Review

Neonatology
formerly Biology of the Neonate

Neonatology 2008;93:309–315
DOI: 10.1159/000121457

Published online: June 5, 2008

Continuous Positive Airway Pressure and Surfactant

Kajsa Bohlin Baldvin Jonsson Ann-Sofi Gustafsson Mats Blennow

Department of Neonatology, Karolinska University Hospital/Karolinska Institutet, Stockholm, Sweden

Key Words
Pulmonary surfactant · Respiratory distress syndrome · Continuous positive airway pressure

Abstract
Nasal continuous positive airway pressure (nCPAP) is an effective treatment of respiratory distress syndrome. Due to long-standing experience of early nCPAP as the primary respiratory support option in preterm infants, this approach is sometimes labeled 'the Scandinavian Model'. Mechanical ventilation is potentially harmful to the immature lungs and cohort studies have demonstrated that centers using more CPAP and less mechanical ventilation have reduced rates of bronchopulmonary dysplasia. However, there is a lack of evidence in the form of larger, randomized controlled trials to prove the superiority of either method. Surfactant is essential in the treatment of respiratory distress syndrome and has generally been reserved for infants on mechanical ventilation. With the development of INSURE (INtubation SURfactant Extubation), in which surfactant is administered during a brief intubation followed by immediate extubation, surfactant therapy can be given during nCPAP treatment further reducing need for mechanical ventilation. In this review the history, current knowledge and techniques of CPAP and surfactant are discussed.

Introduction

Pulmonary disorders represent one of the most common diagnoses in infants admitted to neonatal units. The overall incidence of any form of acute lung disease in the newborn is approximately 3% [1–4]. Respiratory distress syndrome (RDS) and transient tachypnea of the newborn are the most common specific diagnoses, followed by infection/pneumonia. As expected, the incidence of respiratory disorders increases with decreasing gestational age and birth weight [5]. In infants with birth weight between 501 and 1,500 g more than 50% have signs of RDS, increasing to almost 90% in infants below 750 g [6, 7]. Over the last three decades neonatal care has changed dramatically. Improvement in ventilatory support, antenatal corticosteroid treatment and the introduction of exogenous surfactant replacement are major contributors to the greatly reduced morbidity and mortality from neonatal lung disease. Antenatal corticosteroid treatment clearly reduces the incidence of RDS in randomized controlled trials [8, 9]. However, in the few population-based, epidemiological trials available, the overall incidence of RDS remains at about 1% [3, 4]. The explanation for this may be the increasing numbers of viable extremely premature infants. In a recent study from northern Finland the overall incidence of RDS did not change significantly during 1990–1995 compared to 1996–1999, although a shift towards increasing numbers of more immature infants was

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1661–7800/08/0934–0309$24.50/0

Accessible online at:
www.karger.com/neo

Mats Blennow, MD, PhD
Department of Neonatology, K78
Karolinska University Hospital Huddinge
SE–141 86 Stockholm (Sweden)
Tel. +46 8 585 81428, Fax +46 8 585 87545, E-Mail mats.blennow@ki.se

noted [10]. The changing patient population creates a challenge in understanding and applying the optimal respiratory management for the individual infant.

RDS is caused by a developmental deficiency of pulmonary surfactant [11]. In addition, RDS is associated with delayed absorption of fetal lung water due to defective sodium transport mechanisms [12]. Although the pathways for surfactant synthesis are present, the surfactant stores are insufficient until approximately 32 weeks of gestation and, in consequence, the greatest risk factor for RDS is prematurity. The elevated surface tension resulting from surfactant deficiency leads to alveolar collapse at the end of expiration, atelectasis, uneven inflation and regional alveolar overdistension, which produces epithelial injury and pulmonary edema. Superimposed lung injury from mechanical ventilation and high concentrations of inspired oxygen may trigger the release of proinflammatory cytokines which further impair surfactant function and predispose to the development of chronic lung injury [13]. Surfactant replacement treatment significantly reduces mortality in infants with RDS [14]. The introduction of surfactant therapy in the US was reflected in an accelerated reduction in mortality from RDS and was the single most important factor for the decrease in overall neonatal mortality rate in the early 1990s [15]. Despite the effectiveness of surfactant treatment in the acute phase of RDS and new ventilation techniques such as high frequency oscillation and volume target ventilation, bronchopulmonary dysplasia (BPD) remains an important adverse outcome in preterm infants and its incidence is correlated with use of mechanical ventilation [16]. Continuous positive airway pressure (CPAP) is a means of providing respiratory support without mechanical ventilation. CPAP stabilizes the chest wall, reduces airway resistance and increases functional residual capacity, thereby improving lung volumes and oxygenation [17]. Infants with mild RDS can often be managed on CPAP alone without the need for surfactant treatment [18, 19]. There are data from animal studies suggesting that CPAP elicits an attenuated inflammatory response in alveolar washes compared to mechanical ventilation [20] and that surfactant treatment followed by CPAP results in less severe morphological lung injury than surfactant together with mechanical ventilation [21]. Although physiologically appealing and, in parts of the world, associated with positive clinical experiences and outcomes, CPAP as a primary respiratory support option for preterm infants with RDS remains controversial due to lack of data on effectiveness from recent randomized trials [22].

