Surfactant Therapy

11

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Abstract

Pulmonary surfactant is the evolutionary solution to the problem of surface tension and air breathing. Without surfactant, each breath would require inordinate energy expenditure to expose the huge intrapulmonary surface to inspired air, and life on land, at least as we know it, would be virtually impossible. Pulmonary surfactant exists in the alveolar hypophase in a complex microstructure of phospholipid-rich aggregates with incorporated four distinct surfactant proteins, each with their own function. Pulmonary surfactant serves two primary functions in the lungs. It is first and foremost a surface-active agent that lowers and varies surface tension to reduce the work of breathing, stabilize alveoli against collapse and overdistension, and lessen the hydrostatic driving force for edema fluid to transudate into the interstitium and alveoli. In addition, the specific apoprotein components of lung surfactant have been found to play an important role in the lung's innate immune response.

The crucial physiological importance of lung surfactant in respiration is demonstrated by the fact that a lack of this material in premature infants contributes to the development neonatal respiratory distress syndrome, a potentially fatal disease process. Exogenous surfactant replacement is now standard of care in the treatment of premature infants, and can be argued as being the most important discovery in pediatric medicine in the past 30 years. Despite this breakthrough in the treatment of neonatal lung disease, it is clear that the pathophysiology of acute pulmonary injury outside of the neonatal period is much different, and multifactorial, including inflammation, surfactant dysfunction, vascular dysfunction, edema, oxidant injury, ventilation/perfusion mismatching, and injury to alveolar, capillary, and other pulmonary cells. Clinical studies of multiple surfactant preparations in multiple target populations have resulted in unequivocal results. Therefore, the use of exogenous surfactants for the treatment of acute lung disease outside of the neonatal period is much more uncertain and complex, and remains the subject of on-going research.

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Overview of Lung Surfactant and Exogenous Surfactant Therapy

Pulmonary surfactant is the evolutionary solution to the problem of surface tension and air breathing. Without surfactant, each breath would require inordinate energy expenditure to expose the huge intrapulmonary surface (70 m^2, which is approximately the size of a badminton court) to inspired air, and life on land, at least as we know it, would be virtually impossible. One of the first insights into the existence of surface tension forces in the lungs came from the study of von Neergaard in 1929 [1]. Von Neergaard observed that it took nearly twice as much pressure to inflate excised animal lungs with air as it did with fluid. He speculated that since inflating the lungs with an aqueous solution eliminated the air/liquid interface in the alveoli, the additional work required to inflate the lungs with air must be incurred in overcoming surface tension forces at that interface. Von Neergaard's work was supported several decades later in studies by Gruenwald [2] and Mead [3], which further documented the importance of surface tension forces in respiration. Moreover, additional studies indicated that surface tension forces were moderated in the normal lungs by the action of surface-active agents (i.e., surfactants). Work by Pattle [4] in 1955 suggested that the stability of bubbles in the foam expressed from the lungs was related to surfactants that acted to *abolish the tension of the alveolar surface*. Clements [5], Brown [6], and Pattle [7] subsequently confirmed the existence of surfactants in the lungs by further surface tension and biochemical studies.

The crucial physiological importance of lung surfactant in respiration was demonstrated by the early finding that a lack of this material in premature infants contributed to the development of hyaline membrane disease (HMD, later called the neonatal respiratory distress syndrome or RDS) [7, 8]. This finding spurred further research into the function and composition of surfactant. However, clinical interest was significantly dampened by initial unsuccessful attempts by Robillard et al. [9] and Chu et al. [10, 11] in the 1960's to use aerosolized dipalmitoyl phosphatidylcholine (DPPC), the major phospholipid component of pulmonary surfactant, to treat HMD in premature infants. This lack of success was misunderstood as indicating that HMD was not due to surfactant deficiency and, consequently, that surfactant replacement was not an efficacious treatment [11]. Fifteen years of biophysical, biochemical, and animal research was required to reverse this clinical misconception, and establish a firm scientific basis for exogenous surfactant therapy (see Notter [12] for detailed review). Basic science research made it clear that DPPC alone is not a biologically active lung surfactant, and that the aerosolization techniques used by Robillard et al. [9] and Chu et al. [11] were ineffective for alveolar delivery. In 1980, Fujiwara et al. [13] reported the first successful use of exogenous surfactant therapy in premature infants with RDS, although it was another decade before FDA-licensed surfactant drugs were available in the United States. Exogenous surfactant therapy is now a standard of care for the treatment and prevention of RDS in premature infants, but the utility of this treatment approach in other conditions such as clinical acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is less certain and remains the subject of on-going research as detailed later.

Pulmonary Surfactant and Its Functions

Pulmonary surfactant serves two primary functions in the lungs. It is first and foremost a *surface active agent* that lowers and varies surface tension to reduce the work of breathing, stabilize alveoli against collapse and over-distension, and lessen the hydrostatic driving force for edema fluid to transudate into the interstitium and alveoli. In addition, specific apoprotein components of lung surfactant have been found to play an important role in the lung's innate immune response.

Surface Tension and Surfactants

Molecules at the interface between two phases (solid, liquid, or gas) are subjected to specialized conditions that generate associated forces, which manifest as *interfacial tension*. Surface tension is the common name given to the interfacial tension at a liquid-gas interface. In biological systems, the most prevalent liquid-gas interface involves a water-based fluid layer contacting air, as occurs in the alveoli of mammals. In the absence of lung surfactant, surface tension at the alveolar interface would be quite high – on the order of 50 mN/m for tissue fluid that contains non-specific soluble proteins and other endogenous solutes [12]. The surface tension of aqueous fluids is high because water is a strongly polar substance with significant intermolecular attractive forces. Liquid (water) molecules at the interface have a strong attraction toward the bulk of the liquid with no equivalent attractive

forces above the surface since molecules in the gas (air) are so dilute. These unbalanced forces cause the surface to minimize its area, giving rise to surface tension. In a construct such as a spherical bubble, surface tension forces necessitate a pressure drop to maintain the interface at equilibrium against collapse. As described by Laplace in the eighteenth century for a spherical bubble, this pressure drop (ΔP) is directly proportional to the surface tension (γ) and inversely proportional to the radius of curvature (R), i.e., $\Delta P = 2\gamma/R$.

Surfactants are molecules that have an energetic preference for the interface. Molecules that are surface active at an air-water interface all share the characteristic of being amphipathic, that is, possessing both polar and non-polar regions in their structure. Pulmonary surfactant is largely composed of phospholipids that are molecules with polar phosphate *headgroups* and non-polar fatty chains or *tails*. This structure gives phospholipids an energetic preference for the interface in that they can orient with the polar headgroup in the aqueous hypophase and the non-polar hydrocarbon moieties in the air. Lung surfactant also contains essential proteins that have regions of polar and non-polar structure, and these proteins interdigitate with phospholipid molecules in the interfacial film and in bilayers/lamellae in the aqueous phase. A surfactant film at an air-water interface acts to lower surface tension because the attractive forces between surfactant molecules and water molecules are less than those of water molecules for each other (if this were not true, and the surfactant molecules had a stronger attraction for water, they would necessarily go into solution rather than being at the interface). The presence of a surfactant film thus reduces the net attractive force between interfacial region and bulk liquid molecules, lowering surface tension as a function of surfactant concentration. In the lungs, the surfactant film at the alveolar interface has powerful consequences for pressure-volume (P-V) mechanics and respiratory function.

