Alveolar Surfactant and ARDS

W. Seeger, A. Günther, and H. D. Walmrath

Introduction

The acute respiratory distress syndrome (ARDS) characterizes different states of acute impairment of pulmonary gas exchange. Underlying noxious events may directly affect lung parenchyma from the alveolar side (e.g. gastric acid aspiration), or – more classically – the lung vasculature may be the primary target site of circulating humoral or cellular mediators activated under conditions of systemic inflammatory events such as sepsis or severe polytrauma [1]. Key pathophysiological features of the initial "exudative" phase of ARDS include:

1) increased capillary endothelial and alveolar epithelial permeability.
2) leakage of protein rich edema fluid into interstitial and alveolar spaces.
3) increased pulmonary vascular resistance with maldistribution of pulmonary perfusion.
4) alveolar instability with formation of atelectases and ventilatory inhomogenities.
5) severe disturbances of gas exchange characterized by ventilation-perfusion mismatch and extensive shunt flow.

This exudative phase may persist for days to weeks, and full recovery without persistent loss of lung function is possible during this period. New inflammatory events, such as recurrent sepsis or acquisition of secondary (nosocomial) pneumonia, may repetitively worsen the state of lung function and then progressively trigger proliferative processes with mesenchymal cell activation and rapidly ongoing lung fibrosis. Thus, within a few weeks, the lung architecture may become dominated by thickened fibrotic alveolar septae and large interposed airspaces ("honeycombing"). Prognosis is very poor during this phase of ARDS, and only partial recovery of lung function may be achieved in the few survivors from this late phase of disease.

The alveolar space of all mammalian lungs is covered by a complex surfactant system, which is essential to make alveolar ventilation and gas exchange feasible at physiological transpulmonary pressures. It is mainly composed of lipids (90%) and proteins (10%) [2–5]. Apart from a minor amount of neutral lipids (10–20%), phospholipids (PL, 80–90%) represent the predominant class of lipids in this surface lining material. Among those, phosphatidylcholine (PC, 70–80% of PL, 50–60% substituted with the saturated palmitic acid) and phosphatidylglycerol (PG, 10% of PL, bearing a large percentage of unsaturated fatty acids) represent

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the predominant classes; phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI) and sphingomyelin (Sph) are regularly found in low percentages [2]. About half the protein mass of the alveolar lining layer represents the surfactant specific apoproteins (SP)-A (28 kDa), SP-B (8 kDa), SP-C (5 kDa), and SP-D (43 kDa) (all molecular weights given for reducing conditions [3–5]). The predominant, and with respect to some compounds, exclusive source of the different lipid and protein components of the alveolar surfactant system is the type II alveolar epithelial cell. A complex and yet not fully understood interaction between phospholipids and surfactant apoproteins results in far-reaching reduction in the alveolar surface tension, approximating to near zero (mN/m) values at end expiration, with a limited increase in surface tension upon alveolar surface enlargement during inspiration [6]. Such extreme low surface tension may only be achieved by dense "packing" of some rigid lipid material such as dipalmitoyl-PC in the surface film. However, characteristics of fluidity are similarly essential for removal of surface film compounds into the bulk phase during surface (over)-compression and rapid re-entry and re-spreading of these compounds upon re-expansion of the surface area. Studies focusing on the biophysical properties of individual surfactant compounds (for review see [2–6]) underlined the importance of dipalmitoyl-PC and unsaturated PG, and elaborate a key role for the highly hydrophobic low molecular weight apoproteins SP-B and SP-C in adsorption facilities and dynamic surface tension lowering properties [7–10].

More recent studies demonstrate a metabolic cycle of the secreted surfactant material within the alveolar space. Surfactant material retrieved by bronchoalveolar lavage (BAL) fluid may be separated by density or high speed centrifugation into different subfractions defined as small and large surfactant aggregates. The highly surface active large surfactant aggregates comprise lamellar bodies, tubular myelin and multilamellar vesicles, and are thought to represent the precursor fraction of the alveolar lining layer, whileas small surfactant aggregates consist mainly of small, unilamellar vesicles, which largely represent the degradation products of the lining layer and possess poor surface activity [11]. A conversion of the large to the small aggregates may be encountered upon periodic surface area changes and in presence of an enzymatic activity, which can be blocked *in vitro* and *in vivo* by serin protease inhibitors [12]. However, this enzyme, recently entitled surfactant convertase, has not been identified.

Although several authors reported on a cooperative effect of SP-A with the hydrophobic apoproteins on adsorption kinetics [7,13,14], the predominant function of this protein may be the regulation of the surfactant pool size in the alveolar space. SP-A binds to dipalmitoyl-PC, promotes the uptake of phospholipids into type II cells via receptor-operated events, and inhibits secretion of surfactant compounds by this cell type [15–17]. In addition, SP-D and SP-A might be involved in host defense mechanisms of the lower airways *in vivo*, as they function as opsonins for alveolar macrophage phagocytosis of bacteria and viruses *in vitro* [18–21].

