# Rationale for Surfactant Therapy in Pneumonia

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## Introduction

Pneumonia remains an important cause of morbidity and mortality, despite advances in antimicrobial therapy. Pneumonia causes injury to the terminal alveolo-capillary unit, which is followed by increased alveolar permeability, pulmonary edema and hemorrhage, and may lead to respiratory failure. It has been demonstrated that the pulmonary surfactant system becomes impaired in pneumonia, causing decreased compliance, atelectasis, pulmonary edema, ventilation-perfusion mismatch, intrapulmonary shunting, and an impaired arterial oxygenation [1–3].

Pulmonary surfactant, produced by alveolar type II cells, is composed of phospholipids and 4 specific surfactant proteins, and forms a lipid layer coating the alveolar and bronchial epithelium. Its primary function is to reduce surface tension at the air-liquid interface of the terminal airways, which promotes alveolar expansion during inspiration and prevents alveolar collapse at expiration [4]. This layer is the initial surface that invading microorganisms contact when entering the alveoli, and accruing evidence suggests a double role for surfactant in pneumonia: It is involved in primary host defense against inhaled pathogens and is simultaneously a target in pneumonia [2, 3, 5].

Human necropsy studies in the 1960s already demonstrated a decreased surfactant activity in lung involved in pneumonia [6]. Although to date the impaired surfactant function in pneumonia has been verified by a great number of studies, precise mechanisms are still unclear. Possible pathways include a direct interaction of pathogens with the surfactant film, damage to alveolar type II cells affecting surfactant synthesis, and surfactant inactivation by inflammatory mediators and/or protein-rich alveolar edema [2, 3, 7].

Because surfactant dysfunction plays a role in the pathogenesis of pneumonia, beneficial effects can be expected from exogenous surfactant therapy. A few reports have demonstrated an improvement in lung function after intratracheal instillation of surfactant in animals and humans suffering from acute respiratory failure caused by pneumonia [1, 2]. It has moreover, been postulated that the excellent spreading properties of exogenous surfactant in the lung and its capacity to re-expand atelectatic areas could be exploited for delivering antimicrobial agents directly to the sites most wanted in pneumonia [8]; that is, within the alveolar space and the lung interstitium. Studies in this area are very limited but the first experimental results suggest that the use of pulmonary surfactant-antibiotic mixtures is a promising approach for treatment of severe pneumonia [9].

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The current chapter will, after a brief description of the pulmonary surfactant system, outline the existing evidence for surfactant abnormalities in pneumonia. It will present the few experimental and clinical data on exogenous surfactant therapy in pneumonia and discuss the concept of using exogenous surfactant as a carrier for antimicrobial agents.

## The Pulmonary Surfactant System

The pulmonary surfactant system has been the subject of extensive research during the past three decades. Many aspects on composition, metabolism and function of pulmonary surfactant have been elucidated and will only be discussed briefly here (for reviews see [1, 4, 5, 10–12]).

### Composition and Metabolism

The extracellular compound of pulmonary surfactant can easily be harvested by broncho-alveolar lavage (BAL) of the whole lung with saline and is essentially similar between several mammalian species. Surfactant consists predominantly of lipids (80–90%), proteins (10%), and small amounts of carbohydrates. Of the total lipid weight, the phospholipids (Table 1) represent 80–90% of which dipalmitoylphosphatidylcholine (DPPC) is most abundantly present and the principal surface tension reducing compound [10].

Four surfactant specific proteins (SP) have been identified and named in the sequence of their discovery: surfactant proteins A, B, C and D [10]. SP-A and SP-D are hydrophylic proteins whereas SP-B and SP-C are highly hydrophobic proteins. The surfactant proteins have been accredited various roles in the intra-alveolar metabolism of surfactant and the dynamics of the surface film. In addition SP-A and SP-D belong to the so called collectins and apparently play a role in the innate immunity of the lung [11].

