Respiratory support in the newborn

Respiratory support of the newborn infant is a challenging situation in neonatology. The immature lung is especially prone to develop bronchopulmonary dysplasia (BPD), a multifactor disease related to the use of mechanical ventilation and oxygen therapy in very preterm newborn infants. The role of respiratory support is still not well established, but the evidence suggests that less invasive respiratory support is associated with the highest survival without BPD. Different modalities of respiratory support will be discussed in terms of improving lung function with a low risk of lung damage.

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Key points

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1. Noninvasive respiratory support can decrease the risk of lung damage in preterm infants, but nasal CPAP alone is probably not enough to prevent bronchopulmonary dysplasia.
2. Exogenous surfactant administration in combination with noninvasive respiratory support appears to be an effective therapy in preterm infants with RDS.
3. Noninvasive mechanical ventilation, synchronised with the patient, can decrease the need for invasive mechanical ventilation and also probably the risk of BPD.
4. New invasive respiratory support systems adapted to the patient's needs will probably decrease ventilator-induced lung injury and decrease the duration of mechanical ventilation.

At delivery, transition from *in utero* to postnatal respiration occurs. In a term baby, a well developed lung is made ready to breathe shortly after birth. The fetal lung is involved in many physiological mechanisms but not in blood gas exchange. Fluid production is one of the most important functions of *in utero* lungs, and this production contributes to amniotic fluid formation and also to the growth and development of the fetal lung[1]. A few days/hours before delivery the production of fluid is decreased due to the effect of endogenous catecholamine enabling rapid clearance of lung fluid at birth allowing gas transfer[2]. Not only is a well-developed lung important to postnatal function, but also a lung which produces adequate amounts of surfactant, and has an effective antioxidant system.

Due to premature delivery an immature and growing lung sometimes has to begin breathing having an inadequate anatomy and also an insufficient surfactant and antioxidant content. This means that respiratory support is required in the premature newborn infant immediately or shortly after delivery[3]. However respiratory support, particularly mechanical ventilation, can damage the fragile and immature lung contributing to the development of bronchopulmonary dysplasia (BPD), the chronic lung disease of neonates[4-6].

Much has evolved in the knowledge of prevention of BPD, and new techniques of respiratory support aim to do this, by helping the premature infant to breathe but decreasing the risk of lung damage and BPD.

Lung physiology following delivery

Establishing the lung residual capacity is a difficult problem in an immature and wet lung, and once the lung is open, keeping the gas in the lung and recruiting enough numbers of air spaces is a challenging situation. In the term and near term newborn, this is normally done by decreasing the intrathoracic pressure at birth using the respiratory muscles. Once the air comes into the lungs, two important mechanism are involved in keeping air in the lung[7]:

- pulmonary surfactant – which keeps the airspaces open by counteracting the high surface tension forces within the alveoli, preventing differential inflation of the alveoli and decreasing the work of breathing
- closure of the glottis during expiration. After decreasing the intrathoracic pressure in the thorax during the first inspiration, the glottis closes before expiration is finished and with the glottis closed the respiratory muscles continue to contract, dramatically increasing the intrathoracic pressure[7]. This high pressure equalises across the lungs and overcomes the opening pressure of most of the air spaces so they open and remain open.

Both mechanisms are important for alveolar recruitment in the normal lung after delivery, but are probably even more important in the immature lung, where the amount and quality of endogenous surfactant is inadequate and the closing pressure of the lung is higher.

Institution of mechanical ventilation from the first minutes of life by

introduction of an endotracheal tube prevents this normal mechanism occuring after delivery, and may lead to "induced" respiratory distress syndrome (RDS), increasing inflammation and triggering some of the mechanisms involved in the genesis of BPD[8].

Thus prevention of intubation and mechanical ventilation is desirable to decrease the risk of RDS and BPD[9]. However supporting the immature lungs of the preterm newborn without damaging them is one of the most difficult questions to be resolved[4-6].

