

Alveolar surfactant and adult respiratory distress syndrome

Pathogenetic role and therapeutic prospects*

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Summary. The adult respiratory distress syndrome (ARDS) is characterized by extended inflammatory processes in the lung microvascular, interstitial, and alveolar compartments, resulting in vasomotor disturbances, plasma leakage, cell injury, and complex gas exchange disturbances. Abnormalities in the alveolar surfactant system have long been implicated in the pathogenetic sequelae of this life-threatening syndrome. This hypothesis is supported by similarities in pulmonary failure between patients with ARDS and preterm babies with infant respiratory distress syndrome, known to be triggered primarily by lack of surfactant material. Mechanisms of surfactant alterations in ARDS include: (a) lack of surface-active compounds (phospholipids, apoproteins) due to reduced generation/release by diseased pneumocytes or to increased loss of material (this feature includes changes in the relative composition of the surfactant phospholipid and/or apoprotein profiles); (b) inhibition of surfactant function by plasma protein leakage (inhibitory potencies of different plasma proteins have been defined); (c) “incorporation” of surfactant phospholipids and apoproteins into polymerizing fibrin upon hyaline membrane formation; and (d) damage/inhibition of surfactant compounds by inflammatory mediators (proteases, oxidants, nonsurfactant lipids). Alterations in alveolar surfactant function may well contribute to a variety of pathophysiological key events encountered in ARDS. These include decrease in compliance, ventilation-perfusion mismatch including shunt flow due to altered gas flow distribution (atelectasis, partial alveolar collapse, small airway collapse), and lung edema formation. Moreover, more

speculative at the present time, surfactant abnormalities may add to a reduction in alveolar host defense competence and an upregulation of inflammatory events under conditions of ARDS. Persistent atelectasis of surfactant-deficient and in particular fibrin-loaded alveoli may represent a key event to trigger fibroblast proliferation and fibrosis in late ARDS (“collapse induration”). Overall, the presently available data on surfactant abnormalities in ARDS lend credit to therapeutic trials with transbronchial surfactant administration. In addition to the classical goals of replacement therapy defined for preterm infants (rapid improvement in lung compliance and gas exchange), this approach will have to consider its impact on host defense competence and inflammatory and proliferative processes when applied in adults with respiratory failure.

Key words: Adult respiratory distress syndrome – Alveolar surfactant – Surfactant phospholipids – Surfactant apoproteins – Surfactant inhibition – Hyaline membranes

The adult respiratory distress syndrome (ARDS) is characterized by 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 primary target site of circulating humoral or cellular mediators activated under conditions of systemic inflammatory events such as sepsis or severe polytrauma [102, 103]. Key pathophysiological features of the initial “exudative” phase of ARDS include: (a) increase in capillary endothelial and alveolar epithelial permeability, (b) leakage of protein-rich edema fluid into interstitial and alveolar spaces, (c) increase in pulmonary vascular resistance with maldistribution of pulmonary perfusion, (d) alveolar instability with formation of atelectases and ventilatory inhomogeneities, and (e)

Abbreviations: ARDS=adult respiratory distress syndrome; IRDS=infant respiratory distress syndrome; PC=phosphatidylcholine; PG=phosphatidylglycerol; PE=phosphatidylethanolamine; PS=phosphatidylserine; PI=phosphatidylinositol; Sph=spingomyelin; BAL=bronchoalveolar lavage; TNF=tumor necrosis factor

* Dedicated to Prof. Dr. N. Zöllner on the occasion of his 70th birthday

severe disturbances in 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 well possible during this period of acute respiratory distress. 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 composed mainly of lipids ($\approx 90\%$) and proteins ($\approx 10\%$) [28, 41, 42, 120]. Apart from a minor amount of neutral lipids ($\approx 10\text{--}20\%$), phospholipids ($\approx 80\text{--}90\%$) represent the predominant class of lipids in this surface lining material. Among those, phosphatidylcholine (PC; $\approx 70\text{--}80\%$ of phospholipids, 50–60% substituted with the saturated palmitic acid) and phosphatidylglycerol (PG; $\approx 10\%$ of phospholipids, bearing a large percentage of unsaturated fatty acids) represent the predominant classes; phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), and sphingomyelin (Sph) are regularly found in low percentages. About half of 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; [23, 41, 46, 85, 90]). The predominant, and in some compounds exclusive, source of the different lipid and protein components of the alveolar surfactant system are the alveolar epithelial cells type II [41, 46, 90]. A complex and yet not fully understood interaction between phospholipids and surfactant apoproteins results in far-reaching reduction in the alveolar surface tension, approximating zero (mN/m) values at end expiration, with limited increase in surface tension upon alveolar surface enlargement during inspiration. Such extremely 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 reentry and respreading of these compounds upon reexpansion of the surface area. Tubular myelin, a unique morphological structure appearing in the alveolar subphase, appears to be of major functional importance in this context [26, 114, 125]. Studies focusing on the biophysical properties of individual surfactant compounds (for review see [46, 90, 120]) have underlined the importance of dipalmitoyl-PC and unsaturated PG and elaborated a key role of the highly hydrophobic low molecular weight apoproteins SP-B and SP-C for adsorption facilities and dynamic surface tension lowering properties [24, 47, 83, 92, 93, 108–110, 122, 123, 127, 128]. Although several authors have reported on a cooperative effect of SP-A with the hydrophobic apoproteins on adsorption kinetics [19, 47, 71, 92, 98], 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 [74, 95, 100]. 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* [64–66, 116].