Early CPAP Experiences

Gregory et al. [23] first introduced CPAP for newborns in 1971. In the original paper the pressure was delivered by endotracheal tube to 18 infants and via a head chamber to the remaining 2 infants in the study. At this time ventilators were not designed for newborns and mechanical ventilation was only used as an ultimate refuge often with very poor outcome. The head chamber or so-called Gregory box rapidly gained interest around the world and its effectiveness was striking. Mortality in RDS decreased by more than half, from 35–55 to 15–20% [24]. In the late 1970s and 1980s the focus for respiratory care shifted towards mechanical ventilation, partly due to the rapid development of infant ventilators and thus the use of CPAP declined. In Scandinavia however, the tradition of early CPAP was maintained. A variety of devices and strategies to apply CPAP have been used, including face masks, nasal prongs, nasopharyngeal tube and endotracheal tube. CPAP with short nasal prongs is advantageous because it is relatively atraumatic, intubation is avoided and access to the baby is allowed, as opposed to CPAP with a face mask. With the newer, improved nasal prongs increased work of breathing is no longer a significant obstacle [25]. In Scandinavia two devices have been predominant: the Benveniste valve and the Östersund-CPAP, the latter developed into the Infant Flow Driver [26].

New Interest in CPAP

With increasing appreciation of the 'open lung concept' in RDS and the role of mechanical ventilation in the development of lung injury and chronic lung disease, the use of early nasal CPAP (nCPAP) as a primary respiratory support in preterm infants is again gaining interest worldwide. In 1987, Avery et al. [27] in a survey of 8 North American neonatal units found the lowest incidence of BPD in the center practicing early nCPAP instead of initial mechanical ventilation. Horbar et al. [28] later confirmed these results, and van Marter et al. [16] reported that after multivariate analyses to adjust for baseline risk, most of the increased risk for BPD among very-low-birthweight infants could be explained simply by the initiation of mechanical ventilation. A recent bi-center study comparing infants with gestational age <28 weeks in Boston and Stockholm revealed that in Boston, where all infants were primarily intubated in the delivery room and CPAP was used less often compared to Stockholm, significantly more infants required oxygen supplementation at 40

weeks [29], suggesting better outcomes with the less invasive approach. In a previous survey from Stockholm of all infants below 1,500 g birth weight, 59% of infants were managed with early nCPAP or supplemental oxygen as their sole respiratory support. Failure of nCPAP and need for mechanical ventilation was significantly associated with presence of RDS and gestational age <27 weeks [30]. This illustrates the importance of surfactant supplementation in this group of infants and indeed the numbers requiring mechanical ventilation can be reduced by implementing a protocol such as INSURE (see below) [31]. Among the few randomized studies, Tooley and Dyke [32] recently confirmed that even very preterm infants could be successfully managed with nCPAP after surfactant treatment. However, for very preterm infants it remains uncertain whether it is better to initiate mechanical ventilation from birth or use nCPAP as the primary intervention [22]. Reports from the COIN study of 610 infants born at 25–28 weeks of gestation showed that almost half of the infants in the CPAP group required intubation during the first 5 days of life [33]. Despite that, the odds ratio for death or oxygen treatment at 28 days favored early CPAP over mechanical ventilation. Other outcome measures were similar, apart from pneumothorax, which was increased with CPAP. These results suggest that even very preterm infants may benefit from early CPAP.

