# 10
# Pulmonary Surfactant: Biology and Therapy

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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 (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 because 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 et al. [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 physiologic importance of lung surfactant in respiration was shown 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 stimulated the interest of physicians, spurring 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 1960s 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 caused by 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 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 ongoing 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, stabilizes alveoli against collapse and overdistension, and lessens 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 an *interfacial tension*. Surface tension is the common name given to the interfacial tension at the liquid–gas interface. In biologic systems, the most prevalent liquid–gas

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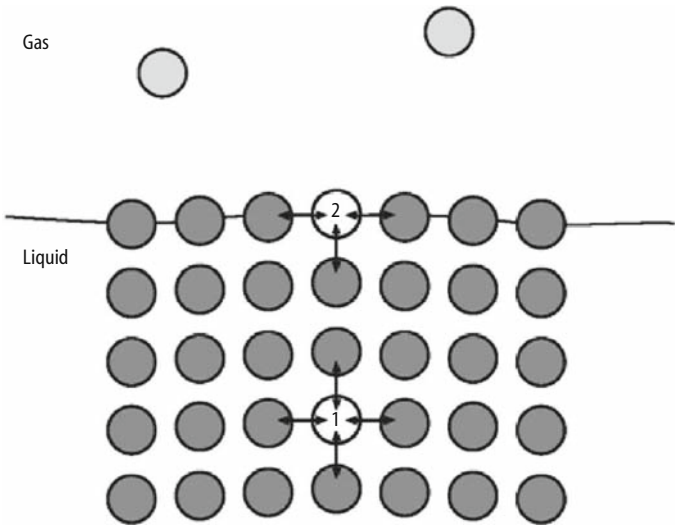


**Figure 10.1.** Molecular forces leading to surface tension at a liquid–gas interface. Attractive forces from nearest neighbors are illustrated for an idealized bulk liquid molecule (1) and an interfacial region molecule (2) contacting a gas. Because the gas is much more dilute, gas molecules exert a negligible attraction on interfacial molecules compared with the liquid. This leads to an unbalanced inward attractive force that causes the surface to minimize its area, generating surface tension. (From Notter [12], with permission from Taylor & Francis Group.)

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 dynes/cm for tissue fluid that contains nonspecific 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 because molecules in the gas (air) are so dilute. These unbalanced forces cause the surface to minimize its area, giving rise to surface tension (Figure 10.1). 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 18th century for a spherical bubble, this pressure drop ($\Delta P$) is directly proportional to the surface tension ($\gamma$) and inversely proportional to the radius of curvature (R), that is, $\Delta P = 2\gamma/R$.

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 nonpolar regions in their structure. Pulmonary surfactant is largely composed of phospholipids that are molecules with polar phosphate *head groups* and nonpolar fatty chains or *tails*. This structure gives phospholipids an energetic preference for the interface in that they can orient with the polar head group in the aqueous hypophase and the nonpolar hydrocarbon moieties in the air. Lung surfactant also contains proteins that have regions of polar and nonpolar 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 unbalanced 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 (PV) 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 apoproteins. Surfactant molecules in the hypophase adsorb to the air–water interface, which is energetically preferred as described above. The resulting surface 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 compared with 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 (Figure 10.2). Small alveoli resist collapse at end expiration because their surface tension is low, and alveolar inflation is better distributed during inhalation because 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 PV mechanics. The physiologic consequences of surfactant deficiency or dysfunction are profound, as seen in the diffuse atelectasis, uneven inflation, and severe ventilation/

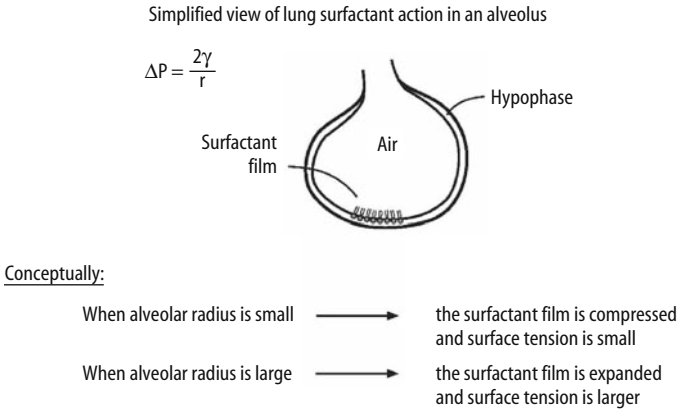


**Figure 10.2.** Schematic showing the effects of lung surfactant on pulmonary pressure–volume (P–V) behavior based on the Laplace equation. The pressure drop ($\Delta P$) necessary to maintain alveoli at equilibrium is proportional to surface tension ($\gamma$) and inversely proportional to radius (r), i.e., $\Delta P = 2\gamma/r$ (Laplace's law for a sphere). By lowering and varying surface tension as a function of alveolar size (radius), lung surfactant acts to stabilize pulmonary P-V mechanics as shown schematically. Surfactant also greatly decreases the overall work of breathing by a generalized lowering of surface tension throughout the alveolar network. See text for discussion.