Surfactant deficiency has been established as the primary cause of the respiratory distress syndrome in preterm infants (IRDS), and transbronchial application of natural surfactant preparations has been proven to be beneficial in this disease

[22, 23]. Surfactant abnormalities may also be involved in the sequelae of pathogenetic events in ARDS; however, due to the diversity of underlying triggering mechanisms and the complexity of pathophysiological events, any evaluation of the role of surfactant in this disease is much less certain. This review focuses on three questions:

1) What is the present evidence for surfactant abnormalities in patients with ARDS?
2) Which pathophysiological events encountered in the course of ARDS may be ascribed to surfactant abnormalities?
3) What are the acute effects of a transbronchial surfactant administration in ARDS in view of gas exchange and compliance?

These aspects aim to provide a rational basis for the question, whether transbronchial surfactant application might become a safe and general therapeutic approach in patients with ARDS as it is in IRDS.

Alteration of Surfactant in ARDS

Early post-mortem investigations in lungs from patients who had died with ARDS, provided the first evidence of severe impairment of surfactant function [24]. More direct proof was provided by biophysical analysis of BAL fluids obtained by flexible bronchoscopy during the active state of the disease [25–28]. Compared to normal volunteers, BAL samples of these patients showed increased minimal surface tension and decreased hysteresis of the surface tension/surface area relationship, two critical variables of surfactant function

Table 1. Impairment of surface activity in ARDS

Authors	Ref.	material	method	variable	change[a]
– Hallman et al.	[26]	protein-complexes[b]	BAL, lipid Balance	Wilhelmy	γ_{min} ↑_
– Pison et al.	[27]	BAL[c]	Wilhelmy Balance	Hysteresis γ_{min}	↓ ↑
– Gregory et al.	[25]	surfactant pellet[d]	BAL, crude Surfactometer	Bubble γ_{max}	γ_{min} ↑ ↑
– Günther et al.	[28]	surfactant pellet[d]	BAL, crude Surfactometer	Bubble γ_{max}	γ_{min} ↑ ↑

[a] Change as compared to normal volunteers

[b] BAL was centrifuged twice (140 × g, supernatant; 10 000 × g pellet) and was subjected to a discontinuous sucrose density gradient (100 000 × g). Material between 0.2 and 1.3 M sucrose ("lipid-protein complex") was used

[c] BAL was separated from cells by centrifugation at 300 × g, no further preparation

[d] BAL was separated from cells by centrifugation at 450 × g, supernatant was centrifuged at 48 000 × g, the resulting "crude surfactant pellet" was resuspended in saline and used for bubble measurements – γ_{min} – minimum surface tension, γ_{max} – maximum surface tension

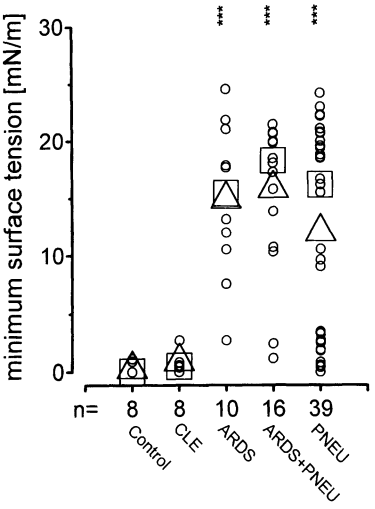

Fig. 1. Biophysical surfactant properties of isolated large surfactant aggregates. For controls and the different groups of patients, all single events (○), means (△) and median (□) values are indicated. Surface tension [mN/m] at minimum bubble size after 5min of film oscillation (γ_{min}) is given. Phospholipid concentration was 2 mg/mL; n-numbers are given in the x-axis. All groups were compared to controls; p is indicated by * ($p < 0.05$), ** ($p < 0.01$) or *** ($p < 0.001$). CLE: cardiogenic lung edema, ARDS : Acute respiratory distress syndrome, PNEU: Severe pneumonia necessitating mechanical ventilation, ARDS + PNEU: ARDS and lung infection. (From [28] with permission)

in vivo (Table 1, Fig. 1). Recently, elevated minimal surface tension values were also determined for surfactant samples obtained from patients being at risk for ARDS [25]. Several factors may underlay such a loss of surface activity in ARDS.

Lack of Surface-Active Compounds and Change in Phospholipid, Fatty Acid and Apoprotein Profiles

Clinical studies addressing the phospholipid composition of surfactant samples obtained from patients with ARDS revealed three important features. First, the overall content of phospholipids was found to be decreased in 2 of the 4 studies performed to date. In addition, this decrease appeared to be dependent on the severity of ARDS [25]. Second, the relative amounts of the 2 functionally most important phospholipids, PC and PG, were markedly depressed in all 3 studies (Table 2). Most strikingly, the PG levels decreased by >80% in 3 of the studies; the decrease in the percentage of PC was more moderate in all investigations. However, the degree of palmitoylation, especially the relative amount of dipalmitoylated PC (DPPC), was found to be severely reduced in patients with ARDS (not given in detail). Third, all studies demonstrated an increase in the relative amounts of PI, PE and Sph.