Surfactant lipids and proteins are synthesized in type II cells and secreted into the alveolar space. Synthesis and/or secretion of surfactant are known to be influenced by a number of different stimuli [10]. Once secreted, the surfactant is transformed into specific structures called tubular myelin, from which the insertion of phospholipids into the air-liquid interface is thought to take place. The surface film changes dynamically during respiration, with phospholipids continuously incorporated in and removed from the surface film [10]. Clearance of surfactant material from the

**Table 1.** Percentual distribution of phospholipid fraction. (From [10] with permission)

| | |
|---|---|
| Phosphatidylcholine of which 50% DPPC | 75% |
| Phosphatidylglycerol | 10% |
| Phosphatidylethanolamine | 5% |
| Phosphatidylinositol/Phosphatidylserine | 5% |
| Sphingomyelin | 5% |

alveoli seems predominantly accomplished by re-uptake in the type II cells and uptake by alveolar macrophages [12].

### Surfactant Functions and Properties

The lungs have a continual elastic tendency to collapse which is caused by the recoil tendency of the tissue and, most pronounced, by the surface tension at the air-liquid interface in the lung. By reducing surface tensions at the air-liquid interface, pulmonary surfactant promotes alveolar stability at end-expiration and reduces alveolar opening pressures, as explained by the law of Laplace. That is, the pressure that is required to keep the alveolus expanded (P) is directly proportional to the tension in the alveolar wall (y) divided by the alveolar diameter (r): $P = 2y/r$. Surfactant reduces the surface tension at the air-liquid interface and the degree of surface tension reduction is closely tuned to the alveolar radius. As alveolar size decreases during expiration, the surface film becomes enriched in DPPC which accounts for the very low surface tension (close to 0 dynes/cm) needed to prevent alveolar collapse [1, 4, 10].

Surfactant further protects against the formation of lung edema by stabilizing the fluid balance in the lung. In general, the forces that influence the circulation of liquid at the alveolo-capillary level in the lungs include: plasma colloid osmotic pressure on the one side, and capillary hydrostatic pressure, interstitial colloid osmotic pressure and alveolar surface tension on the other. As surface tension increases, the combined forces for moving fluid into the alveoli increases, resulting in pulmonary edema [4, 13].

Pulmonary surfactant not only lines the alveoli, but also the narrow conducting airways. Increasing evidence supports the concept that pulmonary surfactant maintains openness of those small airways. A lack of bronchial surfactant may thus cause airway obstruction or collapse of small bronchioli with air trapping [4, 14, 15].

Finally, there is accruing evidence that pulmonary surfactant plays a role in the primary host defense in the lung. Surfactant may impede pathogen adherence to epithelial surfaces and facilitates mucocilliary clearance. Furthermore, surfactant components stimulate alveolar macrophages, that is, phagocytosis, intracellular degradation and migration. SP-A and SP-D are members of a collectin class and may function as opsonins inhibiting infectivity of various organisms directly and by enhancing phagocytosis. In addition, an immunosuppressive effect may exist, as surfactant components decrease the stimulatory effects of antigens on pulmonary and blood monocytes. The immunosuppressive effects are predominantly in association with the surfactant lipids. Thus far, more questions than answers remain on the role of surfactant in pulmonary host defense, especially concerning its *in vivo* relevance (for review see [5, 11]).

## Surfactant Impairment in Pneumonia

Both human and animal studies have provided evidence that pneumonia is attended with significant changes in pulmonary surfactant composition and function (Table

2). The data is derived from extracts or lavage samples of lungs from patients or animals with pneumonia of, in most cases, known microbial etiology. In spite of the diversity between studies, the changes in pulmonary surfactant in pneumonia can roughly be characterized as: 1) increased surface tension, 2) a decrease in the amount of phospholipids recovered, 3) a shift in the phospholipid or fatty acid profile of the samples, and 4) changes in the amount of surfactant proteins recovered (Table 2). Shifts in phospholipid profiles are often expressed as ratios, e.g. the concentration of phosphatidylcholine (lecithin) to sphingomyelin is referred to as the L/S ratio.