Surfactant deficiency has been established as the primary cause of the respiratory distress syndrome in preterm infants (IRDS), and transbronchial administration of natural surfactant preparations has been proven to be beneficial in this disease [22, 49]. 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 in ARDS, any evaluation of the role of surfactant in this disease is much less certain. This review focuses on two questions: (a) What is the present evidence for surfactant abnormalities in patients with ARDS? (b) Which pathophysiological events encountered in the course of ARDS may be attributed to surfactant abnormalities? These aspects aim to provide a rational basis for the more general question of whether transbronchial surfactant administration may become a profitable therapeutic approach in patients with ARDS as it is in IRDS.

Alteration of surfactant in ARDS

In early postmortem investigations in lungs from patients who had died in ARDS, initial evidence for severe impairment of surfactant function was

Table 1. Impairment of surface activity in ARDS

	Material	Method	Variable	Change*
Hallman et al. [39]	BAL, lipid-protein complexes ^a	Wilhelmy Balance	τ min	↑
Pison et al. [87]	BAL ^b	Wilhelmy Balance	Hysteresis τ min	↓ ↑
Gregory et al. [29]	BAL, crude surfactant pellet ^c	Bubble Surfactometer	τ min τ max	↑ ↑

τ min, minimum surface tension; τ max, maximum surface tension; * Change as compared to normal volunteers

^a 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

^b BAL was separated from cells by centrifuged at 300 g, no further preparation

^c BAL was separated from cells by centrifugation at 450 g, supernatant was centrifuged at 48 000 g, and the resulting "crude surfactant pellet" was resuspended in saline and used for bubble measurements

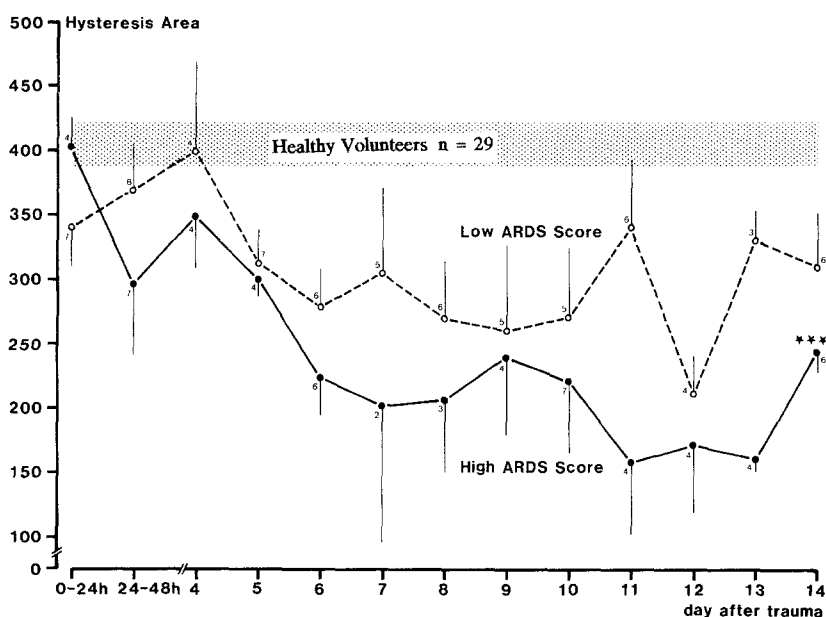


Fig. 1. Time course of surface tension hysteresis area determined in lung lavage material from severely traumatized patients with high and low ARDS scores. Repetitive flexible bronchoscopy for serial determination of alveolar surfactant function was performed within 14 days after trauma; the number of samples for each posttrauma day is indicated. Biophysical measurements were undertaken in diluted surfactant material in the Wilhelmy balance/Langmuir trough system; the hysteresis of the surface tension-surface area relationship is given (arbitrary units). Shaded area, mean \pm SE for healthy volunteers. The groups with high and low ARDS scores differ significantly ($P < 0.001$). (From [87])

obtained [86]. More direct proof was provided by studies of this group and of other investigators with biophysical analysis of bronchoalveolar lavage fluids (BAL) obtained by flexible bronchoscopy during the active state of the disease [29, 39, 87]. 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 presumably most critical variables of surfactant function in vivo (Table 1). In addition, the extent of impairment of biophysical surfactant function was correlated with the severity of ARDS (Fig. 1). Recently, elevated minimal surface tension values were also determined for surfactant samples obtained from patients at risk for ARDS [29]. Several factors may underlie such loss of surface activity in ARDS;

those discussed below are the following: lack of surface-active compounds (phospholipids, apoproteins), change in phospholipid and apoprotein profiles, inhibition of surfactant function by plasma protein leakage, "incorporation" of surfactant in fibrin/hyaline membranes, and damage to surfactant compounds by inflammatory mediators (proteases, oxidants, nonsurfactant lipids, etc.).