Effects of Lung Surfactant on Respiratory Physiology

Pulmonary surfactant exists in the alveolar hypophase in a complex microstructure of phospholipid-rich aggregates with incorporated surfactant proteins (apoproteins). Surfactant material in the hypophase adsorbs to the air-water interface, which is energetically preferred as described above. The resulting interfacial surfactant film is compressed and expanded during breathing, and lowers and varies surface tension in a dynamic fashion. As alveolar size decreases during exhalation, the surfactant film is compressed and surface tension reaches very low values (<1 mN/m as compared to 70 mN/m for pure water at 37 °C). As alveolar size increases with inspiration, the surfactant film is expanded and surface tension proportionately increases. This dynamic variation of surface tension with area allows alveoli of different sizes to coexist stably at fixed pressure during respiration (Fig. 11.1). Small alveoli resist collapse at end-expiration because their surface tension is low. Consequently alveolar inflation is better distributed during inhalation since the ratio of surface tension to area is more uniform in different sized alveoli. Moreover, by reducing surface tension throughout the lungs, surfactant decreases the pressures (work) needed for pulmonary inflation. There is a direct connection between the surface activity of lung surfactant and pulmonary pressure-volume (P-V) mechanics. The physiological consequences of surfactant deficiency or dysfunction are profound, as seen in the diffuse atelectasis, uneven inflation, and severe ventilation/perfusion mismatching present in the lungs of preterm infants with RDS. The physiological roles of lung surfactant, and the surface properties that generate them as described above, are summarized in Table 11.1.

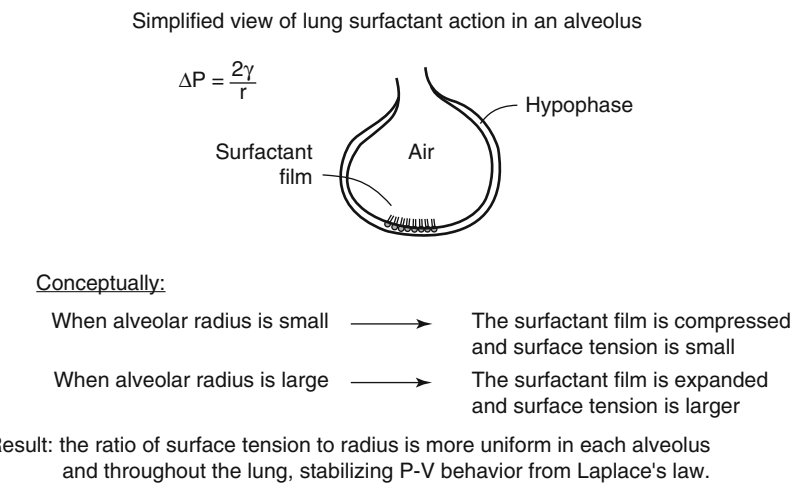

Fig. 11.1 Schematic showing the effects of lung surfactant on pulmonary pressure-volume behavior based on the Laplace equation. The pressure drop (ΔP) necessary to maintain alveoli at equilibrium is proportional to surface tension (γ) and inversely proportional to radius (r), i.e., $\Delta P = 2\gamma/r$ (Laplace's Law for a sphere). By lowering and varying local surface tension as a function of alveolar size (radius), lung surfactant acts to stabilize pulmonary P-V mechanics as shown schematically in the figure. Surfactant also greatly decreases the overall work of breathing by a generalized lowering of average surface tension throughout the alveolar network. See text for details

Table 11.1 Physiological actions and surface properties of functional lung surfactant

Physiological actions of functional surfactant
Reduces the work of breathing (increases lung compliance)
Increases alveolar stability against collapse during expiration
Improves alveolar inflation uniformity
Reduces the hydrostatic driving force for edema formation
Biophysical (surface) properties of functional surfactant
Adsorbs rapidly to the air-water interface
Reaches very low minimum surface tensions during dynamic compression
Varies surface tension with area during dynamic cycling
Respreads from surface collapse phases and other film-associated structures during cycling

Based on data from Notter [12]
See text for discussion

Table 11.2 Average mass composition of lung surfactant lipids and proteins

Phospholipids	88–90 %
Phosphatidylcholine (PC)	80 %
Saturated PCs	55–65 %
Unsaturated PCs	35–45 %
Anionic phospholipids (PG, PI, PS)	15 %
Other phospholipids	5 %
Neutral lipids	3–6 %
Cholesterol, cholesterol esters, glycerides	
Surfactant protein[a]	6–9 %
SP-A, SP-B, SP-C	

Based on data from Notter [12]
Weight percents shown are averages for alveolar surfactant obtained by bronchoalveolar lavage (BAL) in multiple studies. In practice, specific lung surfactant composition varies with animal species, age, and the size-distribution of aggregate fractions isolated from BAL (not shown)
Phospholipid abbreviations: *PC* phosphatidylcholine, *PG* phosphatidylglycerol, *PI* phosphatidylinositol, *PS* phosphatidylserine
[a]Tabulated protein content includes only the biophysically-active surfactant proteins (SP-A, SP-B, SP-C)

Biophysically-Functional Composition of Lung Surfactant

The surface behavior of lung surfactant results from molecular interactions between its lipid and protein components. An average mass composition of lung surfactant is given in Table 11.2. Functional surfactant contains primarily phospholipids and three active surfactant proteins (SP)-A, B, and C. A fourth protein (SP-D) that does not participate in surfactant biophysics but is important in host-defense along with SP-A (see below) also exists. Phosphatidylcholines (PCs) are the major phospholipid class in lung surfactant, including DPPC as the most prevalent single component. DPPC and other disaturated phospholipids form rigid, tightly-packed surface films capable of reducing surface tension to very low values under dynamic compression (<1 mN/m as noted earlier). Lung surfactant also contains fluid unsaturated PCs as well as a range of other phospholipid classes with a mix of saturated and unsaturated compounds. Fluid phospholipids increase the respreading of lung surfactant films so that material ejected from the interface during compression re-enters the film during expansion and remains available for subsequent respiratory cycles. Neutral lipids in lung surfactant also may help increase film respreading. Surfactant proteins have crucial biophysical actions in facilitating the adsorption of phospholipids into the air-water interface, and SP-B and SP-C also act within the surface film itself to refine its composition, to increase respreading, and to optimize surface tension lowering during dynamic cycling.

A summary of the molecular characteristics and activities of the lung surfactant proteins is given in Table 11.3. The two small hydrophobic surfactant proteins SP-B and SP-C are found in approximately equal amounts in endogenous surfactant (together totaling about 1.5–2 % by weight relative to lipid), and are vital to surface activity. SP-B, which is the most active of the two in increasing adsorption and overall dynamic surface activity [12, 15–19], is a particularly important component of functional surfactant. The presence or absence of these hydrophobic proteins in exogenous lung surfactants is a crucial factor in their efficacy as pharmaceutical agents as described later. Genetic deficiency of SP-B is associated with fatal respiratory distress in infancy [20–23], and infants with hereditary SP-B deficiency do not survive beyond the first days of life without surfactant replacement and ultimately lung transplantation [20, 24–26]. Conditional knockout studies have also shown that adult mice rendered acutely deficient in SP-B develop severe respiratory distress, with evidence of surfactant dysfunction and pulmonary inflammation despite maintaining normal levels of SP-C [27]. Mice that are left SP-B deficient die with pathology resembling ARDS, but abnormalities are reversed and mice survive if SP-B synthesis is restored [27]. Although SP-C is less physiologically crucial than SP-B based on such studies, mutations in SP-C in humans have been associated with diffuse interstitial pneumonitis and the early development of emphysema [28].

