Review

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Mechanisms to Explain Surfactant Responses

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Key Words

Respiratory distress syndrome · Bronchopulmonary dysplasia · Lung development · Preterm infant

Abstract

Surfactant is now standard of care for infants with respiratory distress syndrome. Surfactant treatments are effective because of complex metabolic interactions between surfactant and the preterm lung. The large treatment dose functions as substrate; it is taken up by the preterm lung and is reprocessed and secreted with improved function. The components of the treatment surfactant remain in the preterm lung for days. If lung injury is avoided, then surfactant inhibition is minimized. Prenatal corticosteroids complement surfactant to further enhance lung function. The magic of surfactant therapy results from the multiple interactions between surfactant and the preterm lung.

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Introduction

Surfactant treatments have been the standard of care for infants with respiratory distress syndrome (RDS) since about 1990. The development of surfactant is one of the great success stories in neonatal care because the therapy specifically treats surfactant deficiency and changes the pathophysiology and outcome of RDS. Most clinicians who use surfactant do not appreciate the research that was essential to learning why surfactant works so well for most infants. Surfactant works because of the quite complicated biophysical and metabolic effects within the preterm lung. These effects are modified by clinical variables such as antenatal steroids, lung injury and gestational age.

What Is RDS?

Infants with RDS have low surfactant lipid pools <10 mg/kg relative to the surfactant lipid pool sizes in term infants of perhaps 100 mg/kg [1]. The fetal human lung is in the saccular stage of development during the period of viability from 23 weeks' gestation to the initiation of secondary septation (alveolarization) which begins at about 32 weeks' gestation. The structure of the preterm lung with RDS limits lung function in a number of ways. Although the saccular lung can exchange gas, the diffusion distance for gas is increased and surface area for gas exchange relative to metabolic rate is decreased. The low lung gas volume of the preterm (20–40 ml/kg b.w.) relative to the term infant (50 ml/kg) or the adult (80 ml/kg) makes the preterm lung susceptible to overdistention and injury with mechanical ventilation [2]. Injury and edema will develop if the lung is allowed to breathe from an inadequate functional residual capacity or is injured by overstretch. However, the lungs of infants with RDS are, in most cases, not injured at birth and most injuries and edema result from care practices.

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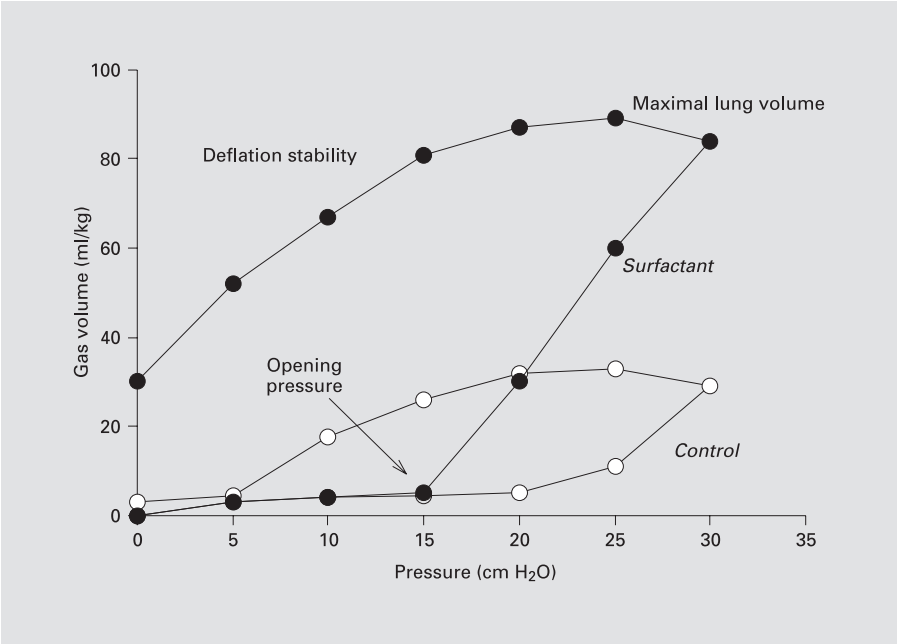

Fig. 1. Representative pressure-volume curves for a surfactant-deficient preterm lung and a surfactant-treated lung. Surfactant facilitates inflation of the lung from a lower pressure, permits the lung to open to a higher volume and prevents the lung from collapsing when pressure is decreased (deflation stability). Data adapted from Rider et al. [4].

Table 1. Variables that contribute to the distribution of surfactant in the lungs

Property	Effect
Surface activity	Causes rapid adsorption and spreading
Gravity	Surfactant distributed by gravity in large airways
Volume	Higher volumes, cause better distributions
Rate of administration	Rapid administration improves distribution
Ventilator settings	Pressure and PEEP help clear airways of fluid
Fluid volume in lung	Higher volumes of fetal lung fluid or edema fluid improve distribution

What Is Surfactant?

