Physiological based CPAP for preterm infants at birth

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General discussion

Introduction

Preterm infants often fail to aerate their lungs and require respiratory support immediately at birth in order to initiate pulmonary gas exchange. To minimise the risk of injury, respiratory support in the delivery room (DR) has shifted from elective intubation and mechanical ventilation towards non-invasive support (1-3). While the effectiveness of non-invasive respiratory support is dependent on infants having a patent airway, if the infant is not breathing at birth (apneic) the larynx is mainly closed and only opens during a breath (4-7). Recent research has focussed on stimulating spontaneous breathing using repetitive tactile stimulation, caffeine and adequate oxygenation (8-10). However, there is no data on the optimal CPAP level needed to assist preterm infants establish and maintain adequate lung aeration (11-14).

Lung aeration is predominantly driven by the transpulmonary (across the airway wall) pressure gradient generated during spontaneous breathing. Hypothetically, the application of continuous positive airway pressure (CPAP) increases the transpulmonary pressure to enhance lung aeration (Figure 1). Currently, 4-8 cmH_2O CPAP is recommended in the DR (15, 16). However, this has predominantly been extrapolated from CPAP support used in the neonatal intensive care unit (NICU), where CPAP is used to support infants hours to days after birth when the lung is well aerated. This is strikingly different to the DR setting, where CPAP is used to promote lung aeration and infants undergo major physiological changes at birth.

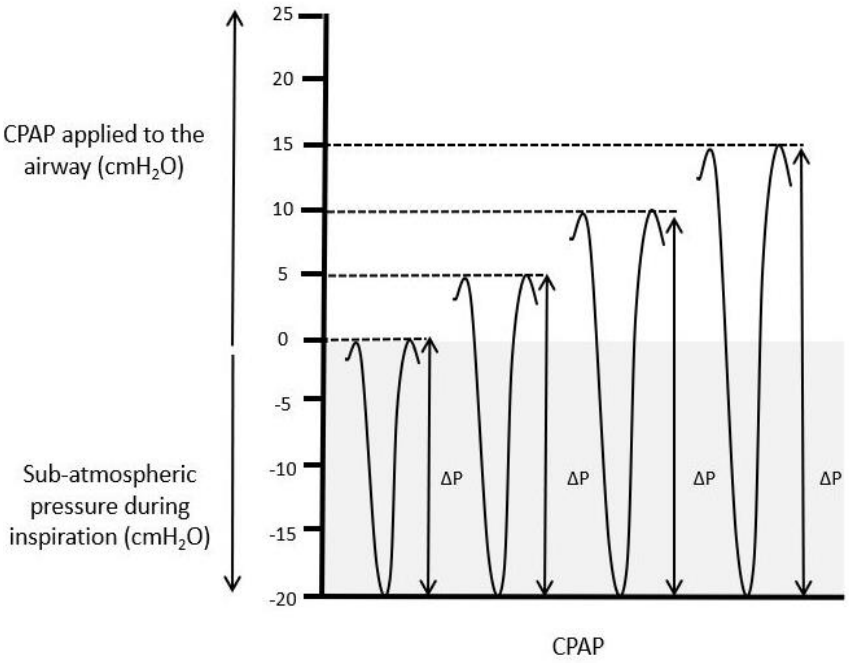

Figure 1. The use of higher CPAP levels increases the transpulmonary pressure (ΔP).

Physiological based CPAP

Physiological based (PB)-CPAP considers the physiological changes that are required to transition from fetus to a newborn (Figure 1). *In utero*, the future airways are filled with lung liquid. Immediately at birth, the role of CPAP is to increase the pressure gradient generated by inspiration and assist the movement of lung liquid across the distal airway wall into the interstitial tissue. This process occurs across the distal airsacs and so requires the distal movement through the airways. As a result, initially the resistance in the airways is high due to the high viscosity of liquid (compared with air) and to its movement across the airway epithelium (11-13). As such a high pressure gradient is needed to overcome the high airway resistance (17, 18). Once the lungs become aerated and liquid accumulates in the interstitial tissue, the role of CPAP converts to maintaining lung aeration. During this phase of the transition, airway resistance is considerably lower (~100 fold), but lung recoil increases due to the formation of surface tension and interstitial tissue pressure are increased which promote alveolar collapse and liquid re-entry at end-expiration (11-13, 17-22). At this time, continuation of high CPAP levels risk over-expanding the lungs and lower levels are sufficient to fulfil the role in maintaining aeration. If the CPAP decrease is guided by real time parameters, PB-CPAP can be individualized and CPAP levels suit the different phases of the transition.

