Spontaneous breathing and respiratory support of preterm infants at birth

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CHAPTER 1

General introduction

Introduction

The first few minutes after birth represent the most stressful period of physiological adaptation that humans undergo. The first breaths following birth are characterized by a transition from liquid to air-filled lungs, release of surfactant, creation of lung volume with air at end of expiration (functional residual capacity; FRC), increase in pulmonary blood flow and establishment of a regular respiration. Uniform aeration of the lung and retention of an appropriate FRC are required to facilitate effective gas exchange and improve an infant's oxygenation which in turn improves the infant's heart rate. If an infant does not achieve this transition promptly, intervention from the caregiver is required. This neonatal "resuscitation" comprises, in most cases, only adequate ventilation (1). Chest compressions and medication are rarely needed during resuscitation and are often secondary to improper ventilation (1).

Perinatal care has improved and the majority of infants needing ventilation at birth are preterm infants. Preterm infants have difficulty aerating their lungs after birth because of poor respiratory muscle strength, surfactant deficiency, a compliant chest wall (2;3) and impaired lung liquid clearance (4-6). To create and maintain FRC, most of them need respiratory support during this transitory phase.

In the last decade caregivers for neonates have been guided by international resuscitation guidelines (7). Little distinction is made between the ventilatory approach of term and preterm infants at birth (7). Ventilation of preterm infants at birth is primarily extrapolated from adult resuscitation and observational data gathered 30 years ago in term and near-term infants. Milner reflected on the difficulties in performing studies in this area and stated in 1982 that it was unlikely that answers will be provided by further studies on newborn babies and that progress will depend on careful animal experimentation (8). Since then, most of the new data in this area have been obtained in experimental animals and used as advice for new guidelines.

Between 1960 and 1986 observational data were gathered immediately after birth from small numbers of spontaneously breathing term infants and used to develop the international guidelines for neonatal resuscitation (9-16). Thereafter no more data became available, probably reflecting the difficulties in performing clinical studies in this area. There are no data describing how preterm infants breathe and aerate their lungs immediately after birth. It may be inappropriate to assume that the results of studies of term infants also apply to preterm infants. Many preterm infants breathe spontaneously at birth and manage to create an FRC with only non-invasive nasal continuous positive airway pressure (CPAP) as support (17-23).

Knowledge of the normal spontaneous breathing patterns immediately after birth would help us understand how the preterm infant creates and maintains an FRC, and how we should ventilate and support a preterm infant in the delivery room when breathing is inadequate.

Neonatologists are familiar with the concept of ventilator induced lung injury (24;25) and prefer to apply ventilation strategies in the neonatal intensive care unit (NICU) that are gentle to the lung (26). At birth, the lungs of preterm infants are most vulnerable and injury can happen with the first manual inflations (27-33). It seems logical that a similar gentle approach should be applied to reduce lung injury during the first few minutes of life, especially in preterm infants.

Many clinicians still advocate intubation and ventilation as common practice in the resuscitation of preterm infants at birth (34;35). Others opt for an alternative approach consisting of nasal CPAP, started directly after birth, which is a gentle and effective non-invasive attempt to support non-compliant lungs (18;20;21;36-44). Interestingly, both strategies were not based on randomized clinical trials.

Improving ventilatory support for infants in the delivery room offers considerable potential for improving short- and long-term outcome.

Outline of the thesis

The general aim of this thesis was to gather data that will lead to a better understanding of spontaneous breathing and improvement of the ventilatory management of preterm infants at birth. This thesis reports the results of ten reviews and original studies in this area and has been divided in two parts.

Part 1 • Breathing at birth

In **chapter 2** the literature about infants' first breaths is reviewed. We discuss how lung liquid is cleared, where it goes, how FRC is created and maintained and current knowledge about the spontaneous breathing patterns adopted by infants immediately after birth.

We investigated the spontaneous breathing patterns of preterm infants immediately after birth. Hot-wire anemometry was used to measure respiratory variables in mechanically ventilated infants and in spontaneously breathing infants by attaching the equipment to a face mask (45-49). This technique is less cumbersome and less stressful to the infant than methods described in earlier studies (9-16). The research team of Professor Colin Morley and Associate Professor Peter Davis in the Royal Women's Hospital, Melbourne, Australia, are well-known for their extensive experience in using a hot-wire flowmeter during resuscitation at birth to measure respiratory variables. Collaboration with them has led to the first studies reporting the spontaneous breathing patterns in preterm infants in the first minutes after birth.

The aim of the observational studies presented in **chapter 3 and 4** was to investigate the spontaneous breathing patterns of preterm infants immediately after birth. In **chapter 3** we present physiological recordings of very preterm infants. These recordings were made during CPAP support at birth. It was not appropriate to use a face mask without also providing CPAP. We therefore repeated the study, presented in **chapter 4**, in more mature preterm infants, who did not need respiratory support, and compared the breathing patterns with those of term infants at birth.

Part 2 • Respiratory support at birth

In **chapter 5** the literature on respiratory support of very preterm infants at birth is reviewed. We discuss not only the available evidence for current practice, but also the accumulating data for a different approach towards respiratory support at birth.

We performed retrospective studies of the respiratory support at birth of preterm infants born in the Leiden University Medical Center in the Netherlands. During that period we increasingly used early nasal CPAP as primary strategy. Nasal CPAP was started on arrival in the NICU, not in the delivery room. In addition, to ensure early surfactant rescue treatment, we maintained a low threshold for intubation. The aim of the cohort-study presented in **chapter 6** was to investigate whether changing to early nasal CPAP while maintaining a low threshold for intubation for surfactant reduced the need for intubation < 72 hours of age in very preterm infants. The case-control study in **Chapter 7** was designed to compare the

pulmonary course and outcome of very preterm infants with respiratory distress syndrome who failed early CPAP with infants who were intubated in the delivery room.

In **Chapter 8** a randomized controlled clinical trial is presented comparing the traditional ventilatory approach with a new method, which combined a number of techniques that theoretically could improve the respiratory outcome of preterm infants. The aim was to test the hypothesis that a sustained initial inflation followed by early nasal CPAP, using a pressure-limited mechanical device, is a more effective and less injurious management strategy in preterm infants than conventional intervention.

Collaboration with the research group of Professor Stuart Hooper has provided the opportunity to perform experimental studies, presented in **chapter 9,10 and 11**, using plethysmography and phase contrast X-ray imaging, which is an ideal imaging technique to observe the rate and spatial pattern of lung aeration and visually demonstrate the effect of ventilation strategies at birth. In these studies preterm rabbit pups were delivered by caesarean section, placed within a water-filled plethysmograph (head out) and imaged as they were mechanically ventilated using a randomly allocated ventilation technique. The aim was to investigate the effect of 5 cm H_2O PEEP or no PEEP, and different durations of sustained inflation on the pattern of lung aeration and FRC recruitment in a 28 day preterm rabbit model ventilated immediately after birth. In **chapter 9** we investigated the effect of PEEP, in **chapter 10** combinations of PEEP and a 20 sec sustained inflation, and in **chapter 11** different durations of sustained inflations.

In **chapter 12** the main findings of the thesis are discussed, together with some future perspectives and proposals for future research. A summary is presented in **chapter 13** (in Dutch in **chapter 14**).

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