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Review

How to overcome surfactant dysfunction in meconium aspiration syndrome?☆

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ABSTRACT

Surfactant dysfunction in meconium aspiration syndrome (MAS) is caused by meconium components, by plasma proteins leaking through the injured alveolocapillary membrane and by substances originated in meconium-induced inflammation. Surfactant inactivation in MAS may be diminished by several ways. Firstly, aspirated meconium should be removed from the lungs to decrease concentrations of meconium inhibitors coming into the contact with surfactant in the alveolar compartment. Once the endogenous surfactant becomes inactivated, components of surfactant should be substituted by exogenous surfactant at a sufficient dose, and surfactant administration should be repeated, if oxygenation remains compromised. To delay the inactivation by inhibitors, exogenous surfactants may be enriched with surfactant proteins, phospholipids, or other substances such as polymers. Finally, to diminish an adverse action of products of meconium-induced inflammation on both endogenous and exogenously delivered surfactant, anti-inflammatory drugs may be administered. A combined therapeutic approach may result in better outcome in patients with MAS and in lower costs of treatment.

1. Introduction

Function of pulmonary surfactant may be diminished by a number of exogenous and endogenous factors. Thus, surfactant dysfunction may occur in many respiratory diseases, such as acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), or meconium aspiration syndrome (MAS).

2. Meconium aspiration syndrome (MAS)

2.1. Incidence of MAS

MAS occurs in the term and post-term newborns. A bodily waste discharged by a fetus – meconium – may be present in the amniotic fluid of 10–15% of all newborns. However, just in 1–2 per 1000 of them, the signs of MAS with characteristic hypoxemia, hypercarbia, acidosis, combined in most severe cases with persistent pulmonary hypertension may develop several hours after labor. The meconium-stained amniotic fluid may be aspirated during the first breaths of a newborn, but the contamination with meconium may occur as a response to stress accompanying fetal asphyxia or stimulation of vagal nerves during an intrauterine development (Dargaville and Mills, 2005).

2.2. Pathophysiology of MAS

The pathophysiology of MAS is complex. In the acute phase (about 15 min of meconium aspiration), obstruction of large airways is dominant. This period is characterized by increased lung resistance and functional residual capacity, decreased lung compliance, acute hypoxemia, hypercarbia, and respiratory acidosis. Signs of the later phase (>60 min after the aspiration) result from meconium movement down to the smaller airways. In the terminal bronchioles and alveoli, meconium triggers inflammation, collapse of airways and alveoli, and inactivation of pulmonary surfactant. The meconium-induced inflammation is mostly mediated by neutrophils and macrophages, the activation of eosinophils and lymphocytes plays a lesser role in this process.

There are several pro-inflammatory substances present in meconium (de Beaufort et al., 2003), such as interleukins (IL)-1β, -6, -8, TNFα, proteolytic enzymes including phospholipase A_2, heme, free fatty acids, bilirubin, cholesterol, bile acids, etc. increasing chemotaxia of neutrophils and their leak through the alveolocapillary membrane. In addition, these substances may stimulate the production of other bioactive cytokines and reactive oxygen species (ROS) from neutrophils, macrophages, and pulmonary fixed cells. Released bioactive substances, activation of complement and coagulation, increased expression of inducible nitric oxide (NO) synthase, and other processes lead to destruction of basal membranes of epithelium and endothelium, damage surfactant, and

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increase leak of liquid, proteins and cells from the blood and interstitium into the alveolar space.

In addition to the acute effects, MAS has the long-term consequences concerning the lung function. For example, an increased bronchial reactivity and wheezing which are observed in children who had overcome MAS as neonates. However, these sequelae may be attributable to the ventilation neonates suffering from MAS with high concentrations of inspired oxygen rather than to the immunogenic or allergenic effect of meconium, as MAS usually appears as a single situation and meconium contains a low amount of proteins.

3. Pulmonary surfactant

Pulmonary surfactant is a complex of phospholipids, neutral lipids, proteins, and saccharides which is synthesized in type II pneumocytes. Surfactant, lowering the surface tension, stabilizes alveoli and terminal airways at the end of expiration, decreases suction forces into alveoli, and thereby prevents lung edema. Surfactant participates in the lung protection and defense, as it works as anti-inflammatory agent. Furthermore, surfactant enhances removal of inhaled particles and senescent cells outside the alveolar compartment (Dargaville and Mills, 2005).

4. Dysfunction of surfactant in MAS

As reviewed by Zuo et al. (2008), reduced surface activity of surfactant due to its inhibition or inactivation may result from:

1. interference with adsorption of phospholipids and their ability to form a functional film of surfactant,
2. inability of surfactant film to reach low values of the surface tension in compression,
3. incapability of proper re-spreading of phospholipids during expansion.