## Possible Pathways

There are several pathways along which an impairment of the surfactant system may develop in pneumonia (Fig. 1). Pathogens can directly interact with the extracellular surfactant pool or cause a surfactant impairment through interactions with type II cells, through induction of an inflammatory response or by destroying the integrity of the alveolo-capillary membrane. Proteases [16], phospholipases [7, 17], or oxygen radicals [18] released by microorganisms and/or inflammatory cells can directly affect the surfactant. Further, type II cell function may be affected by virus replication [19], bacterial cytotoxic agents, or oxygen radicals [20] and interleukins released by inflammatory cells leading to alterations in surfactant composition and/or a decreased surfactant synthesis. Type I and/or type II cell lysis and/or proteolytic activity derived from microorganisms [21] or inflammatory cells can, finally, damage the alveolo-capillary membrane leading to a protein-rich edema. It is well-established that plasma proteins are capable of inactivating pulmonary surfactant [7]. Dependent on the pathogen involved, one or more of the above mentioned mechanisms may contribute to a surfactant dysfunction. So far, however, ample data are available to support the proposed mechanisms and much await experimental proof.

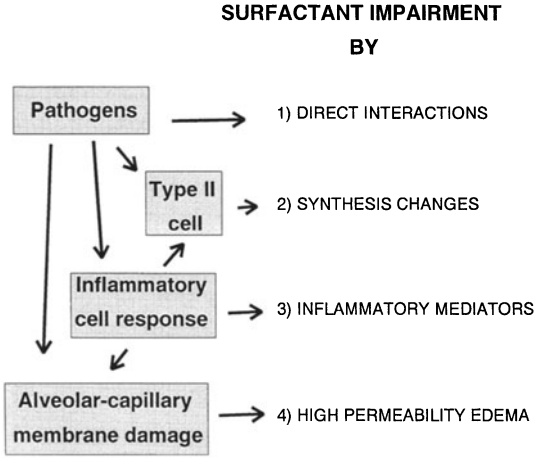


**Fig. 1.** Pathways along which a surfactant impairment may develop in pneumonia. Pathogens can directly interact with the extracellular surfactant pool or cause a surfactant impairment through interactions with type II cells, through induction of an inflammatory response or by destroying the integrity of the alveolar capillary membrane.

**Table 2.** Reported changes in surfactant phospholipid composition in pneumonia

| Authors | Ref | Micro-organism | Animal | Sample source | Total PL | Quantitative | | | | | | | Percentual distribution | | | | | | | Ratio / other | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PC | PG | PE | PS | PI | SPH | LysoPC | PC | PG | PE | PS | PI | SPH | LysoPC | | |
| **Experimental** | | | | | | | | | | | | | | | | | | | | | |
| *Viral* | | | | | | | | | | | | | | | | | | | | | |
| Stinson et al | [22] | influenza A | mice | chopped lung washing | – | ↓(DSPC) | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Engen and Brown | [23] | Bovine herpes-virus-1 | calves | BAL | – | – | – | – | – | – | – | – | ↓PC | ns | ↑PE | ns | ns | ns | ns | – | – |
| Engen and Brown | [23] | Para-influenza-3 | calves | BAL | – | – | – | – | – | – | – | – | ↓PC | ns | ↑PE | ns | ns | ns | ns | – | – |
| *Bacterial* | | | | | | | | | | | | | | | | | | | | | |
| Von Wichert and Wilke | [37] | Myco-plasma pulmonis | pig | tissue homo-genates | ↑PL | – | – | – | – | – | – | – | ↑PC | – | ns | ns | ns | ↓SPH | – | – | – |
| Sachse | [28] | Pasteurella multicoda | pigs | BAL | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | ↓PC/PI | ↓PG/PE |
| Tahvanainen and Hallman | [30] | Endotoxin | guinea-pig | BAL | ns | ↓PC | ↓PG | ns | ns | ns | ↑SPH | ↑LysoPC | ↓PC | ↓PG | ns | ns | ↑PI | ↑SPH | ↑LysoPC | – | – |
| King et al | [26] | Pseudo-monas aeruginosa | baboons | BAL | – | ↓(DSPC) | – | – | – | – | – | – | – | – | – | – | – | – | – | ↓PG/PI | |
| *Parasitic* | | | | | | | | | | | | | | | | | | | | | |
| Kernbaum et al | [40] | Pneumo-cystis carinii | rat | BAL | ↓PL | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Sheehan et al | [39] | Pneumo-cystis carinii | rat | BAL | ↓PL | ↓PC | ↓PG | ↓PE | ↓PS | ↓PI | ↓SPH | ns | ↓PC | ns | ns | ns | ns | ↑SPH | ns | – | – |

