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# Aerosolized Medications for Altering Lung Surface Active Properties

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## **Introduction**

Aerosol inhalation is an effective way to deliver medications into the lung (eg, bronchodilators and steroids). Surface active material might also be effectively delivered by aerosol into lungs with altered surface active properties. This article addresses this concept by reviewing the following topics: surface active properties of the lung; diseases that alter these properties; therapeutic surfactants; instillation techniques; aerosol techniques; other aspects of surfactant aerosolization; and surface active materials other than surfactant.

## **Surface Active Properties**

Normal lung expansion is accomplished by inspiratory muscle contraction generating a negative pleural pressure that, in turn, inflates the lung. Lung mechanical properties that resist inflation include the inherent elasticity of lung tissue and the airway resistance. An important feature in all mammalian lungs is the presence of surface active lin-

ing material in the alveoli. This material consists of a variety of phospholipids, the most common being dipalmitoyl phosphatidyl choline.<sup>1,2</sup> This material is naturally associated with a number of proteins (SP-A,B,C,D) that facilitate spreading and have anti-inflammatory effects. Together, these materials greatly reduce the surface tension of the alveolar membrane and, as a consequence, allow the lung to inflate with relatively small transpulmonary pressure generation. In Figure 1, a lung with surface active material is compared to a lung without this material. Note the much higher pressure requirements (and thus lower calculated compliance) that result when the surface active material is not present or not functioning properly.

## **Diseases with Altered Surface Active Properties**

There are two fundamentally different types of diseases that involve surfactant dysfunction. The first category is surfactant depletion syndromes. The second category is surfactant dysfunction syndromes.<sup>3,4</sup>

In humans, surfactant depletion syndromes usually involve premature infants. In the normal human neonate at birth, as much as 50–100 mg/kg of surfactant are present in the lungs.<sup>3</sup> This material spreads with the first breath and properly establishes the appropriate surface tension necessary for normal ventilation. In the premature infant, the amount of surfactant can be markedly reduced. Indeed, in severe respiratory distress syndrome (RDS), the surfactant amount is generally < 5 mg/kg, and the recoil pressures of the lungs are so high that many units either do not open or else collapse during expiration. This leads to shunt,

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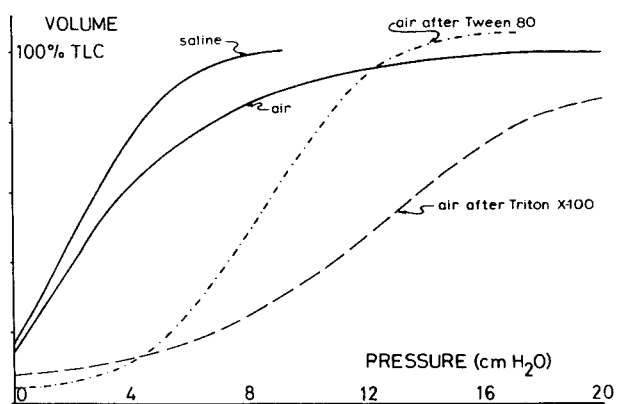


Fig. 1. Pressure-volume plot illustrating effect of surface active material on lung mechanical properties. The solid line represents the pressure-volume relationships of a normal lung. The dashed line represents the pressure-volume relationship of a lung in which surface active material has been destroyed by a detergent. Note the severe worsening of lung compliance when surfactant is not present. (From Hoppin FG, et al. Lung recoil. In Macklem P, Mead J. Handbook of physiology. Bethesda: American Physiologic Society; 1986: 195–216, with permission.)

hypoxemia, right ventricular dysfunction, and, potentially, death.

Diseases involving dysfunctional surfactant include many adult respiratory disorders (eg, acute respiratory distress syndrome [ARDS], pneumonia, interstitial lung disease).<sup>4</sup> In the normal adult lung, the surfactant pool is less than in the neonate, generally in the range of 5–15 mg/kg. In these disease states, the absolute amount of phospholipid may actually be normal (or even elevated). However, surfactant properties are often disrupted by inflammatory mediators, and there are disturbed surfactant metabolism and recycling phenomena. Figure 2 illustrates the time course of abnormal surfactant behavior in adults with trauma-related acute lung injury.

