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Surfactant and the Acute Respiratory Distress Syndrome (ARDS)

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The Acute Respiratory Distress Syndrome (ARDS) is a pulmonary complication resulting from a variety of initial insults, all of which involve an overwhelming inflammatory response within the host.[1,2] Typical events that may elicit this response include "direct" insults to the lung such as gastric aspiration, near drowning, or toxic fume inhalation, or more commonly "indirect" or non-pulmonary insults that eventually involve the lung due to widespread systemic inflammation. Examples of such indirect insults include systemic sepsis (usually arising from the gut), multiple trauma, and pancreatitis. Regardless of the etiology, the ultimate consequence of ARDS is diffuse alveolar damage and respiratory failure. The current definition used to identify patients with ARDS includes the presence of severe hypoxemia and decreased lung compliance, which are the consequences of an increased permeability pulmonary edema rather than cardiogenic edema.[2] Despite a greater understanding of the pathophysiology of ARDS, this disease continues to cause significant morbidity and mortality ranging from 30% to 50%.

Over the last several years, various treatment strategies have been evaluated for patients with ARDS, but unfortunately, few have resulted in a significant improvement in outcome.[3-6] One important factor responsible for this lack of success is the heterogeneous nature of the illness. Although a variety of etiologies or "insults" may ultimately lead to ARDS and fulfill the physiologic criteria for diagnosis, each may have different pathophysiologic processes and/or severities at the time of therapeutic intervention. It is possible that an effective treatment modality for a particular patient with ARDS may need to specifically target the pathophysiologic process involved in this patient. As a result, many interventions have been deemed ineffective for ARDS in general, and therefore abandoned despite the possibility that some patients may have benefited from the therapy. In addition, most clinical studies evaluating new therapies are not designed to include sufficient numbers of patients to conduct reliable subgroup analyses at the end of the trial, which could potentially identify some patients who would benefit. The end result is that therapy for ARDS remains essentially supportive, involving fluid and pressure support, as well as mechanical ventilation to maintain gas exchange.

One therapeutic approach currently being evaluated in patients with ARDS is the administration of exogenous surfactant into these patients' lungs. The following sections will outline the rationale for testing this treatment modality, the current status of clinical trials evaluating exogenous surfactant in patients with ARDS, and the current and future research directions for surfactant therapy in ARDS and other lung diseases.

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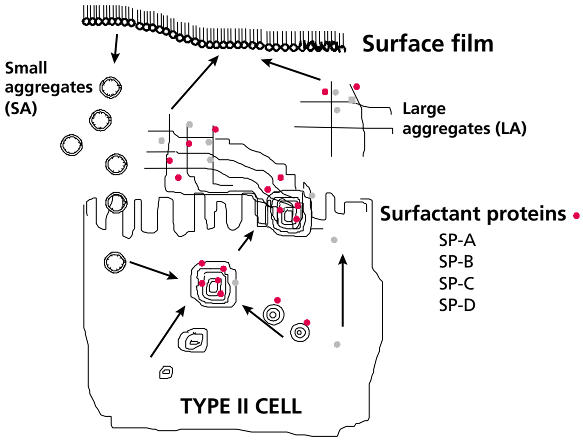
What is surfactant?

Pulmonary surfactant is a lipoprotein complex synthesized within, and secreted from, alveolar type II cells (Figure 1).[7,8] Once secreted into the airspace, surfactant forms a continuous film at the air-liquid interface. This organized film is composed of various phospholipids, with the predominant lipid being the desaturated form of phosphatidylcholine, dipalmitoylphosphatidylcholine (DPPC). There are also four surfactant-associated proteins called SP-A, SP-B, SP-C, and SP-D.[8] Two of these proteins are very hydrophobic (SP-B and C) and closely associate with the lipids to lower surface tension at the air-liquid interface. The other two proteins are hydrophilic (SP-A and D) and may be secreted independently of the lipids. They have host defence functions distinct from other surfactant components.