**Table 2.** Continued

| Authors | Ref. | Micro-organism | Sample source | Total PL | Quantitative | | | | | | | Percentual distribution | | | | | | | Ratio / other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | PC | PG | PE | PS | PI | SPH | LysoPC | PC | PG | PE | PS | PI | SPH | LysoPC | |
| **Patient studies** | | | | | | | | | | | | | | | | | | | |
| Günther et al | [49] | Miscellaneous | BAL | ↓PL | – | – | – | – | – | – | – | ↓PC | ↓PG | ns | ns | ↑PI | ↑SPH | ns | – – |
| Baughman et al | [47] | Bacterial | BAL | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | ↓Palmitic acid |
| LeVine et al | [50] | Bacterial | tracheal aspirates | – | ns | – | – | – | – | ↑SPH | – | – | – | – | – | – | – | – | ↓PC/SPH |
| LeVine et al | [50] | Viral | tracheal aspirates | – | ns | – | – | – | – | ns | – | – | – | – | – | – | – | – | ↓ PC/SPH |
| Escamilla et al | [52] | HIV/PCP | BAL | ns | ↓PC | ↓PG | ↓PE | ns | ns | ↑SPH | ↑LysoPC | ↓PC | ↓PG | ↑PE | ↑PS | ↑PI | ↑SPH | ↑LysoPC | |
| Sternberg et al | [54] | HIV/PCP | BAL | ↓PL | – | – | – | – | – | – | – | – | – | – | – | – | – | – | ↓Diacylglycerol |
| Meignan et al | [56] | HIV/ miscellaneous | BAL | ns | ns | ↑PG | – | – | – | – | – | – | – | – | – | – | – | – | ↑Cholesterol |

Total PL = total phospholipid; PC = phosphatidylcholine; PG = phosphatidglycerol; PE = phosphatidylethanolamine; PI = phosphatidylinositol; SPH = sphingomyelin; LysoPC = lysophosphatidylcholine; DSPC = disaturatedphosphatidylcholine; – means not measured or reported, ns = not significantly changed.

## Experimental Viral Pneumonia

In influenza A virus pneumonia in mice, an increased surface tension together with a decreased disaturated phosphatidylcholine (DSPC) content was found as early as 2 days after infection, decreasing progressively to minimal values at 10 days after infection [22]. This was observed in uncollapsed, and even more pronounced in collapsed infected lung tissue, and also in lung tissue that was not filled with edema. Morphological examination revealed swelling and degeneration of alveolar type II-cells. It was suggested that injury and destruction of type II cells by the virus were the principal causes of the reduced surfactant activity [22].

Virus replication in type II cells may play a prominent role in surfactant disturbances in viral pneumonia. In mink kits, infection with aleutian mink disease parvovirus causes interstitial pneumonia resulting in a fatal respiratory failure [19]. Hyperplasia and hypertrophia of type II cells was observed and virus replication together with a decreased SP-C mRNA could be detected in type II cells by double in situ hybridization [19]. Finally, in calves exposed to bovine herpes virus-1 or parainfluenza-3 virus, changes in the phospholipid profile of BAL fluid have been reported [23].

## Experimental Bacterial Pneumonia

Bacteria may directly interfere with surfactant function, as demonstrated in the studies by Rose and Lindberg [24]. Gram-negative rods, such as *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, demonstrated a marked ability to destroy the surface tension reducing capacity of surfactant after *in vitro* incubation. *Streptococcus pneumonia*, accordingly had an adverse effect on surface tensions, but other Gram-positive bacteria, such as *Staphylococcus aureus* and *Streptococcus pyogenes* did not exhibit this ability. A variety of bacteria secrete phospholipase C and this enzyme is capable of destroying surfactant and affecting its activity [7, 17]. *In vitro* studies have demonstrated a complete degradation of DPPC in the presence of lipase and phospholipase C synthesized by *Pseudomonas aeruginosa* [25].