Administering surfactant might benefit surfactant depletion syndrome and surfactant dysfunction syndrome. One might anticipate greater efficacy, however, from surfactant administration in a depletion syndrome, where surfactant is supplying simple replacement, as compared to surfactant administration in a surfactant dysfunction syndrome involving more complex processes. Indeed, as discussed in more detail below, this has been the case in a number of clinical studies performed in the last 20 years.

#### Surface Active Substances Available for Exogenous Administration

Over the past 20 years a variety of different surfactants have been developed (Table 1).<sup>1–4</sup> A number of these are so-called natural surfactants in that they come from lavage of animal lungs (eg, porcine or bovine surfactants). An

advantage to this type of surfactant is that many of the surface active-related proteins are also present.

It is also possible to manufacture various phospholipids that have surface active lowering properties. The most widely used of these is simple dipalmitoyl phosphatidyl choline (Exosurf). An obvious disadvantage to these simple phospholipids is that they lack the surface active-related proteins of natural surfactants. In recent years, however, these simple phospholipids have been combined with genetically engineered surface active-related proteins to create a synthetic surfactant that has more properties comparable to the natural surfactants.

Nonphospholipid substances can also have surface active lowering properties. A class of drugs that has created considerable interest is perfluorocarbon and the specific compound perflubron.<sup>5,6</sup> These compounds are interesting in that they are highly oxygen soluble and can actually replace gas in the alveolar space. Although perflubron can be used to provide total ventilation, most current studies focus on the use of perflubron only to replace gas in the functional residual capacity. Under these circumstances, perflubron thus functions as “liquid positive end-expiratory pressure” to recruit alveoli (Fig. 3) and substantially reduce lung recoil pressures.

Surfactant can be administered in a variety of ways (Table 2). Direct instillation is the simplest, but transient gas exchange and hemodynamic effects can occur during the procedure (“fluid bolus” effect: Fig. 4).<sup>7,8</sup> In addition, distribution of instilled fluid follows gravity, which may or may not be optimal. An alternative approach is to aerosolize the surfactant with jet or ultrasonic devices.<sup>9–12</sup> Aerosol delivery to the lungs is always going to be less than with direct instillation, simply because aerosol is wasted in ventilator circuitry and upper airway deposition.<sup>13</sup> Lung delivery of an aerosol can be further reduced if particle sizes are too large (ie,  $> 5 \mu\text{m}$  mass median aerodynamic diameter), if aerosol delivery is not coordinated with a slow inspiration and breath-hold, or if airways (especially artificial airways) are long and narrow.<sup>13</sup> Indeed, estimates of lung delivery of aerosolized surfactant are generally  $< 10\%$  of delivered dose,<sup>14–17</sup> although under conditions where particle sizes are small and artificial airways are short and wide, this may be several-fold higher.<sup>7,18</sup> Despite this reduced delivery, advantages of the aerosol route include a reduced “fluid bolus” effect and the ability to provide continuous dosing. Also, aerosolized surfactant distributes according to ventilation<sup>12,16</sup> and, thus, its distribution to various lung units will differ from the gravity-dependent distribution of instilled surfactant. Depending on regional lung mechanical properties, this different distribution effect may or may not have gas exchange or mechanical advantages over the direct instillation technique. It is also possible to combine these approaches (ie, use an initial instillation and then follow it with an aerosol).

