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## Surfactant Treatment of Respiratory Failure Induced by Hydrochloric Acid Aspiration in Rats

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**Background:** The surfactant system seems to be involved in the pathophysiology of respiratory failure caused by hydrochloric acid (HCl) aspiration. This study was an investigation of the effect of different treatment strategies using an exogenous surfactant preparation on lung function of rats suffering from respiratory failure after intratracheal HCl instillation.

**Methods:** In rats anesthetized with halothane, nitrous oxide, and oxygen, tracheotomy was performed and the lungs were mechanically ventilated. Respiratory failure was induced by intratracheal instillation of HCl (0.1 N, 3 ml/kg). After the  $P_{aO_2}$  decreased to <200 mmHg, the animals were randomly divided into five groups. Group I received no treatment; group II received a natural surfactant preparation intratracheally (200 mg/kg); group III underwent bronchoalveolar lavage (BAL) with saline, followed by surfactant treatment (200 mg/kg); and groups IV and V underwent BAL with saline and a diluted surfactant suspension (3.3 mg/ml in 30 ml/kg), respectively. Groups IV and V received a second and third BAL 60 and 120 min after the first lavage. Blood gas analysis and protein measurements in BAL fluids were performed.

**Results:** Gas exchange improved in Groups III and V only. Protein concentrations were high in all BAL fluids. In the rats receiving BAL three times (groups IV and V), a decrease in protein concentration was observed.

**Conclusions:** From these results, it was concluded that plasma-derived proteins (which are known to inhibit surfactant function) are washed out of the alveoli by BAL, resulting in improved efficacy of surfactant treatment. (Key words: Lungs; acid aspiration; bronchoalveolar lavage; exogenous surfactant therapy; respiratory failure.)

MASSIVE aspiration of gastric contents is one of the most feared complications of general anesthesia and is an important cause of the adult respiratory distress syndrome (ARDS) (for review, see Gibbs and Modell and

Fowler *et al.*<sup>1,2</sup>). Adult respiratory distress syndrome caused by aspiration of gastric contents is characterized by deterioration of gas exchange requiring mechanical ventilation with high inspiratory oxygen concentration, high inspiratory pressure, and positive end-expiratory pressure (PEEP), and is associated with a mortality rate of over 90%.<sup>2</sup> Hydrochloric acid (HCl) causes direct damage to the alveolar-capillary membrane, leading to influx of protein-rich edema fluid into the alveolar space.<sup>3-6</sup> These plasma-derived proteins are known to be potent inhibitors of pulmonary surfactant function.<sup>7-13</sup>

Several studies have been performed in which animals suffering from respiratory failure caused by HCl aspiration were treated with surfactant. Kobayashi *et al.*<sup>6</sup> demonstrated that surfactant instillation could only partly restore gas exchange in rabbits suffering from respiratory failure caused by HCl aspiration after intraalveolar lung edema was removed by bronchoalveolar lavage (BAL) with saline. Lamm *et al.*<sup>14</sup> showed improved lung recoil in rabbits receiving surfactant 5 min after HCl aspiration, but no effect was seen on blood gases. Strohmaier *et al.*,<sup>15</sup> in a study on rabbits suffering from respiratory failure caused by HCl aspiration, also were unable to improve oxygenation after surfactant treatment. In a recent study using this model, we reported that surfactant, when given as a bolus at 200 mg/kg body weight after development of respiratory failure, was only able to prevent further deterioration of lung function, but was unable to improve gas exchange.<sup>16</sup> For this reason, the current study was designed to investigate whether it is possible to improve blood gases to almost normal values using an exogenous surfactant preparation in rats suffering from respiratory failure caused by HCl aspiration. Different surfactant substitution regimes are investigated; the removal of edema fluid from the alveolar space with a diluted surfactant suspension was of particular interest.

The surfactant preparation used in this study has proven to be highly effective in improving gas exchange and lung mechanics in various animal models of re-

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spiratory failure of differing etiologies<sup>17-19</sup> and in newborns suffering from respiratory failure caused by congenital diaphragmatic hernia.<sup>20</sup>

## Materials and Methods

### Exogenous Surfactant

The surfactant used in these experiments is a freeze-dried natural surfactant isolated from bovine lungs in basically the same manner as previously described.<sup>21</sup> It consists of approximately 90% phospholipids and 1% hydrophobic surfactant-associated proteins (so called SP-B and SP-C), the remainder being other lipids, such as cholesterol, glyceride, and free fatty acids. There is no SP-A (the largest surfactant-associated protein, molecular weight 26–38 kDa) in this surfactant preparation. Surfactant was suspended in saline.

