The Role of Pulmonary Surfactant in the Pathogenesis and Therapy of ARDS

B. Lachmann

Introduction

There are many functional and pathologic similarities between the adult respiratory distress syndrome (ARDS) and the respiratory distress syndrome (RDS) of premature newborn infants, including a lack of surfactant in the alveolar spaces and airways [1, 2]. In ARDS, however, surfactant deficiency is a complication of lung injury rather than, as in neonatal RDS, a primary etiologic factor.

This article will describe the normal function of the pulmonary surfactant system and, by explaining the mechanisms which lead to disturbances in function, to illustrate the central role of surfactant deficiency in ARDS and, finally, to show that abnormalities in blood gases and lung mechanics can be restored to "normal" by tracheal instillation of surfactant.

Normal Physiologic Function of the Pulmonary Surfactant System

Mechanical Stabilisation of the Lung Alveoli

The integrity of the surfactant system of the lung is a prerequisite for normal breathing with the least possible effort. The surfactant system produces this effect by decreasing the surface tension of the interface between alveoli and air. This provides an explanation as to why we have to generate a pressure of only 4–8 cm H_2O during each inspiration, whilst at the air-liquid interface only the surface tension of plasma is present and then a pressure of 25–40 cm H_2O (depending on the radius of the alveoli) has to be generated for each inspiration. This is a well-known symptom in immature newborn babies with respiratory distress syndrome and in adults with respiratory failure. In alveoli with different radiuses, an equal lowering of surface tension would not, however, produce stabilisation of the alveolar system. It would, according to the law of Laplace ($P = 2\gamma/r$; P = pressure in the bubble, γ = surface tension, r = radius of the bubble) lead instead to the collapse of the smaller bubble or alveoli, and to their emptying into the larger ones. Since alveoli in vivo do not exhibit such behaviour, one may conclude that the second remarkable quality of the alveolar lining layer is that it can change the surface tension, dependent on the size of the alveoli.

J. L. Vincent (ed.), *Update 1987*

Surfactant as Anti-oedema Factor

Another function of the pulmonary surfactant system is stabilisation of the fluid balance in the lung and protection against lung oedema [3] (Fig. 1). In general, alveolar flooding will not occur as long as the suction force in the pulmonary interstitium exceeds the pressure gradient generated by surface tension in the alveolar air-liquid interface. Since this pressure gradient is inversely related to the radius of the alveolar curvature, there is, for each combination of interstitial resorptive force and average surface tension, a critical value for surface tension and for alveolar radius, below which alveolar flooding occurs.

Surfactant and Local Defence Mechanisms

Observations in patients have shown that, following a decrease in lung compliance (thus, surfactant deficiency), pneumonia will often develop, despite the application of high doses of antibiotics. Therefore, it is possible that the surfactant system is also involved in local defence mechanisms of the lung. It has been demonstrated that alveolar phagocytic macrophages ingest only bacteria (or destroy them intracellularly) in the presence of sufficient surface active material [4]. In this context surfactant seems to reduce the surface forces of bacterial membranes and is also an energy-rich substrate which balances the macrophages' high rate of metabolism. Recently we have demonstrated that the pulmonary surfactant system may also be involved in protecting the lung against its own mediators, (e.g. angiotensin II) and in protecting the cardio-circulatory system against mediators produced by the lung.

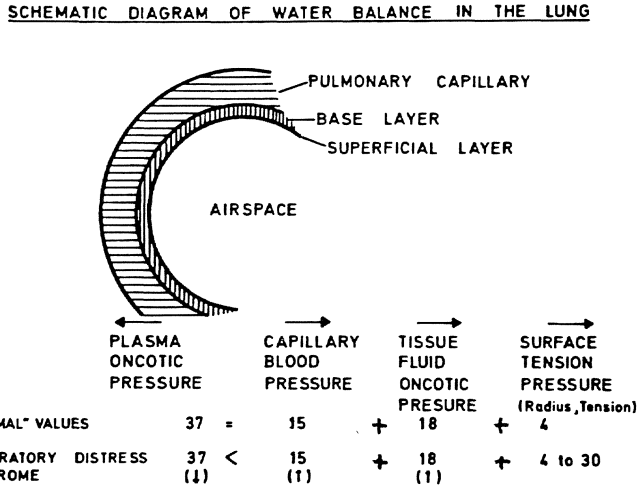

Fig. 1. Simplified schematic diagram representing the factors influencing the fluid balance in the lung

