Spontaneous breathing and respiratory support of preterm infants at birth

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CHAPTER 13

Summary

Introduction

Preterm infants may have difficulty aerating their lungs at birth and most of them need respiratory support during this transitory phase. Clinicians are guided by international resuscitation guidelines, but recommendations are based on few data. At birth, the lungs of preterm infants are most vulnerable, but little distinction has been made between the ventilatory approach of term and preterm infants at birth. The general aim of this thesis was to gather data that could lead to a better understanding of spontaneous breathing and improvement of the respiratory support of preterm infants at birth. Various aspects of this subject are presented using data obtained from reviews, clinical studies (retrospective, observational and randomized controlled trials) and experimental animal studies.

In **Chapter 2** an overview of the literature of spontaneous breathing of infants at birth is presented. This review discusses the available knowledge about the first spontaneous breaths and the breathing patterns adopted by infants at birth. The lung expands more easily with spontaneous inspirations than inflations, most probably because artificially applied inflations do not adequately duplicate the first spontaneous breaths. The transpulmonary pressure generated by inspiratory efforts plays a critical role in airway liquid clearance and aeration of the lung. How very preterm infants with poor respiratory muscle strength, surfactant deficiency, compliant chest walls and impaired lung liquid clearance defend their lung gas volumes immediately after birth is poorly understood.

In **Chapter 3** we described the first study of spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure (CPAP) immediately after birth. We recorded airway flow, tidal volumes and airway pressure using a hot wire flow meter placed between the T-piece of a resuscitation device and mask. We frequently observed prolongation of expiration in very preterm infants treated with facemask CPAP immediately after birth, predominantly characterized by a breath hold. This braking of expiration is recognized as an attempt to defend lung volume. Our speculation is that techniques of positive pressure ventilation that mimic expiratory braking might improve the effectiveness of respiratory support in the delivery room.

In **Chapter 4** we studied the spontaneous breathing patterns in more mature preterm infants, without any respiratory support, immediately after birth and compared those with the patterns of term infants. Immediately after birth an open face mask, with a hot wire flow meter attached, was placed on their face and air flow was recorded. Both preterm and term infants frequently brake expiration, most often represented by a crying pattern. The crying pattern has not been described before but appears to be a method of breathing that uses expiratory braking and facilitates lung volume recruitment. We have shown that preterm infants use significantly more expiratory breath holds to defend their lung volume.

In **Chapter 5** an overview of the literature of ventilation of preterm infants at birth is presented. This review discusses the data available for current recommendations, but also the data available for a different approach towards respiratory support of preterm infants at birth. Different aspects of positive pressure ventilation are discussed, such as the amount of peak pressure, initial prolonged inflation, application of positive end expiratory pressure (PEEP), the device and interface to use, use of CPAP for support of spontaneous breathing, surfactant administration and the FiO_2.

In **Chapter 6** a cohort study is reported investigating whether changing our policy to early nasal CPAP, while maintaining a low threshold for intubation for surfactant administration, reduced the need for intubation < 72 hours of age in very preterm infants. Several cohort studies comparing before and after introducing early nasal CPAP have shown a decrease in intubation rate. However, high FiO_2 thresholds (> 0.6-1.0) were used as an indication that early nasal CPAP had failed and the infants should be ventilated and treated with surfactant and our study reports the use of early nasal CPAP while maintaining a low FiO_2 threshold (> 0.4) for surfactant treatment. We demonstrated that general use of early nasal CPAP and intubation of only those who have obvious and continuing respiratory difficulty, significantly reduced the need for intubation, even when early surfactant rescue treatment was ensured by maintaining a low threshold for surfactant administration.

In **Chapter 7** a case-control study is presented comparing the pulmonary course and short-term outcome of very preterm infants with respiratory distress syndrome, who failed early nasal CPAP and a control group of infants, matched for gestational age, who were intubated in the delivery room. The study groups were patients admitted during a time period that early nasal CPAP was used more and more often in our nursery, 65 % of the infants with RDS were intubated in the delivery room and 33% started with early nasal CPAP therapy. Early nasal CPAP therapy failed in 2 out of 3 infants. There were no differences in morbidity and mortality except for less bronchopulmonary dysplasia in the early nasal CPAP group. Although the characteristics and pulmonary course parameters were not significantly different between the groups and no clear intubation criteria were maintained in the delivery room, a bias could have occurred. The infants intubated in the delivery room may represent the sickest neonates with more severe respiratory distress syndrome. We therefore could only conclude that a trial of early nasal CPAP at birth is not detrimental and may be justified in case of respiratory distress syndrome.

