Physiological based CPAP for preterm infants at birth

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General introduction

Introduction

Although most infants are born after 37 completed weeks of gestation, 10.6% of all liveborn infants are born preterm (1). Preterm birth can be categorised, based on gestational age, into late preterm (32-37 weeks gestation), very preterm (28-32 weeks gestation) and extremely preterm (<28 weeks gestation) (2). As the mortality, morbidity and required medical assistance are all inversely related to the duration of pregnancy, infants who are born extremely preterm are affected the most and require intensive care for a long period (1, 3, 4). These extremely preterm infants are most vulnerable immediately after birth when they exchange the intrauterine environment for an air-filled environment and undergo a major transition from the fetal to newborn state. Most preterm infants require respiratory support instantly after birth, and in recent years, the respiratory support strategies provided during the neonatal transition have undergone major changes (5). To further improve these support strategies, we need to consider the underlying physiological changes that characterise the respiratory transition at birth.

The respiratory transition at birth

During pregnancy, the fetal lung is a liquid filled organ. The fetal lung produces liquid that accumulates within the airway during fetal life. The larynx is predominantly closed and liquid only leaves the lung via the trachea during brief moments of fetal breathing movements. The accumulation of liquid creates a pressure gradient between the airways and the environment, which maintains the lungs in a distended state that is crucial for lung growth and development. Indeed, the volume of liquid retained in the future airways is greater than the volume of air in an aerated lung after birth. Blood flow in the pulmonary vessels (PBF) is low as the vessels are vasoconstricted and pulmonary vascular resistance (PVR) is considerably higher than systemic vascular resistance. As the placenta functions as a low resistance pathway, a substantial part of cardiac output flows through the placenta which provides gas exchange during the pregnancy and provides a considerable part of the venous return to the heart (6-10). After birth, the placenta will be separated from the fetal circulation and the liquid-filled in utero environment will be replaced by a gaseous ex utero environment. For an infant to survive, gas exchange needs to shift from the placenta to the lungs and the airways need to be cleared of liquid to allow the entry of air and the onset of pulmonary gas exchange. Also, PVR needs to decrease and PBF needs to increase considerably, to facilitate gas exchange. This increase in PBF is also important for further cardiovascular changes that are required when transitioning from a fetus to newborn infant.

The first steps of lung liquid clearance can commence when labour starts. During the stress of active labour, the release of adrenaline and vasopressin can increase, which stimulates sodium uptake across the airway epithelium, thereby reversing the osmotic gradient and promoting liquid absorption into lung interstitial tissue (11-13). The uterine contractions during active labour can also increase transpulmonary pressure causing liquid to leave the

infant through its nose and mouth (14-16). So, active labour prior to delivery, contributes to the removal of some lung liquid before birth and before the first inhalation of air.

Once the infant is born, gas exchange needs to be established in the lungs for which the airway liquid needs to be cleared from the remaining liquid and aerated. Unless the infant is displaying constant and regular breathing, the larynx will be predominantly closed immediately after birth, but opens during each inspiration allowing air to enter the lung (17). The primary facilitator that drives air to flow into the lungs is transpulmonary pressure. With each inspiration, liquid leaves the airways and enters lung tissue, while air enters the lungs, and so lung liquid is cleared in a stepwise fashion, with each breath enhancing lung aeration (18, 19). At the beginning of this process, airway resistance is high due to the viscosity of liquid, compared to air, and its movement through the distal airways and across the distal airway wall. As a result, the liquid is forced to accumulate in the interstitial lung tissue (20, 21).

