

Review

Lung surfactant in subacute pulmonary disease

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Abstract

Pulmonary surfactant is a surface active material composed of both lipids and proteins that is produced by alveolar type II pneumocytes. Abnormalities of surfactant in the immature lung or in the acutely inflamed mature lung are well described. However, in a variety of subacute diseases of the mature lung, abnormalities of lung surfactant may also be of importance. These diseases include chronic obstructive pulmonary disease, asthma, cystic fibrosis, interstitial lung disease, pneumonia, and alveolar proteinosis. Understanding of the mechanisms that disturb the lung surfactant system may lead to novel rational therapies for these diseases.

Keywords: asthma, interstitial pulmonary fibrosis, pneumonia, pulmonary alveolar proteinosis, pulmonary surfactant

Introduction

Lung surfactant is a highly surface active substance that is synthesized by alveolar epithelial type II cells and composed of approximately 80% phospholipids, 10% proteins, and 10% neutral lipids. The predominate phospholipids are phosphatidylcholine (PC) and phosphatidylglycerol; phosphatidylinositol and sphingomyelin contribute to the total concentration. Two of the surfactant-associated proteins, SP-A and SP-D, have important host defense properties [1], while the remaining two, SP-B and SP-C, are intensely hydrophobic and interact with surfactant phospholipids to optimize surface tension lowering function. After synthesis, surfactant is stored in lamellar bodies and subsequently secreted in an organized tubular myelin form, which exists in the alveolar lining fluid subphase. It is from tubular myelin that the surfactant film is formed.

Surfactant recovered by alveolar lavage may be separated by centrifugation into two fractions: a highly surface active sedimenting fraction termed 'large aggregates', composed of lamellar myelin, tubular myelin and lipid arrays; and a poorly surface active, nonsedimenting 'small aggregate'

fraction. Surfactant not only maintains alveolar stability, but it is also present in small airways and promotes their patency [2]. Alveolar surfactant is the major source of surfactant found in both distal and proximal airways.

Mechanisms of surfactant dysfunction

A variety of pathologic processes may modify surfactant abundance, structure, and/or function. Genetic alterations of coding or noncoding regions of SP-B or SP-C may be related to the development of pulmonary disease in the adult [3,4]. Surfactant inactivation can be the result of functional inhibition in the presence of such substances as albumin, hemoglobin, fatty acids, or arachidonic acid. Such inactivation can be overcome by addition of excess surfactant [5]. In addition, proteolytic enzymes or phospholipases can cleave surfactant components with consequent loss of function. Other processes that can cause surfactant inactivation include nitration and oxidation, with consequences that include inactivation of SP-A [6]. Accelerated conversion of surfactant from the highly functional large aggregate form to the poorly functioning small aggregate form is another mechanism of surfactant inactivation.

Obstructive lung disease

Asthma

Models of airway closure suggest a theoretical use of surfactant in asthma, and clinical studies have suggested that surfactant from asthmatics is functionally impaired [7,8]. The main mechanism of this impairment is thought to be the influx of inhibitory proteins into the airways, although changes in surfactant composition may occur [9]. Data from animal experiments also suggest a role for surfactant in the pathogenesis of asthma. Becher found that sensitized guinea pigs that have had surfactant prophylactically administered show attenuated bronchiolar constriction in response to ovalbumin challenge [10]. Other investigators have shown in animal models of asthma that even though there is little change in the amount of surfactant, it may be in a less functional form. Cheng and colleagues demonstrated that, in a guinea-pig model of chronic asthma, the content of large surfactant aggregates was decreased [11]. The surfactant pool size was also decreased. Thus, these findings suggest enhanced conversion to small aggregate forms and either that the amount of surfactant secreted may be decreased or that there is increased uptake of the extracellular surfactant.

In the setting of either chronic or acute asthma, products of inflammatory cells (including proteases and reactive oxygen and nitrogen species) and airway edema may contribute to surfactant dysfunction. At present, the contribution of surfactant in the asthmatic process is unclear.

Clinical use of surfactant in asthma is currently under investigation. A study in which 12 asthmatic children received aerosolized bovine surfactant indicated that there was no change in forced vital capacity, forced expiratory volume in 1 s, peak expiratory flow, and mean forced expiratory flow during the middle half of the forced vital capacity [12]. In another clinical trial, 11 adult asthmatic patients with stable airway obstruction six hours after an asthma attack were given aerosolized surfactant [13]. All patients showed an improvement in pulmonary function. Larger trials are indicated to evaluate these observations.