Due to the late detection and – in case of SP-B and SP-C – the extreme hydrophobic nature of the surfactant apoproteins, appropriate analytical techniques for the measurement of these essential surfactant compounds have only recently become available; SP-C quantification in BAL samples is still an unresolved problem. Two recent studies measuring SP-A and SP-B in BAL samples from patients with ARDS demonstrated an impressive decline of SP-A (Table 3). SP-B loss was

Table 2. BAL phospholipid-profile[a]

%	PC	PG	PI	PE	PS	SPH	LPC
Control (n = 17)	83.1 ± 0.9	8.6 ± 0.6	3.2 ± 0.2	1.7 ± 0.2	1.2 ± 0.3	0.8 ± 0.2	0.1 ± 0.1
CLE (n = 10)	83.3 ± 0.8	7.3 ± 1.0	4.3 ± 0.7	1.5 ± 0.1	1.3 ± 0.2	1.2 ± 0.2	0.1 ± 0.1
ARDS (n = 15)	81.9 ± 1.1	3.5 ± 0.7[d]	6.5 ± 1.0[b]	1.9 ± 0.3	1.8 ± 0.5	3.5 ± 0.9[c]	0.3 ± 0.1
ARDS + PNEU (n = 28)	76.8 ± 2.6	2.4 ± 0.3[d]	8.0 ± 0.8[d]	2.6 ± 0.3	1.7 ± 0.3	5.2 ± 0.9[d]	0.2 ± 0.1
PNEU (n = 64)	79.2 ± 1.0	5.2 ± 0.4[d]	5.5 ± 0.4[b]	2.4 ± 0.3	2.4 ± 0.4	4.3 ± 0.6[d]	0.2 ± 0.1

[a] For controls and the various patient groups, the different phospholipid classes are given in percent of total phospholipids; mean values ± SE are depicted. All groups were compared to controls, and p is indicated by [b] ($p < 0.05$), [c] ($p < 0.01$) or [d] ($p < 0.001$).

PC : phosphatidylcholine, PG: phosphatidylglycerol, PI: phosphatidylinositol, PE: phosphatidylethanolamine, PS: phosphatidylserin, SPH: sphingomyelin, LPS: lysophosphatidylcholine, CLE :cardiogenic lung edema, ARDS : Acute respiratory distress syndrome, PNEU: Severe pneumonia necessitating mechanical ventilation, ARDS + PNEU: ARDS and lung infection. (From [28] with permission)

Table 3. BAL apoprotein contents[a]

	SP-B				SP-A			
	ng/ml	μg/ml[u]	% PL	% Prot	ng/ml	μg/ml	% PL	% Prot
Control (n = 20)	740 ± 85	94 ± 15	3.0 ± 0.3	1.4 ± 0.3	1533 ± 175	148 ± 31	6.2 ± 0.7	2.8 ± 0.4
CLE (n = 13)	628 ± 42	119 ± 13	2.5 ± 0.3	0.5 ± 0.1[c]	1013 ± 111	182 ± 21	4.5 ± 0.8	1.0 ± 0.3[c]
ARDS (n = 15)	867 ± 131	62 ± 16	3.3 ± 0.4	0.6 ± 0.2[c]	849 ± 96[b]	54 ± 14[b]	3.5 ± 0.5	0.7 ± 0.3[d]
ARDS + PNEU (n = 35)	818 ± 78	63 ± 22[b]	6.3 ± 0.8[c]	0.3 ± 0.0[d]	747 ± 79[c]	71 ± 35[c]	7.8 ± 1.5	0.3 ± 0.0[d]
PNEU (n = 86)	737 ± 43	58 ± 9[b]	5.5 ± 0.5[b]	0.4 ± 0.0[d]	876 ± 75[c]	66 ± 10[c]	6.2 ± 0.6	0.5 ± 0.1[d]

[a] BAL SP-B and SP-A levels are displayed for controls and the different groups of patients. Values are given for concentrations in the original lavage fluid (ng/ml), concentrations corrected for the urea quotient (μg/ml[u]), apoprotein-phospholipid ratios (%; wt/wt) and apoprotein-total protein ratios (%, wt/wt). All groups were compared to controls; p is indicated by [b] ($p < 0.05$), [c] ($p < 0.01$) or [d] ($p < 0.001$).

CLE: cardiogenic lung edema, ARDS: Acute respiratory distress syndrome, PNEU: Severe pneumonia necessitating mechanical ventilation, ARDS + PNEU: ARDS and lung infection. (From [28] with permission)

particularly prominent in the large surfactant aggregate fraction (see below). Again, some decrease of these functionally important compounds was also observed in patients at risk for ARDS [25].

The reported changes in lavage phospholipid and apoprotein content in patients suffering from ARDS are very much reminiscent of biochemical profiles characterized in neonates with immature lungs and IRDS [2]. They are thus likely to reflect injury of type II pneumocytes, with altered lipid and apoprotein metabolism and/or secretion by this cell type. In addition, the increase in PI, PE and Sph may be due to some surfactant "contamination" with membrane phospholipids from different injured cell types, and there may be leakage of plasma phospholipids under conditions of increased endothelial and epithelial permeability. Finally, as will be discussed below, incorporation of phospholipids into hyaline membranes might also contribute to the alterations in phospholipid and apoprotein profiles.

Alteration of Surfactant Subtype Distribution

Under physiological conditions, nearly 80–90% of the extracellular surfactant material is retrieved among the fraction of large surfactant aggregates (Fig. 2). This subfraction possesses a high SP-B content and excellent surface activity. Under conditions of ARDS, however, increase of the small surfactant aggregates at the expense of the large surfactant aggregates is encountered and is paralleled by a loss of SP-B and surface activity within the large surfactant aggregates (Fig. 2).