### Animal Study

This protocol was approved by the Animal Care and Use Committee of the Erasmus University Rotterdam, the Netherlands.

The studies were performed in 44 male adult Sprague-Dawley rats (body weight 300–350 g). After induction of anesthesia with nitrous oxide, oxygen, and halothane, (65/33/2%) a tracheotomy was performed and a catheter was inserted into the carotid artery. Anesthesia was maintained with pentobarbital sodium (60 mg · kg<sup>-1</sup> · h<sup>-1</sup> intraperitoneally) and muscle relaxation was attained with pancuronium bromide (0.5 mg · kg<sup>-1</sup> · h<sup>-1</sup> intramuscularly). The lungs were ventilated with a Servo Ventilator 900 C (Siemens-Elma, Solna, Sweden) at the following ventilator settings: pressure-controlled ventilation,  $F_{I_{O_2}} = 1.0$ , ventilation frequency = 30/min, peak airway pressure ( $P_{peak}$ ) = 14 cmH<sub>2</sub>O, PEEP = 2 cmH<sub>2</sub>O, and inspiratory/expiratory ratio = 1:2. After reaching steady state ( $P_{a_{O_2}} > 500$  mmHg), 38 rats received 1.5 ml/kg HCl intratracheally (0.1 N; pH = 1.0) while lying on their right side, followed by a bolus of air (30 ml/kg). This was immediately followed by instillation of 1.5 ml/kg HCl, while rats were lying on their left side, again followed by a bolus of air; six rats received saline (2 × 1.5 ml/kg) instead of HCl and served as controls. Directly after instillation,  $P_{peak}$  was increased to 26 cmH<sub>2</sub>O and PEEP to 6 cmH<sub>2</sub>O in all rats; these ventilator settings were maintained throughout the observation period.

After  $P_{a_{O_2}}$  decreased to <200 mmHg (within 1–2 h) in rats receiving HCl, the animals were randomly di-

vided into five groups: group I (n = 7) received no treatment; group II (n = 8) received surfactant intratracheally; in group III (n = 7), the lungs were lavaged with saline followed by intratracheal surfactant instillation; and in groups IV and V (n = 8 per group) the lungs were lavaged with saline or a diluted surfactant suspension, respectively, at two time points. The first lavage was after  $P_{a_{O_2}}$  values decreased to <200 mmHg, followed by a second lavage 60 min after the first. The amount of saline used in all bronchoalveolar lavages was always 30 ml/kg body weight at 37° C; the amount of surfactant in the diluted surfactant suspension (group V) was 3.3 mg phospholipids/ml (100 mg phospholipids/kg body weight). The amount of surfactant used for intratracheal instillation in groups II and III was 200 mg phospholipids/kg body weight at a concentration of 50 mg phospholipids/ml.

Blood samples for measurement of  $P_{a_{O_2}}$  and  $P_{a_{CO_2}}$  were taken from the carotid artery of each rat before intratracheal HCl (or saline) instillation, at regular intervals postinstillation and at 5, 30, and 60 min after treatment (ABL 330; Radiometer, Copenhagen, Denmark). In groups IV and V, blood gas analyses were also performed at 5, 30, and 60 min after the second lavage.

### Bronchoalveolar Lavage Fluid

Bronchoalveolar lavage (BAL) was performed in the following groups for measurement of total protein concentration and surface tension properties. At the end of the experiments (*i.e.*, 60 min after the second BAL), groups IV and V were lavaged for the third time with saline (37° C; 30 ml/kg). Bronchoalveolar lavage fluids of group III and the first, second, and third BAL fluids from groups IV and V were prepared as described below. To compare all BAL samples with BAL samples from healthy control animals, the rats of the control group were lavaged 2 h after saline instillation. The BAL fluids of the different groups were prepared as follows: all samples were centrifuged for 15 min at 2,000 g to remove cell material. Protein concentration was measured in all samples using a modified Lowry method,<sup>22</sup> with bovine serum albumin as standard. Also, surface activity in BAL fluid was measured with the Wilhelmy balance (E. Biegler GmbH, Mauerbach, Austria) by applying 500  $\mu$ l of BAL fluid to the surface of a saline-filled trough. Surface area was reduced and expanded at a cycle speed of 0.33/min. Maximal and minimal surface tensions were measured after three cycles at 100% and 20% surface area, respectively.