Nasal CPAP

At present there is limited evidence from clinical trials, but data from the literature suggests that some of the smallest preterm newborns can be supported from delivery with nasal continuous positive airway pressure (nCPAP)[10] or noninvasive positive pressure ventilation (nIPPV) to protect their lungs[11] (**FIGURE 1**). Using this noninvasive approach from delivery decreases the need for invasive mechanical ventilation and exogenous surfactant administration, but there is conflicting data regarding the effect on BPD. There is currently a large randomised trial of NIPPV versus CPAP underway to answer whether or not NIPPV is genuinely better at reducing BPD (NIPPV Trial).

Nasal CPAP has been used for many years and was first described by Gregory and colleagues in 1971[12] to obviate the need for intubation, to prevent reintubation after extubation and to treat apnoea of prematurity. There are basically two different mechanisms to generate CPAP – by increasing pressure using flow or by increasing pressure using resistance:

- The high flow devices use a low resistance in the expiratory limb of the circuit and increase pressure with flow by generating a differential jet effect. The classical device of this group is the Benveniste jet device[13]. The Infant Flow Driver (IFD) system is a sophisticated variation of the Benveniste jet device, where pressure is generated at the nasal level, by a generator connected directly to short binasal prongs. By adjusting the flow, pressure is controlled.
- Bubble CPAP is a traditional mechanism, introduced in the early 1970s, which provides pressure support by increasing the resistance via underwater gas bubbling.

Although there is not enough evidence to determine which of these mechanisms for creating nCPAP is better, some authors do prefer the IFD[14,15].

FIGURE 1 Extremely low birthweight baby on CPAP using infant flow driver system.

Humidified high flow nasal cannula can also generate pressure at the nasal prongs but it is not a recommended method due to the difficulty in knowing exactly what pressure has been generated and the lack of clinical evidence. More studies need to be done before this therapy can be recommended in preterm infants[16,17]. Different nasal interfaces have been used, but the short binasal prong devices are more effective than single prongs in reducing the likelihood of the short-term adverse outcomes of re-intubation and respiratory failure[18].

Although nasal CPAP can be effectively used even in extremely preterm infants, to prevent intubation at delivery, not all preterm newborns can be managed in this way. Failures of using only nCPAP occur because of the need to treat RDS with surfactant, which requires intubation, and also because of apnoea or inadequate respiratory effort[10-19].

Also using only nCPAP can lead in some instances to an increase in the risk of air-leaks and pneumothorax, and there is no evidence that BPD is decreased.

Nasal CPAP and surfactant administration

It has been shown that with the decrease in the use of invasive mechanical ventilation, there is a decrease in the use of surfactant in preterm infants, but probably there is a trend of increasing the risk of BPD[20]. The combined effect of prompt extubation to nCPAP after surfactant administration has been demonstrated to be effective, compared to nCPAP alone, in decreasing the need for invasive mechanical intubation with a trend of reducing the risk of BPD in a group of preterm infants with a gestational age of 27 to 32 weeks[21].

So the combined effect of nCPAP with surfactant administration soon after delivery would appear to be a good approach to managing RDS. The question then is how to select the target population which requires surfactant – not only to decrease the number of preterm infants who receive surfactant and do not need it, but because the administration of surfactant needs to be done through an endotracheal tube, although there are some instances from the literature of giving surfactant without intubation[22].

A recommended approach is to give surfactant when the FiO_2 is 45% or higher, but also any time there is a need for intubation in the preterm infant[23] and probably the earlier the surfactant is given the more effective it is.

Synchronous non-invasive mechanical ventilation

Nasal CPAP relies on the spontaneous minute ventilation generated by the patient to be effective, so in some instances sending pressure cycles of ventilation through a nasal interface can be a better support to the infant. There is some evidence to show that noninvasive ventilation produces less inflammation compared to conventional invasive ventilation in neonatal animal models [24].

These pressure cycles can be sent to the

patient by a classical intermittent positive pressure ventilator (IPPV), and some authors have demonstrated a beneficial effect of this modality of ventilation[25-27]. The efficacy of this noninvasive ventilation can be improved, and some of the side effects described reduced, by synchronising the positive pressure of the device with the inspiration of the infant[28,29].