Nursing during CPAP

Good quality nursing during CPAP care is of uttermost importance. The success of the treatment relies on optimal positioning of the baby, maintaining patency of the upper airways and avoiding loss of the positive airway pressure. The latter is especially important during delivery of CPAP through nasal prongs, when opening of the mouth frequently results in loss of airway pressure. Key points for CPAP nursing care are given in table 1. A baby under optimal CPAP care is shown in figure 1.

How we wean from CPAP is an important, but often neglected role influencing the final result. Weaning by slowly reducing CPAP pressures has been shown to be superior to weaning by time pauses, often referred to as 'training' the infant off CPAP [34]. Logically, pausing can result in alternating hyperinflation with collapse of alveoli (atelectotrauma) known to be associated with development of BPD.

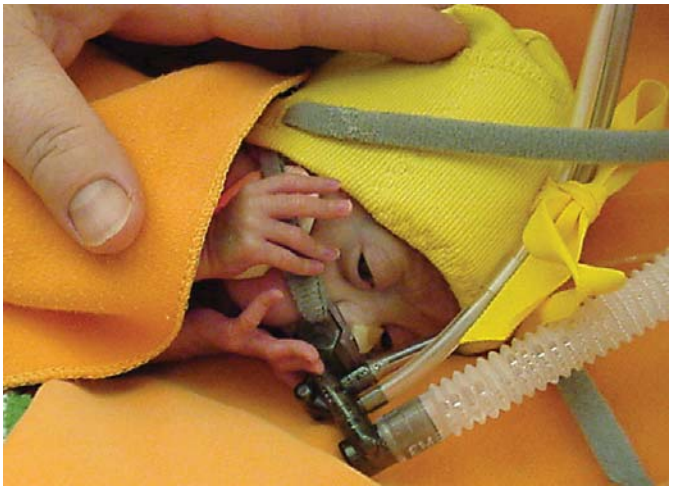

Fig. 1. CPAP and nursing. Extremely preterm infant during nCPAP care. Please note loose fitting of nasal prongs, comfortable nesting and positioning of infant.

Table 1. Key points for CPAP nursing care

– Infants on CPAP are completely dependent on open nasal passages.
– Find the optimal body position for the infant (NIDCAP).
– Use preterm pacifier to minimize loss of pressure from open mouth.
– Try to avoid suctioning the nose and use saline drops instead, then suction the oropharynx.
– Use adequate humidification of gases.
– Avoid using excessive force when fixating the nasal prongs.
– The nosepiece should not be pulled tightly against the nose, rather positioned from under the nose.
– Use the largest size prong that will sit without support in the nose.
– Inspect the fixation when you see that the nosepiece is pressing too tightly against the nose or the CPAP pressure is difficult to hold.
– Change to a larger prong as the baby grows.

Surfactant Era

The story of surfactant research began in 1929 with von Neergaard demonstrating that lowering surface tension of the air/liquid interface stabilized the alveoli [35]. Later, in 1955 Pattle described an insoluble layer that could abolish the tension of the alveolar surface [36]. A couple of years later Clements showed that compression of surface films from animal lung extracts lowered sur-

face tension providing the first demonstration of surface active material from the lung [37, 38]. Before that, in 1903, Hochheim described hyaline membranes in the lungs of infants with respiratory distress [39]. In the late 1940s and 1950s hyaline membrane disease was recognized as the most common cause of death in preterm infants. The hallmark of the disease, the histological finding of hyaline membranes, was not seen at birth but they formed soon afterwards as a result of atelectasis and lung injury. Gruenwald [40] first proposed the linkage between elevated surface tension and hyaline membrane formation in 1947. This was confirmed in 1959 when Avery and Mead showed that lung extracts from preterm infants dying of hyaline membrane disease were unable to lower surface tension, and they associated this with deficiency of surface active material [11]. In the 1960s pulmonary surfactant underwent further biochemical and functional characterization. During the 1970s ground-breaking experimental work of surfactant replacement in animal models performed by Robertson and Enhörning [41–45] led to the first successful trial of endotracheal surfactant administration to preterm infants with RDS in 1980 by Fujiwara et al. [46]. The efficacy and safety of surfactant therapy was further established by several multicenter trials which showed that it dramatically decreased neonatal mortality and pulmonary air leaks [47–51]. In 1990, the American Food and Drug Administration approved the clinical use of exogenous surfactant and since then it has become one of the cornerstones in the care of preterm infants with RDS.