Lack of surface-active compounds and change in phospholipid and apoprotein profiles

As summarized in Table 2, clinical studies addressing the phospholipid composition of surfactant samples obtained from patients with ARDS have revealed three important features. First, the overall content of phospholipids was found to be de-

Table 2. Phospholipid content and profile in ARDS

	Hallmann et al. [39]		Pison et al. [87]			Gregory et al. [29]		
	Normal	ARDS	Normal	Low-score ARDS	High score ARDS	Normal	At risk	ARDS
	(μM)	(μM)	($\mu\text{g/ml}$)	($\mu\text{g/ml}$)	($\mu\text{g/ml}$)	($\mu\text{M/ml}$)	($\mu\text{M/ml}$)	($\mu\text{M/ml}$)
PL ^a	0.6	0.6	84.1	65.7	65.1	7.99	3.48	2.47
	% ^b	% ^b	% ^b	% ^b	% ^b	% ^b	% ^b	% ^b
PC	73	59.5	62.8	56.3	48.1	76.27	73.32	62.64
PG	12.4	0.3	10.02	1.6	1.88	11.58	7.26	6.48
PI	2.7	3.1	8.32	13.54	13.95	3.88	4.71	6.94
PE	2.6	4.3	4.82	13.65	18.68	3.32	4.9	5.86
Sph	3.7	17.5	7.37	12.28	14.21	1.45	1.56	5.45

^a Concentration of phospholipids; BAL and sample preparation as detailed in Table 1

^b Percentage of total phospholipids

Table 3. Surfactant apoprotein content in ARDS

	Pison et al. ^a		Gregory et al. ^b		
	Normal	ARDS	Normal	At risk	ARDS
SP-A ($\mu\text{g/ml}$)	2.74	1.49	123.64	49.28	29.88
SP-B (ng/ml)	n.m.	n.m.	1.28	0.89	0.57

^a BAL was separated from cells by centrifugation at 180 g; concentrations given for original lavage fluid; from [89]

^b Cell-free BAL was concentrated by centrifugation at 48000 g; concentration given for "crude surfactant pellet;" from [29]

creased in two of the three studies performed to date. In addition, this decrease in total phospholipids appeared to be dependent on the severity of ARDS. Second, the relative amounts of the two functionally most important phospholipids, PC and PG, were markedly depressed in all three studies. Most strikingly, the PG levels decreased by over 80% in two of these studies; the decrease in the percentage of PC was more moderate in all three investigations. 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 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, one also measuring SP-B, in BAL samples from patients with ARDS have demonstrated an impressive decline of these surfactant

apoproteins (Table 3). Again, some decrease in these functionally important compounds was also observed in patients at risk for ARDS.

The reported changes in lavage phospholipid and apoprotein contents in patients suffering from ARDS are very much reminiscent of biochemical profiles characterized in neonates with immature lungs and IRDS [120]. 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 discussed below, incorporation of phospholipids into hyaline membranes may also contribute to the alterations in phospholipid and apoprotein profiles.

Inhibition of surfactant function by plasma protein leakage

Leakage of plasma proteins into the alveolar space may substantially contribute to surfactant alterations in ARDS. Measurements of the protein content in BAL samples from these patients persistently show markedly increased levels 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 (see e.g., [87]; Fig. 2). Experimental studies in vitro and in vivo have demonstrated that admixture of blood, serum, plasma, or alveolar washings obtained during states of plasma leakage may severe-

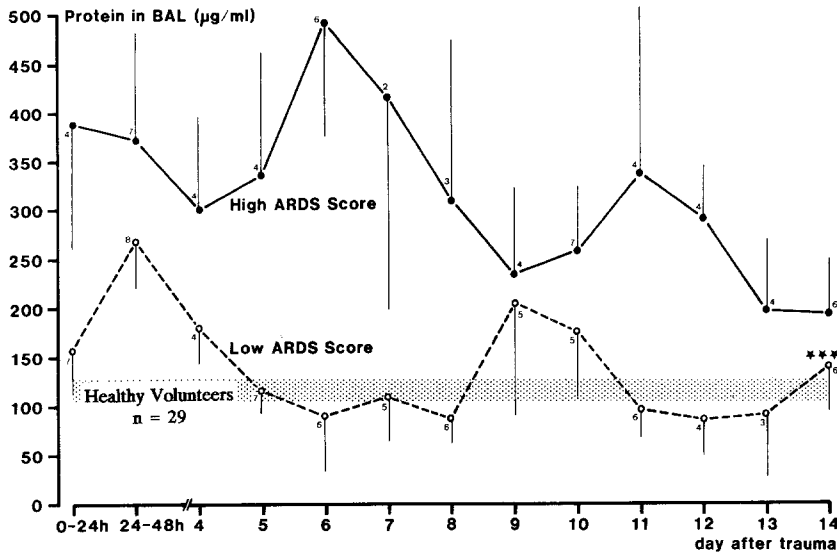


Fig. 2. Time course of BAL protein content in severely traumatized patients with high and low ARDS scores. Repetitive flexible bronchoscopy for serial determination of alveolar surfactant function was performed within 14 days after trauma; the number of samples for each post-trauma day is indicated. *Shaded area*, mean \pm SE of BAL protein concentration in healthy volunteers. The groups with high and low ARDS scores differ significantly ($P < 0.001$). (From [87])