Once the surface film is formed, respiratory motion results in expansion and compression of the film, the former facilitating newly-secreted surfactant to adsorb onto the air-liquid interface, while compression of the film causes some components of the surfactant film to be released into the sub-phase as small vesicular forms. These forms may then be taken back up into the type II cell for recycling, or cleared from the airspace entirely. This process represents the metabolic lifecycle for pulmonary surfactant.[9] Investigators have also demonstrated that two distinct structural forms of surfactant exist within the alveolar space; these can be separated based on their buoyant density.[10] Freshly secreted surfactant consists of lamellar bodies and tubular myelin-like forms called large surfactant aggregates (LA), while the small vesicular forms are called small aggregates (SA). LA are the metabolic precursors of SA and have superior functional activity compared to SA when tested both in vitro and in vivo. In the normal lung, there is a consistent proportion of LA relative to SA, although this ratio may be disturbed in acute lung injury.[7,11]

Figure 1: Surfactant is synthesized within the type II cells as a lipoprotein complex and secreted as lamellar bodies into the alveolar subphase. These unravel to form tubular myelin forms (LA), which are the precursors to the surface film. With respiratory motion, small vesicular forms are "squeezed out" of the surface film as small aggregates (SA). These may then be cleared from the air space or taken back up into the type II cell for recycling.



What is the role of pulmonary surfactant?

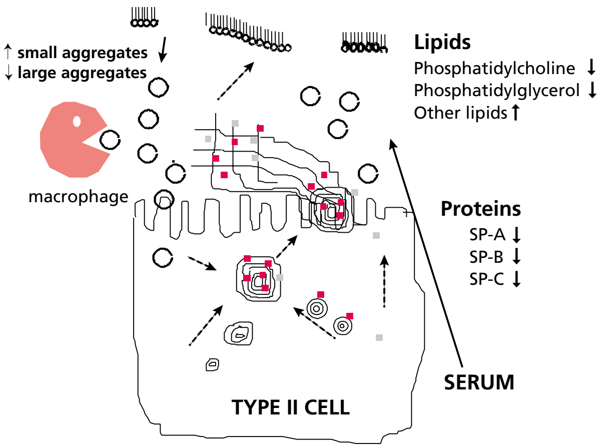
The major function of pulmonary surfactant is to lower surface tension (T) within the alveolar space thereby maintaining alveolar stability.[8,12] This function is best described using LaPlace's law ($\Delta P=2T/r$) where the pressure gradient (ΔP) across the alveolar surface is directly proportional to the surface tension at the air-liquid interface (T) and inversely proportional to the radius (r) of the alveolus. As one exhales and the surface film is compressed, surfactant is responsible for decreasing the surface tension and maintaining a constant pressure gradient across the alveolus. This serves to prevent alveolar collapse and minimize the formation of pulmonary edema due to changes in pressure gradients. DPPC is the major component of surfactant responsible for surface tension reduction, although it has been shown that both SP-B and SP-C are required for optimal formation and maintenance of the surface film at the air-liquid interface.[13]

Pulmonary surfactant has also been shown to play a role in host defence.[14,15] In addition to enhancing ciliary movement and particle clearance from the airways, some surfactant components have been shown to have anti-inflammatory, antibacterial, and antiviral functions. Both in vitro and in vivo studies have demonstrated that the surfactant proteins SP-A and D have important roles in protecting the host from various inflammatory and infectious insults.[15,16] These non-biophysical properties suggest that pulmonary surfactant alterations may play a role in the inflammatory component of lung injury which, for the most part, occurs before significant lung dysfunction is present. Further in vivo studies are required to probe the significance of surfactant host defence properties in the development and progression of various lung diseases.

How is surfactant altered in ARDS?