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*Statistical Analysis*

All data are expressed as mean  $\pm$  SD. For PaO<sub>2</sub> and PaCO<sub>2</sub> data, a two-factor mixed-design ANOVA (group by repeated measures [time]) was used. For analysis of BAL parameters, a one-way between-subjects ANOVA (group) was used. When significant differences between and/or within groups occurred, these differences were further analyzed (Student-Newman-Keuls test). Statistical significance was accepted at  $P \leq 0.05$ .

**Results***Animal Study*

Before instillation of HCl, PaO<sub>2</sub> values were high ( $536.3 \pm 29.9$  mmHg) and there was no significant intergroup difference. Hydrochloric acid instillation decreased PaO<sub>2</sub> values to approximately 140 mmHg ("Pre"). After treatment, there was a statistically significant increase in PaO<sub>2</sub> values in rats undergoing BAL followed by surfactant (group III) and rats undergoing lung lavage with the surfactant suspension (group V). The PaO<sub>2</sub> values did not increase in the other groups. The PaO<sub>2</sub> values of control rats receiving saline instead of HCl remained high after 2 h of ventilation ( $550.5 \pm 27.7$  mmHg). For other statistically significant differences, see figure 1.

Table 1 shows the PaCO<sub>2</sub> values for each group. There are no significant differences in PaCO<sub>2</sub> values between all groups at any time. The PaCO<sub>2</sub> values remained low in control rats that received saline instead of HCl ( $36.5 \pm 3.50$  mmHg).

Table 2 shows the blood gases of rats whose lungs were lavaged with saline, and rats whose lungs were lavaged with the surfactant suspension (groups IV and V, respectively) after the first and second lavage. After the second lavage, there appears to be an increase in PaO<sub>2</sub> values in both groups compared with PaO<sub>2</sub> values after the first lavage; however, this increase is not significant. For statistically significant differences, see table 2.

*Bronchoalveolar Lavage Fluid*

Table 3 gives the recovery percentage, protein concentration, and surface tension properties of BAL fluid samples. The control lavages are from rats that received saline instead of HCl. The protein concentrations in BAL samples of control animals are much lower compared with all other groups, whereas there are no differences between the other groups. Maximal and min-

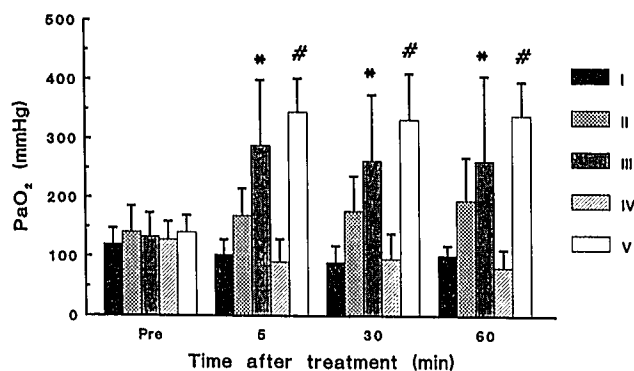


Fig. 1. PaO<sub>2</sub> values (mean  $\pm$  SD) of different groups after HCl instillation; after PaO<sub>2</sub> values decreased below 200 mmHg (= Pre), rats were divided into five groups: group I received no treatment, group II received surfactant (200 mg/kg), group III was lavaged with saline followed by surfactant treatment (200 mg/kg); and groups IV and V were lavaged with saline or a diluted surfactant suspension (3.3 mg/ml), respectively. \*Statistically significant differences between group III and pretreatment, group I and group IV. #Statistically significant differences between group V and pretreatment, groups I, II, and IV.

imal surface tensions of the BAL samples of rats undergoing lung lavage with a diluted surfactant suspension are significantly lower compared with all other groups. The minimal surface tensions of BAL samples of sick animals undergoing lung lavage with saline are significantly higher compared with healthy controls.

