

# Surfactant administration in neonates: A review of delivery methods

Nina Nouraeyan MD<sup>1</sup>, Alicia Lambrinakos-Raymond MD<sup>1</sup>, Marisa Leone RRT<sup>2</sup>,  
Guilherme Sant'Anna MD PhD FRCPC<sup>3</sup>

N Nouraeyan, A Lambrinakos-Raymond, M Leone, G Sant'Anna. Surfactant administration in neonates: A review of delivery methods. *Can J Respir Ther* 2014;50(3):91-95.

Surfactant has revolutionized the treatment of respiratory distress syndrome and some other respiratory conditions that affect the fragile neonatal lung. Despite its widespread use, the optimal method of surfactant administration in preterm infants has yet to be clearly determined. The present article reviews several aspects of administration techniques that can influence surfactant delivery into the pulmonary airways: the bolus volume, injection rate, gravity and orientation, ventilation strategies, alveolar recruitment, and viscosity and surface tension of the fluid instilled. Based on the present review, knowledge gaps regarding the best way to administer surfactant to neonates remain. From the available evidence, however, the most effective way to optimize surfactant delivery and obtain a more homogeneous distribution of the drug is by using rapid bolus instillation in combination with appropriate alveolar recruitment techniques.

**Key Words:** Neonatology; Preterm infant; Respiratory distress syndrome; Review; Surfactant administration; Ventilation

Treatment with exogenous surfactant has saved the lives of thousands of premature babies in the past few decades (1). The therapeutic efficiency of a given surfactant preparation correlates with its lipid and protein composition (and other factors), but it is also highly dependent on the technique used for administration. It is important to use a delivery strategy that optimizes surfactant distribution into the pulmonary airways to maximize its beneficial effects (2). In 2014, the Committee on Fetus and Newborn – American Academy of Pediatrics published a clinical report on the use of surfactant replacement therapy for respiratory distress in the preterm and term neonate (1). Among several recommendations, the report stated that “the optimal method of surfactant administration in preterm infants has yet to be clearly proven”. Unfortunately, the scientific literature provides conflicting and limited data regarding the methods or techniques of surfactant administration. The majority of studies were performed long ago and tested in more mature infants (gestational age >28 weeks), which does not reflect the population of preterm infants that actually undergo endotracheal intubation and surfactant treatment. Moreover, respiratory care has changed substantially since these studies were conducted.

Exogenous surfactant preparations must spread rapidly and efficiently into the air-liquid interface once instilled in the proximal airways, with the goal of achieving a homogenous distribution throughout the lungs. However, rapid administration of liquid into the lungs may elicit transient oxygen desaturation and bradycardia, or significant complications such as severe airway obstruction, pulmonary hemorrhage, pneumothoraces or pulmonary hypertension (3). Therefore, surfactant should be administered according to a well-established protocol under the supervision of clinicians and respiratory therapists experienced in tracheal intubation, ventilator management and general care of the premature infant.

## L'administration de surfactant chez les nouveau-nés : une revue des modes de libération

Le surfactant a révolutionné le traitement du syndrome de détresse respiratoire et d'autres troubles respiratoires qui endommagent le fragile poumon néonatal. Malgré l'utilisation généralisée du surfactant son mode optimal d'administration n'est pas clairement établi chez les nourrissons prématurés. Le présent article traite de divers aspects des techniques d'administration, qui peuvent influencer sur la libération du surfactant dans les voies respiratoires : le volume du bolus, le rythme d'injection, la gravité et l'orientation, les stratégies de ventilation, le recrutement alvéolaire, ainsi que la viscosité et la tension de surface du liquide instillé. D'après la présente revue, il reste des lacunes quant au meilleur moyen d'administrer le surfactant aux nouveau-nés. Cependant, selon les données probantes, pour en optimiser l'administration et obtenir une distribution plus homogène, il est préférable de procéder à un bolus rapide, combiné à des techniques pertinentes de recrutement alvéolaire.

### BOX 1

#### Modes of delivering surfactant into the pulmonary airways

- Bolus administration
  - One dose: complete dose given within a single time frame
  - Multiple doses: total dose divided into two or more amounts (aliquots) and given separately in time
- Continuous infusion (slow administration of the surfactant preparation)
- Nebulization: suspension of aerosolized surfactant that is subsequently inhaled

The present article reviews several aspects of administration techniques that can influence the delivery of surfactant into the lungs: the bolus volume, injection rate, gravity and orientation, ventilation strategies and development of airway obstruction, alveolar recruitment, and viscosity and surface tension of the fluid instilled. A surfactant administration protocol that was developed and implemented in our unit, based on the best available evidence, is included in Appendix 1.