Smoking and chronic obstructive pulmonary disease

Smoking plays a role not only in the pathogenesis of the alveolar destruction and airway inflammation found in chronic obstructive pulmonary disease (COPD) patients, but also in altering surfactant composition and function. As reviewed by Hohlfeld *et al.*, smokers are likely to have a decrease in the phospholipid content of bronchoalveolar lavage (BAL) fluid and impaired surface activity of surfactant recovered from BAL fluid [7]. Smoking might affect surfactant homeostasis and function through both direct and indirect mechanisms. The particulate phase of cigarette smoke has been demonstrated to impair surfactant function directly. Also, type II pneumocytes exposed direct-

ly to cigarette smoke in culture have decreased secretion of PC [14].

Indirectly, cigarette smoking causes airway inflammation with subsequent effects on surfactant function due, in part, to products of activated neutrophils. The activity of neutrophil elastase is particularly augmented, as constituents of cigarette smoke (nitrites and oxidants) can inactivate α_1 -proteinase inhibitor, a critical inhibitor of elastase activity. In addition, cigarette smoke can activate macrophages, resulting in increased oxygen radical production [15].

The aggregate effects of cigarette smoke on lung surfactant are likely to result in a significant loss of surface tension lowering function and increase in pressure gradient across the alveolar wall. As extracellular matrix components of the alveolar wall may be partially disrupted in the chronic smoker, this increased pressure gradient may contribute to alveolar wall rupture and the development of emphysema.

Host defense functions of surfactant may also be impaired in the chronic smoker. Levels of both SP-A and SP-D are decreased in BAL fluid recovered from chronic smokers and, given the importance of these two surfactant proteins in host defense, these changes may contribute to the increased incidence of respiratory infections [16].

There is limited information on the value of surfactant treatment of patients with COPD. In a single study of the effect of surfactant phospholipid in COPD, patients with chronic bronchitis who received aerosolized phospholipid three times daily for two weeks had a modest improvement in airflow compared to that in patients who received saline [17].

Cystic fibrosis

Analysis of BAL fluid from adults with cystic fibrosis (CF) discloses a decrease in the content of intact SP-A and evidence of proteolytic cleavage of SP-A [18,19]. As SP-A may be of critical importance in host bacterial defense [1], its loss may predispose to lung infection in CF patients. Surface tension lowering function of surfactant from CF patients is also impaired, and alterations in surfactant lipid composition may contribute to this impairment. A pilot study investigating the consequences of administering a natural surfactant aerosol to CF patients daily for five days showed no evidence of acute or short-term benefit [20].

Pneumonia

Surfactant recovered in BAL fluid from patients with pneumonia has reduced PC and phosphatidylglycerol content, and alterations in fatty acid composition. These changes are qualitatively similar to those observed in patients with acute respiratory distress syndrome. In addition, the amount of SP-A is also decreased and surfactant surface tension lowering function is impaired, due, in part, to the al-

terations in lipid components [21]. As found in other conditions where hydrophilic surfactant protein content is diminished, host defense functions may be impaired. Limited experience with selective bronchial instillation of surfactant in a patient with pneumonia has suggested the possibility of benefit [22].

Interstitial lung disease

Idiopathic pulmonary fibrosis

Recent changes in the definition of idiopathic pulmonary fibrosis (IPF) may confuse interpretation of prior clinical studies. The pathological classification of usual interstitial pneumonia is now commonly called IPF, whereas previously patients who had a more cellular IPF were classified as having nonspecific interstitial pneumonia. Given that the nomenclature is confusing, existing data may be from a mixture of patients with usual interstitial pneumonia and nonspecific interstitial pneumonia. Nevertheless, IPF studies suggest that the total amount of surfactant phospholipid is decreased and that the composition is altered, with a decrease in the fractional content of phosphatidylglycerol and an increase in that of phosphatidylinositol and sphingomyelin. In addition, the concentration of large surfactant aggregates is also decreased in patients with IPF, as is the surface tension lowering ability of this surfactant [23].

Decreases in the SP-A content of BAL fluid from patients with IPF have also been reported. Günther *et al.* found that the concentration of SP-A in BAL fluid was 1121 ± 252 ng/ml versus 1529 ± 136 ng/ml in BAL fluid from control patients [23]. When normalized to phospholipid, the values also showed a modest but significant decrease. These changes in surfactant apoprotein and phospholipid levels may be due to underlying parenchymal destruction in patients with IPF.