Table 4 gives the protein concentrations in the first, second, and third BAL samples from groups IV and V. In both groups, there is a significant decrease in protein concentrations between the first and third BAL samples. The difference in protein concentrations between groups IV (third BAL) and V (third BAL) is statistically significant. There is no statistically significant difference in either maximal or minimal surface tensions between the first, second, and third BAL samples of group IV; the same is true for group V (data not shown). The differences in surface tension between BAL samples of groups IV and V, as shown in table 3, also exist for the second and third BAL.

**Discussion**

Massive aspiration of HCl with low pH leads to damage of the alveolar-capillary membrane which, in turn, leads to increased permeability to, and intraalveolar accumulation of, plasma proteins.<sup>3-6</sup> These proteins have proven to be potent surfactant inhibitors.<sup>7-13</sup> The resulting impaired surfactant function leads to accu-

Table 1. Pa<sub>CO2</sub> Values of All Groups

Group	N	Control	Pre	After Treatment		
				5 min	30 min	60 min
I	7	30.7 ± 3.19	58.1 ± 15.8	53.0 ± 11.6††	62.4 ± 23.1	76.0 ± 13.6††
II	8	34.8 ± 4.58	67.5 ± 20.3	67.5 ± 13.9	68.6 ± 10.3	65.6 ± 8.81†
III	7	32.6 ± 4.78	65.1 ± 15.8	65.9 ± 23.4	57.3 ± 15.2	57.4 ± 18.7
IV*	8	31.5 ± 3.61	57.6 ± 13.3	52.3 ± 8.10	49.9 ± 10.3	54.3 ± 4.12††
V*	8	33.1 ± 3.25	65.1 ± 16.4	63.8 ± 10.8	57.3 ± 8.66	57.1 ± 5.32†

Data are mean ± SD (mmHg). Control = before HCl instillation; Pre = after HCl instillation and before treatment.

\* After the first BAL treatment.

† One animal died.

mulation of edema fluid in the alveolar space. Also, as a result of diminished surfactant function, surface tension on the alveolar wall increases, leading to increased retractive forces across the alveolar-capillary membrane, with subsequent formation of atelectasis and mismatch of the ventilation-perfusion ratio, leading to hypoxemia. The damage to the surfactant system and the fact that surfactant is no longer produced as a result of damage to the surfactant producing type II pneumocytes<sup>4</sup> makes treatment of this pathologic entity with surfactant plausible.

The results in the current study demonstrate that ventilation with 100% oxygen and increased inflation pressure and PEEP to the levels used in this study were not able to maintain high Pa<sub>O2</sub> levels in rats after HCl aspiration. Also, surfactant instillation without prior lavage did not restore lung function. The best way to treat these animals appears to be either to lavage the lungs with saline, directly followed by intratracheal instillation of a high dose of surfactant, or to lavage the lungs with a diluted surfactant suspension, as evidenced by an increase in Pa<sub>O2</sub>.

The decrease in Pa<sub>O2</sub> values after HCl aspiration could not be explained by a fluid challenge, as demonstrated by Pa<sub>O2</sub> values remaining high in rats receiving saline instead of HCl.

It has been hypothesized that the mechanism of inhibition of surfactant by proteins is based on competition for space at the air-liquid interphase.<sup>9,12</sup> Thus, the way to overcome the inhibition of surfactant by these proteins would be to get a relatively high surfactant concentration in relation to the amount of proteins. This favorable surfactant/inhibitor (S/I) ratio can be achieved in two ways.

First, by treating the animals with a large dose of surfactant (without prior lavage), a high S/I ratio could be achieved. The results from the current study demonstrate no increase in Pa<sub>O2</sub> values after instillation of surfactant at a dose of 200 mg/kg in animals suffering from respiratory failure after HCl aspiration, although a further decrease in Pa<sub>O2</sub> values seemed to be prevented at this surfactant concentration. Also, in comparable studies<sup>6,15</sup> on animals suffering from respiratory failure caused by HCl aspiration, surfactant only was