Inhibition of Surfactant Function by Plasma Protein Leakage

Leakage of plasma proteins into the alveolar space may contribute substantially to surfactant alterations in ARDS. Measurements of the protein content in BAL samples from these patients persistently show markedly increased levels when compared to normal controls. Protein leakage is an early event in the sequence of pathogenetic events in ARDS, and is related to the severity of the disease [28]. Experimental studies *in vitro* and *in vivo* have demonstrated that admixture of blood, serum, plasma or alveolar washings obtained during states of plasma leak-

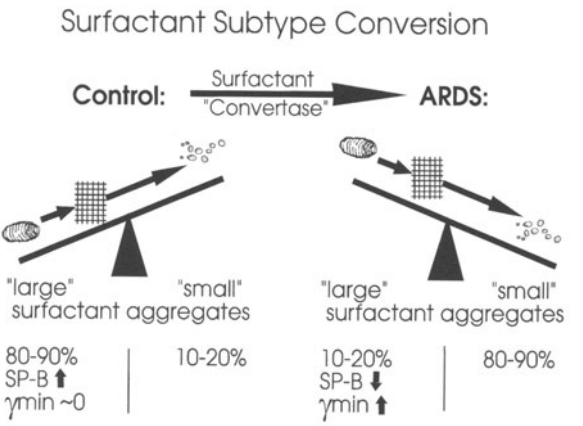

Fig. 2. Changes in the surfactant subtype distribution and the biophysical activity and SP-B content of large surfactant aggregates in the development of ARDS. (For details see text)

Table 4. Protein inhibition of pulmonary surfactant[a]

Varying degree of "protein-resistance" among different surfactants: relevant compounds SP-B > SP-C > SP-A
Inhibitory Capacity: Fibrinoligomers/-polymers ⩾ Fb(g)lysisproducts > Fbmonomers, Fbg > Hemoglobin > Albumin
Polymerising Fibrin = "Surfactant-trap" (phospholipids and hydrophobic apoproteins)
"Specialized" alveolar Fibrinpolymer characterized by - incorporation of pulmonary surfactant with - promotion of alveolar collapse - lower susceptibility towards fibrinolytic enzymes - altered mechanical properties (e.g. rigidity ↓)
Restoration of regular surface tension properties by fibrinolytic approaches possible (release of surface active material)

[a] The table summarizes the current knowledge concerning the inhibition of surfactant function by plasma protein, especially the influence of fibrinogen (Fbg), fibrin monomers (Fb monomers) and fibrin oligo/polymers (Fb oligo/polymers). For details see text

age may severely compromise biophysical surfactant function (Table 4) [29–32]. Among different proteins involved, albumin [13, 29, 33, 34], hemoglobin [35], and in particular fibrinogen or fibrinmonomer [9, 13, 29, 34, 36, 37] possess strong surfactant inhibitory properties (Table 4). Concerning fibrinogen, it has been demonstrated that its potency to inhibit surfactant function depends on the surfactant apoprotein profile. Surfactant preparations lacking hydrophobic apoproteins are extremely sensitive to fibrinogen inhibition, and less sensitivity is noted in the presence of both SP-C and SP-B in near physiological quantities [9, 38]. In addition, a further reduction of surfactant sensitivity to fibrinogen is achieved by supplementation of phospholipid and hydrophobic apoprotein-based surfactants with SP-A [13].

"Incorporation" of Surfactant in Fibrin/Hyaline Membranes

Intra-alveolar accumulation of clot material, characterized as "hyaline membranes", is commonly found in ARDS and other acute or chronic inflammatory diseases of the lung [39–42]. In the alveolar milieu, the extrinsic coagulation pathway represents the predominant clotting sequence. Alveolar macrophages express and shed procoagulant activity, which is mainly attributable to tissue factor in compound with factor VII [43–46]. This alveolar procoagulant activity was found to be markedly increased in ARDS patients (possibly because of local macrophage activation [45–49]), and in several experimental models of lung injury (Fig. 3) [50–53]. By contrast, concentrations of urokinase-type plasminogen activator, representing the predominant fibrinolysis pathway within the alveolar spaces [45, 53–55], were noted to be decreased in lavage fluids from patients with ARDS. Concomitantly, increased levels of plasminogen-activator-inhibitor-1 and 2-antiplasmin were detected [45, 48, 53, 56]. Moreover, surfactant phospholipid mixtures

