous injury at the onset of treatment exhibited a poor response to the surfactant due to nonuniform distribution (19). In other studies, a rapid bolus administration of surfactant resulted in a more uniform distribution of the material compared with a slow tracheal instillation technique when tested in a surfactant-deficient model (32). Unfortunately, these techniques have not been further evaluated in other more clinically relevant models of lung injury reflecting ARDS. Finally, previous studies have shown that larger volumes of surfactant used for instillation resulted in a more uniform distribution pattern of the surfactant. Van der Bleek and colleagues (33) showed that when the volume of a given dose of surfactant was increased from 2 to 16 ml/kg, the pulmonary distribution of the material was more uniform. Unfortunately, physiological outcome did not parallel improvements in distribution in this study, and optimal volumes of instillation for patients with ARDS have yet to be determined. Clinically, volumes in excess of 4 ml/kg may not be tolerated in patients with severely injured lungs, as seen in the results of some animal studies showing a significant deterioration in gas exchange immediately after a bolus dose of surfactant was administered (18). Although this strategy may therefore be limited as an option to improve surfactant distribution in patients with ARDS, we did show different distribution patterns of exogenous surfactant in the present study, even with smaller volumes of surfactant.

The method of mechanical ventilation utilized after the exogenous surfactant was administered also influenced the outcome of animals in the present study, as reflected by the different responses within each surfactant treatment group. We compared two different Vt by using conventional ventilatory techniques, both of which are used in the clinical setting for adult patients with ARDS. Moreover, these particular ventilatory strategies have previously been shown to influence physiological outcomes in non-surfactant-treated animals with acute lung injury (14). In that study, low-Vt ventilation strategies (5 ml/kg) resulted in superior outcomes compared with larger Vt ventilation strategies (10 ml/kg), as reflected by a significantly greater deteriora-

Interestingly, in our study, oxygenation values measured 3 h after the onset of mechanical ventilation were similar for the three ventilatory groups when the surfactant was more uniformly distributed (4 ml/kg group). This finding confirms the hypothesis that these two factors are closely related and contribute significantly to the physiological response one observes after exogenous surfactant is administered to injured lungs. Consistent with previous studies, peak airway pressure values did not appear to have a significant effect on oxygenation in the present study (13). Although animals in both groups 1 and 3 had similar PIP values over the period of ventilation, significantly different outcomes with respect to gas exchange values were observed in these two groups. Indeed, previous studies have shown that it is the volume administered to patients during mechanical ventilation that is responsible for lung injury rather than the pressure effects (6). Furthermore, the dynamic change in lung volume induced by higher Vt seems to be more harmful than static changes in lung volume induced by PEEP.

Although oxygenation values immediately after surfactant treatment have traditionally been used as a guide for determining optimal treatment strategies, our results suggest that this variable as a sole outcome measure may not be adequate. For example, the superior oxygenation responses observed in animals ventilated with the higher PEEP values in the present study were subsequently associated with a higher mortality rate due to barotrauma. In these particular animals, oxygenation values immediately before death were relatively high and similar to those in other animals within the group, with no suggestion of deteriorating lung function before death. The mechanism responsible for the observed barotrauma in these animals is unknown; however, it is clear that oxygenation responses alone are not sufficient for monitoring patients treated with exogenous surfactant. Adequate preclinical studies are required to determine optimal Vt and PEEP.
values that should be used in patients receiving exogenous surfactant. It is likely, for example, that specific ventilatory strategies utilized immediately after exogenous surfactant administration will differ from those used several hours later.

In conclusion, we have shown that, for optimal physiological responses to exogenous surfactant, lower VT strategies should be utilized when mechanical ventilation involving conventional distribution pattern of exogenous surfactant administration and the distribution of the surfactant may be nonuniform, ventilation strategies using lower VT should result in superior overall outcomes. Although adequate PEEP levels may provide a benefit in the early posttreatment phase, optimal levels of PEEP should be determined to avoid barotrauma.

The authors thank Dr. Dave Bjarneson of BLES Biochemicals for supplying the bovine lipid extract surfactant and Larry Stitt for statistical assistance.

The work was supported by the Medical Research Council of Canada.

Address for reprint requests: C. L. Kerr, Lawson Research Institute, 268 Grosvenor St., London, Ontario, Canada N6A 4V2 (E-mail: ckerr@ulian.uwo.ca).

Received 21 August 1997; accepted in final form 15 April 1998.

REFERENCES