Table 2. Pa<sub>O2</sub> and Pa<sub>CO2</sub> Values after Repeated BAL

Group	N	Control	Pre	After First BAL			After Second BAL		
				5 min	30 min	60 min	5 min	30 min	60 min
IV (1st/2nd)									
Pa <sub>O2</sub>	8	539.1 ± 25.8	128.3 ± 30.9	90.3 ± 38.7	95.1 ± 43.1	81.0 ± 30.7††	99.8 ± 32.5††	131.4 ± 57.9	129.5 ± 68.1
Pa <sub>CO2</sub>		31.5 ± 3.61	57.6 ± 13.3	52.3 ± 8.10	49.9 ± 10.3	54.3 ± 4.12	41.8 ± 10.9§	42.1 ± 7.98	42.5 ± 9.21
V (1st/2nd)									
Pa <sub>O2</sub>	8	536.0 ± 30.7	144.7 ± 28.8	345.2 ± 56.5*	332.2 ± 77.4	340.0 ± 56.8†	411.0 ± 45.3	418.9 ± 53.7	388.5 ± 87.6†
Pa <sub>CO2</sub>		33.1 ± 3.25	65.1 ± 16.4	63.8 ± 10.8	57.3 ± 8.66	57.1 ± 5.32	55.6 ± 7.26	50.9 ± 5.88	53.7 ± 6.93

Data are mean ± SD (mmHg). Control = before HCl instillation; Pre = after HCl instillation and before BAL treatment.

\* P < 0.05 between pre-BAL and 5 min after BAL.

† One animal died.

§ P < 0.05 between first BAL and second BAL treatments.

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Table 3. BAL Parameters of Different Groups

Sample Group	N	Recovery (%)	Protein (mg/ml)	Surface Tension (mN/m)	
				Maximal	Minimal
III	5	97.0 ± 2.45	7.14 ± 1.26	59.7 ± 1.82‡	32.1 ± 1.00‡
IV*	5	100.0 ± 8.16	7.95 ± 1.29	60.1 ± 0.41§	32.2 ± 0.42**
V*	6	97.5 ± 3.82	7.50 ± 0.97	54.9 ± 3.28¶	16.6 ± 2.19¶
Control	6	94.2 ± 5.32	0.40 ± 0.39†	63.1 ± 3.16	24.9 ± 2.55

Data are mean ± SD. Control = BAL fluid of control rats receiving saline instead of HCl.

\* Fluid from first BAL treatment.

†  $P < 0.01$  between control and other groups.

‡  $P < 0.05$  between maximal/minimal surface tension of III and other sample groups, except IV.

§  $P < 0.05$  between IV and V.

¶  $P < 0.05$  between V and other groups.

\*\*  $P < 0.05$  between IV and other sample groups, except III.

not able to restore gas exchange. A possible explanation is that surfactant, at the concentration used, is directly inhibited by a high concentration of inhibitors. Another explanation could be that the edema fluid and the atelectatic areas form a mechanical barrier, preventing surfactant from entering the alveolar spaces. However, in another study,<sup>23</sup> surfactant instillation at very high doses (280–350 mg/kg) was able to restore gas exchange in guinea pigs suffering from severe respiratory failure caused by protein-rich lung edema after intravenous instillation of antilung serum. Thus, in the latter study, a more favorable S/I ratio was obtained by giving a large amount of surfactant. Recently, Kobayashi *et al.*<sup>24</sup> investigated the ability of surfactant mixed with edema fluid at several ratios to restore lung function in immature rabbit fetuses, as measured by tidal volume at preset insufflation pressures. It was demonstrated that surfactant (25 mg/ml) mixed with edema fluid at a protein to lipid ratio (P/L ratio) of 2.2 was capable of restoring lung function, whereas surfactant mixed with edema fluid at P/L ratio of 11.2 was not. Surface tension properties of these mixtures demonstrated high mini-

mal surface tensions at  $P/L \geq 3.4$  and low surface tensions at  $P/L \leq 1.8$ .