#### BOLUS ADMINISTRATION AND INJECTION RATE

There are two common modes of delivering surfactant into the pulmonary airways: bolus infusion (one or multiple aliquots); or continuous infusion (2) (Box 1). Surfactant has also been given by nebulization; however, because this method and preparation remain under investigation, it will not be reviewed here.

In general, slower techniques of surfactant bolus administration have been noted to be inferior to the rapid bolus technique (4). When rapid bolus infusions were compared with slow bolus or continuous

<sup>1</sup>Department of Pediatrics; <sup>2</sup>Department of Respiratory Therapy; <sup>3</sup>Faculty of Pediatrics; McGill University Health Centre, Montreal, Quebec  
Correspondence: Dr Guilherme Sant'Anna, 2300 Upper Street, Room C-912, Montreal, Quebec H3H 1P3.

Telephone 514-412-4400 ext 22389, fax 514-412-4356, e-mail guilherme.santanna@mcgill.ca

infusions in several animal studies, they were noted to be superior in terms of overall distribution of the surfactant and a faster rate of improvement of oxygenation and lung compliance (5,6). However, side effects, such as transient bradycardia and decreased blood pressure, were noted with rapid bolus administration. At present, the rapid bolus technique remains the recommended method of surfactant administration.

Cassidy et al (7) showed that the method of liquid instillation affects how the liquid distributes within the lung. The best method allowed the formation of a liquid plug in the trachea at the beginning of surfactant instillation. The liquid was then driven to the distal parts of the lung by ventilation, resulting in quicker spread in a few breaths and more uniform liquid distribution throughout the lungs. Transit and delivery times depend on plug volume, among other factors. Although the exogenous surfactant takes in the order of minutes to reach the alveoli, the lowering of surface tension at the distal ends occurs very rapidly – within seconds – as the result of the compression of the endogenous surfactant (8).

### GRAVITY AND ORIENTATION

When surfactant is administered slowly (slow infusion and/or slow rate of ventilation), the distribution is dependent on the orientation of the airways with respect to gravity (4,5,9). This could lead to overinflation of the parts of the lung receiving surfactant and result in bronchopulmonary dysplasia (6). Improved homogeneity is achieved with supine compared with upright positioning. Animal models have also shown greater epithelial cell injury at slower propagating speeds (10). In a randomized control trial (11), there was no difference in clinical outcomes when two fractional doses of surfactant were given in two body positions, compared with four fractional doses given in four positions.

### VENTILATION STRATEGIES AND DEVELOPMENT OF AIRWAY OBSTRUCTION

Surfactant has been administered either by disconnecting the infant from the ventilator and applying bagging, or by continuing ventilation during the procedure. Using beractant at a volume of 4 mL/kg, Zola et al (11) conducted a multicentre, randomized control trial comparing three different strategies of surfactant instillation: two doses, removing patient from the ventilator; two doses, continuing ventilation during the procedure; and four doses, removing patient from the ventilator. Ventilation during all three procedures was performed by using pre-treatment pressures: fraction of inspired oxygen ( $FiO_2$ ) = 1.0; respiratory rate at least 60 breaths/min; and an inspiratory time of 0.5 s. There were no significant differences among the three procedures. A similar study was conducted by Valls-i-Soler et al (12), who compared two methods. The first was bolus delivery (two aliquots) of poractant alfa at a volume of 2.5 mL/kg, with the patient removed from the ventilator and hand-bagged for 1 min with the same  $FiO_2$  used before the procedure and adjusting the peak inflation pressure (PIP) for adequate chest expansion. The second method was delivery via a side hole, in which a full dose of surfactant was rapidly given in 60 s via a 3.5 Fr catheter introduced through a side hole. Mechanical ventilation was not interrupted, but PIP was increased by 10% for 5 min. Both procedures were equally effective, but a slight significant increase in the partial pressure of carbon dioxide ( $PCO_2$ ) at 5 min of dosing was observed in the side-hole group, indicating decreased minute ventilation, likely related to some degree of airway obstruction.