Recent data suggest that serum SP-A levels may be of value in predicting the course of patients with IPF. Takahashi *et al.* found that patients with normal serum SP-A levels had a better prognosis than those with elevated serum levels [24]. They also found that elevated serum SP-D levels correlated with the rate of decline of vital capacity and total lung capacity. McCormack *et al.* also found that BAL fluid levels of phospholipid and SP-A, and the SP-A/phospholipid ratio (SP-A/PL) could be used to predict the outcome [25]. Patients who had a SP-A/PL ratio of less than $29.6 \mu\text{g}/\mu\text{mol}$ had a five-year survival rate of 30% whereas those who had a SP-A/PL ratio greater than $29.6 \mu\text{g}/\mu\text{mol}$ had a five-year survival rate of 68%. The benefit of surfactant as a therapy in IPF has not been investigated.

Sarcoidosis

Sarcoidosis is a multisystem, granulomatous disease with a predilection for involvement of the lung. The concentration of SP-A in BAL fluid is either unchanged or increased,

but when normalized to phospholipid content, the SP-A/PL value may be decreased relative to controls. The SP-B levels in BAL fluid are increased, but when normalized to phospholipid, values are unchanged relative to controls [23,26]. According to most reports, the amount and fractional content of surfactant phospholipid recovered in BAL fluid from patients with sarcoidosis is unchanged from controls. As with IPF the surface activity of surfactant in patients with sarcoidosis is impaired and there is a reduction in the large aggregate pool size [23]. The responsible mechanisms and pathophysiologic relevance of these observations are unclear.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis, also called allergic alveolitis, may be due to a wide variety of antigenic stimuli. The fractional content of large surfactant aggregates and the phospholipid content of BAL fluid from these patients is not significantly different from that of healthy patients, although subtle differences in the fractional content of phosphatidylglycerol and sphingomyelin have been reported [23]. Changes in the level of SP-A are conflicting, with reports of both significant decreases [23] and increases [26]. SP-B levels are reported to be the same as those of controls [23].

Pulmonary alveolar proteinosis

The adult form of pulmonary alveolar proteinosis (PAP) is a rare idiopathic disease characterized by massive accumulation of surfactant in alveoli. The exact defect is unclear, but it may be related to lack of granulocyte-macrophage colony-stimulating factor (GM-CSF) or GM-CSF receptor β_c chain. These defects contribute to reduced clearance of surfactant from the alveoli. Mice deficient in GM-CSF show the same clinical disease as humans with PAP [27]. When GM-CSF knockout mice were given exogenous GM-CSF by inhalation for five weeks, the histopathology, PC pool size, and SP-B concentrations returned to normal. Withdrawal of inhaled GM-CSF resulted in return to the alveolar proteinosis phenotype. Mice lacking the GM-CSF receptor β_c chain also had the same histopathology as the GM-CSF deficient mice, but the concentrations of PC and of the surfactant proteins were lower, indicating that the severity of PAP symptoms may be regulated by different mutations. Other clinical reports indicate that some cases of idiopathic PAP may be due to an autoimmune disorder. Neutralizing antibodies to GM-CSF have been described in certain patients with PAP [28]. Other investigators have shown that there is marked heterogeneity of mass and charge in the SP-A isoforms in patients with PAP, and elevation in the content of SP-A, SP-B, and SP-C occurs [29,30]. It is unclear whether these lung surfactant modifications are secondary effects or have a pathogenic role.

The traditional method of treating patients with PAP is whole lung lavage with saline. Recent trials, however, have

examined the value of recombinant GM-CSF administration. In a preliminary study, Kavuru and colleagues showed that the use of GM-CSF was beneficial in increasing the partial pressure of oxygen in arterial blood and decreasing the alveolar-arterial oxygen gradient in four patients with PAP [31]. This is a promising area of clinical investigation that will require additional clinical investigation.

Conclusion

In acute diseases, surfactant has been used in the treatment of infant respiratory distress syndrome and meconium aspiration and is now used as a standard of care. Many trials have also been performed with surfactant as therapy for acute respiratory distress syndrome. This review article focuses on the role of surfactant in a variety of subacute diseases. While much remains to be learned, both clinical and laboratory data continue to provide insights that might provide novel treatments in the future.

Abbreviations

BAL = bronchoalveolar lavage; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; GM-CSF = granulocyte-macrophage colony-stimulating factor; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary alveolar proteinosis; PC = phosphatidylcholine; SP = surfactant-associated protein; SP-A/PL = surfactant-associated protein-A/ phospholipid ratio.

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