Surfactant Proteins and Innate Immune Function

Pulmonary surfactant is also important in innate (non-adaptive) pulmonary host defense. The epithelial lining of the lungs is critically positioned to participate in the neutralization and clearance of inhaled microorganisms and other particles. Two of the surfactant proteins (SP-A and SP-D) are members of a family of proteins called collectins that play a vital role in the innate host defense of the lung

Table 11.3 Molecular characteristics and activities of lung surfactant proteins

Surfactant protein (SP)	Selected characteristics and functions
SP-A	MW 26–38 kDa (monomer), 228 AA in humans
	Most abundant surfactant protein, relatively hydrophilic
	Acidic glycoprotein with multiple post-translational isoforms
	C-type lectin and member of the collectin family of host defense proteins
	Forms an active octadecamer (six triplet monomers)
	Aggregates and orders phospholipids (Ca^{++}-dependent)
	Necessary for tubular myelin formation (along with SP-B, Ca^{++})
	Enhances ability of lung surfactant to resist biophysical inhibition
	Has biological importance in host-defense and in helping to regulate surfactant reuptake/recycling/metabolism
SP-B	MW 8.5–9 kDa (monomer), 79 AA in humans (active peptide)
	Most essential SP for increasing adsorption and overall dynamic surface activity
	Contains both hydrophobic residues and charged residues (10 Arg/Lys and 2 Glu/Asp)
	Secondary structure has 4–5 amphipathic helices plus turn/bend and β-sheet regions
	Has significant biophysical interactions with both lipid headgroups and fatty chains
	Necessary for tubular myelin formation (along with SP-A, Ca^{++})
	Can form functional dimers and other oligomers in addition to acting as a monomer
	Fuses/disrupts lipid bilayers, promotes lipid insertion/adsorption into the interface, and enhances lipid mixing and spreading in surface films
SP-C	MW 4.2 kDa (monomer), 35 AA in humans (active peptide)
	Most hydrophobic SP, with only two charged residues (Arg/Lys)
	Contains two palmitoylated cysteine residues in humans
	Monomer is primarily α-helical in structure, with a length that spans a lipid bilayer
	Can form dimers/oligomers, but also detrimental non-specific beta (amyloid-like) forms
	Primary functional biophysical interactions are with hydrophobic phospholipid chains
	Disrupts and fuses lipid bilayers, promotes lipid adsorption, and enhances film spreading
SP-D	MW 39–46 kDa (monomer), 355 AA in humans
	Has significant structural similarity to SP-A
	C-type lectin and member of the collectin family of host defense proteins
	Oligomerizes to a dodecamer (four triplet monomers)
	Not implicated in lung surfactant biophysics, but facilitates host defense and may also participate in surfactant metabolism

Adapted from [12, 14]

MW molecular weight, *AA* amino acids

([29–32] for review). SP-A and SP-D are synthesized and secreted by alveolar type II cells and also by non-ciliated bronchiolar cells (Clara cells) in the airways [29, 30].

As a class, collectins are large multimeric proteins composed of an N-terminal cysteine-rich region, a collagen-like region, an alpha helical coiled *neck* region, and a carbohydrate recognition domain (CRD) [29–31]. The basic collectin structure is a trimer of the polypeptide chain, but different collectins have different degrees of higher order oligomerization [31]. SP-A forms octadecamers (6 trimers), while SP-D preferentially accumulates as dodecamers (4 trimers). The carboxy-terminal domains of SP-A and SP-D are responsible for their lectin (carbohydrate binding) activity, and trimeric clusters of the peptide chains are required for high-affinity binding to multivalent ligands. Both proteins bind to the mannose or glucose sugars present in most microbial ligands, although SP-A preferentially binds to the dimannose repeating unit in gram-positive capsular polysaccharides and SP-D to the glucose-containing core oligosaccharides of gram-negative lipopolysacharide (LPS) [29]. Both can also interact with lipids; SP-A with phospholipids and the lipid A domain of gram-negative LPS, and SP-D with the lipid and inositol moieties of phosphatidylinositol.

SP-A and SP-D can bind, agglutinate, and opsonize a variety of pathogens as well as induce chemotaxis, phagocytosis, and provoke killing by phagocytic cells. Table 11.4 lists selected organisms bound by SP-A and/or SP-D. While no specific diseases associated with deficiencies of these proteins in humans have been described, murine knockout models have elucidated their role in host defense. SP-A deficient mice have normal surfactant homeostasis and respiratory function, but enhanced susceptibility to a number of different bacteria, viruses, and parasites [29, 33, 34]. The phenotype of SP-D deficient mice is somewhat confusing in that these animals develop a lipoproteinosis-like disease that

makes effects on innate immunity difficult to separate from lung injury-induced inhibitory changes in surfactant function [35]. Nonetheless, SP-D can be shown to similarly bind, agglutinate, and opsonize a variety of pathogens [29, 36, 37].

Surfactant Metabolism and Recycling

Much is known regarding the complex metabolism of pulmonary surfactant ([12, 38–46] for review). Lung surfactant is synthesized, packaged, stored, secreted and recycled in type II epithelial cells in the alveolar lining. The phospholipid components are synthesized in the endoplasmic reticulum and transported through the Golgi apparatus to the lamellar bodies, while surfactant proteins are translated in the usual fashion and then undergo extensive post-translational processing. SP-A, SP-B and SP-C [47–51], but not SP-D [52, 53], are found in lamellar bodies.

Lamellar bodies are subcellular organelles, and their contents are composed of tightly packed membrane-like structures that are effectively identical in composition to surfactant obtained from the alveolar space. Lamellar bodies make their way to the cell surface where their contents are extruded into the alveolar hypophase and unwind into a lattice-like construction called tubular myelin [54–56] (Fig. 11.2). Tubular myelin is a regularly spaced lattice of phospholipid bilayers studded with regularly spaced particles thought to be SP-A. SP-B and calcium are also required for tubular myelin formation [56, 57] and are present in its lattice structure. In addition to tubular myelin, a variety of other size-distributed surfactant aggregate forms (lamellar, vesicular, and non-specific) exist in the alveolar hypophase [12]. Lung surfactant adsorbs from tubular myelin and other active aggregates to form a complex mixed lipid/protein film at the alveolar hypophase-air interface as described earlier.

Lung surfactant has a finite life span in the alveoli and then is cleared from the alveolar space. As much as 90 % of the surfactant cleared from the alveolar space is taken up and recycled by type II pneumocytes, with the highest uptake percentages found in newborn compared to adult or premature animals ([12, 38, 58, 59] for review). Alveolar macrophages are responsible for only about 10–15 % of surfactant clearance, and a smaller percentage (<5 %) is cleared via the airways. Studies using labeled surfactant introduced into the airways have demonstrated direct uptake by type II pneumocytes, repackaging in lamellar bodies, and eventual re-secretion [60]. The half-life for turnover of human surfactant is variable, and has been reported to range from 1 to 24 h in

Table 11.4 Interactions of lung surfactant collectins with bacterial ligands

	Bacterial ligand	Collectin
Gram-negative bacteria		
Pseudomonas aeruginosa	LPS?	SP-A, SP-D
Klebsiella pneumoniae	LPS core (cap-phenotype)	SP-D
	Capsule (di-mannose)	SP-A
Escherichia coli	LPS core	SP-D
	Not defined	SP-A
H. influenzae, type A	P2 outer membrane protein	SP-A
Gram-positive bacteria		
Group B Streptococci	Not defined	SP-A
Staphylococcus aureus		
Cowan I strain	Not defined	SP-A
Clinical isolate	Not defined	SP-A
Streptococcus pneumoniae	Not defined	SP-A

Based on data from Crouch and Wright [29]

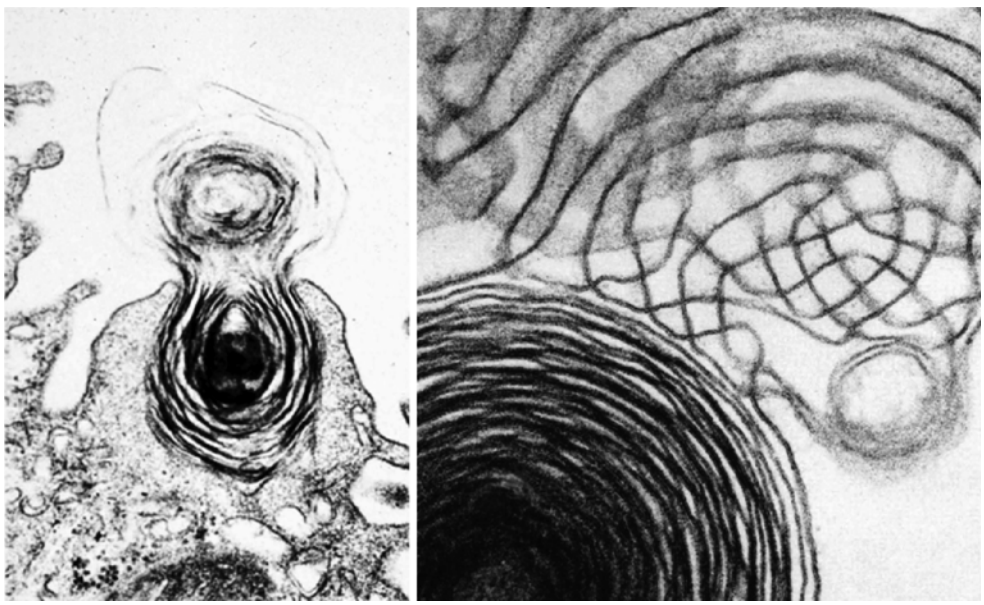

Fig. 11.2 Lung surfactant secreted from a lamellar body and resulting tubular myelin. Lamellar body contents being extruded from a type II pneumocyte (*left image*), which subsequently "unwind" into tubular myelin in the alveolar hypophase (*right image*). Formation of tubular myelin requires phospholipids, SP-A, SP-B, and calcium. Alveolar surfactant also exists in a variety of other large and small aggregate microstructural forms in addition to tubular myelin (Reprinted from Williams [54]. © 1977 Rockefeller University Press)