A prospective study was performed in smaller and more immature preterm infants receiving their first or second dose of surfactant while being ventilated in assist control volume guarantee mode (13). A small volume of poractant alfa (1.25 mL/kg) was given as a single bolus using a closed technique during ventilation (ventilation not interrupted during administration). Ventilator parameters were recorded before, during and after administration. A complete cessation (ie, obstruction) of flow down the endotracheal tube (ETT) was observed in 21 of 22 (95%) of infants. Following surfactant administration, PIP

increased from a mean of 19 cmH<sub>2</sub>O (range 16 cmH<sub>2</sub>O to 22 cmH<sub>2</sub>O) up to 27 cmH<sub>2</sub>O (range 23 cmH<sub>2</sub>O to 30 cmH<sub>2</sub>O), taking 30 min to 60 min to return to baseline. A significant and prolonged decrease in the delivered tidal volume (obstruction) was noted in the majority of the infants. Airway obstruction immediately after surfactant administration was also noted by Miedema et al (14) in 15 preterm infants receiving surfactant while on high-frequency oscillatory ventilation, despite a lung recruitment manoeuvre used before surfactant administration. Tarawneh et al (3) prospectively evaluated a standardized protocol for a bovine lipid extract surfactant administration using a dose of 5 mL/kg. According to the protocol, surfactant was given in four aliquots using a closed technique without removing the patient from the ventilator. A significant number of extreme low birth weight infants experienced episodes of severe airway obstruction, requiring removal of the ETT followed by reintubation.

Anderson et al (15) investigated the effects of breathing frequency on liquid distribution. At 60 breaths/min, the liquid is first deposited on the airway walls and then transmitted toward the gravity-dependent region of the lung over the ensuing breaths. A more uniform distribution of liquid throughout the lung was obtained. This phase lasted only a few minutes and facilitated the transport of liquid to its target location. After this initial targeted instillation is achieved, normal ventilation using appropriate ventilation rate can be used. The implication for surfactant delivery is that a slow rate of ventilation could result in nonhomogeneous surfactant distribution. This is not the desired outcome because it may inflate parts of the lung receiving surfactant, resulting in lung injury.

### ALVEOLAR RECRUITMENT

Recruitment of the lungs before surfactant treatment can minimize ventilation-induced lung injury and facilitate the distribution of surfactant into the pulmonary airways. In newborn piglets, a volume recruitment manoeuvre using moderately increased tidal volume applied before, during and for an additional 5 min after surfactant administration led to a superior clinical response in terms of gas exchange and lung function, owing to a more homogeneous distribution pattern (16). Surfactant distribution was also evaluated in a study in which a recruitment manoeuvre to determine the optimal peak end-expiratory pressure (PEEP) level was performed in newborn piglets before surfactant administration. In one-half of the animals, an additional recruitment manoeuvre was performed to define a new PEEP level after surfactant administration. Using electrical impedance tomography, an improved spatial distribution of regional lung ventilation was observed in animals that underwent a postsurfactant recruitment manoeuvre. This recruitment manoeuvre was then applied in 15 preterm infants receiving surfactant while on high-frequency oscillatory ventilation. A rapid increase (5 min) followed by stabilization of lung volume was observed, with the most prominent effect in the dependent (dorsal) lung regions, supporting the role of gravity in surfactant distribution.

### VISCOSITY AND SURFACE TENSION OF THE FLUID INSTILLED

Commercial surfactants also differ in surface viscosity. Viscosity is believed to influence the rate, extent and uniformity of distribution of surfactant in the lungs. Preparations with lower surface viscosity are preferred for endotracheal application because it allows a more uniform and rapid distribution of the instilled surfactant with less loss due to coating of the upper airways. The viscosity of surfactant preparations is directly dependent on phospholipid concentration and inversely related to temperature. After 15 min at a temperature of 37°C, viscosity increases exponentially. In fact, after 30 min at this temperature, the viscosity of calfactant and beractant were 20 times higher when compared with values measured at 10 min (17). In an animal experiment, Lewis et al (18) compared beractant and a bovine lipid extract surfactant. A significantly improved distribution was achieved with the bovine lipid extract surfactant, which was demonstrated to have a viscosity eight times lower than beractant.