Since the first report of successful surfactant replacement in preterm infants by Fujiwara et al. [46], more than 35 randomized controlled clinical trials, enrolling over 7,000 infants, have been performed [14, 52]. Surfactant treatment has universally been proven to reduce the need for supplemental oxygen and ventilatory support, decrease the incidence of air leaks and mortality from RDS [15, 53] as well as the risk of neonatal death [54]. In contrast to the great impact on mortality, the incidence of CLD or BPD has not been consistently shown to be decreased [55]. A change in the clinical pattern of BPD has taken place during the surfactant era as the smaller and more immature infants have come to constitute the majority of cases with BPD [56]. The term 'new BPD' has been coined to indicate this change in pathophysiology. However, there is evidence that surfactant treatment reduces the incidence of BPD in infants with a birth weight over 1,250 g [57]. This may imply that barotrauma and volutrauma are more important risk factors for BPD in the more mature infants whereas factors such as developmentally impaired alveolarization and vascularization, poor nutrition and recurrent infections are likely to have a greater impact in very preterm infants.

Combining Surfactant and CPAP

CPAP alone may attenuate the signs of RDS, but in more severe cases surfactant treatment is imperative. In Scandinavia, where nCPAP is traditionally used as the primary respiratory support, a new treatment approach with administration of exogenous surfactant during a brief intubation, followed by immediate extubation to nCPAP, has been implemented. Victorin et al. [58] performed the first study of surfactant treatment in spontaneously breathing infants in Kuwait, at a center where mechanical ventilation was not available. Fourteen newborns with a mean gestational age of 32 weeks and severe RDS were treated with intratracheal bolus doses of surfactant and immediately extubated. Twelve responded with a rapid improvement in oxygenation that was sustained over the 72-hour observation period. In 1994, the Danish group of Verder et al. [59] published the first randomized controlled trial of surfactant instillation during nCPAP and showed that the subsequent need for mechanical ventilation could be reduced by half, from 85% without surfactant to 43% with surfactant treatment. The effect was even more pronounced when the treatment was given early in the course of the disease [60]. Dani et al. [61] recently reported the results of a prospective randomized study showing that immediate reinstitution of nCPAP after surfactant administration reduced the duration of oxygen therapy, need for mechanical ventilation and need for a second dose of surfactant. In Stockholm, a treatment protocol modified from the Danish strategy is used – INSURE (i.e. INtubation, SURfactant Extubation).

The INSURE protocol was implemented in 1998, and a retrospective follow-up recently published [31]. Similar to previous studies, we found that the need for mechanical ventilation was reduced by 50%. The overall use of surfactant increased after introduction of INSURE which is consistent with the most recent meta-analysis comparing early surfactant administration with brief mechanical ventilation to later, selective surfactant treatment followed by continued mechanical ventilation [62]. The provision of surfactant treatment to more patients is a desirable effect associated with INSURE and may have contributed to the reduction in mechanical ventilation rate. Repeated doses of surfactant were rarely needed, an

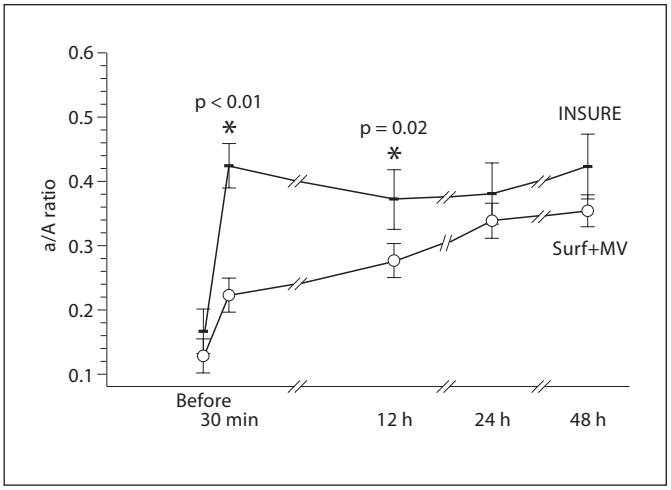

Fig. 2. Oxygenation after INSURE. Infants receiving INSURE treatment and infants receiving conventional surfactant treatment followed by mechanical ventilation (Surf+MV). The oxygenation, as determined by the arterial to alveolar (a/A) ratio, was similar at time of surfactant administration and improved following treatment. In INSURE-treated infants the immediate improvement in oxygenation 30 min after treatment was more pronounced compared to Surf+MV infants, shown by a significantly higher a/A ratio ($p < 0.01$). The improved oxygenation was sustained after INSURE over the 48 h following surfactant treatment. * Indicates significant differences with a $p < 0.05$.

observation also noted in the Danish and Italian studies [59, 60]. Surfactant treatment improved oxygenation in all subjects, but the treatment response appeared to be augmented and sustained after INSURE compared to that in infants given surfactant followed by mechanical ventilation (fig. 2). This observation has been tested in an experimental rabbit study which showed increased surfactant inactivation by lipid peroxidation and impaired lung function, measured as dynamic compliance, after mechanical ventilation compared to spontaneous breathing [63].

