Surfactant Therapy: Beyond a Rescue Therapy for ARDS

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Introduction

In acute respiratory distress syndrome (ARDS) the deficiency of (active) surfactant leads to the progressive deterioration of lung function. If one can reverse the surfactant deficiency one can expect also to improve lung function and ultimately this may reduce the mortality rates in ARDS patients. Therefore, it would be logical to supplement the ARDS lung with exogenous surfactant. Because ARDS is associated with a high mortality rate (>40%) current investigation on surfactant therapy in adults is focused on reducing mortality in these patients by using exogenous surfactant as a rescue therapy. However, in light of the unique properties of surfactant as a rate-limiting factor in the transfer across the alveolo-capillary membrane, as well as its surface tension lowering properties and the critical role of surfactant in pulmonary host defense, in this chapter we present an outline for future applications of exogenous surfactant.

Properties of Surfactant

The normal physiological functions of the pulmonary surfactant system include:

- Mechanical stabilization of lung alveoli: during deflation of the lung a high surface tension would tend to promote alveolar collapse, however, the dynamic surface tension behavior of surfactant prevents this.
- Transport of mucus and inhaled particles: surfactant acts as an anti-glue factor, preventing the development of large adhesive forces between mucus and the bronchial wall [1].
- Protection against lung edema: another important function of surfactant is stabilization of the fluid balance in the lung, especially across the alveolo-capillary membrane. Figure 1 presents a diagram of fluid balance across the lung. The normal plasma oncotic pressure of 37 cmH_2O is opposed by the capillary hydrostatic pressure of 15 cmH_2O, by the oncotic pressure of interstitial fluid proteins of 18 cmH_2O, and by the surface tension conditioned suction pressure of 4 cmH_2O. In general, alveolar flooding will not occur when the surfactant system is functioning properly. However, when the surface tension rises above a critical level, alveolar flooding will occur, leading to influx of proteins into the alveolar space, which results in further inactivation of surfactant. Besides stabilizing the fluid balance across the alveolo-capillary membrane, surfactant is also rate limiting in the transfer of several other molecules across the alveolo-capillary membrane [2].

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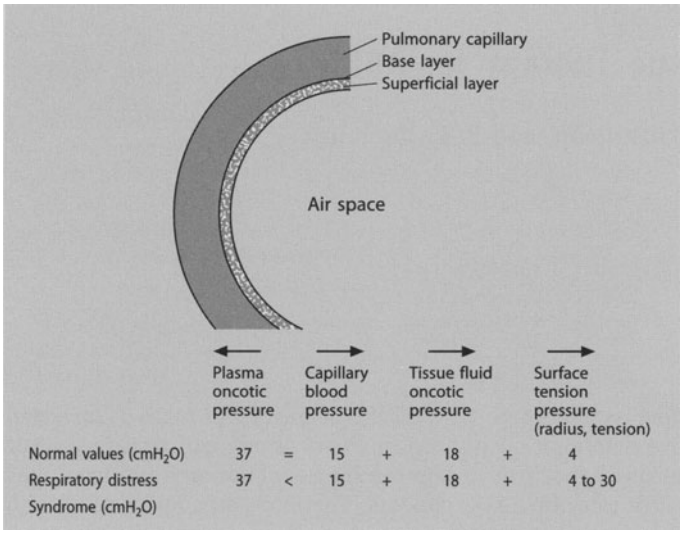

Fig. 1. Diagram showing the factors influencing fluid balance in the lung

- Local defense against infection: it has been demonstrated that surfactant, in particular surfactant protein A (SP-A) and probably SP-D, enhances the antibacterial and antiviral defense properties of alveolar macrophages [3].

Preventive Treatment with Exogenous Surfactant

Our group showed that respiratory failure induced by aspiration of hydrochloric acid could be prevented when exogenous surfactant was given before deterioration of lung function (i.e., within 10 min after acid aspiration), whereas after development of respiratory failure exogenous surfactant served only to prevent further decline of lung function but did not restore gas exchange [4]. When treatment starts in a later stage of lung injury, the amount of inhibitory proteins that have accumulated in the lung require larger amounts of surfactant, or several consecutive administrations, to improve lung function.