The aim of this thesis was to investigate the effect of PB-CPAP in preterm infants at birth. We hypothesized that an initial higher CPAP would improve lung aeration and that adverse effects would be avoided by decreasing CPAP after establishing lung aeration, as these lower levels are sufficient to maintain lung aeration. We investigated the effect of PB-CPAP on lung aeration, oxygenation, breathing effort and potential adverse effects in experimental setting using preterm animal models and tested the feasibility and effect of PB-CPAP in clinical setting.

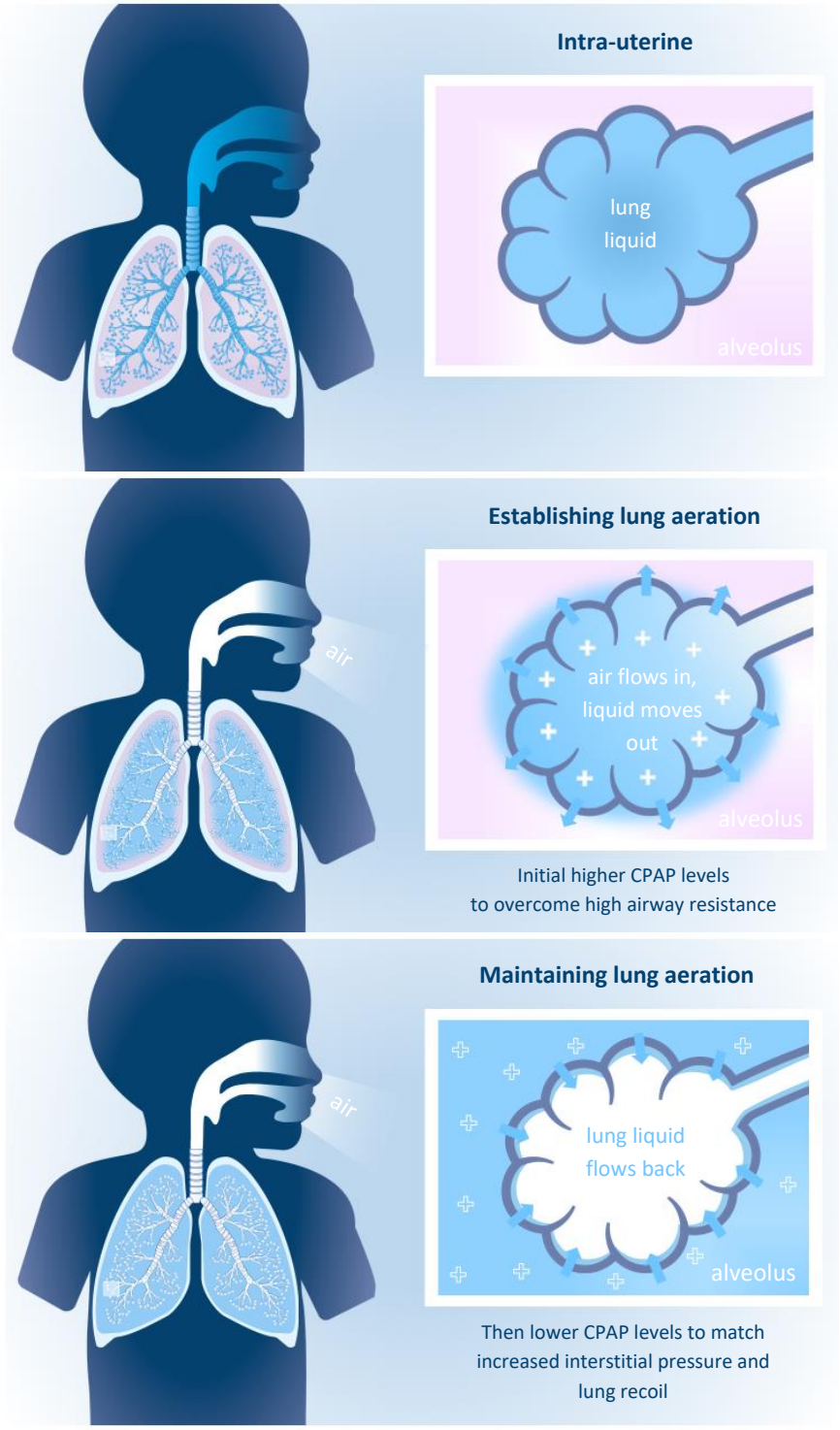

Figure 2. Physiological based CPAP. Image by Lisanne Tollenaar.