Several studies have evaluated surfactant samples recovered via bronchoalveolar lavage (BAL) from patients with severe ARDS.[7,17,18] These studies have consistently shown that surfactant phospholipid composition was altered (decreased phosphatidylcholine and phosphatidylglycerol and increased phosphatidylinositol and sphingomyelin), surfactant protein levels were decreased (SP-A, B and C), and the proportion of the poorly functioning SA forms was increased relative to the superior functioning LA forms (Figure 2). In all cases, the surface tension reducing ability of the surfactant recovered in the BAL samples was impaired. In addition, some clinical reports have evaluated patients "at risk" for ARDS and documented similar, but less marked surfactant abnormalities.[17,18] However, on closer examination of these studies, it was apparent that these patients also had significant lung injury, as all were severely hypoxemic and required mechanical ventilation, but fell just outside the specific oxygenation criteria used to diagnose ARDS. There are no clinical data evaluating the surfactant system of patients at the very early stages of their illness, before significant lung dysfunction is present.

Figure 2: Surfactant alterations in acute lung injury include altered phospholipid and protein composition, an increase in the proportion of small aggregates relative to large aggregates and protein inhibition of surfactant function due to serum protein leakage.



Animal data have provided important insight into the pathophysiologic processes and mechanisms responsible for the surfactant changes observed in acute lung injury. For example, the changes in surfactant phospholipid and protein composition are due to type II cell metabolic abnormalities (ie, altered synthesis and/or secretion) and occur relatively late in the course of the disease, when lung dysfunction is severe.[11] At this point, type II cells are either decreased in total number, or markedly damaged due to the severity of the injury. Another mechanism contributing to surfactant dysfunction is inhibition of the surfactant via leakage of serum proteins into the airspace due to the increased permeability pulmonary edema associated with ARDS.[19] It is believed that the excess protein competes with surfactant molecules for the air-liquid interface, thereby resulting in abnormal adsorption of the surfactant and altered surface tension. Other substances such as phospholipases, oxygen radicals and peroxinitrates, all of which are increased in patients with ARDS, may also affect various surfactant components resulting in altered composition and/or impaired surfactant function. Finally, several studies have shown that the proportion of LA relative to SA was decreased in the injured lung compared to normal lungs.[7,11,20] Mechanisms responsible for these aggregate changes have been probed via studies evaluating the effects of mechanical ventilation on the surfactant system. For example, in vitro studies showed that the conversion of LA into SA was dependent on protease activity as well as a phasic change in surface area.[21] In vivo, when patients are mechanically ventilated, alveolar surface area is determined by the level of positive end expiratory pressure (PEEP) applied, as well as the tidal volume (Vt) utilized. Animal studies have shown that ventilation strategies utilizing lower Vt, or smaller changes in surface area, resulted in less conversion of LA into SA compared to higher Vt.[22] Although the "static" surface area established by the PEEP level did not affect LA conversion, PEEP was important for optimal alveolar recruitment. In models of acute lung injury, the use of higher Vt's resulted in a marked depletion of the functional pool of LA within the airspace, which in turn, contributed to progressive lung dysfunction.[23] Interestingly, a recent NIH study involving patients with ARDS showed that "low stretch" ventilation (Vt = 6 ml/kg) resulted in lower mortality than a "high stretch" ventilator mode (Vt = 12 ml/kg).[24] These data, together with the available animal data, support the concept that surfactant alterations significantly contribute to the progression of lung dysfunction associated with ARDS.

Another important observation from recent animal studies suggests that different types of lung injuries may be associated with specific changes in the surfactant system.[25] For example, in an acid aspiration model in adult rabbits, an acute deterioration of lung function was associated with a marked increase in protein recovered from the airspace of these animals shortly after the acid was instilled. There were no changes in surfactant composition at that point, and the major mechanism responsible for the surfactant dysfunction was protein inhibition. On the other hand, in a rat model of sepsis induced via cecal ligation and perforation, there were minimal amounts of protein recovered from the airspace and few surfactant compositional abnormalities, but there were significant changes in surfactant aggregate forms.[26] Potential reasons for these surfactant differences may be due to the nature of the insult resulting in the lung injury of these two situations (ie, the direct versus indirect) and/or the different severities of the injuries elicited by these insults. The most important issue at this point, however, is that these differences may have important implications with respect to therapeutic interventions. Only with a greater understanding of the various pathophysiologic processes associated with ARDS will optimal treatment strategies be developed.

