Eur Respir J 2002; 19: 787–789
DOI: 10.1183/09031936.02.00284902
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European Respiratory Journal
ISSN 0903-1936

*EDITORIAL*

# Exogenous surfactant in acute respiratory distress syndrome: more is better

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Pulmonary surfactant is a complex of highly active phospholipids and proteins that cover the alveolar epithelial surface of the lungs [1]. Surfactant is synthesized in the alveolar type-II cells, stored in the lamellar bodies, and secreted to the alveolar space where it undergoes complex changes [2]. The composition of lung surfactant in humans is very constant, although it may change in disease states [3]. Phospholipids account for 85% of its composition and the main component is dipalmitoylphosphatidylcholine (DPPC). In addition, surfactant contains different apoproteins, neutral lipids, and carbohydrates [4].

Pulmonary-surfactant dysfunction can lead to acute lung injury and is characterized by alveolar instability, floating, and collapse. These abnormalities have been shown to occur in acute respiratory distress syndrome (ARDS) [5, 6] and infant respiratory distress syndrome (IRDS) [7]. Since the initial report of ARDS by ASHBAUGH *et al.* [5], abnormalities of the surfactant system have been recognized. PETTY and co-workers [8, 9], later reported both qualitative and quantitative abnormalities in the surfactant content of ARDS patients. It is now known that surfactant dysfunction plays a major role in the pathophysiology of ARDS [6, 10], and functional changes have been described not only in patients with established ARDS, but also in patients at risk [10–12]. The main biochemical abnormalities include an 80% fall in the total phospholipid content, decline in the fractional content of DPPC and phosphatidylglycerol and other fractions, and loss of apoproteins (90% of surfactant protein (SP)-A and SP-B) [6, 7]. This loss of alveolar surfactant is due to several factors including the presence of plasma proteins [13], cleavage of phospholipids by serum phospholipases [14], formation of free radical species (including nitrates, lipid peroxidation, *etc.*) [15–17], and conversion to nonfunctional surfactant with more phospholipid aggregates [14].

Exogenous-surfactant replacement has been successfully achieved in IRDS [7], but clinical trials in ARDS have had mixed results. Initial preliminary reports, mainly phase-II multicentre trials, have shown that exogenous artificial surfactant (Exosurf®) [18] or bovine surfactant (Survanta®) [19] in ARDS can improve oxygenation and lung mechanics. The authors' group reported the results of a large, randomized, multicentre, prospective trial involving 725 patients in sepsis-induced ARDS treated with Exosurf® or placebo [20]. This study did not show any improvement in either oxygenation and/or survival benefit of exogenous-surfactant supplementation.

There have been several speculations as to why the Exosurf® trial failed to show any improvement in the physiological parameters and/or survival in patients with ARDS. One explanation could be related to the underlying condition that resulted in ARDS. In the study by GREGORY *et al.* [19], patients had several precipitating aetiologies to ARDS whereas the Exosurf® study was limited to sepsis-induced ARDS. Thus, the aetiology of ARDS may have to be taken into consideration when future studies are designed.

Another potential explanation for the difference in the results, could be related to the surfactant preparation that was utilized. Exosurf® is an exogenous surfactant that does not contain apoproteins and this can affect the onset of action and be inhibited by serum proteins. The study by GREGORY *et al.* [19] used a bovine surfactant that contains two apoprotein constituents, whereas the synthetic preparation contains neither protein nor peptides and needs to achieve an *in vitro* critical concentration in order to exert its effects [16]. These data suggest that for an exogenous surfactant preparation to be effective, it must contain apoproteins.

Finally, the mode of delivery of surfactant may be crucial. In the Exosurf® trial [20], surfactant was delivered by continuous aerosolization, but MACINTYRE *et al.* [21], showed that only 4.5% of aerosolized radiolabelled surfactant reached the lungs thus, >5 μg of 102 μg of aerosolized DPPC·kg$^{-1}$·day$^{-1}$ actually reached the lungs in this study. It is also possible that the small amount of delivered surfactant was inhibited by the same inflammatory mediators associated with ARDS, and therefore had no effect.

In this issue of the *European Resipratory Journal*, GÜNTHER *et al.* [22] reported on the results of 27 patients with ARDS who received 300 mg·kg$^{-1}$ of body weight of natural bovine surfactant extract (Alveofact®) delivered to each segment of the lung *via* a fibreoptic bronchoscope. This study showed that using the bronchoscope to deliver surfactant had no deleterious effects on gas exchange, lung mechanics,

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or haemodynamics. These patients had a significant improvement in oxygenation within 12 h, although it should be noted that in seven patients in whom the gas exchange deteriorated; additional surfactant was administered within the first 24 h. There was a significant decrease in mortality in the study patients, 44% compared to the calculated mortality of 74%. This study further supports the concept that larger volumes of surfactant need to be delivered to these patients in order to have a physiological effect. This investigation has provided several important contributions to the literature. First, the optimal surfactant preparation is very important and should contain apoproteins. Second, in order to achieve a physiological response, surfactant must be administered in large volumes into the adult lungs.

Other investigators have suggested that bronchoscopic instillation of surfactant not only results in delivery of large volumes of the material, but also allows the clinician to perform a bronchoalveolar lavage in order to remove inflammatory mediators. WISWELL *et al.* [23] used a human recombinant protein-B surfactant preparation that was delivered to each bronchopulmonary segment. In this study, the material was suctioned in an effort to remove at least 50% of the volume instilled. These investigators showed that the fluid removed contained large amounts of inflammatory mediators.

The question that needs to be answered is, what happens to the exogenous surfactant once it is delivered into injured lungs? The manuscript by WALMRATH *et al.* [24] in this issue of the *European Respiratory Journal*, reported the impact of exogenous surfactant administration on the biochemical and biophysical properties in patients with severe ARDS and septic shock. These investigators obtained bronchoalveolar lavage samples 3 h prior to, and 15–18 and 72 h after exogenous surfactant administration. Prior to surfactant administration, these patients had a massive alveolar protein load, a reduced percentage of large surfactant aggregates, a loss of phosphatidylcholine, a significant reduction of apoproteins (SP-A, SP-B and SP-C), as well as a reduction in surfactant functional activity. Surfactant administration resulted in a marked increase in the phospholipid pool, but the large alveolar protein load was still present. The surface tension lowering properties were markedly improved, but not fully recovered. These samples also showed a significant effect on the biochemical and functional properties of endogenous surfactant. Therefore, the bronchoscopic administration of surfactant resulted in an improvement of some of the biochemical and biophysical characteristics of surfactant in patients with ARDS.

What are the lessons of these studies for clinicians? Exogenous-surfactant administration in acute respiratory distress syndrome can significantly improve oxygenation and survival, but must be administered in large volumes. Direct bronchoscopic instillation may be one way to achieve these effects. Although surfactant preparations are not approved by the Federal Drug Administration for use in patients with acute respiratory distress syndrome, these data show promise that it may be an important adjunctive therapy in patients with acute respiratory distress syndrome and refractory hypoxaemia.

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