A more viscous liquid yields a more homogeneous distribution, and a less viscous plug penetrates more deeply into the distal airways. There are several surfactant preparations available for use in neonates. A natural bovine lipid extract surfactant is used in the majority of Canadian neonatal units. The biochemical composition of each preparation generally reflects the composition of natural surfactant obtained from the alveolar spaces, at least with respect to the high content of phospholipids and the high proportion of disaturated dipalmitoyl phosphatidylcholine (DPPC). The production procedure should also, in principle, preserve the hydrophobic proteins SP-B and SP-C. Surfactants produced from bronchoalveolar lavage are, in principle, less contaminated with plasmatic and tissue components: bovactant, calfactant, bovine lipid extract surfactant, and a biological product produced from pig lungs in Cuba. Poractant alfa and beractant are examples of surfactant obtained from minced lungs. The resulting proportion of the main surface-active lipid component, DPPC, varies from 70% in beractant, 40% in calfactant, approximately 35% to 56% in poractant alfa, 41% in the bovine lipid extract surfactant and 45% in the biological product produced from pig lungs in Cuba.

### OTHER FACTORS

Experimental studies have demonstrated that the level of endogenous surfactant can have important consequences in surfactant replacement therapy. Pre-existing surfactant can slow the spreading of new surfactant by diminishing the differential in tension between surfactant-rich and surfactant-poor areas (19). In addition, the new surfactant can induce a disturbance through the existing surfactant. Once a patient is treated with the first dose of surfactant, it could be more difficult for subsequent doses to reach the periphery, hindering the overall delivery and efficacy of the product. This could be the reason of the observed decrease in benefits of the administration of three or more doses, compared with one or two doses (20).

### CONCLUSION

The present review discussed some of the mechanisms that influence the instillation of surfactants into the pulmonary airways. In light of the evidence from animal and human studies, we believe that the optimal method for surfactant delivery should include the use of bolus instillation combined with ventilatory strategies before (lung recruitment), during (disconnection and bagging OR increase on ventilator settings to provide sufficient pressure and a rate of 60 breaths/min) and after surfactant administration (lung recruitment). Extra care should be taken when giving surfactant to extreme low birth weight infants because this is a population at higher risk for side effects such as severe episodes of airway obstruction during the procedure (3). As for any protocol, each neonatal intensive care unit should develop a coherent administration strategy with the goal of achieving targeted delivery of surfactant that enhances safety and efficacy of this medication.

### APPENDIX: PROTOCOL FOR SURFACTANT REPLACEMENT ADMINISTRATION AT MCGILL UNIVERSITY HEALTH CENTRE, MONTREAL, QUEBEC

Patient population:

- Patients with respiratory distress syndrome
- Patients with conditions associated with surfactant deficiency such as meconium aspiration syndrome, sepsis and pulmonary hemorrhage as per discussion with the most responsible physician. Although congenital diaphragmatic hernia is associated with surfactant deficiency, the administration of surfactant may result in significant deterioration and, therefore, should be used with caution.

### CRITERIA FOR SURFACTANT ADMINISTRATION

a. **<24 weeks' gestational age:** these infants should be intubated immediately after birth and surfactant given prophylactically (within the first 15 min to 30 min of life). Between intubation and surfactant administration, these infants should be ventilated very carefully with low tidal volume and pressures.

### b. **≥24 weeks' gestational age:**

b.1 For infants intubated immediately after birth, it is recommended that surfactant be given as early treatment (<2 h of age), except if the infant is on room air and minimal ventilatory support on neonatal intensive care unit admission. These infants should be immediately extubated to nasal ventilation or nasal continuous positive airway pressure.

b.2 Infants initially treated with noninvasive ventilation, endotracheal intubation and surfactant administration is recommended under one the following circumstances:

- a) Fraction of inspired oxygen ( $FiO_2$ ) >0.5 (21-23) to maintain oxygen saturation ( $SpO_2$ ) >88% or a partial pressure of arterial oxygen ( $PaO_2$ ) >45 mmHg
- b) Partial pressure of arterial carbon dioxide ( $PaCO_2$ ) >55 mmHg to 60 mmHg with a pH <7.25
- c) Apnea requiring bag and mask ventilation
- d) >6 apneas/6 h
- e) Evidence of significant work of breathing (retractions, grunting and chest wall distortion in infants presenting with increases in oxygen needs)

### PROCEDURE

Physician will assess patient eligibility for surfactant administration and write an order for surfactant to be given. Physician should be at bedside during surfactant administration. The registered respiratory therapist (RRT) will advise the bedside nurse that the patient will be receiving surfactant. The RRT and registered nurse will perform a baseline patient assessment, which should include:

1. Respiratory assessment: respiratory rate, ventilator pressures, tidal volumes and transcutaneous  $PCO_2$  ( $TcPCO_2$ )
2. Chest assessment: air entry, adventitious sounds, symmetry of chest expansion, secretions
3. Vital signs: heart rate, oxygen saturation ( $SpO_2$ ), blood pressure
4. Patient status: awake, asleep, sedated
5. Chest x-ray review to assess endotracheal tube (ETT) position and lung volume

### EQUIPMENT SET-UP

The RRT should set up the equipment as follows

- a) Retrieve surfactant from the freezer and warm to room temperature for no more than 30 min before its use. The vial can be rolled but DO NOT shake it.
- b) Calculate the amount of surfactant needed.
- c) Swab the vial rubber cap with an alcohol swab before introducing needle. Fill syringe with surfactant.
- d) Attached luer lock syringe with medication to luer fitting.
- e) Attach trach care mac cartridge to Y.
- f) Before attaching trach care mac to patient, prime the interval volume of the catheter with medication.
- g) Attach trach care mac adaptor to ventilator circuit and ETT.

### INTERVENTION BEFORE SURFACTANT DELIVERY

The RRT perform the following interventions

1. Pre-oxygenation: the oxygen concentration should be increased to achieve  $SpO_2$  >95% before surfactant delivery.
2. Suction ETT and listen to the air entry.
3. Lung recruitment manoeuvre: Provide five to 10 inflations with pressures 1  $cmH_2O$  to 2  $cmH_2O$  above previous ventilatory settings to assure some lung recruitment before administration, which would facilitate drug distribution into the pulmonary airways.
4. Record all vital signs (heart rate, blood pressure,  $SpO_2$  and  $TcPCO_2$ ).

## SURFACTANT ADMINISTRATION: BACKGROUND INFORMATION (2)

The acute treatment response to surfactant results from the biophysical properties of surfactant AND depends on the rapid distribution of surfactant to the lungs

The magnitude of the distribution problem is generally not appreciated. There are approximately 20 generations (branch points) from the trachea to the respiratory bronchioles and saccules. Therefore, there are approximately 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 nonuniformity at a proximal branch point will be amplified at subsequent branch points.

When surfactant is instilled into a lung, the distribution results from the following principles:

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 the lungs	Higher volumes of fetal lung fluid or edema fluid improves distribution

PEEP Positive end-expiratory pressure

Therefore, **treatment techniques do matter**. Surfactant will distribute to the preterm lung more uniformly when given rapidly and at higher volumes (see Table above).

The slow infusion of surfactant into the lungs to minimize any acute physiological changes during treatment can result in very poor distribution. Using a slow rate of administration could result in a non-homogeneous surfactant distribution, which is not the desired outcome.

Administration of surfactant to extreme preterm infants using multiple aliquots and with the patient receiving mechanical ventilation at the same settings before delivery of the drug was associated with severe episodes of airway obstruction. (3)

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 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.

## SURFACTANT ADMINISTRATION

The RRT should administered surfactant as follows:

1. Surfactant should be delivered through an in-line catheter with the tip located at the mid trachea level.
2. Because the surfactant actually available at the Units is the **bovine lipid extract surfactant** and the dose should be 5 mL/kg (135 mg phospholipids/kg) divided into one or a maximum of two aliquots.
3. Mode of delivery: surfactant should be given as bolus infusion (10 s to 20 s).
4. Infant should be disconnected from the ventilator and bagged by a physician or another RRT with the flow inflating bag or T-piece device at a rate of 60 inflations/min and pressure necessary to push the surfactant effectively into the pulmonary airways.

5. Start the bagging approximately 5 s after initiation of surfactant administration (to give some time for the formation of a fluid plug or column of surfactant into the ETT). The flow rate of the flow inflating bag should be the minimum necessary to provide adequate pressures.
6. Infant should be kept in the horizontal position during the entire procedure.
7. When using more than one aliquot, a minimum period of 30 s to 60 s between the aliquots should be used if infants remained stable.
8. Vital signs and ventilator parameters should be monitored during the delivery process.
9. Details regarding surfactant administration given should be written in the medical records (time, number of aliquots, PIP and PEEP used, vital signs and complications).
10. The ETT should not be suctioned for following 2 h unless signs of significant airway obstruction occur.