animals [12, 38, 58]. SP-A has been found to enhance the uptake of surfactant phospholipids into type II pneumocytes [61–63], and SP-B/C may also influence phospholipid uptake in type II cells [64, 65]. The uptake of exogenously administered surfactants as substrate is thought to be an important factor in the indirect (non-surface active) benefits of surfactant therapy, particularly for relatively inactive preparations with a high DPPC content such as Exosurf® and ALEC® (pharmaceutical surfactants are described in more detail later).

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

The pathophysiology of acute lung injury is multifactorial and includes inflammation, surfactant dysfunction, vascular dysfunction, edema, oxidant injury, ventilation/perfusion mismatching, and injury to alveolar, capillary, and other pulmonary cells. This pathophysiology is described in detail elsewhere in this text. A common aspect of acute pulmonary injury is damage to the cells of the alveolar-capillary membrane (type I and type II alveolar epithelial cells and capillary endothelial cells) with a loss of barrier integrity leading to interstitial and alveolar edema. Another common feature is inflammation. The innate pulmonary inflammatory response is complex, involving the recruitment and activation of circulating leukocytes as well as participation by resident lung cells. A large number of inflammatory mediators and transduction and regulatory pathways are involved in acute pulmonary inflammation and injury (e.g., [66, 67] for review).

ALI/ARDS is a prevalent and potentially lethal condition in adults and children following direct or indirect pulmonary injury from multiple etiologies [67–70]. Common direct causes of acute pulmonary injury include respiratory infection, gastric or toxic liquid aspiration, pulmonary contusion, thoracic radiation, hyperoxia, and noxious gas inhalation, among others. Common indirect (systemic) causes of acute pulmonary injury include sepsis, hypovolemic shock, burn injury, pancreatitis, fat emboli, and generalized body trauma. Acute pulmonary injury also affects infants in addition to older patients. In term infants, while not generally labeled ALI/ARDS, common causes of lung-injury induced respiratory failure include meconium aspiration, pulmonary infection, and sepsis. In preterm infants, acute respiratory failure is most commonly initiated by surfactant deficiency (i.e., RDS), but secondary lung injury and surfactant dysfunction can arise in association with hyperoxia, mechanical ventilation, infection, edema from patent ductus arteriosus, and other factors. In addition to acute respiratory failure, ALI/ARDS can also progress to a fibroproliferative phase that leads to chronic lung injury with tissue remodeling and the initiation of fibrosis. However, surfactant dysfunction is most prominent in the acute phase of ALI/ARDS.

Surfactant Dysfunction in ALI/ARDS

In their original descriptions of ARDS (initially termed "adult" instead of "acute" respiratory distress syndrome), Ashbaugh et al. [71] and Petty and Ashbaugh [72] commented on its similarity to infantile RDS, and Petty et al. [73] reported abnormalities in surfactant function. However, as described earlier, respiratory failure in RDS is initiated by a quantitative deficiency in surfactant that leads to progressive atelectasis and overdistension with decreased lung compliance. Although an element of surfactant deficiency can be present in ALI/ARDS, surfactant dysfunction (inhibition, inactivation) as a consequence of inflammatory injury and edema is generally much more prominent. Extensive basic research has identified many of the mechanisms contributing to surfactant dysfunction in lung injury (for detailed review of lung surfactant inhibition and mechanisms of dysfunction see [12, 18, 74]). Irrespective of whether the initiating event is direct injury from the alveolar side or indirect pulmonary injury from the vascular side, surfactant dysfunction may arise by multiple pathways that include the following (Table 11.5):

1. *Physicochemical interactions with inhibitory or reactive substances*: A prevalent cause of surfactant dysfunction in lung injury is through biophysical or chemical interactions with substances that gain access to the alveolar space following damage to the alveolar-capillary membrane. Albumin, hemoglobin, fibrin, fibrinogen, and

Table 11.5 Pathways and processes that can contribute to surfactant abnormalities in acute inflammatory lung injury

Lung surfactant dysfunction/inactivation
Biophysical inactivation by inhibitory substances in edema or the inflammatory response
Chemical degradation by lytic enzymes or reactive oxygen/nitrogen species
Depletion or detrimental alteration of active large aggregate surfactant subtypes
Alveolar epithelial cell damage or alteration
Type I cell injury and death leading to increased permeability of the alveolar epithelial barrier
Type II cell injury and/or hyperplasia causing altered surfactant synthesis, secretion, recycling
Inflammation and microvascular dysfunction
Capillary endothelial injury with increased microvascular permeability, resulting in interstitial or alveolar edema containing surfactant inhibitors
Inflammatory mediators and products produced by leukocytes and lung cells that exacerbate lung injury or interact chemically/physically with functional surfactant components.

See text for discussion. Surfactant dysfunction and its mechanisms in ALI/ARDS are reviewed in detail by Notter [12] and Wang et al. [74]

Table 11.6 Examples of endogenous compounds that inhibit lung surfactant activity by direct physical or chemical interactions

Biophysical inhibitors
Plasma and blood proteins (e.g., albumin, hemoglobin, fibrinogen, fibrin monomer)
Fluid cell membrane lipids
Lysophospholipids
Fluid free fatty acids
Glycolipids and sphingolipids
Meconium
Chemically-acting inhibitors
Lytic inflammatory enzymes (proteases, phospholipases)
Reactive oxygen and nitrogen species

Adapted from [12, 18, 74]
Tabulated inhibitors are examples only. See text for discussion

other blood or serum proteins have been shown in vitro to impair the surface tension lowering of lung surfactant by competing with the adsorption of its active components into the air-water interface, thus compromising film formation [75, 76]. Other biophysical inhibitors include cell membrane lipids, lysophospholipids, or fatty acids that mix into the interfacial film itself to compromise surface tension lowering during dynamic compression [76–79]. Additional biophysical inhibitors are listed in Table 11.6, which also includes chemically-acting inhibitors such as phospholipases or proteases that can degrade essential surfactant lipids or proteins to impair surface activity [80–82]. Lung surfactant can also be chemically altered by interactions with reactive oxygen and nitrogen species [74]. Fortunately, although surfactant can be inhibited by these physicochemical processes, it has been well-documented, at least in vitro, that dysfunction can be overcome by increasing the concentration of active surfactant even if inhibitors are still present [12, 18, 74].

2. *Altered surfactant aggregates and metabolism*: Another pathway by which surfactant activity can be reduced during lung injury is by depletion or alteration of active large aggregates. As noted earlier, surfactant exists in the alveolar hypophase in a size-distributed microstructure of aggregates, the largest of which typically have the greatest surface activity and the highest apoprotein content [83–90]. The percentage of large aggregates and their content of SP-A and SP-B are reduced in bronchoalveolar lavage from patients with ALI/ARDS [91–93]. Surfactant phospholipid composition can also be altered in patients with ALI/ARDS [93, 94]. Animal models of ALI/ARDS demonstrate that large surfactant aggregates can be depleted or reduced in activity by physicochemical interactions with inhibitors or by changes in surfactant metabolism [86, 95–98]. Although large aggregates can be detrimentally affected in ALI/ARDS, information on total surfactant pools is inconsistent, with both decreased [99–101] and unchanged amounts [94, 102] reported.