If surfactant can prevent aspiration-induced lung injury, we speculated that treatment with surfactant could diminish the lung injury observed by ventilation, ventilator-induced lung injury (VILI). Therefore, using a standard model of VILI, we investigated whether administration of exogenous surfactant has any beneficial effects. In the animals ventilated with high peak inspiratory volumes and low levels of positive end-expiratory pressure (PEEP), inducing VILI, we demonstrated that surfactant prevented impairment of oxygenation and deterioration of lung mechanics, and reduced the permeability to Evans blue [5].

When patients are ventilated for even short periods, this can result in the release of lung injury markers [6]. Verbrugge and colleagues showed that mechanical ventilation for only 7 minutes resulted in release of purines [6]. Instillation of exogenous surfactant before the start of mechanical ventilation reduced this release of this lung injury marker [6].

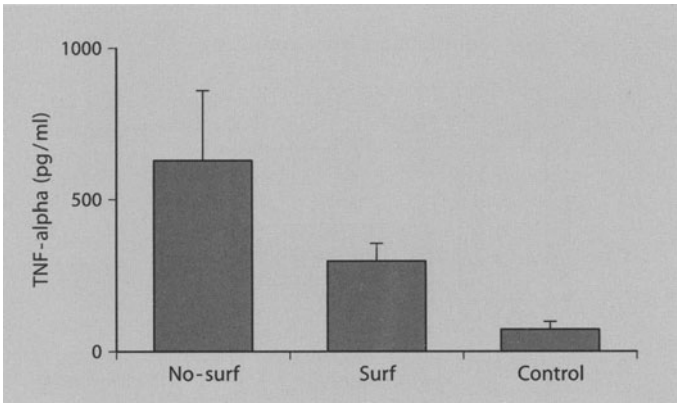

Fig. 2. Tumor necrosis factor (TNF)-α concentration in the broncho-alveolar lavage (BAL) fluid of animals which had a compartmentalized systemic activation of the pro-inflammatory mediator TNF-α. After 20 min of ventilation increased levels of TNF-α are found in the BAL fluid of the animals who did not receive surfactant (*no-Surf*) indicating loss of compartmentalization. In the animals pre-treated with surfactant (*Surf*) there is a significant reduction in loss of compartmentalization. Control animals had no systemic inflammation activation. Adapted from [9]

Mechanical ventilation of a healthy lung can activate the inflammatory cascade. In ARDS lungs, characterized by increased inflammatory activation, mechanical ventilation will augment this activation of the inflammatory process. Although production of the inflammatory mediators is compartmentalized, mechanical ventilation can lead to loss of compartmentalization [7]. This loss of compartmentalization induces a shift of inflammatory mediators across the alveolo-capillary membrane [7], increasing the risk of patients to develop multi-organ failure (MOF) [8]. We have recently demonstrated that this loss of compartmentalization is largely dependent on the function of surfactant, especially its rate-limiting function in the transfer of inflammatory mediators across the alveolo-capillary membrane [9]. Increasing the amount of active surfactant in a lung significantly reduced the decompartmentalization of pro-inflammatory mediators [9] (Fig. 2).

We therefore speculate that the early use of exogenous surfactant as an adjuvant therapy during mechanical ventilation could help reduce the incidence of VILI in patients, diminish the occurrence of MOF due to ventilation, and, thus, help to improve the outcome of patients requiring mechanical ventilation. Finally preventive application of surfactant requires lower amounts of surfactant and could help to reduce overall costs by shortening the ICU stay.