Surfactant and Airway Stabilization

As early as 1970, Macklem et al. [5] drew attention to the significance of stabilization of the peripheral airways and hinted that its lack might cause airway obstruction or collapse of the small bronchi with air trapping. Recently this has been proved in an animal model in our laboratory where it was demonstrated that the pressure needed to open up collapsed bronchi is about 20 cm H_2O. In the same study we also demonstrated that severe impairment of bronchial surfactant can be successfully treated with exogenous surfactant replacement [6].

Surfactant and Transport Function

Besides its role in mechanical stabilisation, bronchial surfactant also has a transporting function for mucus and inhaled particles. This has been proven, in vitro, in a study showing that particles on a surface film move only in one direction if the surface film is compressed and dilated - comparable to the compression and expansion during expiration and inspiration [6, 7]. Furthermore, bronchial surfactant also acts as an antiglue factor, preventing the development of large adhesive forces between mucus particles as well as between mucus and the bronchial wall [8].

A further possible function of bronchial surfactant, which to date has scarcely been discussed, is its masking of receptors on smooth muscle with respect to substances which induce contraction and could lead to airway obstruction. We have recently demonstrated that lining the airway with surfactant in ovalbumin-sensitised guinea pigs prevented significant bronchial obstruction during antigen challenge in these animals [9]. This means that bronchial surfactant could also be involved in asthma. This is further supported by the fact that use of the most effective bronchodilating drugs (corticoids and beta-mimetics) leads to a release of surfactant.

Functional Changes Due to a "Disturbed" Surfactant System

When considering all the physiologic functions of the alveo-bronchial surfactant system it can easily be understood that alteration in its functional integrity will lead to:

- decreased lung distensibility and thus to increased work of breathing and increased oxygen demand by the respiratory muscles
- atelectasis
- transudation of plasma into the alveoli with decreased diffusion for oxygen and CO_2
- inactivation of the surfactant by plasma and specific surfactant inhibitors
- hypoxaemia and metabolic acidosis secondary to increased production of organic acids under anaerobic conditions

- enlargement of functional right-to-left shunt due to perfusion of non ventilated alveoli (the v. Euler-Liljestrand reflex does not "work" in surfactant deficient alveoli)
- decreased production of surfactant as a result of hypoxaemia, acidosis and hypoperfusion. This will lead to a vicious circle and the lung will fail as a gas exchange organ.

Some of these functional alterations within the lung are not typical of primary disturbances in the surfactant system. They may also appear in conjunction with certain diseases, such as bacterial pneumonitis, acute (cardiac) pulmonary oedema, acute exacerbation of chronic lung diseases etc. But all the above-mentioned changes are typical for the respiratory distress syndrome in adults. The mortality rate for ARDS ranged from 40–70% and this high rate is reflected in increasing efforts all over the world to overcome this disease.

Postmortem Characterisation of the Surfactant System

Only a few reports have been published concerning the surfactant system in ARDS. Ashbaugh et al. [2] found increased minimal surface tension in lung extracts from two ARDS patients who had been ventilated artificially for 2–4 days. In our own investigation [10], we used a modified Langmuir balance to evaluate surface properties of lung homogenates from 16 patients with ARDS. We found a significant correlation between the duration of artificial ventilation and the decrease in surfactant activity (Fig. 2, 3a and 3b).