In assessing surfactant dysfunction in ALI/ARDS, it is important to realize that the pathology is not static. The contribution of surfactant dysfunction to ALI/ARDS is dependent on the stage of injury, which commences with an exudative phase involving alveolar-capillary membrane damage and acute inflammation, but may evolve to include elements of fibroproliferation and fibrosis. The superimposition of iatrogenic factors such as ventilator-induced lung injury and hyperoxic injury during intensive care further confounds pathology, as does the multi-organ disease that is frequently present in patients with ALI/ARDS. The multifaceted pathology of lung injury is an important issue when evaluating the potential efficacy of exogenous surfactant therapy in ALI/ARDS.

Surfactant Therapy in ALI/ARDS

The existence of surfactant dysfunction in ALI/ARDS provides a conceptual rationale for therapy with exogenous surfactant, but the use of surfactant preparations having the greatest surface activity and ability to resist inhibition is clearly required. Moreover, to be effective in ALI/ARDS, exogenous surfactant must be delivered and distributed to injured alveoli in the necessary amounts, despite the presence of edema and inflammation. In analogy with initial attempts to treat RDS in premature infants, the first large controlled trial of surfactant replacement in ARDS using the aerosolized protein-free synthetic surfactant Exosurf® was an unequivocal failure [103]. This failure at least partly can be explained by similar reasons to the initial failed neonatal trial, i.e., the use of a surfactant with inadequate activity and an ineffective delivery method. However, surfactant therapy in ALI/ARDS faces more complex challenges than in the case of neonatal RDS, and this therapy remains investigational as detailed below.

Pharmaceutical Surfactants

Although the composition of endogenous pulmonary surfactant is similar throughout mammalian species, this is not true of exogenous surfactant drugs. The degree of resemblance of pharmaceutical surfactants to native surfactant is highly variable, and this has direct consequences for surface and physiological activity. Pharmaceutical surfactants can be divided into three functionally relevant groups: (i) organic solvent extracts of lavaged lung surfactant from animals; (ii) organic solvent extracts of processed animal lung tissue with or without additional synthetic additives; and (iii) synthetic preparations not containing surfactant material from animal lungs (Table 11.7).

Table 11.7 Clinical exogenous surfactant drugs used to treat lung diseases involving surfactant deficiency/dysfunction

I. Organic solvent extracts of lavaged animal lung surfactant
Infasurf® (CLSE, calfactant)
bLES®
Alveofact®
II. Supplemented or unsupplemented organic solvent extracts of processed animal lung tissue
Survanta®
Surfactant-TA®
Curosurf®
III. Synthetic exogenous lung surfactants
Exosurf®
ALEC®
Surfaxin® (lucinactant, KL4)
Venticute® (Recombinant SP-C surfactant)

Adapted from [12, 104]
Infasurf® (ONY, Inc and Forest Laboratories), Survanta® (Abbott/Ross Laboratories), and Curosurf® (Chesi Farmaceutici and Dey Laboratories) are currently FDA-approved in the U.S. for neonatal administration, and Surfaxin® is under active FDA evaluation. Exosurf® (Glaxo-Wellcome) is also FDA-approved, but is no longer used clinically. Details on the composition, activity, and efficacy of these exogenous surfactants in neonatal RDS are reviewed elsewhere (e.g., Refs. [12, 105–109]). The use of these surfactants in ALI/ARDS is discussed in the text, along with the development of new synthetic lipid/peptide exogenous surfactants in current research

Organic solvent extracts of lavaged alveolar surfactant (Category I) contain all of the hydrophobic lipid and protein components of endogenous surfactant, although specific compositional details can vary depending on preparative methodology. Extracts of minced or homogenized lung tissue (Category II) necessarily contain some non-surfactant components, and require more extensive processing that can further alter composition compared to native surfactant. The synthetic surfactants in Category III that have been most widely studied are the early protein-free preparations Exosurf® and ALEC® (artificial lung expanding compound). Exosurf is a mixture of DPPC:hexadecanol:tyloxapol (1:0.11:0.075 by weight) and ALEC is a mixture of 7:3 DPPC:egg PG. These two preparations are no longer in active clinical use because they have been found to have inferior activity compared to animal-derived surfactants [12, 110–115]. Two additional newer synthetic surfactants, KL4 (Surfaxin®, lucinactant) and recombinant SP-C surfactant (Venticute®), are currently undergoing clinical evaluation.

The composition and activity of the animal-derived and synthetic exogenous surfactants in Table 11.7 are discussed in detail by Notter [12], and their efficacy in preventing or treating RDS in clinical trials in premature infants is extensively reviewed elsewhere (e.g., [12, 105–109, 116, 117]). The three animal-derived exogenous surfactant preparations that are currently licensed and used for treating or preventing RDS in preterm infants in the United States are: Infasurf®, Survanta®, and Curosurf®. Infasurf® is a direct chloroform: methanol extract of large aggregate surfactant obtained by bronchoalveolar lavage from calf lungs [12, 19]. Survanta® is made from an extract of minced bovine lung tissue to which dipalmitoylphosphatidylcholine (DPPC), tripalmitin, and palmitic acid are added [12, 19]. Curosurf® is prepared from minced porcine lung tissue by a combination of washing, chloroform: methanol extraction, and liquid-gel chromatography [117]. Surfaxin®, which has recently gained FDA-approval, contains a 21 amino acid peptide (KL4) that has repeating units of one leucine (K) and four lysine (L) residues. This peptide is combined at 3 % by weight with a 3:1 mixture of DPPC and palmitoyl-oleoyl phosphatidylglycerol (POPG) plus 15 % palmitic acid [12]. Venticute® contains synthetic lipids and palmitic acid plus a 34 AA modified human recombinant SP-C that has substitutions of phenylalanine for cysteine at two positions and isoleucine for methionine at another [12].

Relative Activity and Inhibition Resistance of Exogenous Surfactant Drugs

The relative activity and efficacy of surfactant drugs are crucial for evaluating and optimizing therapy. As noted above, direct clinical comparison trials in premature infants and retrospective meta analyses have indicated that current animal-derived surfactants are more efficacious in treating preterm infants than protein-free synthetic surfactants such as Exosurf® (e.g., [12, 109, 112–116]). Differences in clinical activity between surfactants can in many cases be directly linked to their composition. The fact that surfactants derived from animal lungs (Categories I and II, Table 11.7) have greater efficacy than protein-free synthetic surfactants like Exosurf® reflects a lack of synthetic components to adequately replace the highly active hydrophobic surfactant proteins SP-B/C. The surface and physiological activity of Exosurf® is significantly increased by the addition of purified bovine SP-B/SP-C, demonstrating that its synthetic components are not functionally effective in substituting for these active proteins [110]. Animal-derived clinical surfactants themselves also vary markedly in surface activity and ability to resist inhibitor-induced dysfunction based on their apoprotein content and other compositional differences. Laboratory research indicates that the surface and physiological activity of direct extracts of lavaged surfactant (Category I surfactant drugs, Table 11.7) are typically greater than those of other clinical surfactants (Figs. 11.3, 11.4, and 11.5). As an example, the activity and inhibition resistance of Infasurf® are substantially greater than Survanta® in basic biophysical and animal studies [19, 110, 111, 118] (Figs. 11.3, 11.4, and 11.5), and these differences correlate directly with the content of SP-B in the two preparations

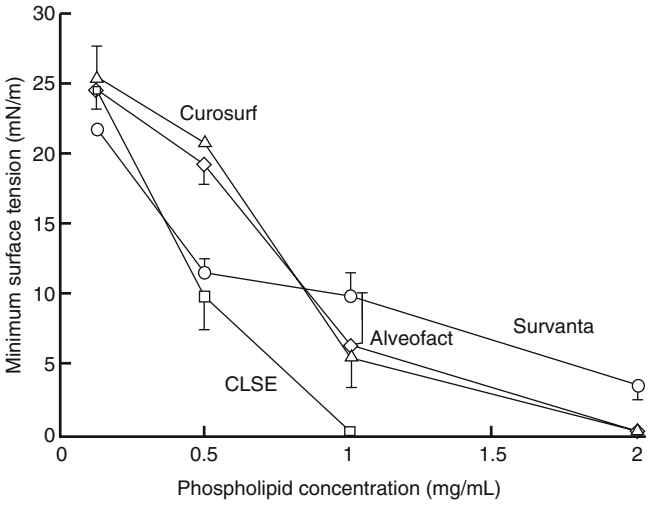

Fig. 11.3 Overall surface tension lowering ability of clinical exogenous surfactants. Minimum surface tension after 5 min of pulsation in a bubble surfactometer (37° C, 20 cycles/min, 50 % area compression) is plotted as a function of surfactant phospholipid concentration for several clinical surfactants. More active surfactants reduce surface tension to lower values at lower concentrations. The surfactants shown vary widely in overall surface tension lowering ability, with the most active being CLSE (Infasurf®, Category I, Table 11.7) (Reprinted from Seeger et al. [111]. With permission from European Respiratory Society)