Two extensive studies reported surfactant alterations in association with pathophysiological alterations in baboons ventilated with 80% oxygen for 6 days, followed by *Pseudomonas aeruginosa* infection and 50% oxygen ventilation for 5 days [26, 27]. Pseudomonas infection caused a decrease in lung function, and surfactant analysis revealed a decrease in DSPC and a loss of surface activity in lavage samples [26]. The phosphatidylglycerol/phosphatidylinositol (PG/PI) ratio was decreased compared with healthy non-ventilated control lungs; however, this decrease was also found in uninfected animals using a similar ventilators protocol [26].

A decrease in the relative PG and increase in the relative PI levels was found in BAL fluid from pigs with a *Pasteurella multocida* pneumonia [28] (Table 2). PG and PI share a common precursor within the surfactant synthesis pathway, and a compositional interchange between PG and PI has also been reported in other respiratory diseases such as idiopathic pulmonary fibrosis, alveolar proteinoses, the adult respiratory distress syndrome (ARDS), and during perinatal life [29].

In guinea pigs, endotracheal instillation of endotoxin caused impaired arterial oxygenation and decreased static compliance within 6 h after instillation [30]. BAL fluid revealed increased surface tensions and decreased total phospholipids, and in the phospholipid profile significantly decreased amounts of DSPC and PG [30] (Table 2). Endotoxin is a constituent of the cell walls of Gram-negative bacteria and is held responsible for many of the inflammatory phenomena associated with Gram-negative infections [31]. The major component lipopolysaccharide (LPS) of endotoxin can form complexes with whole pulmonary surfactant of sheep, and is capable of decreasing surface activity of surfactant *in vitro* [3]. SP-A [32, 33] and SP-D [34] can specifically bind LPS *in vitro*. It has been speculated that this complex formation with LPS has a protective effect, restricting inflammation in the alveoli, rather than a destructive effect on surfactant function [33, 34]. Future studies should clarify the *in vivo* importance of these observations. Lopez and colleagues [35] have demonstrated cytotoxicity of intratracheally instilled LPS to pulmonary epithelial cells causing epithelial desquamation. This may well affect pulmonary surfactant synthesis.

In *Mycoplasma pulmonis*-infected rat lungs, an increased surface tension appeared to be the main cause for a decrease in lung compliance [36]. Increased surface tensions were also found in *Mycoplasma pneumonia* in pigs, in spite of an observed increase in DSPC [37]. This study, however, used whole lung homogenates which include cellular lipids and the increase in phospholipids should therefore be considered with caution.

## Experimental *Pneumocystis carinii* Pneumonia

During its life cycle in the alveolar space, *Pneumocystis carinii* can selectively adhere to alveolar type I cells leading to type I cell degeneration and causing increased alveolo-capillary permeability and pulmonary edema [38]. Studies with a *P. carinii* model in rats have demonstrated a significant decrease in the total amount of phospholipid recovered from BAL fluid [39, 40], changes in phospholipid pattern [39] (Table 2), and an accumulation of SP-A and SP-D in the lung during *P. carinii* pneumonia [41, 42]. Recently, it has been shown that SP-A and SP-D can bind to *P. carinii* organisms and augment attachment of *P. carinii* to alveolar macrophages [42–44]. It has been suggested that *P. carinii* has a pathogen specific effect on SP-A and SP-D homeostasis [41, 45].

## Patient Studies

Sutnick and Soloff [6] already reported in 1964 increased surface tensions in extracts from lungs involved in pneumonia. Since then, several clinical studies have been published demonstrating surfactant abnormalities in pneumonia (Table 2).

Hallman and colleagues [46] studied BAL specimens from patients with respiratory failure and other respiratory diseases among which pneumonia patients. Percentual changes in the phospholipid profile were observed in pneumonia patients in comparison to shifts previously reported in experimental pneumonia, that is decreased PC, PG and increased sphingomyelin [46].

Baughman and coworkers [47] studied fatty acid profiles of non-ventilated patients with bacterial pneumonia. Bacterial pneumonia was characterized by a decrease in palmitic acid which is the major fatty acid component of DPPC. This study clearly demonstrated surfactant abnormalities in bacterial pneumonia before the occurrence of severe respiratory failure. A more recent study from Baughman and coworkers [47] reported a decrease in SP-A levels in non-ventilated patients with bacterial pneumonia, more profound in Gram-positive than Gram-negative bacterial pneumonia [48].