Hallman et al. [11] reported that bronchial lavage fluid from patients with ARDS failed to exhibit normal surfactant activity although its phospholipid content was normal; this finding suggests the appearance of potent surfactant inhi-

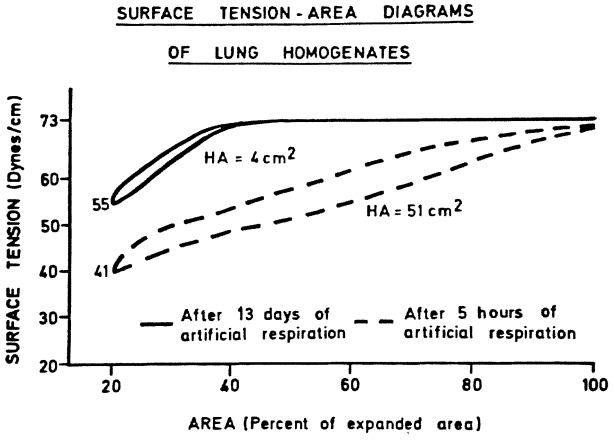

Fig. 2. Typical tension-area diagram of lung extracted from patient with ARDS (solid line) compared with analogous recording from a 30-year old man who died from extrapulmonary causes (dashed line). Note elevated minimal surface tension and reduced hysteresis area (HA) in patient with ARDS. (From Lachmann et al. [10] with permission)

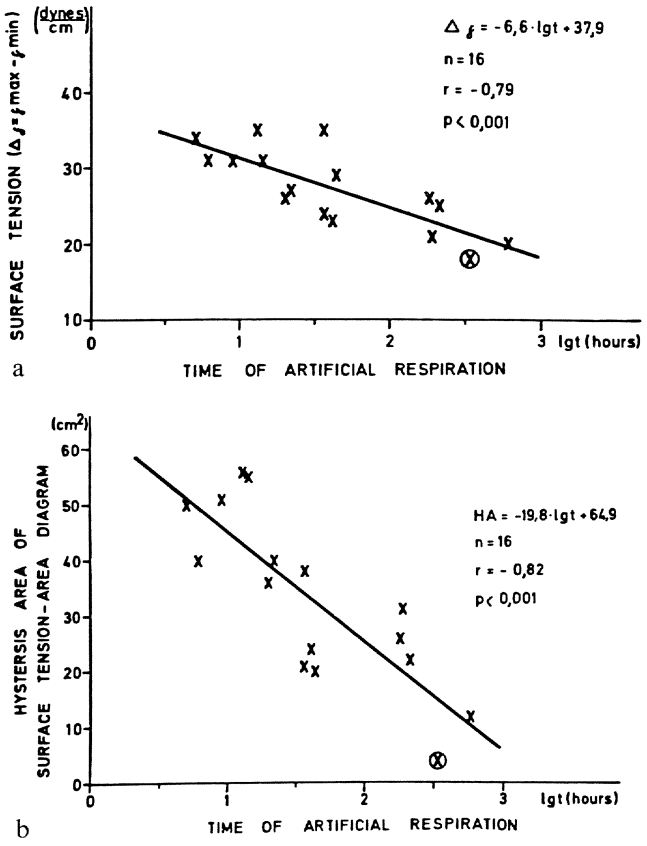

Fig. 3 a Surfactant activity, expressed as difference between maximal and minimal surface tension ($\gamma_{max} - \gamma_{min}$), in lung extracts from 16 patients with ARDS. Values for $\Delta\gamma$ are shown in relation to duration of artificial ventilation. The time scale is logarithmic (log h). X = patient in Fig. 2. (From Lachmann et al. [10], with permission) **b** Hysteresis area (HA) in surface-tension area diagrams of lung extracts from 16 patients with ARDS (as in Fig 3a). Values are shown in relation to duration of artificial ventilation. The time scale is logarithmic (log h). X = patient in Fig. 2. (From Lachmann et al. [10] with permission)

bitors in the airspaces. Similarly, Petty et al. [12, 13] found that surface films formed by lung lavage fluid from ARDS patients had increased compressibility, while minimal surface tension did not differ from control levels. In this study, there was no significant difference in the recovery of total phospholipids between ARDS patients and normal controls. However, in patients with ARDS the phospholipids were qualitively different from those recovered by bronchoalveolar lavage in normal controls and similar to those found in neonatal RDS. Thus, the L/S ratio and the content of the phosphatidylglycerol and saturated phosphatidylcholine were low, whereas sphingomyelin and phosphatidylserine were relatively abundant [11]. Von Wichert and Kohl [14] found decreased dipalmitoylphosphatidylcholine, but increased total phospholipids in lung homogenates from ARDS patients. These biochemical discrepancies might reflect variations in

patient material and sampling procedures. Details concerning the duration of the disease were not reported by Hallman [11] or Petty et al. [12, 13]. Summaries of these few studies lead one to conclude that further postmortem investigation of the pulmonary surfactant system could be an important target for future research.