Conclusion and Future Directions

Early nCPAP, mechanical ventilation and surfactant treatment are all established interventions for preterm infants with RDS. The methods complement each other, but the question of an optimal strategy remains unanswered. The success of CPAP care is very dependent on experience and therefore adequate training of both medical and nursing staff is essential. To date neither early nCPAP nor mechanical ventilation can be said to be superior. The ability to give surfactant during nCPAP appears to be important in very preterm infants and more mature infants with severe RDS. INSURE provides a safe means to administer surfactant to infants on CPAP. Although not yet shown to be effective, aerosolized surfactant may in future become available and there are reports of less invasive surfactant administration through a feeding catheter without intubation [64]. More evidence is clearly needed, although in Scandinavia the long-standing practice of early nCPAP makes randomized trials ethically difficult and the hope is that ongoing studies from other parts of the world, such as the CURPAP study [65], will provide answers to the remaining questions regarding the benefits and risks of nCPAP treatment in preterm infants.

Acknowledgements

The authors wish to thank the neonatal staff at Karolinska, Huddinge and Solna Hospitals for their support and skilled care of these infants.

This work was supported by grants from the Swedish Society of Medicine, the Swedish Freemasons in Stockholm Foundation for Children's Welfare and the Jerring Foundation.

References

1 Bonafe L, Rubaltelli FF: The incidence of acute neonatal respiratory disorders in Padova county: an epidemiological survey. Acta Paediatr 1996;85:1236–1240.
2 Hjalmarson O: Epidemiology and classification of acute, neonatal respiratory disorders. A prospective study. Acta Paediatr Scand 1981;70:773–783.
3 Field DJ, Milner AD, Hopkin IE, Madeley RJ: Changing patterns in neonatal respiratory diseases. Pediatr Pulmonol 1987;3:231–235.
4 Rubaltelli FF, Dani C, Reali MF, Bertin G, Wiechmann I, Tangucci M, Spagnolo A: Acute neonatal respiratory distress in Italy: a one-year prospective study. Italian Group of Neonatal Pneumology. Acta Paediatr 1998;87:1261–1268.