Günther and colleagues [49] studied BAL fluid derived from intubated patients with severe pneumonia from various etiology, ARDS patients, and patients with cardiogenic lung edema. They found in BAL fluid from pneumonia patients, a tendency towards decreased total phospholipid levels, changes in phospholipid profile (Table 2), a decrease in SP-A but not in SP-B levels, and an impaired surface activity. The same study showed that these surfactant abnormalities corresponded to those found in ARDS patients, but were absent in patients with cardiogenic lung edema [49]. Levine and coworkers [50] studied tracheal aspirates from pediatric patients with viral pneumonia or bacterial pneumonia and found in both groups decreased L/S rate and decreased SP-A levels but, no decrease in SP-B levels. The L/S ratio was increased by the time of extubation and correlated weakly with an increase in pulmonary compliance [50].

A number of studies have focused on surfactant abnormalities in *P. carinii* pneumonia in patients infected with the human immunodeficiency virus (HIV) and found decreased levels of total phospholipids [54], changes in phospholipid profile [51–53], and elevated levels of SP-A [54, 55]. There is evidence that infection with HIV itself, without the presence of *P. carinii*, causes increased alveolo-capillary permeability [56] and surfactant abnormalities, i.e. decreased phospholipid [52] and SP-A levels [54].

## Surfactant Therapy in Pneumonia

The increasing evidence for quantitative and qualitative changes in the surfactant system during pneumonia, has led to the hypothesis that surfactant instillation is beneficial in pneumonia. Exogenous surfactant may re-expand and stabilize alveoli and small airways, improve lung volumes, decrease required inspiratory pressures, and enhance alveolar and interstitial fluid resorption in pneumonia. Although surfactant instillation does not directly treat the underlying lung infection, it may invert a progressive decay in lung function.

Instillation of exogenous surfactant preparations derived from natural sources or artificially produced, is to date a well-established therapy in neonates suffering from infant respiratory distress syndrome, known to be triggered primarily by a lack of pulmonary surfactant [57]. Surfactant therapy is currently also under investigation for patients suffering from ARDS [1]. ARDS and pneumonia are closely associated; not only is pneumonia an important antecedent of ARDS, ARDS is also often complicated by secondary pulmonary infection [58]. A few experimental studies have focused on surfactant therapy in pneumonia and a profound number of the ARDS patients treated with surfactant so far, are primary pneumonia patients.

## Experimental Studies

In a Sendai virus model in rats, gas exchange and pulmonary compliance deteriorated after infection, with a lethal outcome within 4 days [59]. Increments of the ventilatory pressures could improve arterial oxygenation on day 2 after infection, but no longer at day 3 after infection (Fig. 2). At this time, keeping the same ventilator settings, replacement therapy with a natural surfactant (200 mg/kg) resulted in a significant improvement of arterial oxygenation [60] (Fig. 2).

Similar improvements in gas exchange were observed in rats with a severe *P. carinii* pneumonia after instillation of 200 mg/kg of a natural surfactant [61]. Furthermore, studies in mice demonstrated that surfactant instillation could correct the decrease in lung compliance and lung volume during severe influenza A pneumonia [62]. Preliminary studies with the same virus in mice showed that surfactant instillation in spontaneously breathing animals at day 5 after infection, could improve survival outcome [63].

Recently, Tashiro and coworkers [64, 65] have reported the results of surfactant treatment in ventilated rats suffering from severe respiratory failure after endotracheal injection of endotoxin. Bolus instillation of a natural surfactant (100 mg/kg body weight) resulted in an improvement of the arterial oxygenation, stable for 3 h after instillation, and an improvement in compliance [64, 65].