Some studies have demonstrated the efficacy of this ventilation in preventing re-intubation after invasive mechanical ventilation and also there is some evidence that this synchronous noninvasive mechanical ventilation can be effective in decreasing the risk of BPD[30,31]. The difficulty lies in the sensitivity of the triggering device detecting the inspiratory effort of the most premature infants with the highest risk of BPD. There are some devices that have demonstrated this efficacy, but large randomised controlled trials are still needed[32].

High frequency mechanical ventilation (HFV)

This modality of using a high continuous distending pressure to recruit the lungs, improving oxygenation and using an infra-tidal ventilation (using tidal volumes smaller than the anatomical dead space delivered at a very high rate of 180 to 900 cycles per minute), to decrease arterial $PaCO_2$, was initially demonstrated in immature animal models of RDS to be an efficient mode of ventilation with a decreased risk of lung damage. There is even some evidence that noninvasive HFV in a premature animal model with RDS can cause less injury compared to conventional mechanical ventilation[33].

This HFV was expected to result in less mortality and less BPD, when used as the primary mode of ventilation in the treatment of RDS in preterm infants, but clinical trials failed to demonstrate such an effect, so there is no evidence that using elective HFV, soon after delivery, can decrease lung injury[34].

Caution should be taken when comparing HFV to conventional ventilation, as HFV can be superior or not depending on how the conventional ventilation is managed. Dani and coworkers[35] using a low PEEP ($3cmH_2O$) and a fast rate in assist/control mode with a Dräger Babylog 8000plus, demonstrated that HFV induced less inflammatory response in the airways compared to conventional mechanical ventilation. However Lista and coworkers[36] found that conventional ventilation with higher PEEP ($5cmH_2O$) and a slow rate backup of the ventilator, enabling the infant to trigger the ventilation in each cycle, induced less inflammation than HFV. So currently we can only say that elective HFV is not necessarily preferred to conventional ventilation in the preterm infant.

Since the current trend of respiratory support is to be as less invasive as possible, HFV is often used as a rescue therapy in most neonatal intensive care units. However even as a rescue therapy, there is not much evidence of its superiority over conventional ventilation. Each HFV device is different, but the most important variable in decreasing $PaCO_2$ is the tidal volume generated by the HFV device[37]. There is a great advantage in monitoring HFV tidal volume, particularly in very preterm infants in whom the risk of brain damage due to changes in $PaCO_2$ is higher. Some devices such as the Dräger Babylog 8000plus can measure it, and the new Dräger VN500 can also adapt the oscillatory pressure (delta pressure) to keep constant the tidal volume and prevent excessive variations in $PaCO_2$.

These new strategies, such as volume guarantee during HFV, should be studied in clinical trials, but look promising as a method of decreasing the possible deleterious effect of variations in tidal volume and $PaCO_2$.

New modalities in conventional ventilation

Patient-triggered ventilation was introduced in newborn ventilators a few years ago, and there is evidence to show that this has advantages over controlled non-triggered ventilation. These benefits are not related to an improvement in survival, but to a decrease in the pressure needed to deliver the tidal volume, as the patient when triggering the ventilator decreases the pressure. There is a decreased risk of asynchrony with the ventilator, a lower risk of air leak, and a shorter duration of mechanical ventilation, among other advantages[38].

Giving the patient the possibility of maintaining minute volume by modifying the spontaneous respiratory frequency is one of the most important improvements in respiratory support for neonates during the last decade. This can be done with assist/control or inspiratory flow synchronisation. Again, to achieve the best synchronisation between the ventilator and the patient, the trigger should be of a high sensitivity and a short delay time in response. Pressure support ventilation (PSV) also modifies the inspiratory time as needed, to ensure enough time to equalise the pressure in the pressure-limiting ventilation modality, or to send the programmed tidal volume in volume-setting ventilation.