5 Chard T, Soe A, Costeloe K: The risk of neonatal death and respiratory distress syndrome in relation to birth weight of preterm infants. Am J Perinatol 1997;14:523–526.
6 Hack M, Fanaroff AA: Outcomes of extremely-low-birth-weight infants between 1982 and 1988. N Engl J Med 1989;321:1642–1647.
7 Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L: Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. Pediatrics 1991;87:587–597.
8 Crowley P, Chalmers I, Keirse MJ: The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1990;97:11–25.
9 Kari MA, Hallman M, Eronen M, Teramo K, Virtanen M, Konisto M, Ikonen RS: Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. Pediatrics 1994;93:730–736.
10 Koivisto M, Marttila R, Kurkinen-Raty M, Saarela T, Pokela ML, Joupila P, Hallman M: Changing incidence and outcome of infants with respiratory distress syndrome in the 1990s: a population-based survey. Acta Paediatr 2004;93:177–184.
11 Avery ME, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child 1959;97:517–523.
12 O'Brodovich H: Immature epithelial Na^+ channel expression is one of the pathogenic mechanisms leading to human neonatal respiratory distress syndrome. Proc Assoc Am Phys 1996;108:345–355.
13 Dreyfuss D, Saumon G: Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 1998;157:294–323.
14 Soll R: Clinical Trials of Surfactant Therapy in the Newborn; in Robertson B, Taeusch H (eds): Surfactant Therapy for Lung Disease. New York, Marcel Dekker, 1995, pp 407–441.
15 Lee K, Khoshnood B, Wall SN, Chang Y, Hsieh HL, Singh JK: Trend in mortality from respiratory distress syndrome in the United States, 1970–1995. J Pediatr 1999;134:434–440.
16 Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, Susser M, Paneth N, Leviton A: Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. Pediatrics 2000;105:1194–1201.
17 Locke R, Greenspan JS, Shaffer TH, Rubenstein SD, Wolfson MR: Effect of nasal CPAP on thoracoabdominal motion in neonates with respiratory insufficiency. Pediatr Pulmonol 1991;11:259–264.
18 Sandri F, Ancora G, Lanzoni A, Tagliabue P, Colnaghi M, Venturea ML, Rinaldi M, Modello I, Gancia P, Salvioli GP: Prophylactic nasal continuous positive airways pressure in newborns of 28–31 weeks gestation: multicentre randomised controlled clinical trial. Arch Dis Child Fetal Neonatal Ed 2004;89:F394–F398.
19 Kamper J, Wulff K, Larsen C, Lindequist S: Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. Acta Paediatr 1993;82:193–197.
20 Jobe AH, Kramer BW, Moss TJ, Newnham JP, Ikegami M: Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatr Res 2002;52:387–392.
21 Nold JL, Meyers PA, Worwa CT, et al: Decreased lung injury after surfactant in piglets treated with continuous positive airway pressure or synchronized intermittent mandatory ventilation. Neonatology 2007;92:19–25.
22 Subramaniam P, Henderson-Smart DJ, Davis PG: Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. Cochrane Database Syst Rev 2005;3:CD001243.
23 Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK: Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med 1971;284:1333–1340.
24 Dunn PM: Respiratory distress syndrome. Continuous positive airway pressure (CPAP) using the Gregory box. Proc R Soc Med 1974;67:245–247.
25 De Paoli AG, Davis PG, Faber B, Morley CJ: Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database Syst Rev 2002;4:CD002977.
26 Moa G, Nilsson K, Zetterstrom H, Jonsson LO: A new device for administration of nasal continuous positive airway pressure in the newborn: an experimental study. Crit Care Med 1988;16:1238–1242.
27 Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, Epstein MF, Fitzhardinge PM, Hansen CB, Hansen TN, et al: Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26–30.
28 Horbar JD, McAuliffe TL, Adler SM, Albersheim S, Cassady G, Edwards W, Jones R, Kattwinkel J, Kraybill EN, Krishnan V, et al: Variability in 28-day outcomes for very low birth weight infants: an analysis of 11 neonatal intensive care units. Pediatrics 1988;82:554–559.
29 Vanpee M, Walfridsson-Schultz U, Katz-Salamon M, Zupancic JA, Pursley D, Jonsson B: Resuscitation and ventilation strategies for extremely preterm infants: a comparison study between two neonatal centers in Boston and Stockholm. Acta Paediatr 2007;96:10–16; discussion 8–9.
30 Jonsson B, Katz-Salamon M, Faxelius G, Broberger U, Lagercrantz H: Neonatal care of very-low-birthweight infants in special-care units and neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation: gains and losses. Acta Paediatr 1997;419(suppl):4–10.
31 Bohlin K, Gudmundsdottir T, Katz-Salamon M, Jonsson B, Blennow M: Implementation of surfactant treatment during continuous positive airway pressure. J Perinatol 2007;27:422–427.
32 Tooley J, Dyke M: Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatr 2003;92:1170–1174.
33 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;358:700–708.
34 Singh S, Bowe L, Clarke P, Glover K, Pasquill A, Robinson MJ, Smith J: Is decreasing pressure or increasing time off the better strategy in weaning VLBW infants from nasal CPAP (abstract)? Europediatrics, Barcelona, October 2006.
35 Neergaard V: Neue Auffassungen über einen Grundbegriff der Atemmechanik. Z Gesamte Exp Med 1929;66:373–394.
36 Pattle RE: Properties, function and origin of the alveolar lining layer. Nature 1955;175:1125–1126.
37 Clements JA: Surface tension of lung extracts. Proc Soc Exp Biol Med 1957;95:170–172.
38 Clements JA, Brown ES, Johnson RP: Pulmonary surface tension and the mucus lining of the lungs: some theoretical considerations. J Appl Physiol 1958;12:262–268.
39 Hochheim K: Über einige Befunde in den Lungen von Neugeborenen und die Beziehung derselben zur Aspiration von Fruchtwasser. Centralbl Pathol 1903;14:537–538.
40 Gruenwald P: Surface tension as a factor in resistance of neonatal lung to aeration. Am J Obstet Gynecol 1947;53:996–1007.
41 Enhörning G, Grossman G, Robertson B: Tracheal deposition of surfactant before the first breath. Am Rev Respir Dis 1973;107:921–927.
42 Enhörning G, Grossmann G, Robertson B: Pharyngeal deposition of surfactant in the premature rabbit fetus. Biol Neonate 1973;22:126–132.
43 Enhörning G, Robertson B: Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. Pediatrics 1972;50:58–66.