## Patient Studies

A few reports have described the effects of surfactant instillation in patients suffering from acute respiratory failure due to pneumonia of different microbial etiology [4, 66, 67]. Lachmann [4] described a 4 year old patient with bacterial pneumonia and acute respiratory failure. This patient received up to 3 doses of a natural surfactant of 150, 100 and 50 mg/kg body weight, respectively. Only after the last dose, a dramatic improvement of gas exchange was observed. 4 h after instillation, the chest X-rays appeared almost 'normal'. Accordingly, improvements in arterial oxygenation were observed after instillation of a natural surfactant in 2 patients with acute

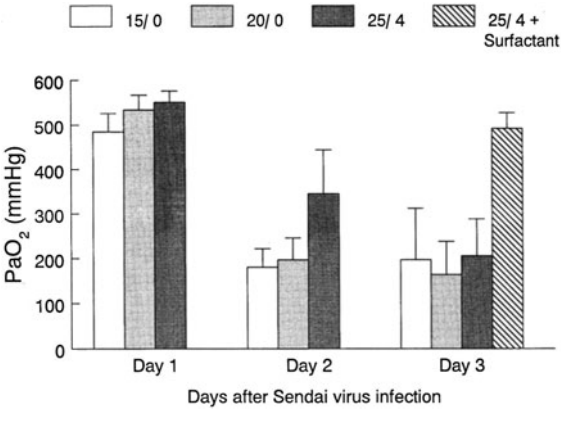


**Fig. 2.** Effects of increased airway pressures (e.g. 15/0 meaning 15 $cmH_2O$ peak inspiratory pressure and 0 $cmH_2O$ PEEP) or intratracheal surfactant instillation on arterial oxygenation ($PaO_2$) during artificial ventilation of rats infected with Sendai virus. At day 3 after infection surfactant instillation significantly increased arterial oxygenation. (From [59, 60] with permission)

respiratory failure due to viral pneumonia by Buheitel and colleagues [66] and by Harms & Herting [67] in 2 neonates suffering from chlamydial pneumonia. One recurrent observation in these reports is the often transient effect after surfactant instillation and the demand for multiple (2 to 3) and high surfactant doses (up to 550 mg/kg body weight) before a stable improvement in lung function is achieved [4, 66, 67]. This has been attributed to the large amount of surfactant inhibitors present in the lung [7].

A similar need for multiple doses was found in a study by Auten and coworkers [68] who studied the effects of surfactant instillation in 7 full term newborns with pneumonia of different etiology. These patients received 1 to 4 doses of 90 mg/kg natural surfactant. Arterial oxygenation improved rapidly after a first and second dose, but was less improved after the subsequent doses [68]. A recent study reported the results of surfactant therapy in acute hypoxemic respiratory failure in pediatric patients of which 13 out of 29 enrolled patients were diagnosed with pneumonia [69]. Patients received a natural surfactant as a bolus up to 4 doses. The overall results demonstrated, according to previous reports, a need for multiple doses in 17 out of 24 initially responding patients, and most profound responses in oxygenation index and ventilatory parameters after the first dose.

So far, only one report has described the effects of selective surfactant instillation in an adult man (aged 71 years, 78 kg) deteriorating from a right lower lobe pneumonia developed after abdominal surgery [70]. This patient received 240 mg of a natural surfactant suspended in 6 mL-saline which was instilled into the affected lobe through a fiber bronchoscope. After instillation, a gradual improvement of oxygenation was observed. This improvement was not as dramatic as usually observed after surfactant instillation, but this might be attributed to the low surfactant dose instilled. One might speculate that the improvement would be more pronounced if surfactant was instilled in a larger dose in the whole right lung.

## Surfactant as a Carrier for Antimicrobial Agents

It has been proposed to use the spreading properties and the inherent therapeutic potential of surfactant for delivering antimicrobial agents to the lung parenchyma [8]. Although each agent with its mode of action in the alveolar space and the lung interstitium could be considered for this administration mode, special interest has gone out to antimicrobial agents. Direct application of antibiotics to the airways offers many potential advantages in the treatment and prevention of pneumonia. Delivery directly to the airways should increase the local effectiveness and reduce the risk for systemic toxicity caused by some antibiotics, e.g. aminoglycosides [71].

Locally administered antibiotics for prevention or treatment of lower respiratory tract infection has been studied extensively. However, despite the high antibiotic dose delivered to the lung, the question of efficacy remains controversial. One explanation includes failure of the antibiotic to reach the infected areas of the lung. When delivered as an aerosol, only a small amount of the nebulized antibiotic dose, around 10%, is actually deposited in the lung. Moreover, with increased airway obstruction and lung damage the amount of aerosol deposited in peripheral regions of the lung decreases [72, 73]. Lung distribution of intratracheally instilled antibiotic

solutions is poorly studied. However, it is known that distribution of intratracheally instilled saline is largely limited to the central regions of the lung [8, 74]. Due to the small diameter of peripheral airways, fluids with a high surface tension, such as saline and water, require high pressures for passage through these airways [75].