Surfactant and Pneumonia

Surfactant (especially SP-A) and alveolar macrophages have a synergistic effect in the defense against bacteria [3]. Studies in patients have shown that, following a decrease in lung compliance (thus, surfactant deficiency), pneumonia will often develop. There are, however, several pathways along which an impairment of surfactant might develop in pneumonia (Fig. 3). Pathogens can directly interact with the extracellular surfactant pool or cause surfactant impairment through interactions

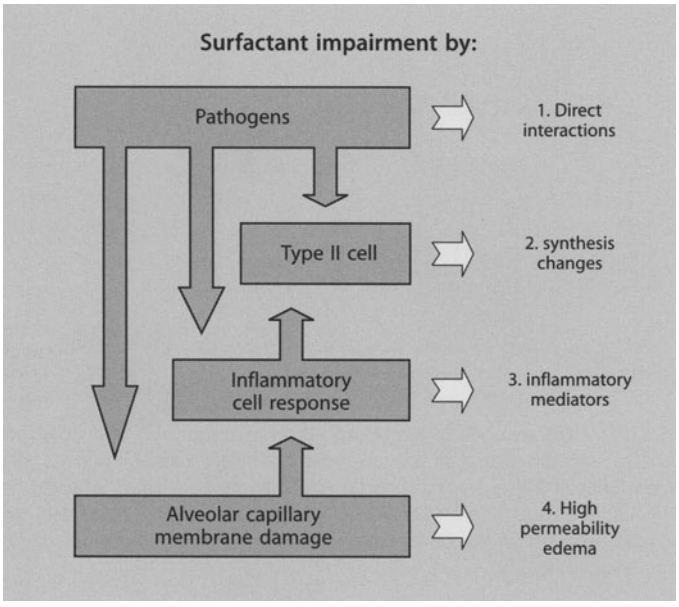

Fig. 3. Pathways along which surfactant impairment may develop into pneumonia. Pathogens can directly interact with the extracellular surfactant pool or cause surfactant impairment through interactions with type II cells, through induction of an inflammatory cell response, or by damaging the integrity of the alveolo capillary membrane

with type II cells, through induction of an inflammatory response, or by destroying the integrity of the alveolar-capillary membrane. Bacteria, bacterial toxins, oxygen radicals, viruses, phospholipases, and proteinases released from inflammatory cells interact directly with the surfactant film. Furthermore, type II cell function may be affected by virus replication, bacterial cytotoxic agents, or oxygen radicals and interleukins (IL) released by inflammatory cells leading to alterations in surfactant composition and/or a decreased surfactant synthesis. Endothelial and epithelial cell lysis and/or proteolytic activity derived from microorganisms or inflammatory cells can, finally, damage the alveolar-capillary membrane leading to high permeability edema. The plasma proteins of the edema will inactivate the surfactant film. Surface tension at the alveolar walls increases, leading to increased suction forces across the alveolo-capillary membrane. This finally results in a vicious circle. Dependent on the pathogen involved, one or more of the above-mentioned mechanisms may contribute to a surfactant dysfunction. Thus, with the proven deficiency of active exogenous pulmonary surfactant in patients with pneumonia, it is rational to assume that replenishment with active surfactant could halt or even reverse the disease process.

We demonstrated the effectiveness of surfactant therapy in different animal models suffering from viral pneumonia or *Pneumocystis carinii* pneumonia [10, 11]. In viral pneumonia, tracheal administration of exogenous surfactant led to improved lung compliance and improved functional residual capacity (FRC), as well as restoration of gas exchange. Similarly, in rats with *Pneumocystis carinii* pneumonia, surfactant instillation led to improvement of arterial oxygenation [10].

In humans suffering from infectious lung diseases, data on treatment with exogenous surfactant are scarce. Lachmann treated a four-year-old patient with bacterial pneumonia and acute respiratory failure. Surfactant was instilled in three doses, in succession (150; 100; 50 mg/kg) and after the last dose of surfactant, gas exchange improved dramatically. Chest X-ray taken four hours after treatment showed nearly 'normal' lungs. The results of first multi-patient studies with surfactant are now being published. Walmrath et al. studying patients with sepsis and established severe ARDS, showed that bronchoscopic application of a natural surfactant (300 mg/kg) improved arterial oxygenation in all patients; in half of the patients a second dose (200 mg/kg) was required [12]. Surfactant can also restore or diminish lung injury due to infections; however, surfactant and surfactant producing alveolar type II cells are susceptible to bacteria and viruses. Nowadays, the interest in improving surfactant therapy while simultaneously preventing and/or treating lung infections is growing.