Exogenous surfactant: rationale and current clinical status

Over the years, numerous studies involving several different animal models have consistently demonstrated surfactant alterations in acute lung injury, and these alterations significantly contributed to the lung dysfunction associated with the injury.[7] There are also a number of studies demonstrating that the administration of exogenous surfactant improved lung function in these animals. These observations not only confirmed the importance of surfactant alterations in the pathophysiology of acute lung injury, but also suggested that exogenous surfactant may be beneficial for patients with ARDS. Indeed, exogenous surfactant has been used successfully for many years in preterm infants with neonatal Respiratory Distress Syndrome (nRDS). Although there are many case reports and pilot studies showing that this treatment may benefit patients with ARDS, there have been only three large, randomized placebo-controlled clinical trials evaluating exogenous surfactant in these patients.

- The first involved a synthetic surfactant preparation (Exosurf) which contains no surfactant-associated proteins.[27] This was delivered as an aerosol over 5 days to patients with severe ARDS; mortality was identical in the treatment and control groups (41%).
- In another study, a natural bovine preparation (Survanta) containing SP-B and SP-C was delivered via tracheal instillation and mortality was lower in the treatment group (17%) than the control group (42%).[28]
- In a more recent, albeit smaller Phase II clinical study, a recombinant SP-C-based surfactant (Venticute) was instilled intratracheally in patients with severe ARDS and outcomes including ventilator-free days and mortality were superior in the treatment group.[29] The results of two separate and much larger Phase III trials evaluating this surfactant in patients with ARDS are pending.

Reasons for the variable outcomes of these trials relate to the different factors that may influence a host's response to exogenous surfactant.[30] For example, animal data have shown that the presence of surfactant proteins is essential for optimal function of the preparation, an important factor that no doubt contributed to the negative results of the Exosurf trial. In addition, delivering surfactant as an aerosol to a patient with a non-uniformly distributed lung injury may result in the bulk of the surfactant being deposited in the less-injured areas of the lung. It is also probable that the amount of surfactant that can be delivered via aerosolization with currently available nebulizers may be insufficient to "rescue" lung function in patients with severe lung injury and significant proteinaceous pulmonary edema. In this situation, an exogenous surfactant preparation that is relatively resistant to protein inhibition and delivered in large doses via tracheal instillation may be necessary.

Similar to its effects on endogenous surfactant, modes of mechanical ventilation utilizing lower tidal volumes with adequate alveolar recruitment (ie, PEEP) have been shown to preserve exogenously administered surfactant in LA forms, and result in a more prolonged duration of response to the surfactant compared to ventilation strategies using higher tidal volumes.[31] Finally, one of the most important factors that may impact a patient's response to exogenous surfactant is the nature and severity of the injury at the time of treatment. Animal data have shown that surfactant may be altered early in the course of lung injury and contribute to the initial stages of the disease, perhaps by influencing the host's inflammatory response.[26] Before contemplating early administration of exogenous surfactant in the clinical setting however, further studies are required including:

- adequate documentation that surfactant alterations are present in patients at risk of ARDS before they are mechanically ventilated,
- evidence that these alterations contribute to disease progression, and
- a greater knowledge as to which surfactant components are most important at this stage of the disease so that appropriate surfactant preparations are utilized.

A relatively sensitive and specific marker that would predict which patients will progress to ARDS would be optimal so that exogenous surfactant would not be given to patients needlessly. Based on this information, it is clear that although exogenous surfactant administration may hold promise as a therapeutic modality for patients with ARDS, more information is required so that optimal treatment strategies can be developed.