It has been shown in experimental studies that pulmonary surfactant is superior to saline in distributing a radioactive colloid within healthy lungs: lung distribution is more peripheral and more homogeneous [8]. Furthermore, surfactant can re-expand non-ventilated atelectatic areas which are, most likely, 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 vehicle. So far, however, only a few studies have addressed this concept.

Two studies demonstrated that interactions between antimicrobial agents and exogenous surfactant exist and can influence the activity of both substances [76, 77]. Timed killing curves of amoxicillin, ceftazidime and tobramycin against 4 pulmonary pathogens in medium with and without additional surfactant revealed a partial inactivation of tobramycin in the presence of surfactant [76]. In additibon, surfactant activity, tested in the lung lavage model in rats, was reduced for tobramycin-surfactant mixtures in saline but unaffected when 0.2 M $NaHCO_3$ was used as solvent [77]. The same study revealed reduced surfactant activity when combined with amphotericin B and amoxicillin. It was concluded from both studies that before using surfactant-antibiotic mixtures, or mixtures of surfactant with other agents in general, alterations in activity of both substances should be considered and carefully examined.

Recent experimental data have supported the concept of surfactant-antibiotic mixtures demonstrating that intratracheal instillation of a surfactant-tobramycin mixture is more effective in protecting mice from death of a respiratory *Klebsiella pneumoniae* infection than intratracheal instillation of tobramycin alone [9] (Fig. 3). It seemed that the previously reported interactions between surfactant and tobra-

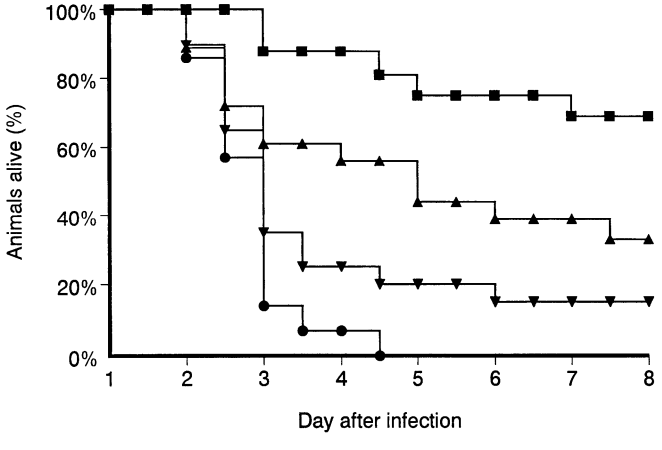


**Fig. 3.** Survival rates of mice infected with *Klebsiella pneumoniae* and treated intratracheally with: 1) surfactant-tobramycin mixture (■), 2) tobramycin alone (▲), 3) surfastant alone (▼) or 4) sham-treatement (●). Survival in the surfactant-tobramycin group was significantly increased compared to the tobramycin group. (From [9] with permission)

mycin played little role in this *in vivo* model. These first indications for the efficacy of surfactant as carrier for antimicrobial agents warrant further studies in this area.

## Conclusion

Experimental and clinical studies have shown that pneumonia is indifferent of the causative pathogen, attended with significant functional and compositional changes in pulmonary surfactant. This surfactant impairment attributes to the impaired lung function in pneumonia. Further studies have shown that impaired lung function in pneumonia can be corrected by instillation of exogenous surfactant. Moreover, exogenous surfactant preparations can be used as a carrier for antimicrobial agents thus improving the efficacy of local antimicrobial therapy in pneumonia. Surfactant therapy offers a potential approach in pneumonia. Many aspects of surfactant therapy, however, still need to be clarified. For instance, it is unclear which patients may benefit most from surfactant therapy, which doses should be used, and which type of surfactant preparation is preferred. Controlled clinical trials for surfactant therapy in severe pneumonia should clarify some of these questions. As for surfactant as a carrier for antibiotics, further experimental studies should establish the efficacy of this new delivery method.

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