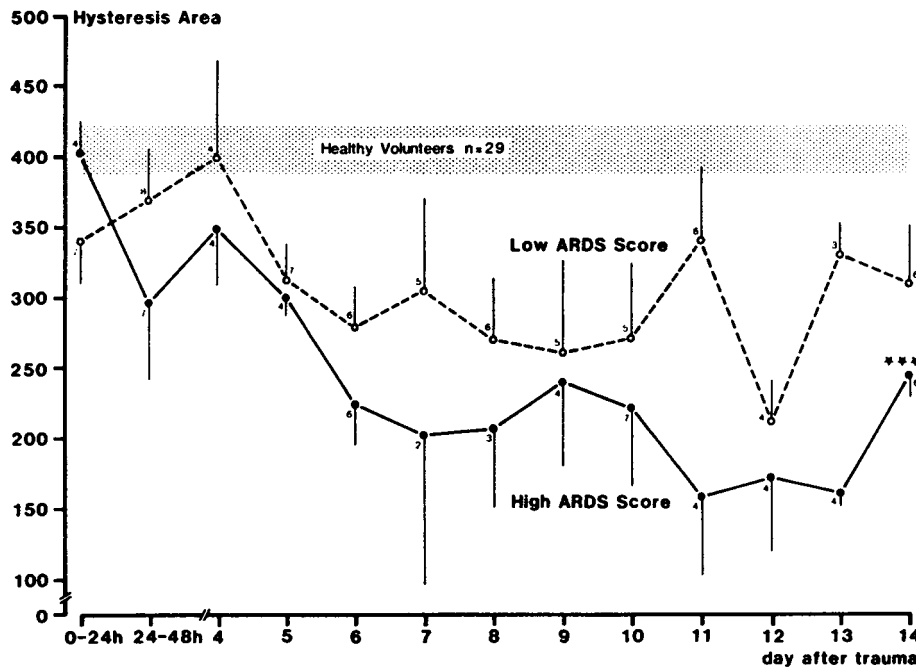


Fig. 2. Time course of surfactant abnormalities in mild/moderate (dashed lines) and severe (solid lines) acute lung injury. On the vertical axis is plotted surface active function (hysteresis area of alveolar lavage fluid). On the horizontal axis is plotted time after initiation of injury. The shaded area depicts normal reference values. Note that important abnormalities in lung surface active properties correlate with the degree of lung injury and can persist for several weeks before recovering. (From Reference 4, with permission.)

Table 1. Surfactants Available for Clinical Use

Natural
Bovine (Survanta, Infasurf, Alveofact)
Porcine (Curosurf)
Synthetic
With proteins (KL4, Venticute)
Without proteins (Exosurf)

### Instilled Surfactant Therapy

The benefits of surfactant replacement were first demonstrated in animal models of infant RDS, using direct instillation.<sup>19,20</sup> The first clinical use of surfactant in RDS was in 1980, and also used the instilled approach.<sup>21</sup> Since then, a number of clinical trials have demonstrated that instillation of both natural and synthetic surfactants into premature infants with RDS dramatically improves lung mechanics, gas exchange, and outcome (Fig. 5).<sup>1</sup>

Standard therapy today for RDS generally involves instilling bolus doses of  $\geq 100$  mg/kg (a full "replacement" dose). With instillation, 100% of the dose enters the airway. However, because instilled surfactant distributes by gravity, the instillation should be followed by turning the infant to achieve effective distribution.<sup>1,3</sup> As noted above, one of the problems with bolus instillation is that the nec-