Pathogenesis of ARDS

The RDS in adults results from a group of diseases of varying etiology and is characterised by an increased capillary permeability, often associated with damage to the alveolar epithelium. The mechanisms responsible for injury to the alveolar-capillary membrane in ARDS are complex and are still under discussion [for review see 15–18]. In brief, activation of complement, a common consequence of trauma, sepsis and other predisposing events, generates mediators (especially C5a) causing intravascular aggregation of leukocytes in the lungs. Aggregated neutrophils injure endothelial cells by producing toxic oxygen radicals. The neutrophils also liberate proteases destroying collagen, elastin and fibronectin and promote further local inflammatory changes by lysis of circulating plasma proteins, including Hageman factor, fibrinogen and complement. In addition, pulmonary antiproteases are inactivated by oxygen radicals and by a therapeutic hyperoxic environment.

This description represents an approximation of the mechanisms causing acute endothelial and interstitial tissue damage in ARDS. However, complement infusion in experimental animals does not lead to the severe pulmonary lesions seen in patients with ARDS. Therefore, some additional factors must be involved. These include abnormalities in blood clotting, such as disseminated intravascular coagulation with formation of microthrombi in pulmonary vessels, local release of prostaglandins, vasoactive amines (histamine, serotonin, kinins and catecholamines), immune complexes, lymphokinins and lymphotoxins, and mediators from the arachidonic acid cascade, as well as influences from the central nervous system. Each of these additional mechanisms are capable of causing a significant disturbance of pulmonary vascular permeability in ARDS.

But all these individual factors which can lead to a pulmonary oedema do not, however, necessarily lead to ARDS. Therefore another system must be involved to explain all these functional changes in ARDS. Thus, if there is a capillary leakage combined with damage to the alveolar epithelium the surfactant system will be responsible for further pathophysiological changes (Fig. 4). Independent of the primary cause of capillary damage, there will be an immediate or moderately slow loss of surface active material from the alveoli and small bronchi which is, however, compensated for by a release of stored surfactant from the type II cells. The progress of the disease depends on the balance between new production and release of surfactant into the alveoli and its inactivation/loss from the alveoli and airways. If the synthesis is reduced e.g. by influenza virus, hypoxia or hyperoxia, an imbalance between new synthesis and demand will result. This will finally lead to a total loss of functional active surfactant, followed by the above-mentioned functional disturbances (changes in the lung) and