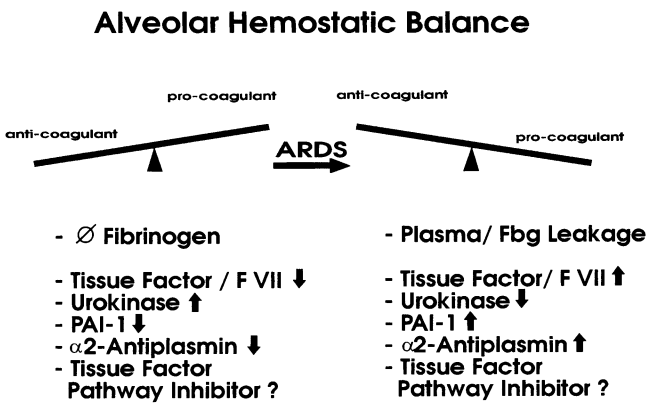

Fig. 3. Increase in procoagulant and decrease in fibrinolytic activity in the alveolar space under conditions of ARDS. (For details see text)

were found to inhibit plasmin-, trypsin- or elastase-induced fibrino(geno)lysis, in particular when combined with the surfactant apoproteins SP-B and SP-C [57,58]. Thus, the hemostatic balance within the alveolar milieu appears to be shifted towards predominance of procoagulant and antifibrinolytic activity in acutely or chronically inflamed lung regions, in particular in ARDS. Recent investigations performed by this group [59] demonstrated loss of surfactant phospholipids from the soluble phase due to binding to/within fibrin strands, when the process of fibrin polymerization occurred in the presence of surfactant material. In parallel, virtually complete loss of surface activity was noted, with fibrin dose-effect curves ranging two orders of magnitude below the corresponding efficacy range of soluble fibrinogen. ^{31}P-NMR-spectrum analysis suggested membrane-like, highly ordered arrangement of the fibrin-associated phospholipids. Overall, these findings obviously suggest "incorporation" of phospholipids (and possibly hydrophobic apoproteins) into nascent fibrin strands. This phenomenon may cause severe loss of functionally important surfactant compounds in areas with alveolar fibrin and hyaline membrane formation. Interestingly, surface activity may be largely restored by application of fibrinolytic agents *in vitro* [58] and *in vivo* (unpublished data), with release of formerly incorporated surfactant material into the soluble phase.

Damage of Surfactant Compounds by Inflammatory Mediators

A variety of inflammatory processes are assumed to underlie the microcirculatory disturbances of ARDS, and mediator generation has also been demonstrated in the alveolar compartment. Free elastase and collagenase activities were repeatedly detected in BAL fluids of patients with ARDS [60,61]; oxidative inhibition of the alveolar α1-proteinase inhibitor indicated oxygen radical generation in this compartment, and increased levels of lysophospholipids (predominantly lyso-

Table 5. Impact of inflammatory mediators on surfactant function : *In vitro* studies

Mediator	Effects
phospholipases (A_2,C)	- generation of lysophospholipids (especially lysoPC) - loss of surface activity - higher sensitivity towards inhibition by plasma proteins - generation of free fatty acids (including arachidonic acid)
cytokines	
- TNF	- pretranslational inhibitory effect on the expression of SP-A and SP-B
proteases	
- elastase	- degradation of SP-A, indirect evidence for degradation of SP-B and SP-C; loss of surface activity
- mixed	- increased conversion of large to small surfactant aggregates?
- oxygen radicals	- decrease in surface activity - induction of lipid peroxidation
lipid mediators	
- arachidonic acid	- decrease in surface activity
- PMN	- decrease in surface activity - degradation of SP-A

PC) [26] suggested increased phospholipolytic activity in the alveolar space. A variety of *in vitro* studies have addressed putative direct inhibitory effects of inflammatory mediators on biophysical surfactant functions. Inhibitory potencies were demonstrated for phospholipases, proteases, oxygen radicals, free fatty acids and activated granulocytes (via release of oxygen radicals), as summarized in Table 5. Presently, however, no data are available to quantify the contribution of such surfactant-inhibitory effects of inflammatory mediators to the impairment of surfactant function in patients with ARDS.

Pathophysiological Consequences of Surfactant Alterations in ARDS

As outlined above, there is strong evidence of severe impairment of the alveolar surfactant system in ARDS, and several mechanisms may underlay this finding. Thus the question arises, whether and to what extent such surfactant alterations contribute to the sequence of pathogenetic events and the loss of lung functional integrity encountered in this disease.

Alteration of Lung Mechanics

Loss of alveolar surface activity increases surface tension thereby causing alveolar instability with formation of atelectases. These features must be expected to result in a marked decrease of lung compliance. This basic finding was, indeed, already described in the very early reports on altered mechanics of post-mortem

analyzed lungs from patients dying with ARDS [24]. In addition, in a variety of experimental approaches using animal models of ARDS, induction of lung injury resulted in a significant decrease in compliance [62–67]. Accordingly, transbronchial application of surfactant was shown to completely or partially restore physiological lung compliance in some of these models [62–67]. In patients with severe ARDS, however, reliable measurements of lung compliance are still difficult to perform, mostly because of uncertainties concerning lung volumes (at which part of the pressure-volume curve does the lung actually range?) and transpulmonary pressures. Moreover, there is presently no reliable *in vivo* technique to differentiate the contribution of increased alveolar surface tension from that of interstitial congestion and on-going fibrosis to the reduction in lung compliance of ARDS patients. It is well conceivable that surfactant alterations predominate in the early phase of ARDS, whereas fibrotic events gain increasing importance in later states of the disease.