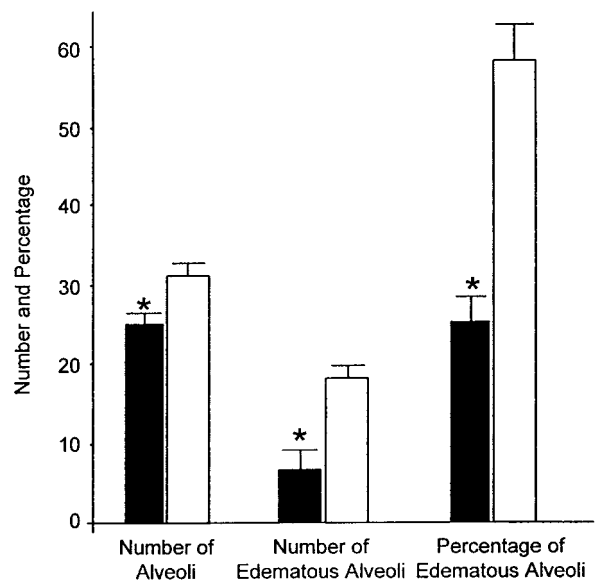


Fig. 3. Effect of instilled perflubron on lung properties in an animal model of acute lung injury. The open bars are gas-ventilated animals, the shaded bars are perflubron-ventilated animals (30 mL/kg perflubron). (From Reference 5, with permission.)

essary 4–5 mL/kg fluid loads into the airway can have substantial airway and hemodynamic effects in the neonate, so careful monitoring of vital signs and appropriate oxygen supplementation is important.

Table 2. Surfactant Delivery Techniques

Instillation
Single or multiple
Preceded by lavage
Aerosol
Alone
Preceded by instillation
Accompany multiple instillations

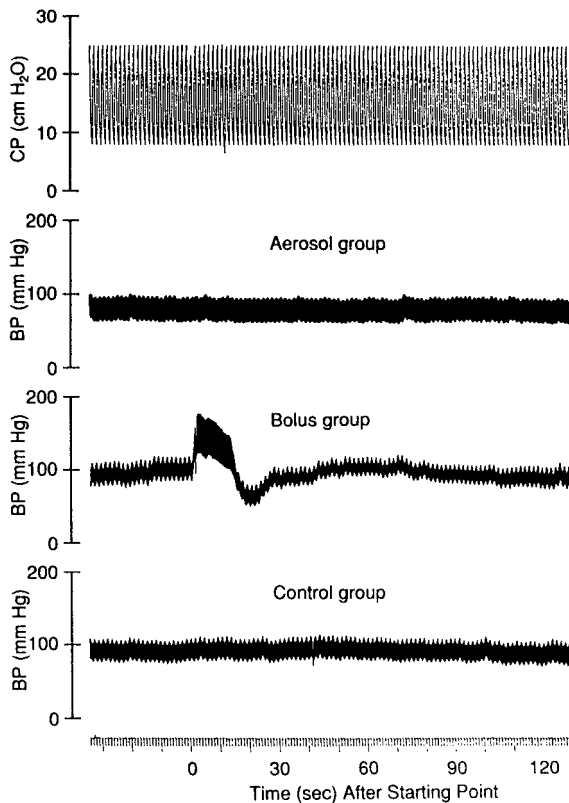


Fig. 4. Effects of a bolus administration of instilled surfactant (5 mL/kg) in an animal model of acute lung injury. Plotted are ventilator circuit pressures (top panel), airway pressures during aerosolized surfactant (second panel), airway pressures during bolus surfactant (third panel), and control (bottom panel). Surfactant administration occurred at time zero. Note that the bolus instillation was associated with substantial hemodynamic effects. (From Reference 8, with permission.)

Because of the success of surfactant replacement therapy in neonates, a number of investigations have attempted to duplicate this success in adult lung injury (eg, ARDS). As noted above, however, in adult lung injury, surfactant dysfunction rather than depletion is usually the issue, so simple replacement strategies that are effective in the premature neonate may not be adequate in adults.

Despite this, promising animal and human studies using instilled surfactant in acute lung injury/ARDS have been

reported. Animal models<sup>8,17,22</sup> have included sheep, rats, and rabbits. In short-term studies, instillation of “infant replacement” doses (eg,  $\geq 100$  mg/kg) has usually shown improved gas exchange and lung mechanics. Similar results have been observed in small human trials.<sup>22–25</sup> In the study by Gregory et al,<sup>23</sup> pharmacologic doses of 4 boluses of 100 mg/kg surfactant seemed to improve gas exchange and perhaps survival in a small group of patients. More impressive was the study by Walrath et al,<sup>24</sup> who used bronchoscopic instillation of  $\leq 300$  mg/kg surfactant and found quite substantial improvement in gas exchange and lung mechanics (Fig. 6). As of this writing, several other clinical trials are underway investigating the use of instilled surfactant in ARDS. One of these trials involves simple bolus techniques through the endotracheal tube. Another, however, uses a more complex approach, which involves first lavaging each segment of the lung with the surfactant and then filling it with additional surfactant.