**Table 10.1.** Physiologic actions and surface properties of functional lung surfactant.

| |
|---|
| Physiologic 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 |

See text for discussion.
*Source:* Adapted from Notter [12].

perfusion mismatching present in the lungs of preterm infants with RDS. The physiologic roles of lung surfactant, and the surface properties that generate them as described earlier, are summarized in Table 10.1.

## Biophysically Functional Composition of Lung Surfactant

The surface behavior of lung surfactant results from molecular interactions between its lipid and protein components. An overall mass composition of lung surfactant is given in Table 10.2. Functional surfactant primarily contains phospholipids and three active surfactant proteins (SP), A, B, and C. A fourth apoprotein (SP-D) that does not participate in surfactant biophysics but is important in host defense (see later) also exists. Phosphatidylcholines (PCs) are the major phospholipid class in lung surfactant, including DPPC as the most prevalent single component. Dipalmitoyl phosphatidylcholine 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, plus 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 reenters 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, increase respreading, and optimize surface tension, lowering during dynamic cycling.

A summary of the molecular characteristics and activities of the four lung surfactant proteins is given in Table 10.3. The two small hydrophobic surfactant proteins (SP-B and SP-C) are found in approximately equal amounts in endogenous surfactant (totaling about 1.5% by weight relative to phospholipid) and are vital to surface activity. Surfactant protein B, which is the most active of the two in increasing adsorption and overall dynamic surface activity [12,14–18], is a particularly important component of functional surfactant. The presence or absence of hydrophobic

**Table 10.2.** Average mass composition of lung surfactant lipids and proteins.

| | |
|---|---|
| Phospholipids | 85%–90% |
| Phosphatidylcholine (PC) | 80% |
| Saturated PCs | 55%–65% |
| Unsaturated PCs | 45%–35% |
| Anionic phospholipids (PG, PI, PS) | 15% |
| Other phospholipids | 5% |
| Neutral lipids | 4%–7% |
| Cholesterol, cholesterol esters, glycerides Protein* | 6%–8% |
| SP-A, SP-B, SP-C | |

*Note:* Tabulated values are averages in weight percent for alveolar surfactant obtained by bronchoalveolar lavage (BAL). Surfactant in BAL contains aggregates of varying sizes that can differ in specific composition (not shown). PC, phosphatidylcholine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine.
*Only biophysically active proteins are tabulated.
*Source:* Notter [12], with permission from Taylor & Francis Group.

**Table 10.3.** Molecular characteristics of lung surfactant proteins.

| Surfactant protein (SP) | Selected molecular characteristics and functional activities |
|---|---|
| SP-A | Molecular weight 26–38 kD (monomer), 228 amino acids 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 ($Ca^{2+}$ dependent) |
| | Necessary for tubular myelin formation (along with SP-B, $Ca^{2+}$) |
| | Enhances ability of lung surfactant to resist biophysical inhibition |
| | Helps regulate reuptake/recycling in addition to aiding host defense |
| SP-B | Molecular weight 8.5–9 kD (monomer), 79 amino acids in humans (active peptide) |
| | Hydrophobic, with 2–3 amphipathic helices plus β-sheet structural regions |
| | Forms dimers and other oligomers of probable functional significance |
| | Has 10 positive Arg/Lys and 2 negative Glu/Asp residues at neutral pH |
| | Interacts biophysically with both head groups and chains of phospholipids |
| | Necessary for tubular myelin formation (along with SP-A, $Ca^{2+}$) |
| | Disrupts and fuses lipid bilayers and promotes lipid insertion/mixing in surface films |
| | Enhances the adsorption, film spreading, and dynamic surface activity of lipids |
| | Most active SP in increasing overall adsorption and dynamic surface activity |
| SP-C | Molecular weight 4.2 kD (monomer), 35 amino acids in humans (active peptide) |
| | Most hydrophobic SP, with only 2 charged Arg/Lys residues |
| | Contains two palmitoylated cysteine residues in humans |
| | Can form dimers and other oligomers |
| | Primarily α-helical in structure, with a length that spans a lipid bilayer |
| | Interacts biophysically primarily with hydrophobic phospholipid chains |
| | Disrupts and fuses lipid bilayers |
| | Enhances the adsorption, film spreading, and dynamic surface activity of lipids |
| SP-D | Molecular weight 39–46 kD (monomer), 355 amino acids in humans |
| | Has significant structural similarity to SP-A |
| | Oligomerizes to a dodecamer (four triplet monomers) |
| | C-type lectin and member of the collectin family of host defense proteins |
| | Not implicated in lung surfactant biophysics |
| | Important in host defense and may also participate in surfactant metabolism |

*Source:* Adapted from Notter [12] and Notter et al. [61].

apoproteins 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 [19–22], and mutations in SP-C have now been associated with diffuse interstitial pneumonitis and the early development of emphysema [23].

## Surfactant Proteins and Innate Immune Function

Pulmonary surfactant is also important in innate (nonadaptive) pulmonary host defense. The epithelial lining of the lungs is critically positioned to participate in the neutralization and clearance of inhaled microorganisms or 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 innate host defense [24–27]. Other collectins include complement, mannan binding lectin (MBL), and conglutinin. Surfactant proteins A and D are synthesized and secreted by alveolar type II cells and also by nonciliated bronchiolar cells (Clara cells) in the airways [24,25].