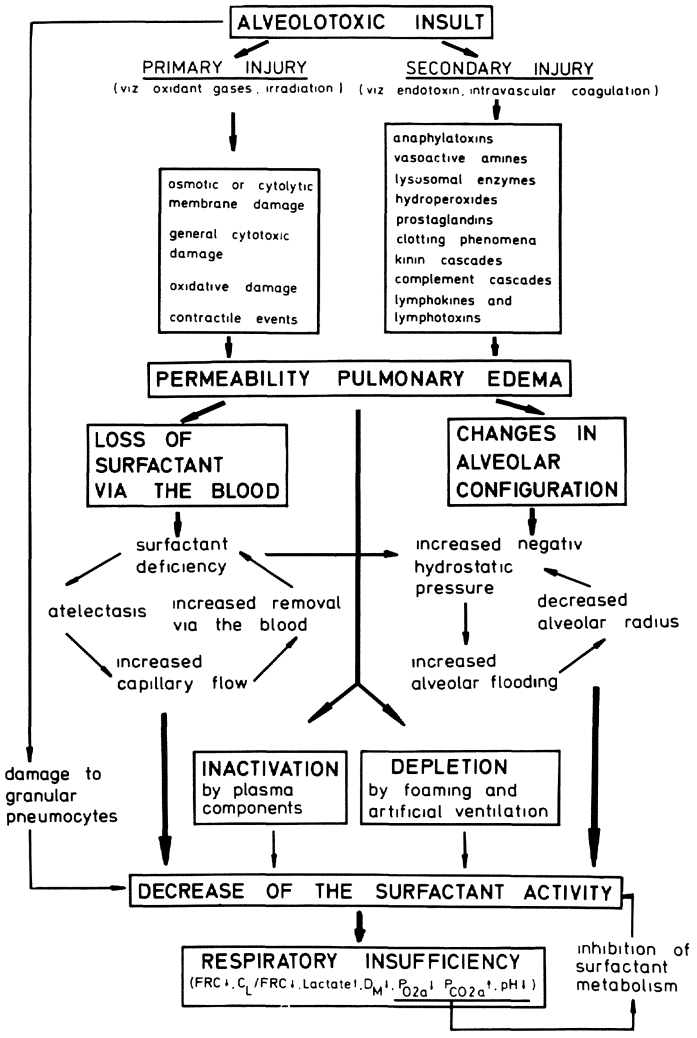

Fig. 4. Pathogenesis of ARDS with special reference to the surfactant system

the lung "finally" fails as a gas exchange organ. The central role of surfactant deficiency in this context is illustrated by recent studies on animal models of ARDS and first clinical trials showing that abnormalities in blood gases and lung mechanics can be restored to "normal" by tracheal instillation of natural surfactant.

Surfactant Replacement in ARDS

Animal Studies

Although many investigators have documented successful treatment, or prevention, of neonatal RDS by tracheal instillation of surfactant, very few reports have been published concerning surfactant replacement in ARDS [19–22]. In 1967, Rüfer showed that surfactant deficiency (induced in isolated rat lungs by bronchoalveolar lavage) can be compensated for by instillation of surfactant into the airways [23].

In experimental ARDS, induced by in vivo lung lavage, tracheal instillation of surfactant lipids results in striking improvement of gas exchange (Fig. 5), even if the treatment is given two hours after the lavage procedure (Fig. 6). Other experiments (in animals receiving surfactant) have documented that the improved blood gases are stable for at least five hours, whereas PaO_2 in control animals remains low, despite ventilation with PEEP and pure oxygen (Fig. 7). Histologic lung sections from surfactant-treated animals showed a uniform pattern of well-aerated alveoli, with only minimal intra-alveolar oedema and hyaline membranes, whereas control animals ventilated with the same respirator setting had extensive atelectasis and prominent hyaline membranes. These results indicate that the ventilator treatment per se is not harmful to the pulmonary parenchyma, provided that alveolar collapse is prevented by surfactant replacement and shear forces thereby avoided.

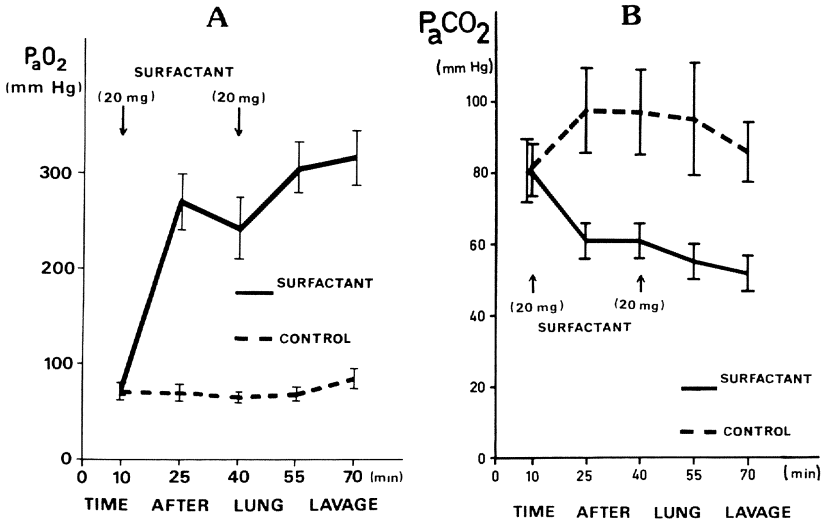

Fig. 5. Effect of surfactant replacement on PaO_2 (A) and $PaCO_2$ (B) in guinea pigs with severe ARDS induced by repeated lung lavage. The animals were ventilated with pressure-controlled ventilation, 100% oxygen, I/E ratio 1:1, frequency 20/min, insufflation pressure 28 cm H_2O and PEEP 5 cm H_2O. Surfactant, made from bovine lung surfactant was administered twice via the tracheal cannula (arrows). Values are given as mean ± SD. (From Lachmann et al. [19, 20] with permission)