### Aerosolized Surfactant Therapy

It is interesting that the first attempts at replacing surfactant in the premature neonate were by the aerosol route.<sup>1,26</sup> The original intent with using the aerosol route was to reduce the effects of the fluid bolus on gas exchange and hemodynamics and to perhaps improve distribution. However, inefficient aerosol systems, coupled with the difficulty in delivering aerosols through an endotracheal tube, made these initial attempts unsuccessful. When the ease and effectiveness of surfactant instillation was subsequently demonstrated, interest waned for using aerosolized surfactant in the premature infant.

Recent animal work with improved aerosol delivery systems suggests that the aerosol route may still be a viable alternative in the premature infant.<sup>7,16,27,28</sup> Moreover, the gas exchange and mechanics benefits seen with the aerosol approach were comparable to those seen with the instillation technique, but required only a fraction of the conventional 100 mg/kg instilled dose (Table 3). Given that airway delivery of an aerosol is always going to be less than with a bolus instillation, especially through narrow artificial airways, it is remarkable that aerosol delivery can be so effective. One reason for this may be the distribution. Specially, as noted above, instilled doses tend to follow gravity, whereas aerosolized doses follow ventilation. Although this may result in inhomogeneous distribution,<sup>16</sup> one might speculate that this could be more beneficial in delivering surfactant to the peripheral regions that need it most. Another issue related to aerosolized delivery is the absence of the “bolus” effect.<sup>8</sup> Finally, a slower, more continuous administration from an aerosol may facilitate spreading of the material or help to penetrate more slowly recruitable lung units.