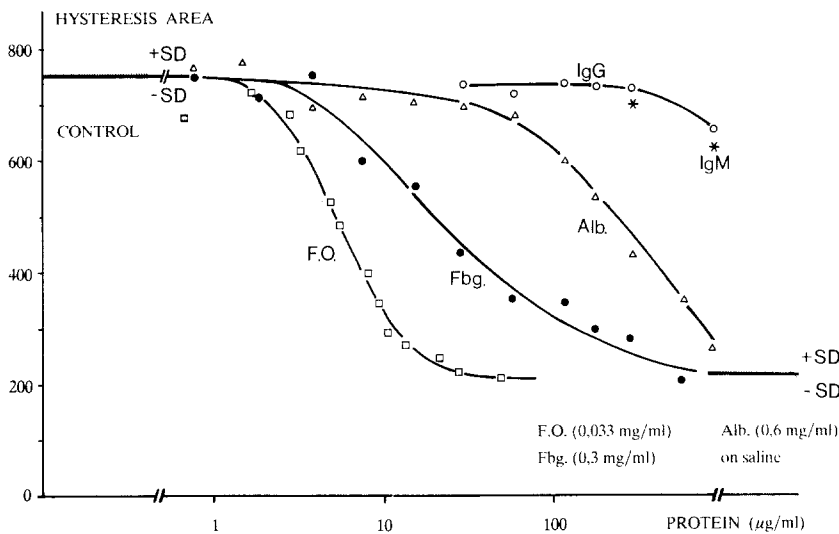


Fig. 3. Dose-effect curves of IgG (human), albumin (bovine; *Alb.*), fibrinogen (bovine; *Fbg.*), and fibrin-monomers/-oligomers (bovine; *F.O.*) on surface tension characteristics of rabbit lung surfactant. Biophysical measurements were undertaken in diluted surfactant material in the Wilhelmy balance/Langmuir trough system (50 μ g/ml phospholipids); the hysteresis of the surface tension-surface area relationship is given (arbitrary units). *Shaded area*, mean \pm SD of hysteresis area of control surfactant without protein addition and of protein effects on pure saline. Fibrinmonomers were first dissolved in a small volume in urea TRIS buffer and then bolus-admixed to the surfactant material; arising large fibrin strands (but not small fibrin oligomers) were removed from the soluble phase by centrifugation before measuring surface tension. [106]

ly compromise biophysical surfactant function [7, 9, 27, 62, 73, 106, 117]. Among different proteins involved, albumin [19, 27, 51, 105], hemoglobin [50], and in particular fibrinogen or fibrinmonomer [19, 27, 52, 84, 99, 105, 108, 109, 115] possess strong surfactant-inhibitory properties (see Fig. 3). Concerning fibrinogen, it has been demonstrated that its potency to inhibit surfactant function depends on the surfactant apoprotein profile. Surfactant preparations lacking the hydrophobic apoproteins are extremely sensitive to fibrinogen inhibition, and least sensitivity is noted in the presence of both SP-C and SP-B in near physiological quantities [109, 121]. In addition, a further reduction in surfactant sensitivity to fibrinogen is achieved

by supplementation of phospholipid- and hydrophobic apoprotein-based surfactants with SP-A [19].

"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 [6, 12, 40, 67, 91, 112]. In the alveolar milieu, the extrinsic coagulation pathway represents the predominant clotting sequence. Alveolar macrophages express and shed a procoagulant activity, which is attributable main-

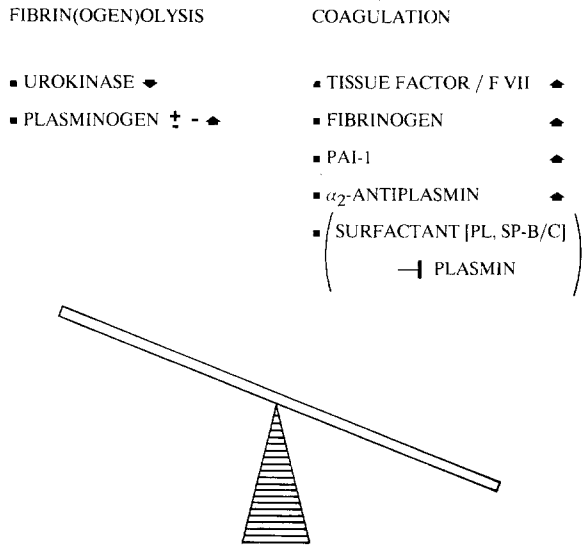


Fig. 4. Hemostatic balance under conditions of ARDS: increase in procoagulant and decrease in fibrinolytic activity in the alveolar space. For details see text. It is hitherto not known whether the plasmin inhibitory capacities of surfactant phospholipids and hydrophobic apoproteins are altered in ARDS