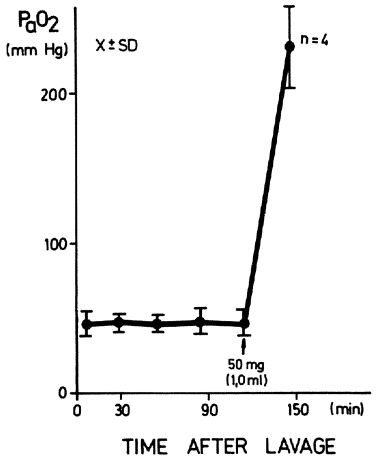

Fig. 6. Cause of PaO_2 in guinea pigs with severe ARDS induced by repeated lung lavage. Surfactant instillation was performed after 2 hours of artificial ventilation. Ventilator settings were unchanged during the entire observation period and were identical to those in Fig. 5. (From Lachmann [22] with permission)

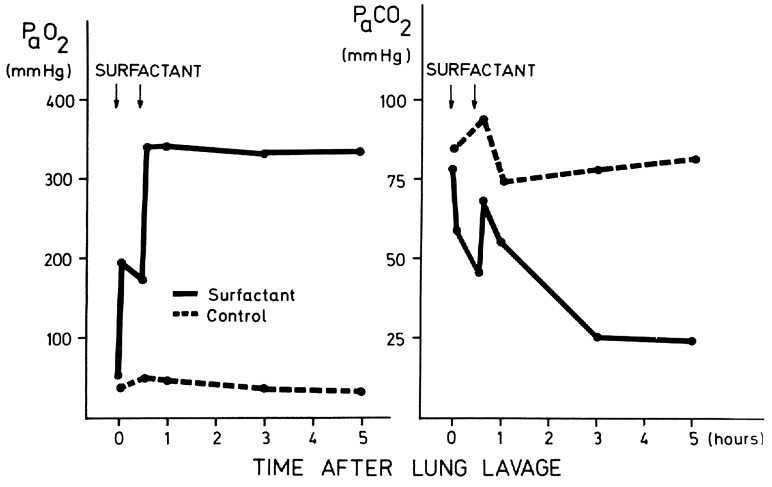

Fig. 7. Sequential recordings of PaO_2 and $PaCO_2$ in two adult guinea pigs subjected to repeated lung lavage, followed by ventilation for 5 hours with pressure-controlled ventilation, 100% oxygen, I/E ratio 1:2, frequency 30/min, insufflation pressure 28 cm H_2O and PEEP 6 cm H_2O. One animal received two tracheal instillations of natural surfactant (each dose 50 mg), 5 and 30 min after lavage (arrows). The improved blood gases, recorded after surfactant replacement, are stable throughout the period of observation. (From Lachmann et al. [20] with permission)

We have also found that surfactant replacement is an effective therapeutic measure in experimental viral pneumonia. In these studies, lung mechanics were recorded in mice 6 days after infection with influenza virus, before and after tracheal instillation of surfactant. Surfactant replacement resulted in a significant augmentation of tidal volumes at insufflation pressure 25 cm H_2O, from 5.8 ± 1.3 to 19.5 ± 6.4 ml/kg (mean $\pm$ SD).

Histologic examination of the lungs, from all animals, showed the interstitial infiltration of mononuclear inflammatory cells, typical of viral pneumonia. Animals receiving surfactant had clearly improved lung aeration in comparison with untreated controls. These findings provide additional indication of the potential therapeutic significance of surfactant replacement in ARDS.