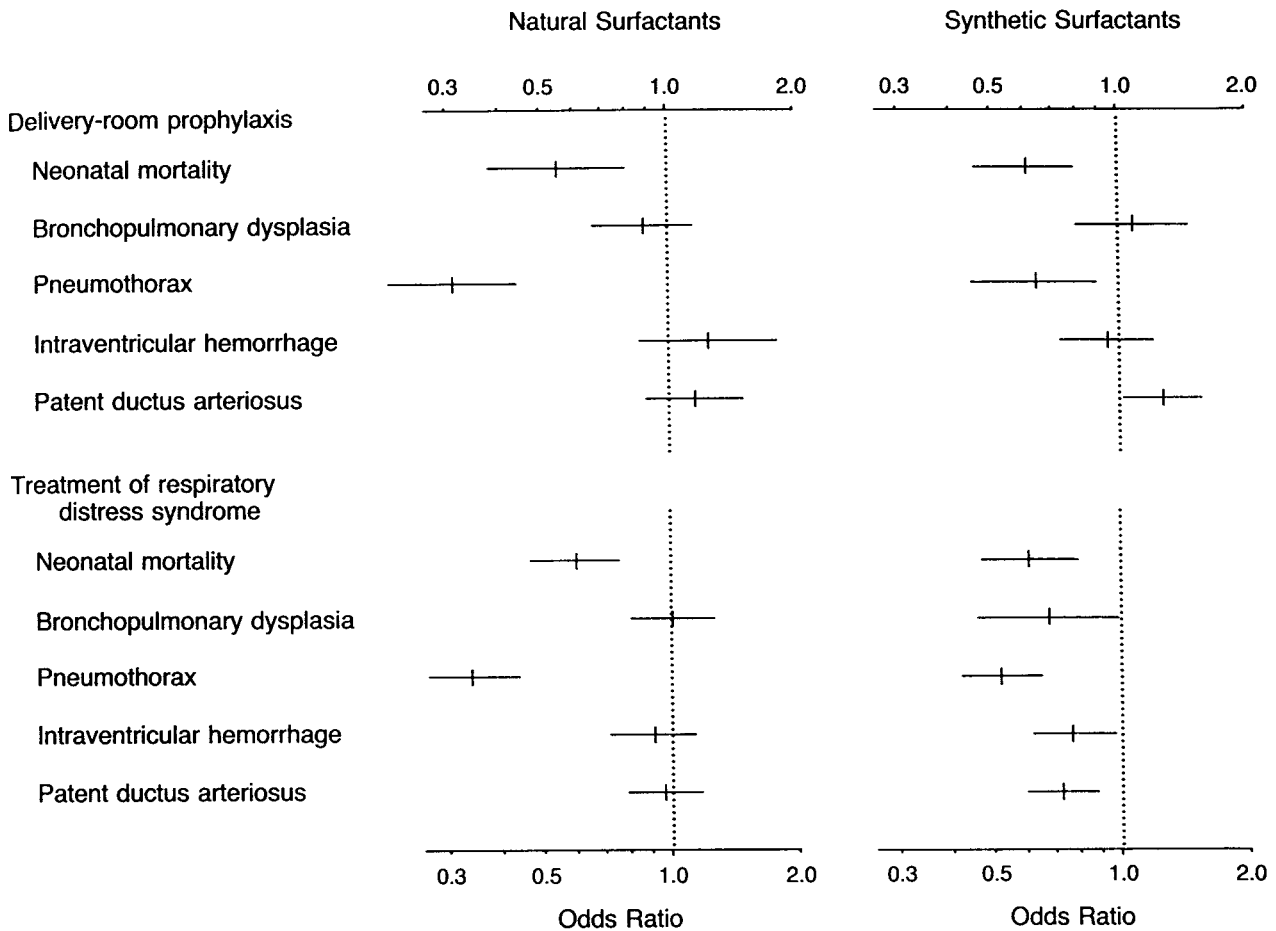


Fig. 5. Odds ratios from 4 meta-analyses of controlled studies showing benefit from instilled surfactant in premature infants with RDS. The 95% confidence intervals are plotted. Ratios to the left of zero favor surfactant treatment. (From Reference 1, with permission.)

Aerosol delivery of surfactant has also been studied in animal models of adult acute lung injury.<sup>8,17,18,22,29,30</sup> As in the premature infant, total delivery from an aerosol to the lungs is always going to be less than with instillation, especially in the presence of an endotracheal tube. Nevertheless, in a variety of animal models, aerosolized surfactant has been shown to provide important gas exchange and mechanics effects comparable to instilled surfactant (Figs. 7 and 8). Unlike the surfactant depletion syndromes, however, the surfactant dysfunction syndromes of acute lung injury seem to require aerosolized doses more comparable to that of the instilled dose (Table 4).

To date, only one randomized trial of aerosolized surfactant has been performed in adults with acute lung injury: the multicenter Exosurf trial.<sup>31</sup> In this study, patients with ARDS were randomized to receive either aerosolized surfactant or aerosolized saline for 5 days. Over 700 patients were randomized, but the trial was stopped because it became clear that the aerosolized surfactant had no benefit. Two major concerns surround this trial and its conclusion that aerosolized surfactant is ineffective. First, the

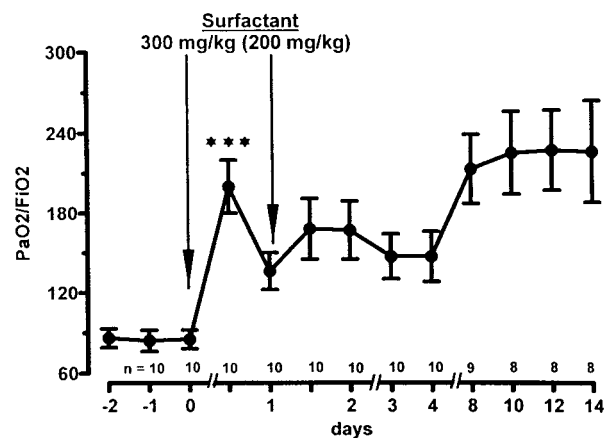


Fig. 6. Effects of bronchoscopically instilled surfactant on arterial partial pressure of oxygen ( $P_{aO_2}$ ) in adult humans with ARDS.  $F_{iO_2}$  = fraction of inspired oxygen. \*\*\* =  $p < 0.001$  for comparison of the  $P_{aO_2}/F_{iO_2}$  values before and after first surfactant application. (From Reference 24, with permission.)