As a class, collectins are large multimeric proteins composed of an N-terminal cysteine-rich region, a collagen-like region, an α-helical coiled *neck* region, and a carbohydrate recognition domain (CRD) [24–26]. The basic collectin structure is a trimer of the polypeptide chain, but different collectins have different degrees of higher order oligomerization [26]. Surfactant protein A forms octadecamers (6 trimers), whereas SP-D preferentially accumulates as dodecamers (4 trimers). The C-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 di-mannose repeating unit in Gram-positive capsular polysaccharides and SP-D to the glucose-containing core oligosaccharides of Gram-negative lipopolysaccharide (LPS) [24]. 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.

Surfactant proteins A and D can bind, agglutinate, and opsonize a variety of pathogens as well as induce chemotaxis, phagocytosis, and provoke killing by phagocytic cells. Table 10.4 lists organisms bound by SP-A and/or SP-D. Although no specific diseases associated with deficiencies of these proteins in humans have been described, murine knockout models have elucidated their role in host defense. Surfactant protein-A–deficient mice have normal surfactant homeostasis and respiratory function but enhanced susceptibility to a number of different bacteria, viruses, and parasites [24,28,29]. 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 changes in surfactant function [30]. Nonetheless, SP-D can be shown to similarly bind, agglutinate, and opsonize a variety of pathogens [24,31,32].

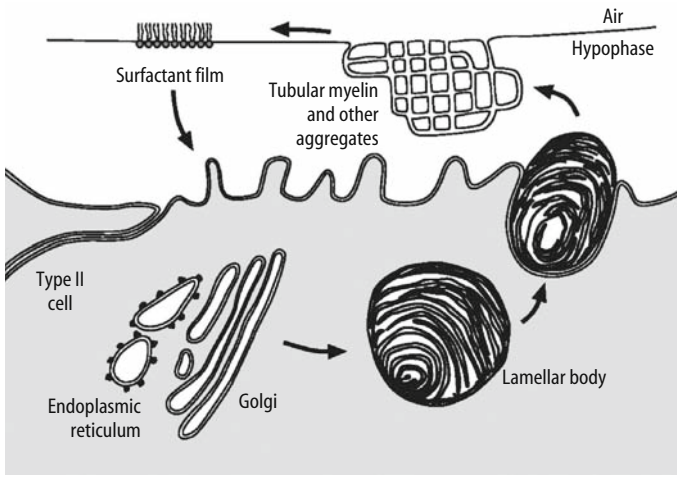


**Figure 10.3.** Schematic overview of the pulmonary surfactant system. The specific lipids and proteins that make up lung surfactant are synthesized, processed, packaged, stored, secreted, and recycled by alveolar type II cells. Surfactant is secreted from lamellar body organelles into the alveolar hypophase, where it forms heterogeneous aggregates (phospholipids plus incorporated apoproteins) that include tubular myelin plus other lamellar/vesicular structures. Surfactant absorbs from these aggregates to form a film at the air–hypophase interface, which acts to lower and vary surface tension during breathing. Over time, "spent" surface-active material in the hypophase is eventually taken up back into the type II pneumocyte for recycling. (From Notter [12], with permission from Taylor & Francis Group.)

**Table 10.4.** Interactions of lung surfactant collectins with bacterial ligands.

| | Bacterial ligand | Collectin |
|---|---|---|
| Gram-negative bacteria | | |
| *Pseudomonas aeruginosa* | Lipopolysaccharide (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 |
| *Haemophilus 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 |

*Source:* Crouch and Wright [24]. Copyright 2001 the Channal Reviews.

## Surfactant Metabolism and Recycling

A good deal of information is now available about the complex metabolism of pulmonary surfactant [e.g., 12,33–41]. Lung surfactant is synthesized, packaged, stored, secreted, and recycled in type II epithelial cells in the alveolar lining (shown schematically in Figure 10.3). The phospholipid components are synthesized in the endoplasmic reticulum and transported through the Golgi apparatus to the lamellar bodies, whereas surfactant proteins are translated in the usual fashion and then undergo extensive post-translational processing. Surfactant proteins A, B, and C [42–46], but not SP-D [47,48], 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* [49–51] (Figure 10.4). Tubular myelin is a regularly spaced lattice of phospholipid bilayers studded with regularly spaced particles thought to be SP-A. Surfactant protein B and calcium are also