44 Enhörning G, Robertson B, Milne E, Wagner R: Radiologic evaluation of the premature newborn rabbit after pharyngeal deposition of surfactant. Am J Obstet Gynecol 1975;121: 475–480.
45 Robertson B, Enhörning G: The alveolar lining of the premature newborn rabbit after pharyngeal deposition of surfactant. Lab Invest 1974;31:54–59.
46 Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T: Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980;1: 55–59.
47 Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. Collaborative European Multicenter Study Group. Pediatrics 1988;82:683–691.
48 Merritt TA, Hallman M, Bloom BT, Berry C, Bernirschke K, Sahn D, Key T, Edwards D, Jarvenpaa AL, Pohjavuori M, et al: Prophylactic treatment of very premature infants with human surfactant. N Engl J Med 1986; 315:785–790.
49 Soll RF, Hoekstra RE, Fangman JJ, Corbet AJ, Adams JM, James LS, Schulze K, Oh W, Roberts JD Jr, Dorst JP, et al: Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. Ross Collaborative Surfactant Prevention Study Group. Pediatrics 1990;85:1092–1102.
50 Hallman M, Merritt TA, Jarvenpaa AL, Boynton B, Mannino F, Gluck L, Moore T, Edwards D: Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. J Pediatr 1985;106:963–969.
51 Fujiwara T, Konishi M, Chida S, Okyama K, Ogawa T, Takeuchi Y, Nishida H, Kito H, Fujimura, Nakamura H, et al: Surfactant replacement therapy with a single postventilatory dose of a reconstituted bovine surfactant in preterm neonates with respiratory distress syndrome: final analysis of a multicenter, double-blind, randomized trial and comparison with similar trials. The Surfactant-TA Study Group. Pediatrics 1990;86: 753–764.
52 Hallman M, Merritt T, Bry K: The fate of exogenous surfactant in neonates with respiratory distress syndrome. Clin Pharmacokinet 1994;26:215–232.
53 Liechty EA, Donovan E, Purohit D, Gilhooley J, Feldman B, Noguchi A, Denson SE, Sehgal SS, Gross I, Stevent D, et al: Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. Pediatrics 1991;88:19–28.
54 Halliday H, Speer CP: Strategies for surfactant therapy in established neonatal respiratory syndrome; in Robertson B, Taeusch HW (eds): Surfactant Therapy for Lung Disease. New York, Marcel Dekker, 1995, pp 443–454.
55 Soll RF, Morley CJ: Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001;2: CD000510.
56 Jobe AH, Bancalari E: Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001; 163:1723–1729.
57 Long W, Corbet A, Cotton R, Courtney S, McGuinness G, Walter D, Watts J, Smyth J, Bard H, Chernick V: A controlled trial of synthetic surfactant in infants weighing 1,250 g or more with respiratory distress syndrome. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal Study Group. N Engl J Med 1991; 325:1696–1703.
58 Victorin LH, Deverajan LV, Curstedt T, Robertson B: Surfactant replacement in spontaneously breathing babies with hyaline membrane disease – a pilot study. Biol Neonate 1990;58:121–126.
59 Verder H, Robertson B, Greisen G, et al: Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994;331:1051–1055.
60 Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, Agertoft L, Djernes B, Nathan E, Reinholdt J: Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103:E24.
61 Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli F: Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks gestation. Pediatrics 2004; 113:560–563.
62 Stevens TP, Harrington EW, Blennow M, Soll RF: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007;4:CD003063.
63 Bohlin K, Bouhafs RK, Jarstrand C, Curstedt T, Blennow M, Robertson B: Spontaneous breathing or mechanical ventilation alters lung compliance and tissue association of exogenous surfactant in preterm newborn rabbits. Pediatr Res 2005;57:624–630.
64 Kribs A, Pillekamp F, Hunseler C, Vierzig A, Roth B: Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age ≤27 weeks). Paediatr Anaesth 2007;17:364–369.
65 Sandri F, Plavka R, Simeoni U: The CURPAP Study: an international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants. Neonatology 2008;94: 60–62.