Impairment of Gas Exchange – V/Q Mismatch and Shunt Flow

Lack of surface active material has been established as a primary cause of severe gas exchange disturbances in IRDS, and dramatic improvements in arterial oxygenation are achieved by transbronchial surfactant application under these conditions [22, 23]. Similarly, experimental approaches in adult animals with removal of alveolar surfactant (lung lavage models [68]) and subsequent transbronchial reapplication of surface active material have underscored the fundamental significance of the alveolar surfactant system for ventilation-perfusion (V/Q) matching in adult lungs [68, 69, 70]. In more realistic models of ARDS, starting with induction of microvascular or alveolar injury, matters are more complex. Shunt (perfusion of atelectatic regions) and blood flow through lung areas with low V/Q ratios (partial closure of alveolar units or small airways) may well be related to an acute impairment of the alveolar surfactant system in such experiments, and transbronchial surfactant application was found to improve gas exchange in models with protein-rich edema formation due to cervical vagotomy [62], acid aspiration [63, 66, 71], induction of pneumonia [72], hyperoxic lung injury [73] and application of N-nitroso-N-methylurethane (NNNMU) [64, 65] or oleic acid [67]. The efficacy of surfactant replacement in these models with induction of lung inflammation is, however, lower than in those with primary surfactant depletion (lavage, preterm newborns), which is most probably attributable to the inhibitory capacities of leaked plasma proteins and inflammatory mediators, as discussed above. Larger amounts of surfactant material are apparently needed under these conditions, in order to surpass, at least partially, such inhibitory capacities.

Lung Edema Formation

Interstitial and alveolar edema is a key finding in ARDS, primarily ascribed to increased endothelial and epithelial permeability in the diseased lungs. Surfactant

alterations may, however, contribute to the disturbances in fluid balance in ARDS. Any increase in alveolar surface tension must be expected to result in a decrease in interstitial and thus perivascular pressures and, according to Starling's law, increase transendothelial fluid fluxes into septal and interstitial spaces. Similarly, increased alveolar surface tension favors transepithelial fluid movement into the alveolar spaces. Several experimental studies have indeed demonstrated extensive lung edema formation due to inhibition of surfactant function *in vivo* by transbronchial detergent application [74, 75], intratracheal injection of bile acid [76], cooling and ventilating at low functional residual capacity (FRC) [77], or plasma lavage [78]. Moreover, the permeability characteristics of the epithelial membrane may be influenced by surfactant deficiencies. Increased transepithelial passage of ^{99m}Tc-DPTA (from alveolar to intravascular space) and labeled albumin (from intravascular to alveolar space) was observed under experimental conditions of surfactant impairment, and the increased fluxes could be reduced by transbronchial surfactant replacement [76, 79, 80]. Similarly, increased epithelial permeability for ^{99m}Tc-DPTA is noted in neonates with IRDS [81]. Concerning patients with ARDS, there is presently no conclusive study evaluating the impact of surfactant abnormalities on lung fluid balance and alveolar epithelial permeability characteristics.

Reduction of Host Defense Competence?

Next to the reduction of surface tension within the alveolar compartment, the pulmonary surfactant system is involved in many host defense properties of the lung. Although not fully understood at the present time, there is evidence that the hydrophilic apoproteins SP-A and SP-D might act as highly effective opsonins, thereby enhancing the phagocytosis of several strains of bacteria and viruses. By contrast, the lipid fraction of pulmonary surfactant is capable of suppressing the activation and proliferative response of lymphocytes, granulocytes and alveolar macrophages. Thus, these aspects are at best mosaics of a complex alveolar host defense system, which largely remains to be defined. The marked decrease in SP-A levels in lungs of ARDS patients (see above) may suggest a loss of opsonizing capacity and increased susceptibility to nosocomial infections.

"Collapse Induration", Mesenchymal Cell Proliferation and Fibrosis

The proliferative phase of ARDS is characterized by progressive mesenchymal cell activation and proliferation, predominantly in atelectatic regions, and may result in widespread lung fibrosis and honeycombing within weeks. Underlying mechanisms may include major roles for the alveolar surfactant system and alveolar fibrin deposition, as schematically depicted in Fig. 4. A corresponding sequence of events was suggested for the pathogenesis of lung fibrosis in general by Burkhardt [40] and termed "collapse induration". Basically, this concept starts with persistent atelectasis at sites of extensive loss of alveolar surfactant function,

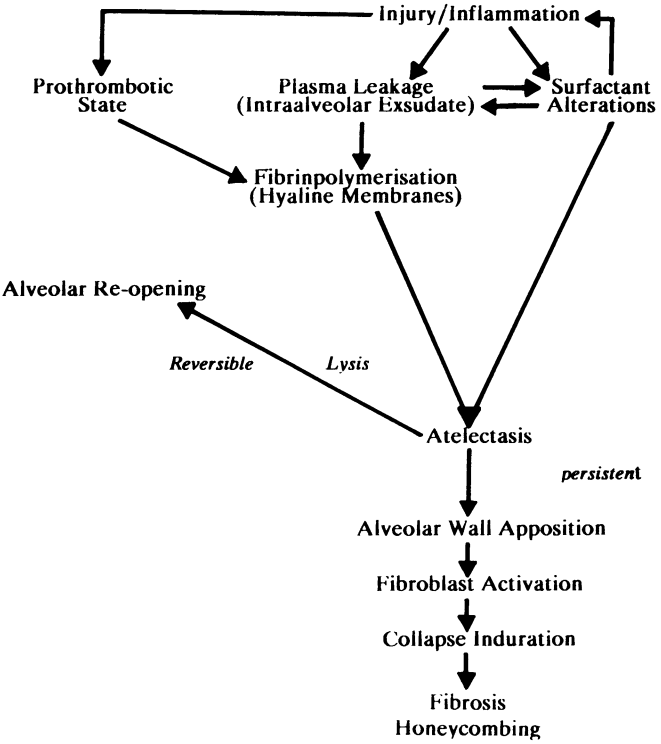

Fig. 4. Possible envolvement of surfactant inhibition and alveolar fibrin deposition in the pathogenesis of fibrosis and honeycombing in protracted ARDS. (For details see text)