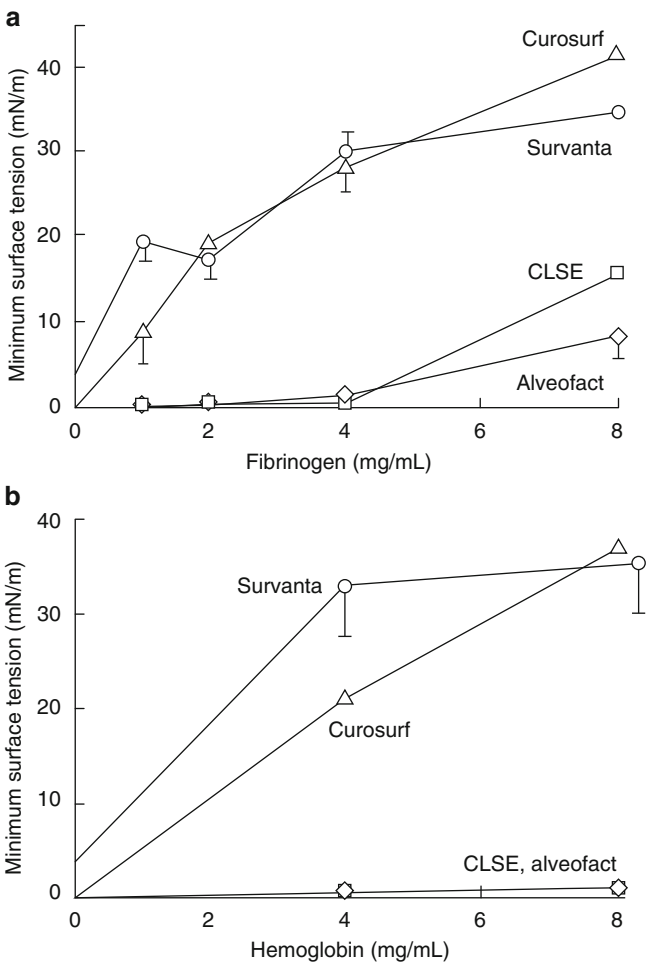

Fig. 11.4 Resistance of clinical surfactants to inhibition by blood proteins. Minimum surface tension of clinical surfactants after 5 min of pulsation in a bubble surfactometer (37° C, 20 cycles/min, and 50 % area compression) is plotted against the concentration of added inhibitory blood proteins (fibrinogen and hemoglobin). Exogenous surfactants that most closely mimic natural surfactant (Category I drugs from Table 11.7) are best able to resist inhibition and reach low surface tension despite high levels of inhibitory proteins. Surfactant phospholipid concentration was constant at 2 mg/ml (Reprinted from Seeger et al. [111]. With permission from European Respiratory Society)

[19, 24, 118]. Survanta® contains only 0.044 % SP-B by weight relative to phospholipid due to losses during processing of lung tissue [19]. In contrast, Infasurf® has a specific SP-B content of 0.9 % by weight (and a total hydrophobic protein content of 1.7 % by weight) equivalent to lavaged calf lung surfactant [19]. As described earlier, SP-B is the most active of the hydrophobic surfactant proteins in enhancing the adsorption and overall dynamic surface activity of phospholipids [15–17, 19, 119, 120]. The addition of SP-B or synthetic SP-B peptides to Survanta® significantly improves its activity towards that of natural surfactant [19, 118, 121] (Fig. 11.5), indicating that the lack of SP-B in this exogenous surfactant is functionally important. Even without SP-B, however, Survanta® still has significantly better activity compared to protein-free surfactants like Exosurf® because of its content of SP-C and other ingredients [12].

New Synthetic Lung Surfactant Development

Recent advances in molecular bioengineering and peptide chemistry provide the potential to design new even more active synthetic lung surfactants than those in Table 11.7, and several approaches are currently being studied ([122–125] for review). One important approach involves synthetic surfactants bioengineered to contain lipids combined with active SP-B peptides that incorporate functionally crucial structural regions of the human protein. Two significant examples of highly active SP-B peptides are the 34 residue Mini-B peptide [126, 127] and the 41 residue Super Mini-B peptide [128]. Mini-B and Super Mini-B both incorporate active N- and C-terminal amphipathic helices from human SP-B, as well as its functional Saposin bend character and key intramolecular connectivities. In addition, Super Mini-B includes an N-terminal lipophilic sequence from human SP-B. Super Mini-B and Mini-B peptides have very high surface and physiological activity when combined with lipids in synthetic surfactants [126, 128]. Synthetic exogenous surfactants containing an SP-B peptide like Super Mini-B or Mini-B can also be bioengineered to contain a second peptide component based on

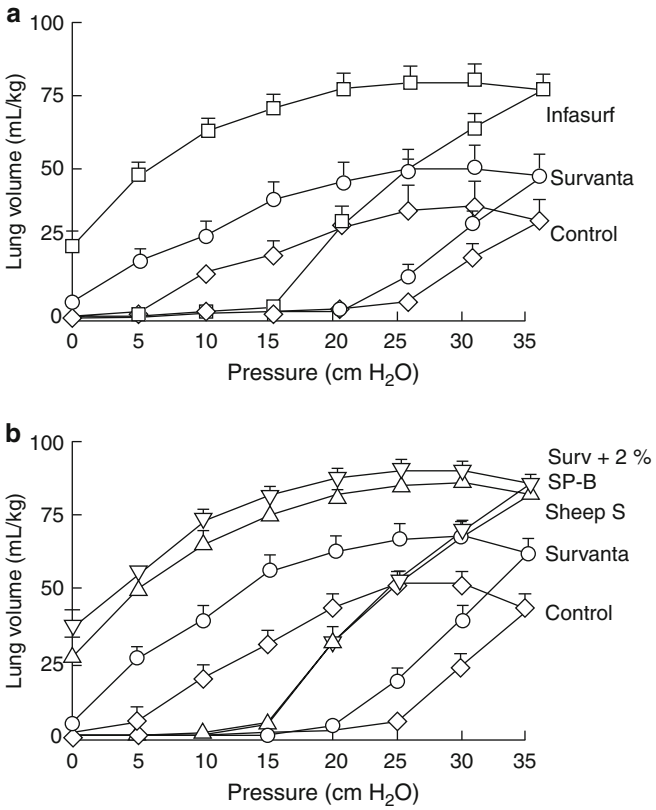

Fig. 11.5 Effects on physiological activity from the addition of purified SP-B to Survanta®. (**a**) Premature rabbit fetuses (27 days gestation) treated with Survanta® or Infasurf®, and untreated controls; (**b**) Premature rabbit fetuses treated with Survanta®, Survanta®+SP-B (2 % by weight by ELISA), natural surfactant from adult sheep (Sheep S), or untreated controls. Infasurf® improved lung mechanics more than Survanta® (**a**), and the importance of SP-B in this behavior is demonstrated by the increased activity of Survanta®+SP-B compared to Survanta® alone (**b**). Surfactants were instilled intratracheally at a dose of 100 mg/kg body weight, and quasistatic pressure-volume curves were measured following 15 min of mechanical ventilation (Reprinted from Mizuno et al. [118]. With permission from Nature Publishing Group)

human SP-C, but designed to be more stable and resistant to amyloid formation that can detrimentally impact the activity of native SP-C. Synthetic surfactants containing SP-B/C peptides can also incorporate novel synthetic phospholipid analog components that are designed to have high surface activity plus beneficial chemical properties like phospholipase-resistance. One particularly active synthetic lipid analog of this kind is DEPN-8, a phospholipase-resistant diether lipid analog of DPPC developed by Notter and co-workers [122, 126, 129–131]. Synthetic surfactants containing DEPN-8 or other phospholipase-resistant lipids plus active SP-B peptides have the potential for particular utility in ALI/ARDS [82, 122, 126, 128, 131–134], where these lytic enzymes can be elaborated in high concentrations during the inflammatory response in injured lungs [135–141].