ly to tissue factor in compound with factor VII [13, 14, 36, 43, 59, 79, 80]. This alveolar procoagulant activity was found to be markedly increased in ARDS patients (possibly because of local macrophage activation [55, 59, 61, 107]) and in several experimental models of acute lung injury [56–58, 60] (Fig. 4). In contrast, concentrations of urokinase-type plasminogen activator, representing the predominant fibrinolysis pathway within the alveolar spaces [10, 15, 43, 59], were noted to be decreased in lavage fluids from patients with ARDS; concomitantly, increased levels of plasminogen activator inhibitor-1 and α 2-antiplasmin were detected [10, 59, 61, 80]. Moreover, surfactant phospholipid mixtures were found to inhibit plasmin-induced fibrinogenolysis, in particular when combined with the surfactant apoproteins SP-B and SP-C [130]. Thus, the hemostatic balance within the alveolar milieu appears to be shifted toward predominance of procoagulant and antifibrinolytic activity in acutely or chronically inflamed lung regions, in particular in ARDS. Recent investigations performed by this group [131] have 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. ³¹P

nuclear magnetic resonance spectrum analysis has suggested membranelike, 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.

Damage to surfactant compounds by inflammatory mediators

A variety of inflammatory processes are thought to underlie microcirculatory disturbances in ARDS, and mediator generation has also been demonstrated for the alveolar compartment. Free elastase and collagenase activities were repeatedly detected in BAL fluids of patients with ARDS [16, 76]. Oxidative inhibition of the alveolar α ₁-proteinase inhibitor indicated oxygen radical generation in this compartment [17], and increased levels of lysophospholipids (predominantly lyso-PC) [39] suggested increased phospholipolytic activity in the alveolar space under conditions of ARDS. A variety of in vitro studies have addressed putative direct inhibitory effects of inflammatory mediators on biophysical surfactant functions. Inhibitory potencies have been demonstrated for phospholi-

Table 4. Impact of inflammatory mediators on surfactant function: in vitro studies

Mediator	Effects
Phospholipases (A ₂ , C)	<ul style="list-style-type: none"> – Generation of lysophospholipids (especially lysoPC) [53] – Loss of surface activity [53] – Higher sensitivity toward inhibition by plasma proteins [18] – Generation of free fatty acids (including arachidonic acid) [38]
Cytokines (TNF)	<ul style="list-style-type: none"> – Pretranslational inhibitory effect on the expression of SP-A and SP-B [126]
Proteases (elastase)	<ul style="list-style-type: none"> – Degradation of SP-A, indirect evidence for degradation of SP-B and SP-C; loss of surface activity [88]
Oxygen radicals	<ul style="list-style-type: none"> – Decrease in surface activity [101, 104] – Induction of lipid peroxidation [104]
Lipidmediators (arachidonic acid)	<ul style="list-style-type: none"> – Decrease in surface activity [104]
PMN	<ul style="list-style-type: none"> – Decrease in surface activity [101] – Degradation of SP-A [101]

pases, proteases, oxygen radicals, free fatty acids, and activated granulocytes (via release of oxygen radicals), as summarized in Table 4. 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 for severe impairment of the alveolar surfactant system under conditions of ARDS, and several mechanisms may underlie this finding. Thus the question arises of 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. The main issues to be addressed in this context are the following: alteration of lung mechanics; impairment of gas exchange (ventilation/perfusion mismatch due to altered gas flow distribution, shunt flow); lung edema formation (hydrostatic gradient, barrier characteristics); reduction in host defense competence (nosocomial pneumonia); up-regulation of inflammatory events; and "collapse induration", fibroblast proliferation and fibrosis.