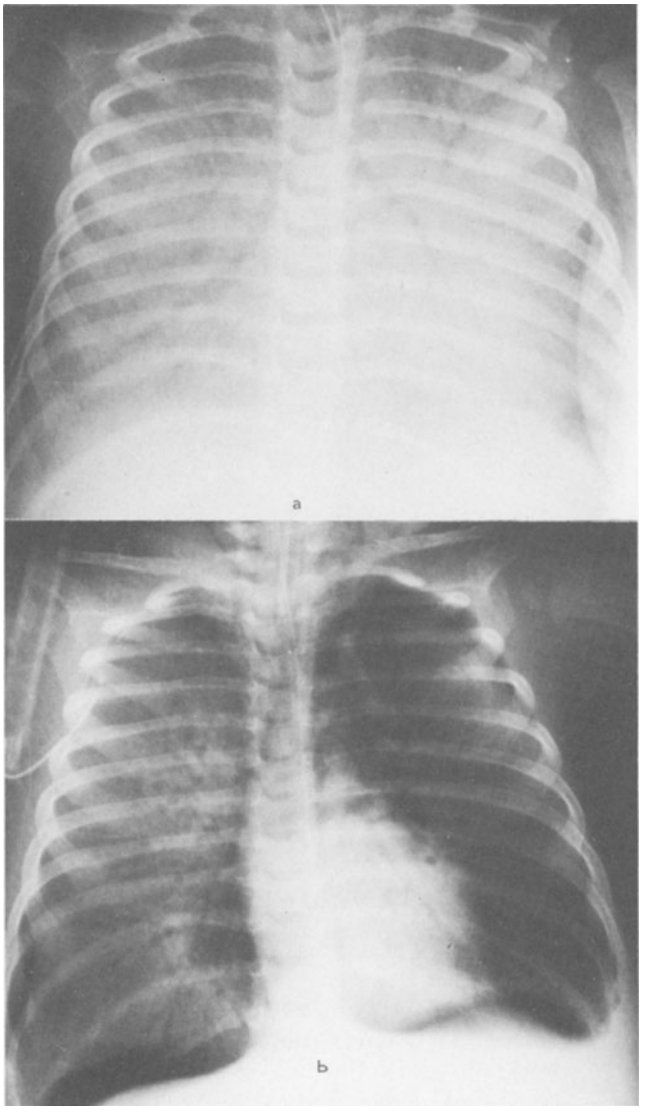

Fig. 8 a, b. X-rays from a child with a severe ARDS immediately before **(a)** and 4 hr after surfactant replacement therapy **(b)**

Surfactant Substitution in Clinical ARDS

In a terminal patient with sepsis and severe ARDS (PaO_2 of 19 mm Hg, despite pressure controlled ventilation with an I:E ratio of 3:1; peak airway pressure of 48 cm H_2O; PEEP 12 cm H_2O; $FIO_2 = 1$), tracheal instillation of natural surfactant (± 2 ml/kg BW; total phospholipid content 55 mg/ml) led, within a few hours, to a dramatic improvement in gas exchange (PaO_2 from 19 mm Hg to 240 mm Hg; $PaCO_2$ from 68 to 45 mm Hg). Chest x-rays, made 20 minutes before surfactant instillation (Fig. 8a) and 4 hours later (Fig. 8b), clearly showed that a near "normal" situation had been restored within this short period of time. These first clinical results already show that lungs from patients with severe RDS, superimposed with virus and bacterial pneumonia, can be re-aerated by tracheal instillation of exogenous surfactant.

Conclusions

On the basis of our current understanding of the lung surfactant system it is established that surfactant serves as an anti-atelectasis factor, an anti-oedema factor, as an essential substrate for local defence mechanisms and for non-ciliar mucous transport and, as shown by our latest results, surfactant is also involved in bronchial obstruction and protection of the lung against pollution. Together with other therapeutic measures such as inhibition of proteases and metabolites of the arachidonic acid cascade, improved control of blood coagulation, complement release and administration of anti-oxidants, surfactant replacement will be one of the most important therapeutic measures in ARDS.