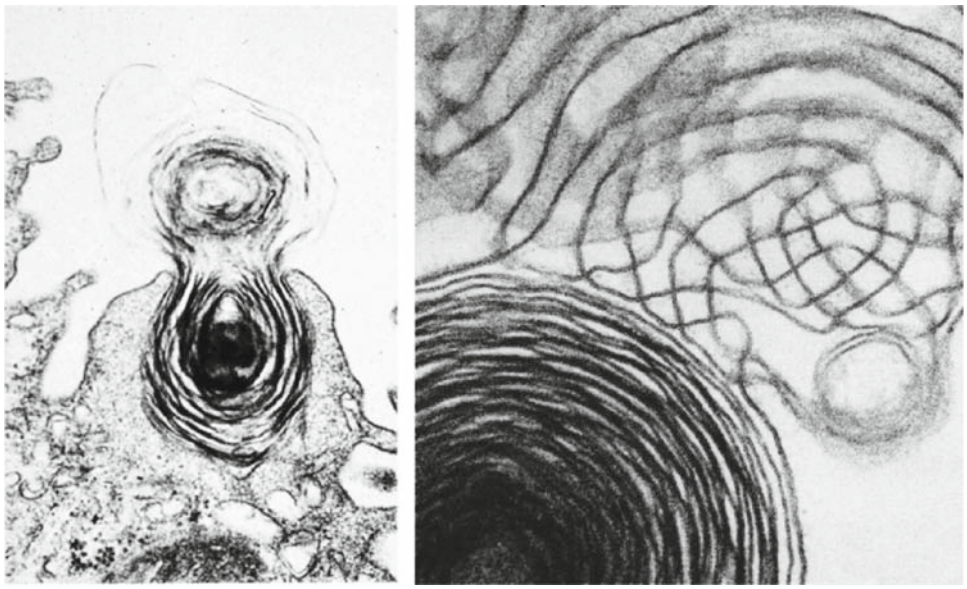

**Figure 10.4.** Lung surfactant secreted from a lamellar body and resulting tubular myelin. Lamellar body contents are extruded from a type II pneumocyte (left) and subsequently "unwind" into tubular myelin in the alveolar hypophase (right). Formation of tubular myelin requires phospholipids, SP-A, SP-B, and calcium. Alveolar surfactant also exists in a variety of large and small aggregate forms in addition to tubular myelin. (From Williams [49], with permission from Rockefeller University Press.)

required for tubular myelin formation [51,52] and are present in its lattice structure. In addition to tubular myelin, a variety of other size-distributed surfactant aggregate forms (lamellar, vesicular, and nonspecific) 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 with adult or premature animals [12,33,53,54]. 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 resecretion [55]. The half-life for turnover of human surfactant is variable and has been reported to range from 1 to 24 hr in animals [12,33,53]. Surfactant protein A has been shown to enhance the uptake of surfactant phospholipids into type II pneumocytes [56–58], and SP-B/C may also influence phospholipid uptake in type II cells [59,60]. The uptake of exogenously administered surfactants as substrate is thought to be an important factor in the indirect (nonsurface-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 Pulmonary Injury

The pathophysiology of acute pulmonary injury (ALI/ARDS) is multifactorial and includes inflammation, surfactant dysfunction, vascular dysfunction, edema, oxidant injury, ventilation/perfusion mismatching, and injury to alveolar, capillary, and other pulmonary cells. 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 (for comprehensive reviews on lung injury and inflammation, see Notter et al. [61]).

In infants, although not generally labeled ALI/ARDS, common causes of respiratory failure include meconium aspiration, sepsis, and pulmonary infection. Although acute respiratory failure in preterm neonates is typically initiated by surfactant deficiency (i.e., RDS), 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 Acute Pulmonary Injury

In their original descriptions of ARDS, Ashbaugh, Petty, and colleagues [62,63] commented on its similarity to infantile RDS, and Petty et al. [64] subsequently reported abnormalities in surfactant function. However, 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 and/or inactivation) as a consequence of inflammatory injury and edema is generally much more prominent. Extensive basic research over the past two decades has identified many of the mechanisms contributing to surfactant dysfunction in lung injury (detailed reviews of lung surfactant inhibition and mechanisms of dysfunction are available [12,17,65]). 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 10.5):

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 other blood or serum proteins have been shown in vitro to diminish 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 [66,67]. Other biophysical inhibitors include cell membrane lipids, lysophospholipids, or fatty acids that mix into the interfacial film itself to impair surface tension lowering during dynamic compression [67–72]. Additional biophysical inhibitors are listed in Table 10.6, which also notes chemically acting inhibitors such as phospholipases or proteases that can degrade essential surfactant lipids or proteins to impair surface activity [71–73]. Lung surfactant can also be chemically altered by interactions with reactive oxygen and nitrogen species [65]. 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 [12,65].

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 [74–81]. The percentage of large aggregates and their content of SP-A and SP-B are reduced in bronchoalveolar lavage from patients with ARDS [82–84]. Surfactant phospholipid composition can also be altered in patients with ALI/ARDS [84,85]. Animal models of ALI/ARDS show that large surfactant aggregates can be depleted or reduced in activity by interactions with inhibitors or by changes in surfactant metabolism [77,86–89]. Although large aggregates can be detrimentally affected in ALI/ARDS, information on total surfactant pools is inconsistent, with both decreased [90–92] and unchanged [85,93] amounts 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 almost certainly dependent on the stage of disease, which commences with an exudative phase involving alveolar–capillary membrane damage and acute inflammation but may evolve to 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 multiorgan 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.