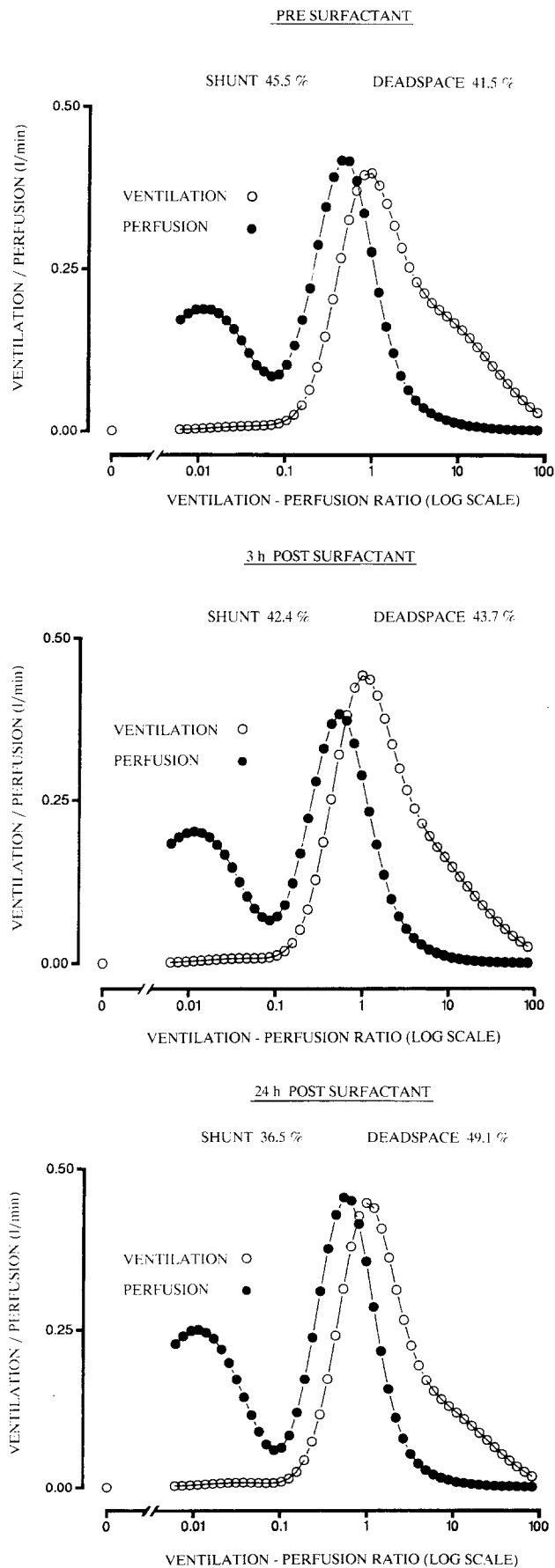
Alteration of lung mechanics

Loss of alveolar surface activity increases surface tension and thereby causes alveolar instability and formation of atelectases. These features must be expected to result in a marked decrease in lung compliance. This basic finding was indeed described even in the very early reports on altered mechanics of postmortem analyzed lungs from patients dying from ARDS [86]. In addition, in a variety of experimental approaches using animal models of ARDS, induction of acute lung injury resulted in significant decrease of compliance [9, 75, 77, 78, 113, 119, 129]. Accordingly, transbronchial administration of surfactant was shown to completely or partially restore physiological lung compliance in some of these models [9, 75, 77, 78, 113, 129]. 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. Future studies of transbronchial surfactant administration in ARDS patients using appropriate techniques to measure lung mechanics may help to determine the contribution of the alveolar surfactant system to altered lung mechanics in these patients.

Impairment of gas exchange: ventilation/perfusion mismatch and shunt flow

Lack of surface active material has been established as primary cause of severe gas exchange disturbances in IRDS, and dramatic improvement in arterial oxygenation is achieved by transbronchial surfactant application under these conditions [22, 49]. Similarly, experimental approaches in adult animals with removal of alveolar surfactant (lung lavage models [97]) and subsequent transbronchial readministration of surface active material have also underscored the fundamental significance of the alveolar surfactant system for ventilation-perfusion matching in adult lungs [8, 37, 97]. In more realistic models of ARDS, starting with induction of microvascular or alveolar injury, matters are more complex. Shunt flow (perfusion of atelectatic regions) and blood flow through lung areas with low ventilation-perfusion ratios (partial closure of alveolar units or small airways) may well be related to acute impairment of the alveolar surfactant system in such experiments, and transbronchial surfactant administration was found to improve gas exchange conditions in models with protein-rich edema formation due to cervical vagotomy [9], acid aspiration [72, 75, 113], induction of pneumonia [118], hyperoxic lung injury [54], and administration of *N*-nitroso-*N*-methylurethane [77, 78] or oleic acid [129]. The efficacy of surfactant replacement in these models with induction of lung inflammation is, however, lower than in models with primary surfactant depletion (lavage, preterm newborns), which is most probably attributable to 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. The same feature is probably true for patients suffering from ARDS. Presently, only few case reports on transbronchial (via bronchoscope) "rescue" administration of natural surfactant preparations in patients with severe ARDS are



available [69, 96]; one example from this group is given in Fig. 5. Some more or less impressive improvement of gas exchange conditions was noted in these trials, suggesting that the use of larger amounts of surfactant material would be more promising. Studies with long-term surfactant administration by use of aerosol techniques have been commenced in ARDS patients, but definite data are yet not available. Further diagnostic and therapeutic approaches will be necessary to elucidate the contribution of impaired surfactant function to the gas exchange abnormalities in ARDS, to define whether this contribution is critically dependent on the phase of the disease (large impact in early ARDS, small impact in late ARDS with fibrosis?), and thereby to provide a rational basis for surfactant replacement trials aimed at acutely improving gas exchange conditions in ARDS patients.

Lung edema formation

Interstitial and alveolar edema is a key finding in ARDS, attributed primarily to increased endothelial and epithelial permeability in the diseased lungs. Surfactant alterations may well contribute, however, 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 administration [11, 81], intra-

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Fig. 5. Gas exchange abnormalities in a patient with severe ARDS: impact of transbronchial surfactant administration. The therapeutic intervention was undertaken in a 38-year-old patient, who developed severe ARDS after extensive gastric acid aspiration, complicated by nosocomial pneumonia. At the time of intervention, he was ventilated for 30 days, and gas exchange was severely compromised in spite of optimizing ventilator settings ($FiO_2 \approx 0.9$ for 1 week). A multiple inert gas analysis of the ventilation/perfusion distribution demonstrated a large percentage of blood flow shifted to areas of a low ratio, accompanied by extremely high shunt flow (45.5%). Rescue administration of a natural surfactant preparation (Curosurf; 50 mg/kg body weight via bronchoscope) was performed; larger amounts of surfactant were not available. Pulmonary shunt flow declined to 36.5% within 24 h, and blood gases improved concomitantly. Further gradual decline in ARDS severity occurred, and the patient was weaned from the ventilator 12 days after surfactant administration