in particular regions with fibrin deposition. Alveolar wall apposition and the fibrin matrix represent a nidus for fibroblast activation, and the alveolar space is definitely lost through deposition of fibrous tissue (collapse induration). Thus, thick indurated septae (or conglomerates of several septae) may exist adjacent to widened (remaining) alveoli to provide the typical morphological image of fibrosis and honeycombing [39, 82]. This concept does not deny an important role of inflammatory mediators, such as TNF, and growth factors for the induction of mesenchymal cell activation in late ARDS. But it provides an explanation for the predominance of fibrosis at sites of persistent atelectasis and fibrin deposition.

Surfactant Replacement in ARDS: Current Status

Against the above background, improvement of alveolar surfactant function appears to be a reasonable approach to augment gas exchange in ARDS patients. Such attempts may include pharmacological approaches to stimulate the secre-

tion of intact surfactant material from type II pneumocytes, but clear evidence that this approach may be effectively used under conditions of acute respiratory failure is lacking. In addition, transbronchial administration of exogenous (natural) surfactant preparations, commonly used in IRDS, may also be employed in ARDS, but will clearly demand larger quantities of material to overcome the surfactant inhibitory capacities in the alveolar space under these conditions. Two pilot studies in this field have been completed. Performing repetitive intratracheal application of Survanta, with cumulative doses between 300 and 800 mg/kg body weight, Gregory and colleagues [83] noted some improvement of gas exchange and even obtained some preliminary evidence for an increase in survival in adults with acute respiratory failure. Our group investigated the safety and efficacy of a bronchoscopic application of a natural surfactant extract (Alveofact) in patients with severe ARDS. All patients fulfilled extracorporeal membrane oxygenation (ECMO) criteria (mean Murray lung injury score ≈ 3.3) and were treated within the first 5 days of disease, i.e. before the onset of major fibrotic processes. Underlying diseases were mostly sepsis and severe pneumonia. At the present time, the study includes 26 patients. 300 mg/kg Alveofact was delivered bronchoscopically in divided doses to each segment of both lungs (total dose 22.5 ± 1.4 g in 375 mL saline), followed by a second application of 200 mg/kg (total dose 15.5 ± 1.05 g in 260 mL saline) 18–24 h later in selected patients. Measurements of gas exchange including ventilation-perfusion characteristics, hemodynamic measurements and BAL was performed before and after surfactant application. As given in Fig. 5, an acute and impressive improvement of the gas exchange was encountered, even during the application procedure. When analyzing the course of gas exchange among all patients, the first surfactant application resulted in an immediate increase of mean PaO_2/FiO_2 from < 90 to ≈ 200 mmHg (Fig. 6), mainly due to a decrease in shunt flow (from ≈ 40 to ≈ 20 %). More than 2/3 of the patients "responded" with a PaO_2/FiO_2 increase of at least 25%. The effect was partially lost within the following hours in some of

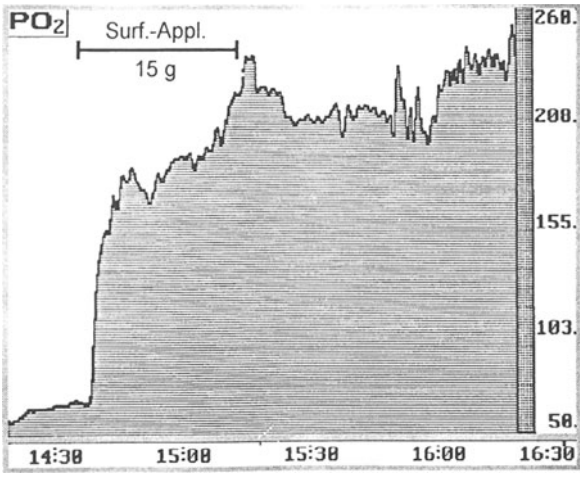

Fig. 5. On-line monitoring of PaO_2 during surfactant application in a 18–year old female with ARDS due to sepsis. As evident from the figure, a far-reaching improvement of oxygention was encountered already within the process of bronchoscopic surfactant application (300 mg/kg body weight Alveofact). The time period of the bronchoscopic procedure is indicated; FiO_2 was set 1.0 throughout. (From [84] with permission)