There are many factors inhibiting the pulmonary surfactant: plasma proteins, unsaturated membrane phospholipids, lysophospholipids, free fatty acids, meconium, supraphysiological concentrations of cholesterol, phospholipases, proteolytic enzymes, ROS, or polutants (Zuo et al., 2008). Several of them participate in surfactant dysfunction in MAS.

4.1. Meconium as an inhibitor of surfactant

4.1.1. Meconium composition

Meconium is a viscous, dark-green substance of pH 5.5–7.0. It consists of amniotic fluid, desquamated epithelial cells, lanugo, vernix caseosa, mucus, blood and gastrointestinal secretes swallowed during the intrauterine life. The dry mass of meconium is formed by mucopolysaccharides, bile acids and bile salts, bilirubin, cholesterol, tri-, di- and monoglycerides, free fatty acids, enzymes including pancreatic phospholipase A_2, proteins, e.g. cytokines IL-1, -6, -8 and TNFα, small amount of lipids, heme, purines, phosphorus, etc. (de Beaufort et al., 2003; Dargaville and Mills, 2005).

Components of meconium may be biochemically divided into a hydrophilic fraction containing proteins and bile pigments, and a hydrophobic fraction containing cholesterol, free fatty acids (palmitic, stearic, and oleic acids), and unsaturated lipids (e.g. triglycerides). Meconium contains approximately 150 mg of proteins, less than 1 mg of total bilirubin, about 49 mg of free fatty acids, 47 mg of triglycerides, and 270 mg of cholesterol per gram of dry mass (Sun et al., 1993).

4.1.2. Components of meconium and their potential to inactivate surfactant

The extent of surfactant inhibition depends on both concentration of surfactant and concentration of surfactant inhibitors (e.g., meconium). If the surfactant concentration is low, even highly diluted meconium inhibits surfactant function, whereas at high surfactant concentrations the effects of even highly concentrated meconium are limited (Sun et al., 1993).

The individual components of meconium possess various potency to inactivate surfactant. For example, bilirubin is able to increase the surface tension already at concentrations of 50 μg/ml or 85 μmol/l. Cholesterol interferes with surfactant ability to reduce surface tension at air-liquid interphase during compression of the surface, which may fluidize the surfactant film and destabilize the alveoli during expiration (Diemel et al., 2002). Similar mechanisms of surfactant inactivation are presumed also in case of free unsaturated fatty acids, bile acids, lysophospholipids, and bilirubin (Zuo et al., 2008).

In addition, bile acids selectively penetrate through the lamelar structures and surfactant monolayer, disintegrate these structures, and alleviate a leak of cholesterol into the surfactant complexes, which further degrades the surfactant function (Lopez-Rodriguez et al., 2011). This type of inactivation may hardly be overcome by higher concentrations of surfactant in the alveoli; thus the way to increase surfactant resistance to inhibition should be searched for.

High concentrations of bile acids increase the production and activation of phospholipase A_2 in the lungs. PLA_2 may directly or indirectly through its products, such as lysophosholipids, affects the surfactant metabolism and it damages the cell membranes (De Luca et al., 2011).

Comparing the effects of hydrophilic and hydrophobic fractions of meconium, Sun et al. (1993) found an elevation of surface tension with increasing concentrations of the meconium fractions, whereas the inhibitory effect on surfactant was about 10-times stronger than that of the hydrophobic fraction. Similarly, in a study by Pallem et al. (2010), both meconium fractions reduced the surface properties of the dipalmitoylphosphatidylcholine (DPPC) film, with a more potent inhibitory effect of the hydrophobic fraction. Thus, it is well appreciated that surfactant dysfunction is even more pronounced in MAS than in the other forms of acute lung injury, as both fractions of meconium act as the potent inhibitors of surfactant.

4.1.3. Mechanisms of meconium action

Meconium may inactivate the surface properties of surfactant by several mechanisms:

1. meconium slows down adsorption of surfactant lipids at the air-liquid interphase and thereby prevents surfactant spread over the alveolar surface;
2. meconium decreases concentration of the surfactant proteins SP-A and SP-B in a time-dependent manner;
3. meconium changes the viscosity and ultrastructure of surfactant;
4. meconium accelerates the transformation of large, surface active aggregates to small, less active ones.

4.1.3.1. Meconium reduces adsorption of phospholipids at air-liquid interphase in alveoli. In in vitro measurements, increasing concentrations of meconium added to surfactant increased gradually the values of minimum and maximum surface tension and prolonged adsorption in a dose-dependent manner (Sun et al., 1993). Similar effects of meconium were observed on DPPC liposomes (Pallem et al., 2010). Negative effects of meconium on surfactant were also measured using a capillary surfactometer, which simulates the situation in terminal airways. In this method, the surface properties of surfactant are expressed by two parameters: initial pressure