**Table 10.5.** 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 present as a result of inflammation |
| Chemical degradation by lytic enzymes or by 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 leading to altered surfactant synthesis, secretion, recycling |
| Inflammation and microvascular dysfunction |
| Capillary endothelial injury leading to increased microvascular permeability and interstitial or alveolar edema that contains surfactant inhibitors |
| Multiple mediators and products produced by leukocytes and lung cells that affect the severity of injury and can directly or indirectly affect alveolar surfactant or type II cells |

See text for discussion. Surfactant dysfunction and its mechanisms in ALI/ARDS are reviewed in detail by Notter [12] and Wang et al. [81].

**Table 10.6.** Endogenous compounds that inhibit lung surfactant activity by physical or chemical interactions.

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

Tabulated inhibitors are examples only. See text for discussion.
*Source:* Adapted from Notter [12], Notter and Wang [17], and Gross [81].

## Surfactant Therapy in Acute Pulmonary Injury

The existence of surfactant dysfunction in ALI/ARDS provides a conceptional rationale for the therapeutic use of exogenous surfactant, but the use of surfactant drugs 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. Similar to 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 [94]. This failure at least partly reflects similar reasons, that is, 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 particularly for adults, as detailed next.

## Pharmaceutical Surfactants

Although the composition of endogenous 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 has direct consequences for surface and physiologic activity. Pharmaceutical surfactants can be divided into three functionally relevant groups: (1) organic solvent extracts of lavaged lung surfactant from animals, (2) organic solvent extracts of processed animal lung tissue with or without additional synthetic additives, and (3) synthetic preparations not containing surfactant material from animal lungs (Table 10.7).

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 nonsurfactant components and require more extensive processing that can further alter composition compared with native surfactant. The synthetic surfactants in category III that have been most widely studied are 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 phosphatidylglycerol (PG). These two preparations are no longer in active clinical use because they have been shown to have inferior activity compared with animal-derived surfactants [e.g., 12,95–100]. Two additional synthetic surfactants, KL4 (Surfaxin®) and recombinant SP-C surfactant (Venticute®), are currently undergoing clinical evaluation.

The compositions and activities of the exogenous surfactants listed in Table 10.7, and their efficacy in preventing or treating RDS in clinical trials in premature infants, are reviewed in detail by Notter [12]. Four exogenous surfactant preparations are currently licensed for clinical use in RDS in the United States: Infasurf®, Survanta®, Curosurf®, and Exosurf® (the latter is no longer used, as noted earlier). Infasurf® is a direct chloroform : methanol extract of large aggregate surfactant obtained by bronchoalveolar lavage from calf lungs [12,56,101]. Survanta® is made from an extract of minced bovine lung tissue to which DPPC, tripalmitin, and palmitic acid are added [12,18]. Curosurf® is prepared from minced porcine lung tissue by a combination of washing, chloroform-methanol extraction, and liquid-gel chromatography [102]. Surfaxin®, which is under active consideration for 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 amino acid modified human recombinant SP-C that has substitutions of phenylalanine for cysteine at two positions and isoleucine for methionine at another [12].

**Table 10.7.** Clinical exogenous surfactant drugs used to treat lung diseases involving surfactant deficiency/dysfunction.

| | |
|---|---|
| **I.** | **Organic solvent extracts of lavaged animal lung surfactant** |
| | Infasurf® (CLSE) |
| | 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® (KL4) |
| | Venticute® (recombinant SP-C surfactant) |

*Note:* Infasurf® (ONY, Inc., and Forest Laboratories), Survanta® (Abbott/Ross Laboratories), and Curosurf® (Chesi Farmaceutici and Dey Laboratories) are currently FDA approved in the United States, and Surfaxin® (KL4) is under clinical evaluation. Exosurf® (Glaxo-Wellcome) is also FDA approved but is no longer used. Details on the compositions, activities, and efficacies of these exogenous surfactants in neonatal RDS are reviewed by Notter [12], and their use in ALI/ARDS is discussed in the text.

*Source:* Adapted from Notter [12] and Enhorning et al. [72].

## Relative Activity and Inhibition Resistance of Exogenous Surfactant Drugs

The relative activities and efficacies of surfactant drugs are crucial for evaluating and optimizing therapy. Differences in efficacy among pharmaceutical surfactants have been demonstrated in comparison trials in premature infants and in retrospective meta-analyses (reviewed by Notter [12]). These differences in surfactant activity can be directly linked to differences in composition. The fact that *natural* surfactants from animal lungs (categories I and II, Table 10.7) have greater efficacy than the protein-free synthetic surfactants Exosurf® and ALEC® reflects the difficulty of substituting for the highly active hydrophobic lung surfactant proteins SP-B/C in synthetic surfactants. The surface and physiologic activities of Exosurf® are significantly increased by the addition of purified bovine SP-B/SP-C, demonstrating that its synthetic components do not adequately replace these active apoproteins [95]. Animal-derived clinical surfactants also differ markedly in their surface activity and ability to resist inhibitor-induced dysfunction based on their compositions.