Animal Studies of Surfactant Therapy in ALI/ARDS

Animal models of ALI/ARDS in which exogenous surfactant therapy has been found to improve respiratory function or mechanics include acid aspiration [142–144], meconium aspiration [145–148], anti-lung serum [149], bacterial or endotoxin injury [150–155], vagotomy [156], hyperoxia [157–161], *in vivo* lavage [121, 162–166], N-nitroso-N-methylurethane (NNNMU) injury [167–169], lung contusion [170], and viral pneumonia [171, 172]. In addition to demonstrating that surfactant therapy has potential benefit in ALI/ARDS, animal studies are also important in comparing surfactant activity under reproducible conditions, as well as in examining other variables of interest for clinical therapy. These variables include the method of surfactant delivery (instillation versus aerosolization), the timing of administration, the effects of different modes of ventilation, the effects of dose, and so forth. For example, animal studies indicate that direct airway instillation is more effective than current aerosol techniques in delivering exogenous surfactant to the alveoli. In addition, these studies demonstrate that early therapy is preferable to later therapy in terms of distributing surfactant to injured lungs ([12] for review). However, despite their utility for assessing the acute effects of exogenous surfactants and comparing preparations and delivery methods, animal models offer limited insight into longer-term morbidity or mortality. For that, one must ultimately turn to human studies.

Human Studies of Surfactant Replacement Therapy in ALI/ARDS

Multiple clinical studies have reported respiratory benefits following the instillation of exogenous surfactants to term infants, children, or adults with ALI/ARDS or related acute respiratory failure [173–192] (Table 11.8). However, many of these were pilot treatment studies or small controlled trials that reported only improvements in acute lung function (oxygenation). Results in sizeable randomized controlled trials of surfactant therapy in ALI/ARDS are more equivocal, particularly in adults.

Infant Investigations

The best-studied application of surfactant therapy in term infants with acute pulmonary injury is in meconium aspiration syndrome [186–190]. Meconium obstructs and injures the lungs when aspirated and is known to cause surfactant dysfunction [194, 195]. Auten et al [186], Khammash et al. [189], and Findlay et al. [190] have all reported significant improvement from surfactant administration in infants with meconium aspiration. The randomized study of Findlay et al.

Table 11.8 Selected clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS)

Study	Patients (N)	Disease or syndrome	Surfactant	Outcomes
Günther et al. [173]	Adults (27)	ARDS	Alveofact	Improved oxygenation Improved surfactant function
Walmrath et al. [174]	Adults (10)	ARDS from sepsis	Alveofact	Improved oxygenation
Spragg et al. [175]	Adults (6)	ARDS from multiple causes	Curosurf	Improved oxygenation and biophysical function
Wiswell et al. [178]	Adults (12)	ARDS from multiple causes	Surfaxin	Improved oxygenation
Spragg et al. [176]	Adults (40)	ARDS, multiple causes	Venticute	Improved oxygenation, decreased IL-6 in BAL
Amital et al. [177]	Adults (42)	Lung transplant	Infasurf	Improved oxygenation, better graft function
Willson et al. [179, 180]	Children (29 & 42)	ARDS from multiple causes	Infasurf	Improved oxygenation
Willson et al. [181]	Children (152)	ARDS from multiple causes	Infasurf	Improved survival
Lopez-Herce et al. [182]	Children (20)	ARDS + post-op cardiac	Curosurf	Improved oxygenation
Hermon et al. [183]	Children (19)	ARDS + post-op cardiac	Curosurf or alveofact	Improved oxygenation
Herting et al. [184]	Children (8)	Pneumonia	Curosurf	Improved oxygenation
Moller et al. [185]	Children (35)	ARDS, multiple causes	Alveofact	Improved oxygenation
Auten et al. [186]	Infants (14)	Meconium aspiration or pneumonia	Infasurf (CLSE)	Improved oxygenation
Lotze et al. [187, 188]	Infants (28 & 328)	ECMO, multiple indications	Survanta	Improved oxygenation, decreased ECMO
Khammash et al. [189]	Infants (20)	Meconium aspiration	bLES	Improved oxygenation
Findlay et al. [190]	Infants (40)	Meconium aspiration	Survanta	Improved oxygenation, decreased pneumothorax and mechanical ventilation
Luchetti et al. [191, 192]	Infants (20 & 40)	RSV bronchiolitis	Curosurf	Improved oxygenation

The tabulated studies of Willson et al. [180, 181], Findlay et al. [190], Moller et al. [185], Lotze et al. [187, 188], Luchetti et al. [191, 192] and Amital et al. [177] were controlled trials, while the remaining studies were uncontrolled treatment trials. See text for details, plus Refs. [67, 68, 104, 193] for added reviews of exogenous surfactant therapy in ALI/ARDS

[190] found reductions in the incidence of pneumothorax, duration of mechanical ventilation and oxygen therapy, time of hospitalization, and requirements for ECMO in 20 term infants treated with Survanta® compared to controls. Lotze et al. [187, 188] also reported favorable results using Survanta® in a controlled trial in term infants referred for ECMO due to severe respiratory failure (meconium aspiration was a prevalent diagnosis in both studies). Twenty-eight infants treated with four doses of Survanta® (150 mg/kg) had improved pulmonary mechanics, decreased duration of ECMO treatment, and a lower incidence of complications after ECMO compared to control infants [187]. A subsequent multicenter controlled trial in 328 term infants also reported significant improvements in respiratory status and the need for ECMO following surfactant treatment [188]. Exogenous surfactant is now used in many institutions to treat respiratory failure in term infants with meconium aspiration or pneumonia, although fewer controlled studies are available for the latter condition. Surfactant therapy has also been studied in infants with congenital diaphragmatic hernia, but its use remains somewhat controversial in this context [196, 197].

Pediatric and Adult Investigations

Surfactant therapy in children and adults with ALI/ARDS has met with mixed success. Improvements in acute respiratory function following exogenous surfactant therapy have been shown in a number of studies in adults and children with ALI/ARDS [173–185] (Table 11.8). However, findings in substantive randomized prospective studies are less positive, particularly in adults. The first large prospective, controlled study of surfactant therapy in adults with ARDS was definitively negative. Anzueto et al. [103] administered nebulized Exosurf® vs. placebo to 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. As described earlier, Exosurf® is no longer used clinically in the United States because of its lower activity compared to animal-derived surfactants, and aerosolization is currently not as effective as airway instillation in delivering surfactant to the distal lung fields. Gregory et al. [198] reported small benefits in oxygenation in a controlled trial in adults with ARDS who received four 100 mg/kg doses of Survanta®, but with no overall advantage in survival in the 43 surfactant-treated patients studied. A study by Spragg et al. [176] using recombinant SP-C surfactant (Venticute®) in adults with ARDS showed immediate improvements in oxygenation, but no longer-term improvement in duration of mechanical ventilation, lengths of stay, or mortality. *Post-hoc* analysis suggested, however, that the response in the subgroup of patients with ARDS due to direct lung injury was strongly positive.

This encouraging result led to a recent follow-up study aimed at determining the impact of Venticute® in adults with direct lung injury, which demonstrated no clinical benefit [199]. However, interpretation of this disappointing finding is complicated by questions raised about the specific surface activity of the newer drug suspension administered in the follow-up investigation [199].