Surfactant from adult animals and humans is a macroaggregate of highly organized lipids and surfactant-specific proteins. The major components that confer the unique ability of surfactant to lower the surface tension on an air-water interface to very low values are the saturated phosphatidylcholine species, surfactant protein B and surfactant protein C [1]. The preterm infant with RDS has low amounts of surfactant that contains a lower percent of saturated phosphatidylcholine species, less phosphatidyglycerol and less of all the surfactant proteins than surfactant from a mature lung. The surfactant from the preterm lung is intrinsically 'immature' in composition and function.

What Are Treatment Responses to Surfactant?

Treatment responses to surfactant empirically can be divided into three stages – an acute response that occurs within minutes, effects that occur over hours, and finally effects that last days or perhaps weeks. The acute treatment response results from the biophysical properties of surfactant and depends on the rapid distribution of surfactant to the lung. The magnitude of the distribution problem is generally not appreciated [3]. There are about 20 generations (branch points) from the trachea to the respiratory bronchioles and saccules. Therefore, there are about 250,000 binary branch points and 500,000 distal airways leading to saccules in the preterm lung. If the distribution is not proportionate to the number of saccules distal to *each* branch point, then surfactant distribution will not be uniform. Any non-uniformity at a proximal branch point will be amplified at subsequent branch points. When surfactant is instilled into a lung, the distribution results from the principles outlined in table 1. Empirically, surfactant distribution is good enough because the lung fields can clear rapidly and oxygenation can im-

prove quickly. However, treatment techniques do matter. Surfactant will distribute to the preterm sheep lung more uniformly when given rapidly at birth because it will mix with fetal lung fluid to increase the volume, and gravity is not a problem in a fluid-filled lung [3]. The slow infusion of surfactant into the lungs to minimize any acute physiologic changes during treatment can result in very poor distribution. Although surfactant distribution in practice is not ideal, it is good enough because of the biophysical properties of the surfactant, and the small amount that is needed regionally in the lung for a treatment response. The practical ways to improve distribution are to position the infant to minimize gravity, to give surfactant quickly in a reasonable volume, and to give the infant enough ventilatory support to quickly clear the airways of fluid.

The effects of the rapid distribution (within seconds to minutes) to the preterm lung are best illustrated by the change in the pressure-volume curve with surfactant treatment [4] (fig. 1). The surfactant-treated fetal lungs begin to inflate at a lower pressure (opening pressure), inflate to a much larger volume, and retain gas on deflation. This effect of surfactant to open the lungs results in a rapid increase in oxygenation that can occur almost instantaneously. The subsequent responses to surfactant treatment result from improved lung mechanics, which may change more gradually and will depend, in part, on the choice of ventilator styles.

Why Do Infants Continue to Improve after Surfactant Treatments?

The persistence of the surfactant treatment response is explained primarily by surfactant metabolism in the preterm lung. Based on measurements in adult, newborn and preterm animals, and more recently in preterm infants, we know that the synthesis of surfactant lipids and proteins from precursors by type II cells is rapid [5]. However, surfactant processing to storage in lamellar bodies and then secretion to the airspaces occurs over many hours. The time from synthesis to peak labeling of surfactant in airway samples is about 3 days in preterm infants with RDS [6]. Therefore, it will take the infant with RDS days to increase the surfactant pool from endogenous synthesis and secretion. Catabolism/clearance/loss of surfactant can be measured from the lung and airspaces in animals and from the airspaces in infants with RDS using tracheal aspirate samples [7, 8]. The consistent result is that both the endogenous and exogenous surfactant components have long half-life values in the airspaces – about 3 days for infants with RDS. The lipids also remain in the lung compartment (airspaces, type II cells, lung tissue) for many days. A treatment dose of 100 mg/kg surfactant exceeds the endogenous alveolar pool in healthy adults by about 20-fold. Therefore, the surfactant dose is large and results in a large increase in the total surfactant pool in the preterm lung that persists for days. Simultaneously, the preterm lung is synthesizing new surfactant.

Part of the magic of surfactant treatment results from how the surfactant interacts with the type II cells. Surfactant components are recycled from the airspaces back to type II cells where the lipids are, in part, diverted into lamellar bodies for resecretion [1]. In general, recycling is more efficient in the preterm than the adult lung. The very long biological half-life values for surfactant in the airspace are explained by continued reuptake and resecretion. The treatment dose of surfactant functions as substrate for recycling in the uninjured preterm lung, resulting in treatment effects that can persist for days.

The second bit of magic is the effect that the preterm lung has on the surfactant used for treatment. Within hours of surfactant treatment the preterm lamb lung improves the function of the surfactant used for treatment [9]. The lung presumably contributes surfactant proteins and recycles the surfactant components for secretion to the lung saccules at the right place and time. Therefore, the persistence of a surfactant response after a single treatment dose results from the uninjured lung integrating the treatment surfactant into normal surfactant metabolic pathways. A single treatment is a cure for the surfactant deficiency disease component of RDS in most infants.