So a great advantage has been achieved by enabling the patient to spontaneously control minute ventilation, the duration of the inspiratory time, and decreasing the breath-to-breath tidal volume variation with the new volume objective ventilation. Volume guarantee is probably the most sophisticated method as it uses the expiratory tidal volume to adjust the next inspiratory pressure as needed, weaning the patient as the lung mechanics and the work of breathing improve[39]. New ventilatory modalities, tested a few years ago[40] are now available, using the concept of minute volume guarantee, so that more physiological ventilation can be provided.

New ventilators will hopefully adapt to the patient's needs, not only as or if the lung improves, but also as the metabolic demands change over the day. Using these new modalities it is clear that more comprehensive ventilation can be provided to the patients associated with a decrease in the damage caused to the lungs.

References

1. **Beall M.H., van den Wijngaard J.P., van Gemert M.J., Ross M.G.** Regulation of amniotic fluid volume. *Placenta* 2007; **28**: 824-32.
2. **Jain L.** Alveolar fluid clearance in developing lungs and its role in neonatal transition. *Clin Perinatol* 1999; **26**: 585-99.
3. **Fanaroff A.A., Stoll B.J., Wright L.L. et al.** NICHD Neonatal Research Network 2007 Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* **196**: 147.e1-148.e1.
4. **Jobe A.H., Hillman N., Polglase G., Kramer B.W., Kallapur S., Pillow J.** Injury and inflammation from resuscitation of the preterm infant. *Neonatology* 2008; **94**: 190-96.
5. **Hillman N.H., Moss T.J., Kallapur S.G. et al.** Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med* 2007; **176**: 575-81.
6. **Hillman N.H., Kallapur S.G., Pillow J.J. et al.** Airway injury from initiating ventilation in preterm sheep. *Pediatr Res* 2010; **67**: 60-65.
7. **Milner A.D., Vyas H.** Lung expansion at birth. *J Pediatr* 1982; **101**: 879-86.
8. **Hutchison A.A., Bignall S.** Non-invasive positive pressure ventilation in the preterm neonate:

reducing endotrauma and the incidence of bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 2008; **93** (1): F64-68.
9. **Jobe A.J.** The new BPD: an arrest of lung development. *Pediatr Res* 1999; **46**: 641-43.
10. **Ammari A., Suri M.S., Milisavljevic V. et al.** Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005; **147**: 341-47.
11. **Davis P.G., Morley C.J., Owen L.S.** Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. *Semin Fetal Neonatal Med* 2009; **14**: 14-20.
12. **Gregory G.A., Kitterman J.A., Phibbs R.H., Tooley W.H., Hamilton W.K.** Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N Engl J Med* 1971; **284**: 1333-40.
13. **Benveniste D., Berg O., Pedersen J.E.** A technique for delivery of continuous positive airway pressure to the neonate. *J Pediatr* 1976; **88**(6): 1015-19.
14. **De Paoli A.G., Morley C.J., Davis P.G., Lau R., Hingeley E.** *In vitro* comparison of nasal continuous positive airway pressure devices for neonates. *Arch Dis Child Fetal Neonatal Ed* 2002; **87**: F42-45.
15. **Courtney S.E., Pyon K.H., Saslow J.G., Arnold G.K., Pandit P.B., Habib R.H.** Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. *Pediatrics* 2001; **107**: 304-08.
16. **Locke R.G., Wolfson M.R., Shaffer T.H., Rubenstein S.D., Greenspan J.S.** Inadvertent administration of positive end-distending pressure during nasal cannula flow. *Pediatrics* 1993; **91**: 135-38.
17. **Dani C., Pratesi S., Migliori C., Bertini G.** High flow nasal cannula therapy as respiratory support in the preterm infant. *Pediatr Pulmonol* 2009; **44**(7): 629-34.
18. **De Paoli A.G., Davis P.G., Faber B., Morley C.J.** Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev* 2008; (1): CD002977.
19. **Morley C.J., Davis P.G., Doyle L.W., Brion L.P., Hascoet J.M., Carlin J.B.** Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med 2008;* **358**: 700-08.
20. **Chong E., Greenspan J., Kirkby S., Culhane J., Dysart K.** Changing use of surfactant over 6 years and its relationship to chronic lung disease. *Pediatrics* 2008; **122**: e917-21.
21. **Rojas M.A., Lozano J.M., Rojas M.X. et al.** Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics* 2009; **123**: 137-42.
22. **Kribs A., Härtel C., Kattner E. et al.** Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. *Klin Padiatr* 2010; **222**: 13-17.
23. **Stevens T.P., Blennow M., Myers E.H., Soll R.** 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, Issue 4. Art. No.: CD003063. DOI: 10.1002/14651858.CD003063.pub3.
24. **Lampland A.L., Meyers P.A., Worwa C.T., Swanson E.C., Mammel M.C.** Gas exchange and lung inflammation using nasal intermittent positive-pressure ventilation versus synchronized intermittent mandatory ventilation in piglets with saline lavage-induced lung injury: an observational study. *Crit Care Med* 2008; **36**: 183-87.
25. **Lemyre B., Davis P.G., De Paoli A.G.** Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. Cochrane Database Syst Rev 2002, Issue 1. Art. No.: CD002272. DOI: 10.1002/14651858.CD002272.
26. **Sai Sunil Kishore M., Dutta S., Kumar P.** Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr* 2009; **98**: 1412-15.
27. **Pantalitschka T., Sievers J., Urschitz M.S., Herberts T., Reher C., Poets C.F.** Randomised crossover trial of four nasal respiratory support systems for apnoea of prematurity in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**: F245-48.
28. **Bhandari V., Finer N.N., Ehrenkranz R.A. et al.** Synchronized nasal intermittent positive-pressure ventilation and neonatal outcomes. *Pediatrics* 2009; **124**: 517-26.
29. **Moretti C., Giannini L., Fassi C., Gizzi C., Papoff P., Colarizi P.** Nasal flow-synchronized intermittent positive pressure ventilation to facilitate weaning in very low-birthweight infants: unmasked randomized controlled trial. *Pediatr Int* 2008; **50**: 85-91.
30. **Bhandari V., Gavino R.G., Nedrelow J.H. et al.** A randomized controlled trial of synchronized nasal intermittent positive pressure ventilation in RDS. *J Perinatol* 2007; **27**: 697-703.
31. **Kugelman A., Feferkorn I., Riskin A., Chistyakov I., Kaufman B., Bader D.** Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. *J Pediatr* 2007; **150**(5): 521-6, 526.e1.
32. **Owen L.S., Morley C.J., Davis P.G.** Neonatal nasal intermittent positive pressure ventilation: what do we know in 2007? *Arch Dis Child Fetal Neonatal Ed* 2007; 92: F414-18.
33. **McCulloch P.R., Forkert P.G., Froese A.B.** Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis* 1988; **137**: 1185-92.
34. **Cools F., Henderson-Smart D.J., Offringa M., Askie L.M.** Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2009; (3): CD000104.
35. **Dani C., Bertini G., Pezzati M. et al.** Effects of pressure support ventilation plus volume guarantee vs. high-frequency oscillatory ventilation on lung inflammation in preterm infants. *Pediatr Pulmonol* 2006; **41**(3): 242-49.
36. **Lista G., Castoldi F., Bianchi S., Battaglioli M., Cavigioli F., Bosoni M.A.** Volume guarantee versus high-frequency ventilation: lung inflammation in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F252-56.
37. **Zimová-Herknerová M., Plavka R.** Expired tidal volumes measured by hot-wire anemometer during high-frequency oscillation in preterm infants. *Pediatr Pulmonol* 2006; **41**: 428-33.
38. **Greenough A., Dimitriou G., Prendergast M., Milner A.D.** Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev* 2008, Issue 1. Art. No.: CD000456. DOI: 10.1002/14651858.CD000456.pub3.
39. **Grover A., Field D.** Volume-targeted ventilation in the neonate: time to change? *Arch Dis Child Fetal Neonatal Ed* 2008; **93**(1): F7-13.
40. **Claure N., Gerhardt T., Hummler H., Everett R., Bancalari E.** Computer-controlled minute ventilation in preterm infants undergoing mechanical ventilation. *J Pediatr* 1997; **131**(6): 910-13.