Biophysical research demonstrates that the surface activity, inhibition resistance, and physiologic effects of extracts of lavaged animal surfactant (category I surfactant drugs, Table 10.7) are greater than those of other clinical surfactants (Figures 10.5 to 10.7) [e.g., 18,95,96]. It has also been shown that differences in apoprotein content can help explain some of these differences in activity [14,16,18,95,103,104]. For example, the activity and inhibition resistance of Infasurf® are substantially greater than those of Survanta® in basic biophysical and animal research [18,95,96,103] (see Figures 10.5 to 10.7), and these differences correlate directly with the content of SP-B in the two preparations [18,103,105]. Survanta® contains only 0.044% SP-B by weight relative to phospholipid because of losses during processing of lung tissue [18]. 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 [18]. As described earlier, SP-B is the most active of the hydrophobic surfactant proteins in enhancing the adsorption and overall dynamic surface activities of phospholipids [14–16,18,106,107]. The addition of SP-B or synthetic SP-B peptides to Survanta® significantly improves its activity toward that of natural surfactant [18,103,104] (e.g., Figure 10.7), indicating that the lack of SP-B in this exogenous surfactant is functionally important. Even without SP-B, however, Survanta® still has

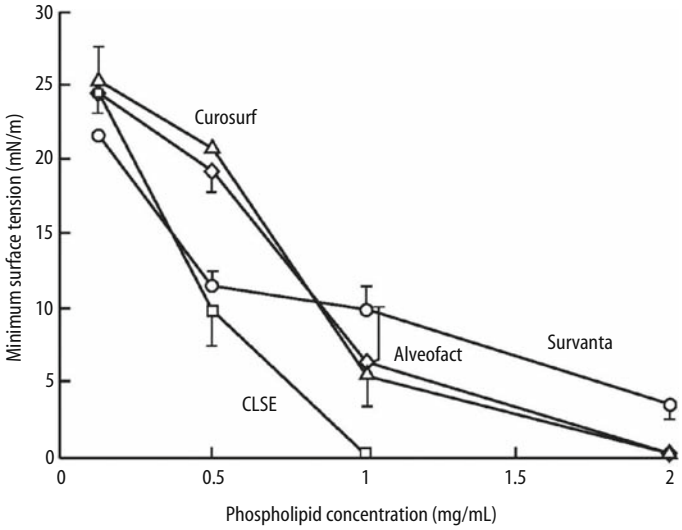


**Figure 10.5.** Overall surface tension lowering ability of clinical exogenous surfactants. Minimum surface tension after 5 min of pulsation in a bubble surfactometer (37°C, 20 cycles/min, 50% area compression) is plotted as a function of surfactant phospholipid concentration for several clinical surfactants. These surfactants vary widely in overall surface tension lowering ability, with the most active being CLSE (Infasurf®, category I, Table 10.7). (Redrawn from Seeger et al. [96].)

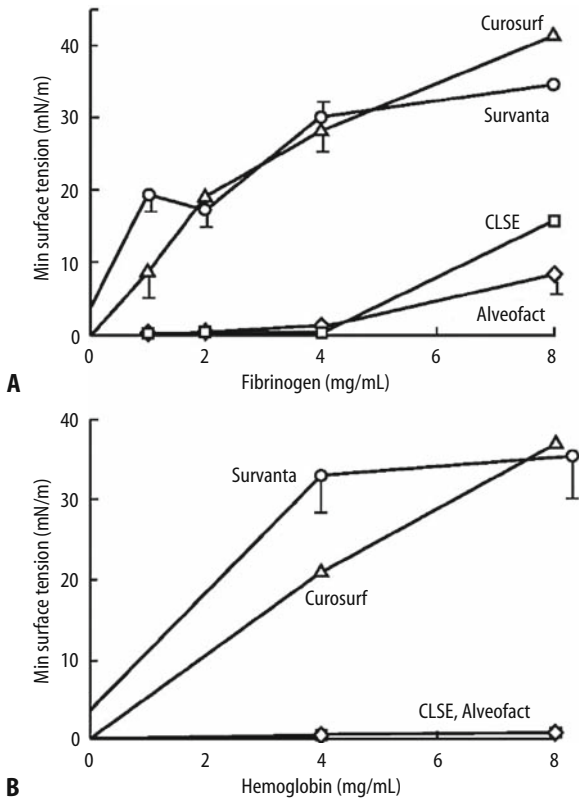


**Figure 10.6.** Resistances of clinical surfactants to inhibition by blood proteins. Minimum surface tension after 5 min of pulsation in a bubble surfactometer (37°C, 20 cycles/min, and 50% area compression) is plotted against the concentration of inhibitory blood proteins (fibrinogen **[A]** and hemoglobin **[B]**). Exogenous surfactants that most closely mimic natural surfactant (category I drugs from Table 10.7) are best able to resist inhibition and reach low surface tension despite high levels of inhibitory proteins. Surfactant phospholipid concentration was 2 mg/mL. (Redrawn from Seeger et al. [96].)