As the lungs become air-filled, this initiates many changes within the cardiopulmonary system. The viscosity of air is markedly lower than that of liquid and, therefore, airway resistance decreases and lung compliance increases as the lung aerates. The abrupt decrease in PVR and increase in PBF is intimately linked to lung aeration. An oxygen induced increase in nitric oxide and increased recoil of alveoli due to the creation of air/liquid surface tension (10) were thought to be primarily responsible for the decrease in PVR. However, recent evidence indicates that the accumulation of liquid in the interstitial tissue triggers a neural reflex, probably via juxta capillary receptors, causing a decrease in PVR and increase in PBF (22). Meanwhile, increased alveoli recoil increases the tendency of alveoli to collapse at end-expiration, which decreases the surface area for gas exchange and increases the required inspiratory effort (23). The liquid that accumulates in the interstitial tissue is replaced in the airways by air, which causes the chest wall to expand and the pressure in the interstitial tissue to rise. The interstitial tissue pressure remains high until the liquid is drained via the lymphatics and blood vessels hours after birth (16, 24, 25). This interstitial pressure causes a tendency for liquid to re-enter the airways during expiration, only to be cleared again during inspiration (18, 19, 26). Infants have several mechanisms to prevent alveolar collapse and to limit liquid re-entry into the lungs. During this phase of transition, the epithelial sodium channels continue to promote liquid absorption back into the interstitial tissue (26). In addition, alveolar type II cells continue to secrete surfactant after lung aeration, which lowers the surface tension, reduce lung recoil and improve lung compliance (27, 28). Infants also use expiratory braking manoeuvres to stop or slow down expiration. During expiration the larynx is (almost) closed while contracting their diaphragm, the airway pressure is increased while the expiratory time is prolonged to prevent airway collapse and liquid re-entry (19, 29-31). Once the infant has achieved a stable breathing pattern, the larynx will remain predominantly open to allow gas exchange (17).

The obstacles for a preterm baby to breathe at birth

While most term infants have no difficulties in dealing with the large and abrupt physiological changes that are required to transition to newborn life, preterm infants can experience much difficulty in transitioning into the newborn state. Preterm infants have lungs that are structurally and functionally immature, they lack the essential components for a smooth transition to newborn life, when pulmonary gas exchange is critical. At 24 weeks gestation, lung development is at the saccular stage, which means that the surface area for gas exchange has not increased as the terminal sacs have not undergo septation to form alveoli and the capillaries have not proliferated to form a narrow air/blood gas barrier. Also, the alveolar epithelium and the surfactant system are still immature when infants are born preterm, before alveolar epithelial cells have had an opportunity to trans-differentiate into type-II cells. Therefore, the alveoli are prone to collapse due to high surface tension, which further reduces the surface area for gas exchange (32-35). In addition, preterm infants have very little epithelial sodium channels and the channels that are present are less functional, meaning preterm infants cannot fully benefit from lung-liquid clearance via this mechanism before birth (13, 36, 37). Also, preterm infants have very compliant chest walls, which makes it more difficult to overcome the lung recoil impeding the increase in gas volume (15, 38, 39). Thus, when infants are born preterm, their lack of fully developed alveoli, surfactant and epithelial sodium channels, as well as the high compliance of the chest wall, make it harder for them to clear lung liquid, prevent alveolar collapse and breathe efficiently after birth.

Respiratory support after preterm birth

Until almost a decade ago, most very preterm infants were electively intubated and mechanically ventilated at birth because they were considered to be incapable of sustaining their respiratory needs. However, when studies (40, 41) showed that mechanical ventilation can be injurious and that non-invasive respiratory support lowers the risk of death or oxygen requirement at 28 days, the focus of respiratory support at birth shifted towards non-invasive application of ventilation. This is most commonly in the form of continuous positive airway pressure (CPAP), to support spontaneous breathing, or intermittent positive pressure ventilation (iPPV) with a positive end-expiratory pressure, to provide artificial ventilation of the lung (5). Both modes, commonly use a face mask to apply this respiratory support.

Although the majority of preterm infants breathe at birth, the respiratory effort is often insufficient (42, 43) or breathing is often missed by the caregiver (44) and so iPPV is deemed necessary. Observational clinical studies (45-47) have shown that the iPPV provided is often inefficient or can be injurious to the preterm infant's lungs and brain. This can occur when high peak pressures are administered, or infants breathe spontaneously during a positive pressure inflation, creating high tidal volumes (48-50). IPPV can be inefficient due to mask leak or airway obstruction, which can occur due to incorrect positioning or applying to much pressure to the mask. In addition, if the infant is apneic or does not have a stable breathing

pattern, the larynx will be predominantly closed immediately after birth, only allowing air to enter the lungs during a spontaneous breath. The larynx will switch to a predominantly open state only after a stable breathing pattern is achieved. This means that when given via a facemask, iPPV delivered to infants who are apnoeic or breathe insufficiently, is often ineffective in ventilating the lungs (17). While iPPV fails to aerate the lungs, hypoxia will worsen and when severe, it is possible that the the larynx will relax, allowing iPPV to ventilate the lungs. However, this far from ideal as hypoxia should be avoided wherever possible as this is associated with higher mortality and morbidities (51).