Surfactant as a Carrier

It has been proposed that the spreading properties and the inherent therapeutic potential of surfactant could be used to deliver antimicrobial agents to the lung parenchyma [13]. Direct application of antibiotics to the airway offers many potential advantages in the treatment and prevention of pneumonia. Delivery direct to the airways should increase the local effectiveness and reduce the risk for systemic toxicity caused by antibiotics, e.g., aminoglycosides [14]. Locally administered antibiotics for prevention and/or treatment of lower respiratory tract infection have been extensively studied [13]. However, despite the high antibiotic dose delivered to the lung, the question of efficacy remains controversial; explanations for this include failure of the antibiotic to reach the infected lung area. When delivered as an aerosol, only a small amount of nebulized antibiotic (around 10%) is actually deposited in the lung. Moreover, with increased airway obstruction, atelectasis and lung damage, the amount of aerosol deposited will be even lower. Lung distribution of intratracheally instilled antibiotic solutions is poorly studied. It is known, however, that distribution of intratracheally-instilled saline is largely limited to the central regions of the lung [15]. Due to the small diameter of peripheral airways, fluid with a high surface tension (such as saline or water) requires high pressures for passage through these airways [16]. Studies have shown that pulmonary surfactant is superior to saline in distributing a radioactive colloid within healthy lungs, as indicated by the more homogenous and peripheral lung distribution; the effectiveness of surfactant as a carrier was even more evident at lower volumes of fluid [15]. Furthermore, surfactant re-expands atelactatic areas, which are most likely to be the infected areas. It is, therefore, expected that intratracheally-instilled antibiotics are more effective when the distribution within the lung is optimized by using pulmonary surfactant as a carrier.

Experimental Studies

Although the idea to use surfactant as a carrier agent was proposed several years ago, data from *in vivo* experimental studies are scarce. Our group was the first to study the effect of a surfactant-tobramycin mixture on mice suffering from respira-

tory infection with *Klebsiella pneumoniae* [17]. It was demonstrated that intratracheal instillation of a surfactant-tobramycin mixture is more effective in protecting mice from death due to a respiratory *Klebsiella pneumoniae* infection than intratracheal instillation of tobramycin alone or of surfactant alone [17]. These results were the first to indicate that exogenous surfactant is an effective carrier agent. It is suggested that one of the advantages of locally administered drugs is the minimization of systemic side-effects of the drugs.

Various surfactant preparations are already commercially available and are being used in the treatment of RDS in neonates. Studies performed in animal models under standardized conditions showed marked differences between several natural and synthetic surfactant preparations in their ability to improve lung function [18]. Natural surfactants containing the hydrophobic proteins SP-B and SP-C (which are more able to withstand inactivation by plasma proteins) are more effective in improving lung function than artificial surfactants, or natural surfactants with low amounts of SP-B and SP-C.

Conclusion

Although use of surfactant as a rescue therapy in ARDS is supported by a large body of evidence, the unique properties of surfactant give rise to other application areas.

Exogenous surfactant therapy can be used to prevent injury caused by mechanical ventilation and help diminish the occurrence of VILI. Thus, when patients require mechanical ventilation the use of surfactant as an adjuvant therapy should be considered. Because surfactant is also rate limiting in transfer of several substances (including inflammatory mediators) across the alveolo-capillary membrane, application of surfactant could reduce the incidence of MOF due to translocation of inflammatory mediators from the lung to the systemic circulation.

Furthermore, we present information on the critical role surfactant plays in the development of pneumonia. Using the low surface tension properties combined with the excellent spreading potential of surfactant, we have outlined the use of a combination of surfactant and antibiotic mixture to improve the effectiveness of antimicrobial therapy. Experimental data show very promising results and warrant future clinical application of the potent combination of antibiotics and surfactant in patients with pnaumonia.

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