Second, a favorable S/I ratio could be achieved by removing the inhibitors from the alveolar space by means of BAL. In the current study,  $Pa_{O_2}$  values increased after surfactant treatment (200 mg/kg) after lung lavage. Similar findings were also reported by Kobayashi *et al.*<sup>6</sup> In our study, although there was no statistically significant difference in  $Pa_{O_2}$  values with rats receiving surfactant after BAL, BAL with a diluted surfactant suspension (100 mg/kg) seemed to be more efficient in restoring gas exchange. Bronchoalveolar lavage with saline alone (without any additional surfactant treatment) was not able to restore gas exchange. The difference between  $Pa_{O_2}$  values of rats lavaged with a diluted surfactant suspension and rats lavaged with saline (not followed by surfactant treatment) may be explained as follows: after removal of a large amount of proteins in both groups, a small amount of surfactant remains in the lungs of the rats lavaged with a diluted surfactant suspension. This appears sufficient to establish surface active material at the air-liquid interphase, allowing improved gas exchange across the alveolar-capillary membrane. Because no surfactant concentration measurements were made in the recovered surfactant suspensions after BAL, no exact data is available on the amount of surfactant remaining in the lungs after BAL. If one tries to estimate the amount of surfactant remaining in the lungs, the following equations can be made: the functional residual capacity (FRC) of the lungs is approximately 10 ml/kg; BAL was performed with 30 ml/kg and almost 100% of the BAL fluid was recovered; the total amount of surfactant in the BAL fluid was 100 mg phospholipids/kg; and this was di-

Table 4. Protein Concentrations in First, Second, and Third BAL

	Group IV	Group V
First BAL	7.95 ± 1.29*	7.50 ± 0.97†
Second BAL	6.11 ± 0.96	5.56 ± 0.84
Third BAL	5.36 ± 0.70	3.99 ± 0.75‡

Data are mean ± SD (mg/ml).

\*  $P < 0.05$  between first BAL and third BAL.

†  $P < 0.05$  between first BAL and both second and third BAL.

‡  $P < 0.05$  between group IV (third BAL) and group V (third BAL).

luted with 10 ml/kg of residual (edema) fluid in the lungs. Considering the mixture of these two concentrations (10 ml/kg = no surfactant; 30 ml/kg = 100 mg surfactant), approximately 25 mg phospholipids/kg remains in the lungs. Considering the amount of surfactant needed to treat respiratory failure caused by HCl aspiration, half the amount of surfactant is needed when BAL is performed with the diluted surfactant suspension, compared with treatment with surfactant after BAL with saline.

Protein concentrations in BAL material from all rats suffering from respiratory failure caused by HCl aspiration were significantly higher compared with protein concentrations in BAL material from healthy control animals. Also, surface tension measurements demonstrated high minimal surface tensions in BAL material from rats suffering from respiratory failure after HCl aspiration, when compared with BAL material from healthy controls. These results indicate that the surfactant system is damaged in animals after HCl aspiration. In BAL material from rats that underwent multiple lung lavage, the protein concentration decreased significantly, both in rats undergoing lung lavage with the diluted surfactant suspension and in those lavaged with saline (table 4). In rats undergoing lung lavage with the diluted surfactant suspension, the decrease in protein concentration was greater compared with those lavaged with saline. Perhaps this indicates repair of the alveolar-capillary membrane, resulting in a decrease of protein influx into the alveoli. The  $P_{aO_2}$  values appeared to increase further after the second lavage with the diluted surfactant suspension, although this increase was not statistically significant (table 2). Thus, although BAL with saline also removes the proteins from the alveolar spaces, surfactant substitution is needed to restore lung function. These results suggest that surfactant inhibitors (e.g., plasma-derived proteins, specific proteases, and cellular breakdown products) can be removed by means of BAL, resulting in improved efficacy of surfactant in restoring lung function.

In conclusion, intratracheal surfactant instillation without prior BAL does not improve pulmonary gas exchange in rats suffering from respiratory failure caused by HCl aspiration; in these animals, gas exchange could be improved after BAL with saline, followed directly by surfactant instillation, or by BAL with a diluted surfactant suspension. It is shown that (multiple) BAL removes edema fluid (containing plasma proteins) from the lungs. It is argued that surfactant treatment can

only succeed when there is a favorable ratio of surfactant to proteins inhibiting surfactant function.

It is difficult to extrapolate from this animal study to the clinical situation. However, if one decides to treat patients suffering from ARDS with surfactant, it might be considered that the amount of surfactant needed to overcome the inhibition by proteins is enormous. From this, it could be speculated that it would probably be more effective to reduce the amount of intraalveolar proteins by means of BAL and then treat with surfactant, or directly by means of BAL with a diluted surfactant suspension. However, the optimal way to perform this in patients has yet to be studied.

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