Controlled studies of surfactant therapy in children with ALI/ARDS have been more encouraging than those in adults. A randomized but unblinded trial by Willson et al. [180] in 42 children at eight centers with ALI/ARDS showed that those receiving Infasurf® (70 mg/kg) had immediate improvement in oxygenation and fewer ventilator days and days in intensive care. This trial followed an initial open label trial by the same group demonstrating improved oxygenation in 29 children (0.1–16 years) treated with instilled Infasurf® [179]. Luchetti et al. [191, 192] have reported two small controlled studies showing that treatment with porcine surfactant (Curosurf®, 50 mg/kg) led to improved gas exchange as well as reduced time on mechanical ventilation and in intensive care for infants with bronchiolitis. A study by Moller et al. [185] reported that children with ARDS had immediate improvement in oxygenation and a lesser need for rescue therapy following treatment with the bovine surfactant Alveofact®, but was underpowered for assessment of more definitive outcomes. A substantial blinded controlled study by Willson et al. [181] in 2005 yielded very positive results in pediatric patients with ALI/ARDS, demonstrating both immediate benefits with regard to oxygenation as well as a significant survival advantage for patients receiving calfactant (Infasurf®) relative to placebo (Table 11.9), particularly in the direct lung injury cohort. The clinically significant results of this study generated a further combined pediatric and adult controlled study of calfactant in patients with direct lung injury. This adult/pediatric study was halted recently due to a lack of efficacy, but interpretations of this negative finding are complicated by questions about the effectiveness of surfactant delivery for the modified clinical drug suspension and administration methods used in the trial (Willson, personal communication). Another recent study involved the testing of the synthetic surfactant Surfaxin® (lucinactant) in a phase 2 study in infants less than 2 years of age with acute hypoxemic respiratory failure (AHRF) [200]. In this study, treatment with lucinactant appeared to be generally safe, and was associated with an improvement in oxygenation and a significantly reduced requirement for retreatment. These findings suggest that lucinactant might improve lung function in infants with AHRF [200], although more data will be required before this can be adequately determined.

None of the above studies showed any significant adverse long-term effects from surfactant administration, although transient hypoxia and some hemodynamic instability surrounding instillation appear common. Transmission of infectious agents or allergic reactions has also not been reported with any of the surfactants currently licensed in the United States.

Table 11.9 Clinical outcomes from a controlled study using exogenous surfactant (Infasurf; calfactant) in pediatric patients with ALI/ARDS

	Calfactant (n = 77)	Placebo (n = 75)	P Value
Mortality			
Died (in hospital)	15 (19 %)	27 (36 %)	0.03
Died w/o extubation	12 (16 %)	24 (32 %)	0.02
Failed CMV[a]	13 (21 %)	26 (42 %)	0.02
ECMO	3	3	–
Use of nitric oxide	9	10	0.80
HFOV after entry	7	15	0.07
Secondary outcomes			
PICU LOS	15.2 ± 13.3	13.6 ± 11.6	0.85
Hospital LOS	26.8 ± 26	25.3 ± 32.2	0.91
Days O_2 therapy	17.3 ± 16	18.5 ± 31	0.93
Hospital charges[b]	$205 ± 220	$213 ± 226	0.83
Hospital charges/day[b]	$7.5 ± 7.6	$7.9 ± 7.5	0.74

Based on data from Willson et al. [181]
In addition to improving mortality and reducing the percentage of patients that failed CMV as reported in the table, instilled calfactant also significantly improved oxygenation index compared to placebo (P = 0.01, data not shown)
Abbreviations: *CMV* conventional mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *HFOV* high frequency oscillatory ventilation, *iNO* inhaled nitric oxide
[a]Some patients that failed CMV had more than one non-conventional therapy (ECMO, iNO, or HFOV)
[b]Costs are given in thousands of dollars

The Future of Surfactant Therapy and Related Combination Therapies in ALI/ARDS

As described in this chapter, surfactant replacement therapy is standard care in the prevention and treatment of RDS in premature infants, and there is basic science and clinical evidence supporting its use in some forms of lung injury-associated respiratory failure. Data suggest that surfactant therapy in ALI/ARDS should be targeted to direct forms of lung injury where it is likely to be most effective (e.g., pneumonia, aspiration, etc.) as opposed to indirect lung injury (sepsis, systemic inflammatory response syndrome, etc.) [176, 181]. Clinical evidence showing the efficacy of surfactant therapy in term infants with meconium aspiration is sufficiently strong that this approach is now frequently used in neonatal intensive care units, and it is also being applied to other forms of neonatal respiratory failure like pneumonia. Clinical data also indicate that surfactant therapy can generate acute improvements in respiratory function in children with direct pulmonary forms of ALI/ARDS. At the same time, a sufficient consensus of controlled clinical trial data

does *not* exist for surfactant administration to be considered a standard therapy in the pediatric intensive care unit for children with ALI/ARDS. It may be argued that well-established basic science evidence of surfactant dysfunction in ALI/ARDS, along with favorable results for surfactant treatment in multiple animal models coupled with respiratory benefits in humans without significant adverse effects, makes a strong rationale for considering surfactant therapy in pediatric patients with direct lung injury and severe acute respiratory failure. From this perspective, the major downside of the therapy is its considerable expense in the context of limited data documenting broadly-improved long-term outcomes in controlled studies.

As emphasized in this chapter, some exogenous surfactants are more active and have better inhibition resistance than others. The severe pathology of lung injury makes it essential that only the most active and inhibition-resistant surfactant drugs be used for meaningful evaluations of the efficacy of this treatment approach. The ability to deliver active exogenous surfactant in adequate amounts to injured lungs is also a crucial factor in achieving efficacy. Currently, tracheal or bronchoscopic instillation as opposed to aerosolization are the standard delivery techniques used clinically. Future work perfecting more efficient aerosol delivery methods would be very valuable in facilitating the clinical use of exogenous surfactant in patients with compromised respiration. In addition, the delivery of instilled exogenous surfactants to injured lungs can possibly be improved by the use of specific administration methods or particular modes/strategies of mechanical ventilation, such as the use of positioning and recruitment maneuvers as were explored in the most successful human surfactant trials. For example, studies have suggested that the distribution and/or efficacy of instilled exogenous surfactant can be improved by jet ventilation [201, 202] and partial liquid ventilation [203–205]. The delivery and pulmonary distribution of surfactant drugs could also potentially be improved by the use of low viscosity formulations to reduce transport resistance after instillation. Whole surfactant and animal-derived exogenous surfactants have complex non-Newtonian, concentration-dependent viscosities that vary significantly among preparations [206, 207]. Finally, extensive experience from surfactant therapy in animal studies and preterm infants suggests that early surfactant administration (i.e., within hours of lung injury) generates improved responses compared to delayed administration, possibly as a result of better intrapulmonary drug distribution coupled with minimized ventilator-induced lung injury. Intuitively, similar advantages might accompany early surfactant administration in patients with ALI/ARDS.

Lastly, a major issue with regard to surfactant therapy in ALI/ARDS involves its potential use in combination with other agents or interventions that target additional aspects of the complex pathophysiology of acute pulmonary injury. This kind of combination therapy approach may be particularly important in adults with ALI/ARDS, where responses to exogenous surfactant have so far been disappointing. Even if exogenous surfactant as an individual agent is mechanistically effective in mitigating surfactant dysfunction and acutely improving respiration in ALI/ARDS, clinical benefits to long-term outcomes may not be apparent in patients due to remaining elements of lung injury pathology. The use of multiple therapeutic agents or interventions based on specific rationales for potential synergy might significantly enhance patient outcomes in complex disease processes involving inflammatory lung injury. The use of exogenous surfactant therapy in the context of specific combined-modality interventions is described in detail elsewhere [67, 208, 209]. Examples of agents that might be synergistic with exogenous surfactant in ALI/ARDS include anti-inflammatory antibodies or receptor antagonists, antioxidants, and vasoactive agents such as inhaled nitric oxide (iNO). In addition, specific ventilator modalities or ventilation strategies that reduce iatrogenic lung injury may be equally important to consider in conjunction with surfactant therapy. Given the known importance of surfactant dysfunction in inflammatory lung injury, it is likely that on-going research will continue to identify specific populations of patients with ALI/ARDS or related acute respiratory failure who can benefit from exogenous surfactant therapy, with or without complementary agents or interventions.

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