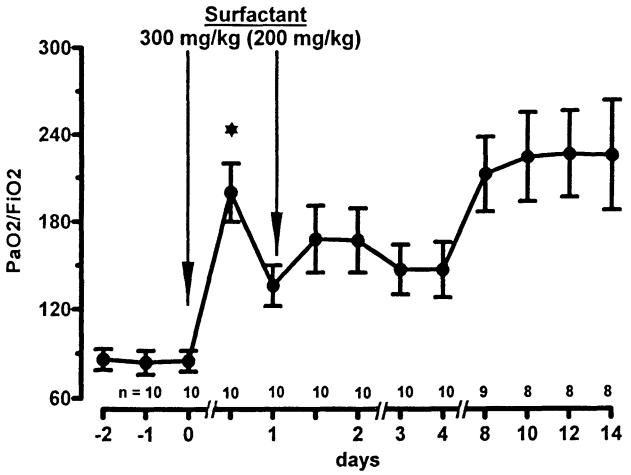

Fig. 6. Time course of oxygenation index (PaO_2/FiO_2) in response to surfactant application. Mean ± SEM of 10 patients are given. 300 mg/kg natural surfactant was delivered bronchoscopically in separate doses to each segment of both lungs in all patients (time zero). In 5 patients, in whom the surfactant-related increase in arterial oxygenation was partially lost within the next hours, a second dose of 200 mg/kg surfactant was applied 18–24 h later. The highest PaO_2/FiO_2 value is given for each day, and for every 12 h within the first 2 days. The number of surviving patients is indicated. (* $p < 0.001$ for comparison of the PaO_2/FiO_2 values before and after the first surfactant application). (From [84] with permission)

the responders, but restored with prolonged improvement of arterial oxygenation by the second application. Initial BAL showed severe alteration of surfactant composition and impaired biophysical surfactant function (Table 6). Surfactant application resulted in a marked, but still incomplete restoration of surfactant properties, with a profound improvement of the phospholipid (PL)-protein ratio, relative content of large surfactant aggregates, relative content of phosphatidylcholine, minimum surface tension in absence as well as in presence of the inhibitory BAL fluid proteins. Analysis of the ventilation-perfusion characteristics revealed that in response to the bronchoscopic surfactant application, formerly collapsed alveoli were re-aerated, yielding a reduction of the intrapulmonary shunt flow and an increase in regions with low and normal ventilation-perfusion ratios.

Conclusion

Profound alterations of the alveolar surfactant system are encountered in ARDS. There is now good evidence that these abnormalities contribute to the severe impairment of gas exchange under these conditions. Transbronchial surfactant application, performed by bronchoscopy by our group, may offer a feasible and safe approach to improve biochemical and biophysical properties of the endogenous

Table 6. BAL variables pre- and post-surfactant application : Comparison to controls and surfactant replacement material

Variables	Patients		Controls	AlveoFact®
	pre	post		
PPR	0.02 ± 0.01	0.23[c] ± 0.1	0.58 ± 0.1	—
LSA (%)	27.7 ± 5.3	68.6[a] ± 8.8	67.0 ± 7.1	> 90
PC (%)	72.6 ± 2.1	85.3[c] ± 1.0	83.1 ± 0.9	87.8 ± 0.4
PG (%)	3.1 ± 0.6	7.2[c] ± 0.9	8.6 ± 0.6	7.6 ± 0.1
SM (%)	7.7 ± 1.3	2.4[c] ± 0.5	0.8 ± 0.2	0.8 ± 0.1
SP-B (% of PL)	3.73 ± 1.15	4.9 ± 1.26	3.0 ± 0.3	3.8 ± 0.7
SP-A (% of PL)	1.0 ± 0.5	0.4 ± 0.1	6.2 ± 0.7	—
γ_{ads} (mN/m)	45.0 ± 1.6	25.6[c] ± 2.8	22.5 ± 0.7	22.2 ± 0.3
γ_{min} (mN/m)	21.6 ± 1.4	9.2[b] ± 2.8	0.25 ± 0.2	0.28 ± 0.3
γ_{ads} + P (mN/m)	43.5 ± 1.5	37.6 ± 2.4	22.7 ± 0.7	—
γ_{min} + P (mN/m)	34.4 ± 2.2	24.2 ± 3.6	0.5 ± 0.3	—

Variables are given for the BAL fluids obtained 3 h prior to (pre) and 15–21 h after (post) the first surfactant administration (mean ± SEM). For comparison, data from 10 healthy controls and the surfactant material used for replacement therapy (measured in triplicate) are displayed. (PPR: ratio of PL to protein in the BAL fluid, LSA: large surfactant aggregates (% of total PL), PC: phosphatidylcholine, PG: phosphatidylglycerol, SM: sphingomyelin, SP-B/A: surfactant protein-B/A (all % of total PL), γ_{ads} and γ_{min}: adsorption and minimum surface tension in the absence or presence (+ P) of supernatant protein). Significance level (comparison of pre- and post-surfactant data) is indicated by [a] ($p < 0.05$) and [b] ($p < 0.01$). (From [84] with permission)

surfactant pool and, by this, the gas exchange conditions in most severe early-stage ARDS. However, a high and/or repetitive dosage regimen appears to be necessary to overcome inhibitory capacities in the alveolar space of these patients and to achieve sustained alveolar recruitment. Forthcoming studies will have to rule out the optimum timing and dosage regimen of such intervention and will have to address the question whether this therapy is capable of reducing the still high mortality of patients with most severe ARDS, and critically consider its impact on inflammation, host-defense and mesenchymal proliferation in the alveolar compartment.

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