Table 5. Host defense properties of the hydrophilic surfactant apoproteins

	SP-A	SP-D
Binding to phospholipids	DPPC	PI
Carbohydrate binding region	+	+
Binding to alveolar type II cells	+ ^a	?
Binding to alveolar macrophages	+ ^a	+
Receptor-mediated binding to peritoneal macrophages, PMN, monocytes	-	?
Alveolar macrophages:		
Chemiluminescence	↑	↑
Chemotaxis	↑	?
<i>Staphylococcus</i> phagocytosis	↑ (≈ × 10)	?
Herpes simplex phagocytosis	↑ (≈ × 15)	?
Aggregation of micro-organisms	?	+
Binding to micro-organism	HSV	gram-negative bacteria, fungi, <i>Pneumocystis</i>
Mediation of binding of gram-negative bacteria to alveolar macrophages	?	+

DPPC, Dipalmitoylphosphatidylcholine; HSV, herpes simplex virus; PI, phosphatidylinositol

^a Receptor-mediated

tracheal injection of bile acid [70], cooling and ventilating at low functional residual capacity [1], or plasma lavage [82]. 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 were reduced by transbronchial surfactant replacement [25, 63, 70]. Similarly, increased epithelial permeability for ^{99m}Tc-DPTA is noted in neonates with IRDS [68]. Concerning patients with ARDS, there is presently no conclusive study to evaluate the impact of surfactant abnormalities on lung fluid balance and alveolar epithelial permeability characteristics.

Reduction in host defense competence?

Nosocomial pneumonia is a feared and frequent complication in ARDS. Involvement of the alveolar surfactant system in lung host defense mechanisms has long been suggested. Direct cytolysis of several cocci upon in vitro incubation with lung lavage material was described in early reports and attributed primarily to free fatty acids in the surfactant material [20, 21]. Synthetic phospholipid mixtures and natural surfactant preparations (presumably lacking the hydrophilic apoproteins) were noted to suppress alveolar macrophage priming [48] and phagocytosis as well as tumor necrosis factor (TNF) secretion [111]; this finding is possibly related to the down-regulation of inflammatory

events in the alveolar compartment under physiological conditions [94]. The PG fraction of the surfactant phospholipids was found to be particularly effective in this context [3–5]. Finally, the hydrophilic surfactant apoproteins SP-A and SP-D were recently noted to possess distinct immunological properties and may contribute substantially to the host defense mechanisms within the alveolar space (Table 5) [64–66, 116]. They apparently serve as opsonizing agents in this compartment and enhance bacterial and viral phagocytosis and killing. Overall, these aspects are at best mosaics of a complex alveolar host defense system, which largely remains to be defined [94]. Studies directly addressing changes in host defense mechanisms due to surfactant alterations in ARDS patients are still lacking. The marked decrease in SP-A levels in these lungs (see above) may suggest loss of opsonizing capacity and increased susceptibility to nosocomial infections.

Up-regulation of inflammatory events?

One typical feature of ARDS is the perpetuation of inflammatory events in the microvascular and alveolar compartments, which may continue even after cessation of the primary noxious event (e.g., sepsis, shock, aspiration). Similarly, as discussed for the host defense mechanisms, our knowledge of the regulation of inflammatory processes in the alveolar compartment is only fragmentary. Alveolar cells such as macrophages, type II pneumocytes, and invading granulocytes are rich sources of lipid mediators and cytokines when appropriate-

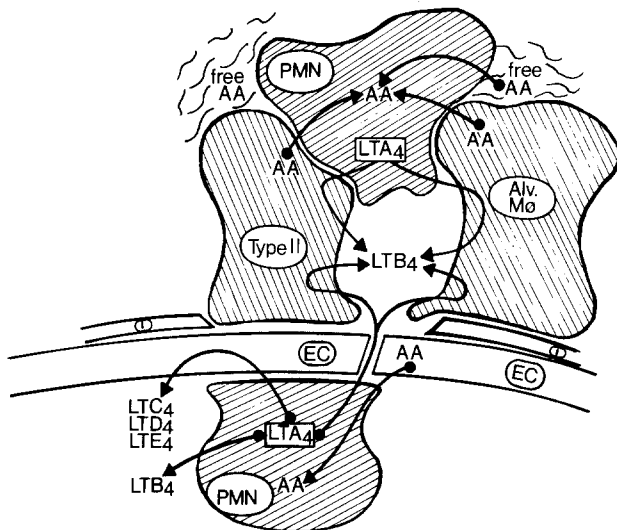


Fig. 6. Intercellular cooperation between granulocytes (PMN) and pulmonary cells in leukotriene (LT) synthesis. Activation of adherent and extravaded PMN by different stimuli results in intercellular shift of the unstable leukotriene precursor LTA_4 to different acceptor cells, such as endothelial cells, alveolar macrophages, and type II pneumocytes. Depending on the enzymatic equipment of these acceptor cells, LTA_4 is metabolized to cysteinyl-LTs (LTC_4 , D_4 , E_4) or LTB_4 . As a countermove, PMN are "fed" with free arachidonic acid (AA) from these LTA_4 acceptor cells, resulting in overall amplification of leukotriene generation. Interestingly, free extracellular AA (contained, for example, in the alveolar surfactant) can substitute for cell-cell shifted AA to perpetuate leukotriene generation in this microenvironment. (Including results from [30–35])