Table 3. Aerosolized Surfactant in Animal Models of Surfactant Depletion Syndromes

Author (year)	Animal Model	Dose	Outcome(s)
Lewis et al (1991) <sup>27</sup>	Premature lambs	2 mg/kg over 120–180 min	Improved mechanics
Li et al (1994) <sup>28</sup>	Lavaged rats	75 mg/kg over 60 min	Improved mechanics and gas exchange
Lewis et al (1993) <sup>16</sup>	Lavaged sheep	8 mg/kg over 180 min	Improved mechanics and gas exchange
Schermuly et al (1997) <sup>7</sup>	Detergent rats	18 mg/kg over 120 min	Improved gas exchange

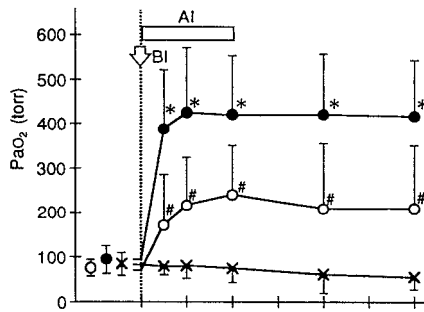


Fig. 7. Arterial partial pressure of oxygen ( $P_{aO_2}$ ) response to surfactant therapy in endotoxin-induced acute respiratory distress syndrome in rats. Animals were treated with either a surfactant instillation (BI, solid circles), aerosolized surfactant (AI) open circles, or served as controls (x). (From Reference 8, with permission.)

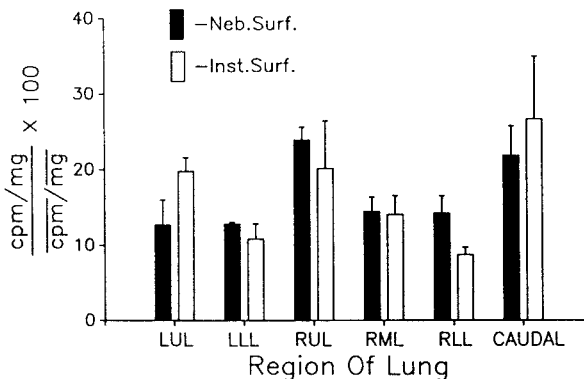


Fig. 8. Distribution of aerosolized (closed bars) versus instilled (open bars) surfactant in a saline lavage sheep model of acute lung injury. On the vertical axis is relative deposition and on the horizontal axis are lobar lung regions. Distribution of surfactant is clearly different with the two techniques. LUL = left upper lung. LLL = left lower lung. RUL = right upper lung. RML = right middle lung. RLL = right lower lung. (From Reference 16, with permission.)

surfactant used was simple dipalmitoyl phosphatidyl choline, an artificial surfactant without any surface active proteins. As noted above, this is a serious concern in adults, who suffer surfactant dysfunction syndrome rather than surfactant depletion syndrome. Under these circumstances, the surfactant-related proteins may be particularly important both for maximizing surfactant function and in providing anti-inflammatory effects. A second concern is that the aerosol-generating system used in this trial was very

ineffective in terms of delivery to lung parenchyma. In a study using radioactive tracers, it was shown that < 5% of the aerosolized material actually made it into the lung.<sup>14</sup> Because of these two serious concerns, it is probably premature to conclude that aerosolized surfactant in adult lung injury is ineffective.