It is clear that spontaneous breathing is essential for effective non-invasive respiratory support and to reduce the need for iPPV. During regular spontaneous breathing, the larynx will open allowing respiratory support to reach the lungs. Although most very preterm infants do breathe at birth (42, 43), their respiratory effort is weak and this should be stimulated and supported in an optimal manner. Enhancing spontaneous breathing will likely reduce the need for iPPV and improve gas exchange, which increases oxygenation and provides a further positive stimulus for breathing. Reaching an increased oxygenation level sooner increases the likelihood of achieving a sustainable and stable regular breathing pattern in the newborn, thereby creating a patent airway that enables any additional respiratory support to be applied (52).

The era of stimulating and supporting spontaneous breathing

In recent years, research has been focusing on stimulating spontaneous breathing using tactile stimulation, caffeine and supplemental oxygen. The most basic intervention to enhance breathing is tactile stimulation, and although it is widely recommended by guidelines (53, 54), the methods of tactile stimulation in the delivery room vary widely (55-59). To date, only one clinical trial (60) has been performed, which showed favourable effects of repetitive tactile stimulation on respiratory effort leading to a significant increase in oxygen saturation.

Caffeine, an adenosine antagonist, is another intervention that was introduced to enhance breathing effort in the delivery room. While caffeine is routinely used in the neonatal unit to promote breathing and reduce the incidence of apnoea, it is not commonly used to improve breathing effort at birth. In a recent trial, caffeine was shown to increase respiratory effort in preterm infants, as indicated by a significant increase in minute volume, tidal volume and the number of recruitment breaths (61).

The use of supplemental oxygen in the delivery room has also been investigated extensively and various clinical trials have been performed to find the optimal initial oxygen concentration (62-64). While there is no convincing evidence, guidelines recommend using low inspired oxygen concentrations initially (0.21-0.3) and to titrate the inspired oxygen content, guided by the infant's preductal oxygen saturation (53, 65). Balancing the use of supplemental oxygen is crucial as hypoxia suppresses spontaneous breathing at birth (66, 67) and increases the risk of death and intraventricular haemorrhages (51). However, hyperoxia

causes tissue damage leading to bronchopulmonary dysplasia and retinopathy of prematurity (68, 69). Recently, Dekker et al. (70) showed that initiating respiratory support with 100% oxygen improves the respiratory effort, oxygenation and reduces the duration of mask ventilation, without increasing exposure to of hyperoxia or the total exposure high inspired oxygen levels, as the inspired oxygen concentration was carefully titrated down, guided by the infant's oxygenation.

While studies have investigated the benefits of stimulating breathing at birth, very little data is available on the optimal approach for supporting their breathing effort. A recent study in animals (71) found that improving the breathing rate does not directly lead to an enhanced degree of lung aeration, indicating that other factors could be involved, such as the depth of inspiration. As the main factor driving lung aeration is the transpulmonary pressure gradient between the airways and interstitial tissue, increasing the CPAP level could increase the transpulmonary pressure gradient. In the era of stimulating and supporting spontaneous breathing, CPAP may be the key facilitator to improve lung aeration and the use of CPAP at birth needs to be evaluated thoroughly.