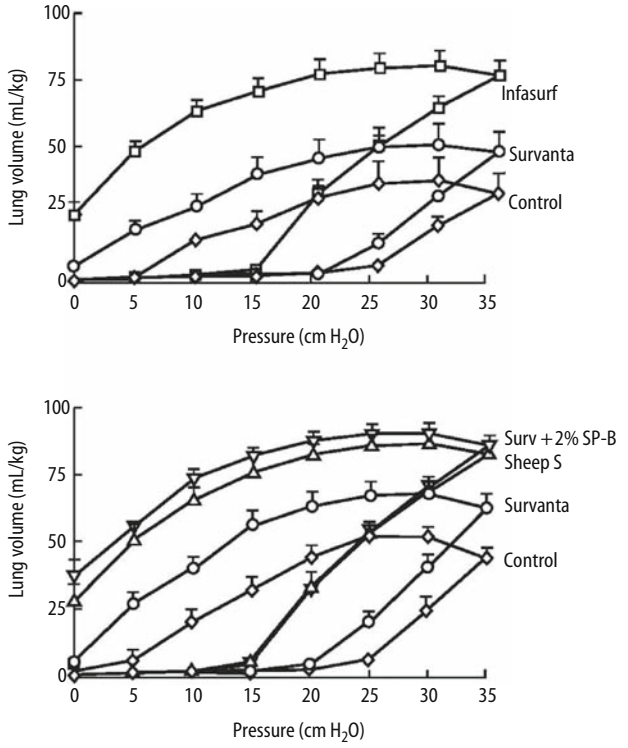


**Figure 10.7.** Effects on physiologic activity of the addition of purified SP-B to Survanta®. **(A)** Premature rabbit fetuses (27 days' gestation) treated with Survanta® or Infasurf® and untreated controls. **(B)** Premature rabbit fetuses treated with Survanta®, Survanta® + SP-B (2% by weight by 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 shown 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. (Redrawn from Mizuno et al. [103].)

significantly better activity than protein-free surfactants like Exosurf® because of its content of SP-C and other ingredients [12].

## Animal Studies of Surfactant Therapy

Animal models of ALI/ARDS in which exogenous surfactant therapy has been shown to improve respiratory function or mechanics include acid aspiration [108–110], meconium aspiration [111–114], anti-lung serum [115], bacterial or endotoxin injury [116–121], vagotomy [122], hyperoxia [123–27], in vivo lavage [104,128–132], N-nitroso-N-methylurethane (NNNMU) injury [133–135], and viral pneumonia [136,137]. 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 on. For example, animal studies indicate that direct airway instillation is more effective than current aerosol techniques in delivering exogenous surfactant to the alveoli and that early therapy is preferable to later therapy in terms of distributing surfactant to injured lungs (reviewed by Notter [12]). 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 this, one must ultimately turn to human studies.

## Human Studies of Surfactant Replacement Therapy

Multiple clinical studies have reported benefits following the instillation of exogenous surfactants to term infants, children, or adults with ALI/ARDS or related acute respiratory failure [138–154] (Table 10.8). However, many of these are small case series or pilot studies and found improvements in only acute lung function (oxygenation). Controlled trials of surfactant therapy in patients with ALI/ARDS have met with mixed success, particularly in studies with adults [94,155]. The clinical experiences with exogenous surfactant therapy in term infants, children and adults are summarized next.

The best-studied application of surfactant therapy in term infants with acute pulmonary injury is in meconium aspiration syndrome [148–152]. Meconium obstructs and injures the lungs when aspirated and is known to cause surfactant dysfunction [156,157]. Auten et al. [148], Khammash et al. [151], and Findlay et al. [152] have all reported significant improvement from surfactant administration in infants with meconium aspiration. The randomized study of Findlay et al. [152] found reductions in the incidence of pneumothorax, duration of mechanical ventilation and oxygen therapy, time of hospitalization, and requirements for extracorporeal membrane oxygenation (ECMO) in 20 term infants treated with Survanta® compared with controls. Lotze et al. [149,150] also reported favorable results using Survanta® in a controlled trial in term infants referred for ECMO because of 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 than control infants [149]. A subsequent multicenter controlled trial with 328 term infants also reported significant improvements in respiratory status and the need for ECMO following surfactant treatment [150]. 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 [158,159].

Studies of surfactant in children and adults with ALI/ARDS have followed the general pattern of initial positive case reports or series followed by more equivocal results in randomized prospective studies. The first large prospective, controlled study of surfactant therapy for adults with ARDS was definitively negative. Anzueto et al [94] administered nebulized Exosurf® versus 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 with animal-derived surfactants, and aerosolization is currently not as effective as airway instillation in delivering surfactant. Gregory et al. [155] 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 recent study by Spragg et al. [160] 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 did suggest, however, that the response in the subgroup of patients with ARDS caused by *direct lung injury* was quite positive, and a follow-up prospective study with this group of patients is currently underway.