### Other Issues with Aerosolized Surfactants

A number of studies have tried to combine aerosolized surfactant with high-frequency ventilation in the infant with RDS. This interesting ventilatory pattern (high velocity gas flow hundreds of times per minute) may help aerosol distribution and, in at least one study in premature infants, the high-frequency approach coupled with aerosolized surfactant had better oxygenation and blood pressure effects than the instillation method.<sup>32</sup>

Aerosolized surfactants have also been tried in airway diseases.<sup>33–35</sup> The rationale behind this is that surfactant in the airways plays an important role in mucus function and airway clearance properties. In two small studies involving cystic fibrosis and chronic bronchitis patients, aerosolized surfactant did not show benefit. In a more appropriately powered larger study,<sup>35</sup> however, two weeks of aerosolized surfactant treatments to outpatients with chronic bronchitis did show improvement in airway function and mucus properties.

An improved delivery system might increase the utility of aerosolized surfactants. As noted above, there may be reasons why the aerosolized route would be preferable to the instilled route. If the deposition could be further improved, especially in patients with endotracheal tubes, the aerosol route might be shown to be a much more cost-effective way of delivering surfactants. One such approach might be the use of intra-airway aerosol delivery system using either jet nebulizers or ultrasonic systems.<sup>36</sup>

### Surface Active Materials Other Than Surfactant

There are surface active materials other than surfactants. In recent years, perfluorocarbon instillation has been studied as a way of recruiting injured/gasless alveoli and improving lung mechanics and gas exchange.<sup>5,6</sup> Indeed, instilled perflubron has in a number of studies been shown to improve gas exchange and lung mechanical function when

Table 4. Aerosolized Surfactant in Animal Models of Surfactant Dysfunction Syndromes

Author (year)	Animal Model	Dose	Outcome(s)
Zelter et al (1990) <sup>29</sup>	Oleic acid sheep	45 mg/kg over 300 min	Reduced lung water on rechallenge
Lewis et al (1991) <sup>17</sup>	NNNMU rabbits	120 mg/kg over 180 min	Improved mechanics
Huang et al (1995) <sup>18</sup>	Oxygen toxic baboons	—	Improved gas exchange
Widner et al (1996) <sup>22</sup>	Kerosene sheep	90 mg/kg over 360 min	Improved mechanics and gas exchange
Tashiro et al (1996) <sup>8</sup>	Endotoxin rats	800 mg/kg over 60 min	Improved gas exchange
Lutz et al (1998) <sup>30</sup>	Endotoxin pigs	40 mg/kg over 240 min	Improved gas exchange

NNNMU = N-nitroso-N-methylurethane

large (eg, full functional residual capacity of 30 mL/kg) fluid volumes are used.<sup>5,6</sup> However, to date there have been no studies of the aerosol route for these particular substances.

### Summary

Surface active material is important in the function of both the infant and adult lung. In the premature infant, surfactant depletion results in the requirement for very high distending pressures to open alveoli. As a consequence, shunt, hypoxemia, and right ventricular dysfunction occur. Surfactant replacement, especially by the direct instillation approach, has been proven effective in improving clinical outcome under these circumstances. Problems with surfactant instillation include the “fluid bolus” effect and concerns about optimal distribution of the instilled material. Recent improvements in aerosol systems have created interest in using aerosol delivery to reduce the total dose of surfactant required to treat RDS.

In adult acute lung injury, surfactant dysfunction, rather than depletion, is the problem. Simple phospholipid replacement strategies thus may not be effective. Instead, surfactant delivery strategies aimed at regional targeting with surfactants having the necessary associated proteins may be the goal in ARDS. In adults, several instillation trials are underway, but there is also a hope that an aerosol strategy might also be tried. The aerosol route may be particularly useful if a high-efficiency aerosol system (eg, one distal to an endotracheal tube) can be shown to be effective.

Other surface active materials exist and there are small studies showing benefit when large instilled doses of these materials are given. These materials, however, have never been studied as aerosols.

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