CPAP strategy in the delivery room

Currently, 4-8 cmH_2O CPAP is widely adopted in the delivery room, but this approach has been extrapolated from strategies used in the intensive care unit. However, scientific evidence to support this pressure range is lacking and the large variability in CPAP protocols used between neonatal centres, highlights this knowledge gap (53, 65, 72). Until recently, only two preclinical studies had investigated the effect of different CPAP levels at birth. In intubated preterm sheep (73), CPAP levels of 8 cmH_2O CPAP improved lung gas volumes and oxygenation compared to 5 cmH_2O CPAP, yet breathing rates were reduced. Similarly, breathing rates of preterm rabbits declined after increasing non-invasive CPAP above 7 cmH_2O (17).

It is also pertinent to note that the available scientific evidence for using specific CPAP levels was extrapolated from animal studies where different positive end-expiratory pressures (PEEP) levels were compared in intubated and mechanically ventilated preterm rabbits (74) and sheep (75-78). While these studies showed that a PEEP level above 8 cmH_2O improved lung aeration and newborn oxygenation, it also caused pulmonary overexpansion, reduced pulmonary blood flow and heart rates and increased the risk on pneumothoraxes. However, these animals were anesthetised, intubated and mechanically ventilated, which is a completely different mode of respiratory support than the application of CPAP in spontaneously breathing preterm infant going through transition at birth. Indeed, although the CPAP level and PEEP level may be the same, the CPAP is the highest positive pressure applied to the airways, whereas PEEP is the lowest pressure and the applied pressures cycle considerably above this during iPPV. Even more important, the animals in these experiments

had already transitioned and lungs were already aerated as they were ventilated prior to the start of the experiment.

Considering the current physiological knowledge of the neonatal transition at birth and the scientific evidence of different CPAP/PEEP levels in preclinical studies, likely that a CPAP strategy that is different from that currently used will be required. Directly after birth airway-liquid needs to be cleared for the lungs to allow the entry of air, and the primary purpose of all respiratory support modes during this stage of transition is to enhance this process. During lung aeration, the lungs are liquid-filled (6, 7) and this liquid moves distally through the airways and across the distal airway wall as air enters the lung. The high viscosity of this liquid means that its movement through the distal airways and across the epithelium, create a high resistance in the airways to the entry of air (20, 21). The only way of overcoming this high resistance is to increase the pressure gradient or to increase the time over which the pressure gradient is applied. As increasing the CPAP level can increase the transpulmonary pressure gradient, a high-CPAP strategy could more easily overcome the high resistance in the airways, clear liquid and promote lung aeration (18, 19, 79, 80). Once the lungs become more aerated and the liquid accumulates in surrounding tissue, the resistance in the airway markedly decreases and the lungs become more compliant and so the required pressure gradient is less. However, with the clearance of liquid into the tissue, the pressure in the interstitial tissue increases, and combined with the formation of surface tension at the air/liquid interfaces alveolar recoil and the pressure gradient for liquid to re-enter the airways increases (16, 23-25). In this phase of the transition, the infant needs to maintain its established lung aeration by preventing re-entry of lung liquid during expiration and alveolar collapse at end-expiration (18, 19, 26). Thus, at this time, purpose of CPAP shifts from promoting lung aeration to maintaining lung aeration by prevention of liquid re-entry, alveolar collapse and supporting spontaneous breathing (81).

Based on the scenario described above, it appears that the applied CPAP level should be dynamic and needs to be changed following the course of lung aeration and its changing role during the transition. Indeed, maintaining high-CPAP levels following lung aeration could cause pulmonary overexpansion as the lungs become more compliant. When considering the low viscosity of air and the decreased airway resistance, lower CPAP levels should be sufficient to maintain aeration and support spontaneous breathing (75-80). A physiological based (PB)-CPAP strategy will match the dynamic nature of the lung's changing physiological state as the infant transitions to newborn life. Initial high-CPAP could enhance lung aeration, but after the lungs become aerated, CPAP can be reduced to maintain aeration while avoiding pulmonary overexpansion (79, 80).

The general hypothesis of this thesis is that preterm infants at birth will benefit from the use of a dynamic CPAP approach with an initial high CPAP level. A CPAP titration strategy with an initial higher CPAP level at birth will enhance lung aeration and better stimulate and support spontaneous breathing when compared to the currently used CPAP range of 4-8 cmH_2O.