References

1. King EG (1976) The adult respiratory distress syndrome: our evolving understanding of hypoxaemic respiratory failure. J Irish Coll Phys Surg 6:39–46
2. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II; 319–323
3. Guyton AC, Moffatt DS, Adair TA (1980) Role of alveolar surface tension in transepithelial movement of fluid. In: Robertson B, van Golde LMG, Batenburg JJ (eds) Pulmonary Surfactant. Elsevier, Amsterdam, pp 171–185
4. Huber G, Mullane J, LaForce FM (1976) The role of alveolar lining material in antibacterial defenses of the lung. Bull Europ Physiopath Resp 12:178–179
5. Macklem PT, Proctor DF, Hogg JC (1970) The stability of peripheral airways. Respir Physiol 8:191–203
6. Lachmann B (1985) Possible function of bronchial surfactant. Eur J Respir Dis 67:49–61
7. Rensch H, von Seefeld H (1984) Surfactant – mucus interaction. In: Robertson B, van Golde LMG, Batenburg JJ (eds) Pulmonary Surfactant. Elsevier, Amsterdam, pp 203–214
8. Reinfenrath R (1983) Surfactant action in bronchial mucus. In: Cosmi EV, Scarpelli EM (eds) Pulmonary Surfactant System. Elsevier, Amsterdam, pp 339–347
9. Lachmann B, Becher G (1986) Protective effect of lung surfactant on allergic bronchial constriction in guinea pigs. Am Rev Respir Dis 133:A118
10. Lachmann B, Bergmann KC, Enders K, et al (1977) Können pathologische Veränderungen im Surfactant-System der Lunge zu einer akuten respiratorischen Insuffizienz beim Erwach-

senen führen? In: Danzmann E (ed) Anaesthesia 77, Proceedings of the 6th Congress of the Society of Anaesthesiology and Resuscitation of the GDR Vol 1. Soc Anaesthesiol and Resuscitation of the GDR, Berlin, pp 337–353
11. Hallman M, Spragg R, Harrell JH, Moser KM, Gluck L (1982) Evidence of lung surfactant abnormality in respiratory failure. J Clin Invest 70:673–683
12. Petty TL, Silvers GW, Paul GW, Stanford RE (1979) Abnormalities in lung elastic properties and surfactant function in adult respiratory distress syndrome. Chest 75:571–574
13. Petty TL, Reiss OK, Paul GW, Silvers GW, Elkins ND (1977) Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with trauma and shock. Am Rev Respir Dis 115:531–536
14. Wichert P von, Kohl FD (1977) Decreased dipalmitoyl-lecithin content found in lung specimens from patients with so-called shock lung. Eur J Intens Care 3:27–30
15. Murray JF (1977) Mechanism of acute respiratory failure. Am Rev Respir Dis 115:1071–1078
16. Pontoppidan H, Rie MA (1982) Pathogenesis and therapy of acute lung injury. In: Prakash O (ed) Applied Physiology in Clinical Respiratory Care. Martinus Nijhoff, The Hague, pp 55–73
17. Cross CE, Hyde RW (1978) Treatment of pulmonary edema. In: Staub NC (ed) Lung Biology in Health and Disease. Vol 7 Lung Water and Solute Exchange. Marcel Dekker, New York, pp 471–513
18. Rinaldo JE, Rogers RM (1982) Adult respiratory distress syndrome: changing concepts of lung injury and repair. N Engl J Med 306:900–909
19. Lachmann B, Fujiwara T, Chida S, Morita T, Konishi M, Nakamura K, Maeta H (1981) Improved gas exchange after tracheal instillation of surfactant in the experimental adult respiratory distress syndrome. Crit Care Med 9:158
20. Lachmann B, Fujiwara T, Chida S, Morita T, Konishi M, Nakamura K, Maeta H (1983) Surfactant replacement therapy in the experimental adult respiratory distress syndrome (ARDS) In: Cosmi EV, Scarpelli EM (eds) Pulmonary Surfactant System. Elsevier, Amsterdam, pp 231–235
21. Berggren P, Curstedt T, Grossman G, Lachmann B, Robertson B (1983) Surfactant replacement in experimental respiratory distress induced by repeated lung lavage. IRCS Med Sci 11:787–788
22. Lachmann B (1985) Surfactant-Therapie bei ARDS. In: Lavin P, Peter K, van Aken H (eds) Intensivmedizin. Thieme, Stuttgart, pp 61–68
23. Rüfer R (1967) Der Einfluss oberflächenaktiver Substanzen auf Entfaltung und Retraktion isolierter Lungen. Pflügers Arch ges Physiol 298:170–184