Controlled studies of surfactant therapy in children with ALI/ARDS have been more encouraging. A randomized but unblinded trial by Willson et al. [143] 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® [142]. Luchetti et al. [153,154] 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. [161] found that children with

**Table 10.8.** Clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS).

| Study | Patients (N) | Disease or syndrome | Surfactant | Outcomes |
|---|---|---|---|---|
| Gunther et al. [138] | Adult (27) | ARDS | Alveofact | Improved surfactant function |
| Walmrath et al. [139] | Adult (10) | ARDS from sepsis | Alveofact | Improved oxygenation |
| Spragg et al. [140] | Adult (6) | ARDS from multiple causes | Curosurf | Improved oxygenation a and biophysical function |
| Wiswell et al. [141] | Adults (12) | ARDS from multiple causes | Surfaxin | Improved oxygenation |
| Willson et al. [142,143] | Children (29, 42) | ARDS from multiple causes | Infasurf | Improved oxygenation |
| Willson et al. [144] | Children (152) | ARDS from multiple causes | Infasurf | Improved survival, and improved ventilation |
| Lopez-Herce et al. [145] | Children (20) | ARDS + postop cardiac | Curosurf | Improved oxygenation |
| Hermon et al. [146] | Children (19) | ARDS + postop cardiac | Curosurf or Alveofact | Improved oxygenation |
| Herting et al. [147] | Children (8) | Pneumonia | Curosurf | Improved oxygenation |
| Auten et al. [148] | Infants (14) | Meconium aspiration or pneumonia | Infasurf (CLSE) | Improved oxygenation |
| Lotze et al. [149,150] | Infants (28, 328) | ECMO, multiple indications | Survanta | Improved oxygenation, decreased ECMO |
| Khammash et al. [151] | Infants (20) | Meconium aspiration | bLES | Improved oxygenation in 75% of patients |
| Findlay et al. [152] | Infants (40) | Meconium aspiration | Survanta | Improved oxygenation, decreased pneumothorax and mechanical ventilation |
| Luchetti et al. [153,154] | Infants (20, 40) | RSV bronchiolitis | Curosurf | Improved oxygenation |

*Note:* Tabulated clinical studies include both controlled and noncontrolled trials as discussed in the text. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RSV, respiratory syncytial virus.

**Table 10.9.** Clinical outcomes from a recent 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* | 13 (21%) | 26 (42%) | 0.02 |
| ECMO | 3 | 3 | — |
| Use of iNO | 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† | $205 ± 220 | $213 ± 226 | 0.83 |
| Hospital charges/day† | $7.5 ± 7.6 | $7.9 ± 7.5 | 0.74 |

*Some patients who failed CMV had more than one nonconventional therapy (ECMO, iNO, or HFOV);

Costs are given in thousands of dollars.

*Note:* In addition to improving mortality and reducing the percentage of patients who failed CMV as reported in the table, instilled calfactant also significantly improved oxygenation index compared with placebo ($p = 0.01$, data not shown). CMV, conventional mechanical ventilation; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide.

*Source:* Willson et al. [144].

ARDS showed immediate improvement in oxygenation and had less need for rescue therapy following treatment with Survanta®, but it was underpowered for more definitive outcomes. Most recently, a blinded controlled study by Willson et al. [144] yielded very positive results in pediatric patients with ALI/ARDS, showing both immediate benefits with regard to oxygenation as well as a significant survival advantage for patients receiving calfactant (Infasurf®) relative to placebo (Table 10.9). 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 and allergic reactions have not been reported with any of the surfactants currently licensed in the United States.

## The Future of Surfactant Therapy and Related Combination Therapies

As described in preceding sections, surfactant replacement therapy is standard 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. Clinical evidence of the efficacy of surfactant therapy for term infants with meconium aspiration is sufficiently strong that this approach is now frequently used in neonatal intensive care units (and is also being applied to other forms of neonatal respiratory failure, such as pneumonia). Controlled trials of surfactant therapy for children with ALI/ARDS also suggest significant benefits, with survival advantages shown in a recent trial [144]. It can be argued that evidence of surfactant dysfunction in ALI/ARDS, along with favorable results for surfactant treatment in animal models and evidence for efficacy in humans without significant adverse effects, makes a strong rationale for considering surfactant therapy for any pediatric patient with pulmonary injury and ALI/ARDS. From this perspective, the major downside of the therapy is its considerable expense. However, it would be ideal if additional questions about the therapy were addressed in research before its indiscriminate adoption.

As emphasized in this chapter, some exogenous surfactants are more active and have better inhibition resistance than others, and this, along with effective delivery, will impact the success of surfactant therapy for ALI/ARDS. It is also likely that surfactant therapy is more applicable for some types of pulmonary injury than others. It is important to note that post hoc analyses in the studies of both Spragg et al. [160] and Willson et al. [144] suggested greater efficacy in direct lung injury (e.g., pneumonia, aspiration) as opposed to indirect lung injury (e.g., sepsis, systemic inflammatory response syndrome). It would obviously be helpful to focus surfactant therapy on the types of lung injury where it has maximal benefit. Also, neonatal data suggest that early surfactant administration generates improved responses compared with delayed administration [e.g., 162], 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.

Finally, a major issue with regard to surfactant therapy in ALI/ARDS involves its potential use in combination with 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 for adults with ALI/ARDS, whose responses to exogenous surfactant have so far been disappointing. The use of multiple therapeutic agents or interventions based on specific rationales for potential synergy has the potential to significantly enhance patient outcomes in complex disease processes such as those involving inflammatory lung injury. The potential use of exogenous surfactant therapy in the context of specific combined-modality interventions is described in detail elsewhere [163,164]. Examples of agents that might be synergistic with exogenous surfactant in ALI/ARDS include antiinflammatory antibodies or receptor antagonists, antioxidants, and vasoactive drugs 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 ongoing 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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