When lung aeration has improved and thus the area for gas exchange is expanded, preterm infants will likely sooner reach an increased oxygenation or require less supplemental oxygen. Promoting spontaneous breathing may also reduce the need for iPPV. When the initial high-CPAP is titrated to a lower level following lung aeration, lower CPAP pressures should be able to preserve aeration and sufficiently support spontaneous breathing.

Aim and outline of this thesis

The general aim of this thesis is to test the hypothesis that; (i) high-CPAP levels improve the neonatal transition of preterm infants at birth by enhancing lung aeration and supporting spontaneous breathing, and (ii) a PB-CPAP approach will prevent adverse events caused by pulmonary overexpansion. For this, we have performed studies investigating different CPAP strategies in spontaneous breathing preterm newborns at birth. This thesis includes a literature review of all available evidence, a bench test and retrospective analysis, preclinical studies that allow us to understand the underlying physiology and a single centre randomised controlled trial.

Although most preterm infants receive 4-8 cmH_2O CPAP directly at birth via mask or prongs, there is a huge variability in CPAP protocols between centres due to the lack of scientific evidence (53, 65, 72). In **Chapter 1** of this thesis, we provide an overview of the scientific evidence available in 2018 on the devices, interfaces and CPAP pressures that are commonly used in the delivery room. In **Chapter 2** we describe a striking example of the huge variability in CPAP strategies currently used between centres in Europe. The difference in CPAP protocols (5-8 vs 12-35 cmH_2O) allowed us to retrospectively perform a matched-pairs analysis comparing at oxygenation and heart rate, delivery room interventions and short-term clinical outcomes.

To understand the effect of different CPAP pressures on the neonatal transition at birth, we performed two preclinical studies in spontaneously breathing animals directly at birth. In the first experiment we explored the supposed main benefit of higher CPAP pressures, which is on lung aeration. We hypothesised that the application of high-CPAP levels would increase the transpulmonary pressure and enhance lung aeration. To test this hypothesis, we delivered rabbits preterm and provided them mask CPAP directly at birth. The preterm rabbits were assigned to different CPAP pressures (0 vs 5 vs 8 vs 12 vs 15 cmH_2O) and CPAP strategies (15 cmH_2O continuous vs titrated). By measuring intra-thoracic oesphageal pressure and imaging the preterm rabbits using phase contrast X-ray imaging, the breathing pattern and the degree of lung aeration were analysed. The results of this preclinical experiment can be found in **Chapter 3**.

Previous preclinical studies in mechanically ventilated preterm sheep (75-78) have found that high-PEEP levels cause pulmonary overexpansion and compromise the cardiovascular system by reducing venous retrun and decreasing PBF. We therefore explored the effect of high-CPAP on the cardiovascular system during the neonatal transition. Prior to the experiment, fetal lambs were instrumented with flow probes and catheters for continuous flow- and pressure measurements. In the first 30 minutes after birth, preterm lambs received 5 or 15 cmH_2O CPAP continuous or 15 cmH_2O CPAP titrated to 8 cmH_2O, after which CPAP pressures were decreased. In **Chapter 4** we highlight the effect of different CPAP pressures on the pulmonary and cerebral blood flow and the jugular venous pressure to investigate any possible physiological consequences of high-CPAP levels.

To extrapolate the results of the preclinical studies into a clinical setting, a single centre randomised clinical trial was performed. In this trial the previously proposed PB-CPAP strategy was compared to standard of care which is 5-8 cmH_2O CPAP. PB-CPAP meant commencing respiratory support at 15 cmH_2O with stepwise titration (-2/2/3 cmH_2O/min) to 8 cmH_2O if the infant met set criteria (spontaneous breathing, oxygenation ≥85%, FiO_2 ≤0.4 and heart rate ≥100 bpm.) The primary outcomes were oxygenation and feasibility. Secondary outcomes included heart rate, delivery room interventions and short-term outcomes. These results are presented in **Chapter 5**.

To conclude, the main findings of the studies presented in this thesis and the future perspectives will be discussed in the **General discussion.** The studies will be summarized in the **English summary** and **Nederlandse samenvatting.**

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