## POSTSURFACTANT ADMINISTRATION

1. Registered nurse should record vital signs immediately after administration is completed and every 10 min for the next hour.
2. RRT should record ventilator parameters every 15 min for the next hour.

## REFERENCES

1. Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics* 2014;133:156-63.
2. Jobe AH. Mechanisms to explain surfactant responses. *Biol Neonate* 2006;89:298-302.
3. Tarawneh A, Kaczmarek J, Bottino MN, Sant'Anna GM. Severe airway obstruction during surfactant administration using a standardized protocol: A prospective, observational study. *J Perinatol* 2012;32:270-5.
4. Fernandez-Ruanova MB, Alvarez FJ, Gastiasoro E, et al. Comparison of rapid bolus instillation with simplified slow administration of surfactant in lung lavaged rats. *Pediatric Pulmonol* 1998;26:129-34.
5. Segerer H, van Gelder W, Angenent FW, et al. Pulmonary distribution and efficacy of exogenous surfactant in lung-lavaged rabbits are influenced by the instillation technique. *Pediatr Res* 1993;34:490-4.
6. Ueda T, Ikegami M, Rider ED, Jobe AH. Distribution of surfactant and ventilation in surfactant-treated preterm lambs. *J Appl Physiol* 1994;76:45-55.
7. Cassidy KJ, Bull JL, Glucksberg MR, et al. A rat lung model of instilled liquid transport in the pulmonary airways. *J Appl Physiol* 2001;90:1955-67.
8. Halpern D, Jensen OE, Grotberg JB. A theoretical study of surfactant and liquid delivery into the lung. *J Appl Physiol* 1998;85:333-52.
9. Hentschel R, Brune T, Franke N, Harms E, Jorch G. Sequential changes in compliance and resistance after bolus administration or slow infusion of surfactant in preterm infants. *Intensive Care Med* 2002;28:622-8.
10. Ghadiali SN, Gaver DP. Biomechanics of liquid-epithelium interactions in pulmonary airways. *Respir Physiol Neurobiol* 2008;163:232-43.
11. Zola EM, Gunkel JH, Chan RK, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. *J Pediatr* 1993;122:453-9.
12. Valls-i-Soler A, Lopez-Heredia J, Fernandez-Ruanova MB, Gastiasoro E. A simplified surfactant dosing procedure in respiratory distress syndrome: The "side-hole" randomized study. Spanish Surfactant Collaborative Group. *Acta Paediatr* 1997;86:747-51.
13. Wheeler KI, Davis PG, Kamlin CO, Morley CJ. Assist control volume guarantee ventilation during surfactant administration. *Arch Dis Childhood* 2009;94:F336-8.
14. Miedema M, de Jongh FH, Frerichs I, van Veenendaal MB, van Kaam AH. Changes in lung volume and ventilation during surfactant treatment in ventilated preterm infants. *Am J Respir Crit Care Med* 2011;184:100-5.

15. Anderson JC, Molthen RC, Dawson CA, et al. Effect of ventilation rate on instilled surfactant distribution in the pulmonary airways of rats. *J Appl Physiol* 2004;97:45-56.
  16. Krause MF, Jakel C, Haberstroh J, Schulte-Monting J, Leititis JU, Orlowska-Volk M. Alveolar recruitment promotes homogeneous surfactant distribution in a piglet model of lung injury. *Pediatr Res* 2001;50:34-43.
  17. Lu KW, Perez-Gil J, Tausch H. Kinematic viscosity of therapeutic pulmonary surfactants with added polymers. *Biochim Biophys Acta* 2009;1788:632-7.
  18. Lewis JF, Goffin J, Yue P, McCaig LA, Bjarneson D, Veldhuizen RA. Evaluation of exogenous surfactant treatment strategies in an adult model of acute lung injury. *J Appl Physiol* 1996;80:1156-64.
  19. Grotberg JB, Halpern D, Jensen OE. Interaction of exogenous and endogenous surfactant: Spreading-rate effects. *J Appl Physiol* 1995;78:750-6.
  20. Long W, Thompson T, Fau, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. The American Exosurf Neonatal Study Group I. *J Pediatr* 1999;118:595-605.
  21. Ammari A, Suri M, Milisavljevic V, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005;147:341-7.
  22. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008;358:700-8.
  23. Finan NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
-