Future directions

The current indication that exogenous surfactant is being evaluated for is established ARDS. As noted, ongoing research is examining the potential for earlier administration in this disease, with the rationale that surfactant may play a role in host defence mechanisms. In this situation, an exogenous surfactant preparation containing appropriate components aimed at down-regulating the host's inflammatory response may be required. Currently, there are no exogenous surfactants available that contain either SP-A or SP-D. Also in this context, exogenous surfactant may be useful for patients with pneumonia, both with respect to its antibacterial/viral properties, as well as its biophysical functions, as it may benefit the lung dysfunction usually associated with these types of infections. Indeed, most diseases involving the lungs also involve some component of inflammation and/or physiologic impairment, thus rationalizing further research probing the contribution of surfactant abnormalities to a variety of lung conditions. Once the role of the surfactant system in these diseases has been determined, and the potential of exogenous surfactant has been evaluated, it is likely that combination therapies will also be of benefit. The addition of antibiotic, anti-inflammatory, or antioxidant agents to exogenous surfactant may prove to be superior to either agent alone, and would capitalize on the spreading and metabolic properties of surfactant to ensure optimal delivery of these compounds. The future of surfactant research is exciting and may enhance our understanding of the pathophysiology of a variety of lung diseases in addition to ARDS.

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Abstracts of Interest

Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits.

VELDHUIZEN RA, MARCOU J, YAO LJ, MCCAIG L, ITO Y, LEWIS JF. LONDON, ON

Alveolar surfactant can be separated into two subtypes; large aggregates and small aggregates. Large aggregates represent the surface active form of surfactant and are the metabolic precursors of small aggregates. Previous studies examined the mechanism by which large aggregates are converted into small aggregates in vitro. We used intratracheal injection of radiolabeled large aggregates in rabbits to probe the aggregate conversion in vivo. After this injection, animals were mechanically ventilated for 60 min. After the animals were killed, the lungs were lavaged, and the percentage of radiolabel present in the small aggregate fraction was determined. Our results showed that ventilation resulted in aggregate conversion and that increases in tidal volume, but not in respiratory rate, correlated with increased conversion. Aggregate conversion in rabbits with acute lung injury correlated significantly with severity of injury. We conclude that a change in surface area (i.e., respiration) is necessary for aggregate conversion in vivo and that the ventilation strategy can affect this conversion. Furthermore, increased aggregate conversion in injured lungs might contribute to increased small-to-large aggregate ratios in these lungs compared with normal lungs.

Am J Physiol 1996;270(1 Pt 1):L152-L158

Treatment of ARDS with rSP-C surfactant

SPRAGG RG, LEWIS J, WURST W, RATHGHEB F. SAN DIEGO, CA.

We have performed a phase two study in North America of rSP-C surfactant (Venticute®) as treatment for ARDS using dose amounts and volumes derived from preclinical studies. Results from this prospective randomized multicenter controlled open-label trial were examined to determine efficacy, as measured by: ventilator free days to day 28 (VFD), area under the p_aO_2/F_1O_2 curve referenced to baseline average (AUC), and safety. Patients were prospectively randomized to receive rSP-C surfactant plus standard therapy or standard therapy alone (STD, n=13). Surfactant doses were given over 24 hr and were: (a) 1 mg rSP-C given up to 4 times (MID, n= 15); or (b) 0.5 mg/kg given up to 4 times (LOW, n= 12). We observed:

	STD	MID	LOW
VFD (mean / median)	7.8 / 6	10.3 / 11	6.6 / 0
Weaned by day 28	54%	53%	42%
AUC	333.6	885.7	446.1
Mortality	46%	20%	33%

Improvement in p_aO_2/F_1O_2 in the MID group was apparent within as little as 4 hrs after the first treatment. No significant adverse events were associated with administration of rSP-C surfactant. These results support the hypothesis that treatment of ARDS patients with exogenous rSP-C surfactant may be of value, and provide a foundation for expanded clinical trials.

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