In **Chapter 8** a randomized controlled trial is described comparing the traditional respiratory approach with a new approach, which combines a number of techniques that theoretically could improve the respiratory outcome of preterm infants. We hypothesized that a sustained inflation followed by early nasal CPAP, using a pressure-limited mechanical device, is a more effective management strategy in preterm infants than our conventional

approach of repeated manual inflations with a self-inflating bag and mask followed by nasal CPAP on admission to the neonatal intensive care unit. We found that this compound respiratory approach decreased the need for intubation < 72 hours after birth, mechanical ventilation during admission, and bronchopulmonary dysplasia. Early nasal CPAP also buys time to differentiate between respiratory distress syndrome and transition problems, which are transient, and reduces the number of preterm infants intubated unnecessarily. Although this trial has shown the importance of early respiratory management for pulmonary outcome (bronchopulmonary dysplasia) in preterm infants, more randomized trials, especially in infants < 28 weeks of gestation, are needed to develop an optimal strategy.

In **Chapter 9, 10 and 11** experimental studies are reported which use preterm rabbit models mechanically ventilated from birth. Functional residual capacity (FRC) and tidal volume were measured using plethysmography and uniformity of lung aeration was imaged by using phase contrast X-ray imaging .

In **Chapter 9** we tested the effect of PEEP on lung aeration at birth. Phase contrast X-ray imaging demonstrated that in the absence of PEEP, air only briefly penetrates into the distal airways during inflation and that the distal airways collapse during expiration. Plethysmography showed that the FRC did not increase above the anatomical dead space volume (2.5 ± 0.8 ml/kg) of the lung in the absence of PEEP. In contrast, the application of 5 cmH_2O PEEP promoted a gradual increase in aeration of the distal airways with each inflation and prevented collapse of the distal airways at end-expiration. As a result, pups ventilated with PEEP achieved significantly greater FRC (19.9 ± 3.2 mL/kg) than pups ventilated without PEEP (1.0 ± 1.5 mL/kg) after 120 inflations. The combination of phase contrast X-ray imaging and plethysmography demonstrated an essential role for PEEP in facilitating lung aeration, accumulating FRC and preventing distal airway collapse at end-expiration in preterm rabbit pups mechanically ventilated from birth.

In **Chapter 10** we examined the effect of PEEP and a 20 sec sustained inflation (SI) on the spatial pattern of lung aeration and FRC recruitment. We found that in preterm rabbit pups a larger FRC was created and maintained in the first 7 minutes after birth when a 20 sec SI was followed by ventilation with PEEP compared to either no SI inflation or no PEEP. PEEP had a larger effect on the formation of FRC than a 20 sec inflation. However, the effects were additive and made it possible to create and maintain a FRC as early as the first inflation following the SI. Importantly, a SI also resulted in uniform lung aeration before the onset of tidal ventilation, but in the absence of PEEP, the lungs failed to retain an FRC, which emphasizes the importance of PEEP. We concluded that preterm infants receiving ventilation at birth should benefit from the application of PEEP, but a combination of the two techniques (initial sustained inflation + ventilation with PEEP) may be better. Thus, it is possible that combining these two techniques during stabilisation of preterm infants will

increase the chance of establishing effective breathing, promote uniform ventilation and reduce the need for intubation in the delivery room.

In **Chapter** 11 we tested the effect of initial inflations lasting 1, 5, 10 or 20 sec on the first inflation volume and FRC immediately after birth. The first inflation volume increased with increasing inflation time; from a mean (SD) of 0.2 (0.1 – 3.1) ml/kg for a 1 sec inflation to 23.4 (19.3 - 30.4) ml/kg for a 20 sec SI. The lung was uniformly aerated, without causing overexpansion, and FRC and tidal volume were fully recruited following a 20 sec SI. Compared to a 1 sec inflation, a 5 sec SI had no extra effect on FRC, but a 10 second SI resulted in a higher FRC at 7 minutes and a 20 second SI resulted in a higher FRC at 20 seconds and 7 minutes after start ventilation. During the first inflation, the rate of lung inflation was lower (3.5 (3.5) mL/kg/sec vs 81.7 (32.1) mL/kg/sec) and the resistance to inflation higher (25.3 (29.6) cmH_2O/(mL/kg/sec) vs 0.38 (0.08) cmH_2O/(mL/kg/sec)) compared with after lung aeration was established. The mean (SD) time taken for 90% of the lung to aerate was 14.0 (4.1) sec using a PIP of 35 cmH_2O. We concluded that in ventilated preterm rabbits, a 10 and 20 sec SI increased the first inflation volume, produced a greater FRC during the first minutes and a 20 sec SI uniformly aerated the lung before the onset of tidal ventilation.

In conclusion, the evidence level for current recommendations for respiratory support of preterm infants at birth is low. The studies presented in this thesis not only contribute to the accumulating evidence for a different approach than currently recommended, but also provide a basis for further research.