The crucial variable for the need for a second dose of surfactant is *lung injury* [10]. The preterm infant with RDS has a low surfactant pool size and if lung injury results in edema, then the proteins in the edema fluid can inhibit surfactant function [11]. The preterm infant can injure the lung with spontaneous breathing if the lung is very surfactant deficient or if positive end-expiratory pressure (PEEP) is not provided to help stabilize the lung. Mechanical ventilation can certainly injure the lung. Once injury has occurred, the airspaces fill with fluid, proteins and inflammatory exudate. Surfactant function can deteriorate by multiple mechanisms that in aggregate are called surfactant inhibition [12]. Lung injury also interferes with the normal metabolism of surfactant by type II cells. The net effect is a loss of biophysical function and a deterioration in lung function. The use of repetitive dosing has decreased in clinical practice, probably because more attention is being paid to avoiding lung injury prior to and after the first dose of surfactant.

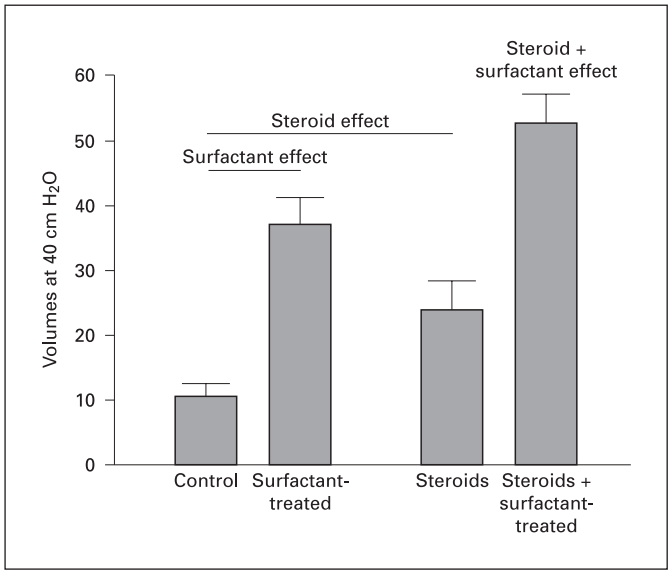

Fig. 2. Lung gas volumes following ventilation of control lambs, lambs treated with surfactant, lambs delivered after cortisol infusions (steroids) and cortisol-infused lambs treated with surfactant. Surfactant treatment or fetal cortisol infusions improved lung gas volumes, and both treatments increased the lung gas volumes more than either treatment. Data redrawn from Ikegami et al. [15].

Clinical Variables That Alter Surfactant Treatment Responses: Gestational Age and Antenatal Corticosteroids

As the fetus matures, lung structure becomes more mature in parallel. The more mature lung responds more favorably to surfactant treatments for a number of reasons [9]. The surface area will be larger, the microvasculature will be better developed, and the lung will be less susceptible to injury. The preterm lung is less effective at improving surfactant function at very early gestational ages. Surfactant from the preterm lung also is easier to inhibit by plasma than is surfactant from the adult lung. The more immature the infant, the more immature the surfactant, the less the metabolic capabilities of the type II cells, and the more interference with surfactant function may be present.

Antenatal corticosteroids have multiple effects on the fetal lung that result in decreased lung mesenchyme, an increased lung gas volume, a decreased tendency of the lung to leak proteins into the airspaces, and increased surfactant. These maturational changes may not be sufficient to prevent RDS. Fortunately, the corticosteroid-mediated effects augment surfactant treatment responses by multiple mechanisms [13, 14]. Antenatal corticosteroids increase lung gas volumes, as do surfactant treatments. The combined treatments result in an additive increase in lung gas volumes [15] (fig. 2). This interaction of antenatal corticosteroids and surfactant occurs at multiple levels. The dose-response curve for the corticosteroid treated lung demonstrates better compliances at lower doses. Also, the sensitivity of surfactant to inhibition is decreased by antenatal corticosteroid treatment.

Is the Incidence of RDS and the Need for Surfactant Treatment Decreasing?

There is no consensus in the neonatal community about the optimal timing of surfactant treatment for RDS. Delivery room treatment is preferable to treatment of established RDS. However, the option to delay intubation and treatment until the infant either demonstrates inadequate respiratory effort or has signs of early RDS has advantages; the infant will not be overventilated as easily during initial stabilization and infants without RDS will not be treated with surfactant. An important question is why many very low birth weight (VLBW) infants do not have RDS? The surprising answer is that in the hands of clinicians who use nasal CPAP very early to assist infants with respiratory transition after birth, surfactant was used to treat only 16% of infants [16]. This is strikingly lower than the recent experience of the Vermont-Oxford Network where almost 80% of similar infants receive surfactant treatment. Many of these infants have been exposed to antenatal corticosteroids and chorioamnionitis, both of which can mature the preterm lung. Many of the VLBW infants that are now born probably have minimal RDS and if lung injury is avoided, the infants may do well with CPAP therapy alone. Several randomized and controlled trials to evaluate surfactant treatment in the delivery room relative to initial stabilization with CPAP are in progress.

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