ly stimulated, and intercellular cooperation in inflammatory mediator generation appears to be of major importance; an example for pulmonary capillary and alveolar leukotriene generation is depicted in Fig. 6. Interestingly, the "level" of leukotriene generation in this system of cell-cell cooperation may be largely up-regulated in the presence of free arachidonic acid (leukotriene precursor fatty acid) in the extracellular space, i.e., the alveolar surfactant system. Such increase in lung tissue and surfactant free arachidonic acid content was indeed observed under conditions of experimental [124] and clinical ARDS [39] and may thus contribute to the perpetuation of inflammatory events. As another example of surfactant involvement in inflammatory processes, Allen et al. [2] recently reported on suppression of interleukin-1 and TNF release from human alveolar macrophages by natural surfactant material, without defining the contribution of single surfactant components to this finding. It is thus easily conceivable that alterations in surfactant composition may have multiple effects on inflammatory processes in the alveolar compartment.

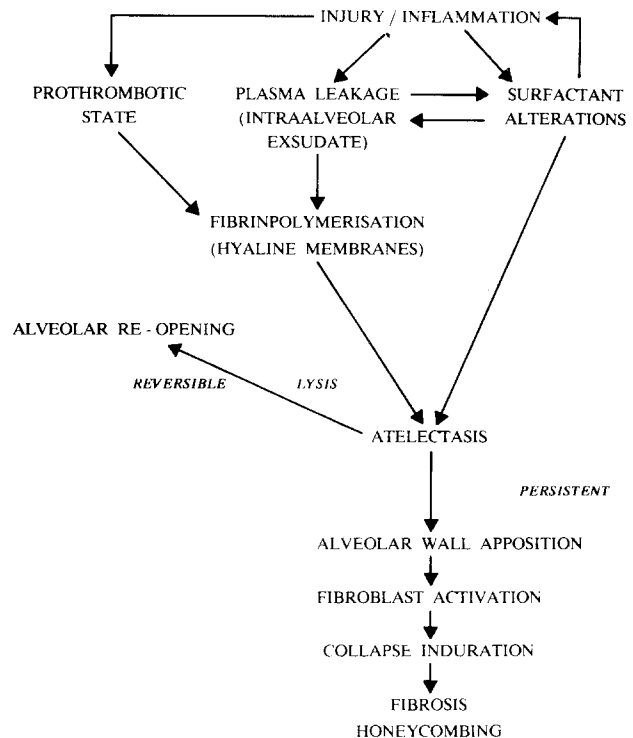


Fig. 7. Possible involvement of surfactant inhibition and alveolar fibrin deposition in the pathogenesis of fibrosis and honeycombing in protracted ARDS. For details see text

"Collapse induration," fibroblast 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 a few weeks. Underlying mechanisms may well include a major role of the alveolar surfactant system and of alveolar fibrin deposition, as depicted schematically in Fig. 7. A corresponding sequence of events was suggested for the pathogenesis of lung fibrosis in general by Burkhardt [12] and termed "collapse induration." Basically, this concept starts with persistent atelectasis at sites of extensive loss of alveolar surfactant function, in particular regions with fibrin deposition. Alveolar wall apposition and the fibrin matrix represent a nidus for fibroblast activation, and the concerned alveolar space is definitely lost by 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 [6, 44, 45]. 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. However, it provides an explanation for the predominance of fibrosis at sites of persistent atelectasis and fibrin deposition.

Conclusion – Perspective

Overall, there is good evidence for the assumption that significant surfactant abnormalities occur under conditions of ARDS, and a variety of mechanisms may contribute to this feature. It is thus conceivable that “classical” consequences of surfactant deficiency such as atelectasis formation and loss of compliance, ventilation-perfusion mismatch and shunt-flow, as well as lung edema formation may be related to such surfactant abnormalities in patients suffering from ARDS. However, the extent to which surfactant-related disturbances contribute to the overall pathophysiological events in ARDS cannot presently be quantified and may depend critically on the phase of the disease. Moreover, surfactant abnormalities may have considerable impact on host defense mechanisms, inflammatory events, and fibrosis generation, but no definite evaluation of these aspects can currently be undertaken due to the scarcity of clinical data in these fields. There is, however, no doubt that all these aspects must be addressed when planning transbronchial surfactant administration as a new therapeutic approach in ARDS. Final “design” of a surfactant to be administered under these conditions will have to use proper administration techniques (preferably some kind of aerosolization), aim at acute improvement in lung mechanics and gas exchange, and critically consider its impact on inflammation, host defense, and mesenchymal proliferation in the alveolar compartment.

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