Which CPAP levels to use for PB-CPAP

In **Chapter 1**, we summarize the available literature of (pre)clinical studies on CPAP levels. We found that there was only one study investigating the effect of CPAP levels at birth and because CPAP and positive end-expiratory pressure (PEEP) are used interchangeably in guidelines (16, 23), we also included studies on PEEP levels at birth. When interpreting these studies, it is important to note that PEEP applied during positive pressure ventilation is substantially different from CPAP during spontaneous breathing (Figure 3). When infants are supported with CPAP, the CPAP level is effectively the highest external pressure applied to the airways as the pressure in the lower airways only transiently increases above the CPAP level to effect expiration. With each breath, the intrathoracic pressure decreases thereby reducing the mean airway pressure (MAP) below the CPAP level. However, when infants are ventilated, PEEP is the lowest pressure applied to the airways as the peak inspiratory pressure increases the MAP. Therefore, the MAP is substantially higher during ventilation with PEEP than with a similar CPAP level used during spontaneous breathing and this may have a different effect on preterm infants. Nevertheless, this was the best available evidence at the time and therefore was still included in our search strategy.

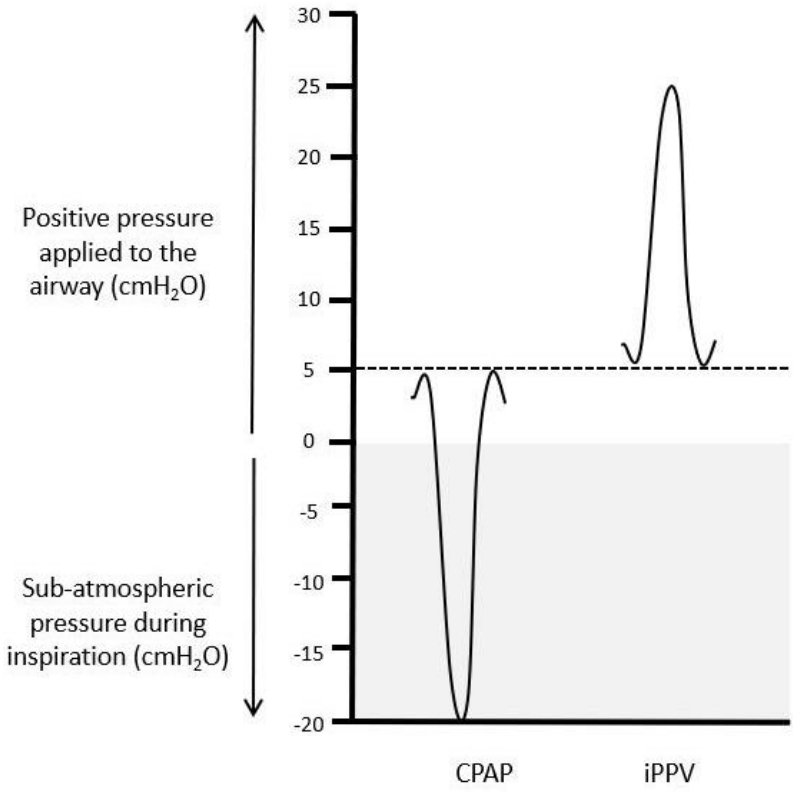

Figure 3. Differences in mean airway pressure during CPAP and iPPV.

There have been a few experimental studies investigating the effect of CPAP/PEEP in intubated preterm animals at birth. CPAP levels were investigated in intubated preterm lambs at birth, demonstrating that 8 cmH_2O CPAP improves lung function and oxygenation when compared to 5 cmH_2O (24). Studies in intubated and ventilated preterm rabbits demonstrated that with decreasing gestational age higher PEEP levels (10 cmH_2O instead of 5 cmH_2O) are needed for establishing lung aeration (18, 25-27). In intubated preterm sheep it was shown that increasing PEEP levels to max 20 cmH_2O improves lung function when compared to a static PEEP levels of 5 cmH_2O (28). In a clinical setting, increasing CPAP is known to positively affect lung function of preterm infants who are admitted to the NICU hours to days after birth (29-32). While there are no clinical studies on CPAP levels at birth, centres that use PEEP levels of 6-15 cmH_2O during mask ventilation at birth have reported a reduction in intubation and mechanical ventilation in the DR when compared to a historical control where 4-5 cmH_2O PEEP was used (33-35).

There were also concerns in using higher pressure levels at birth. When high intra-thoracic pressures are given to preterm infants on the NICU hours to days after birth, this can potentially over-expand the lungs and compromise cardiac output (36-38). Indeed, pulmonary blood flow (PBF) was reduced when 8-12 cmH_2O CPAP/PEEP was applied to intubated preterm lambs during 10-20 min after birth and levels higher than 8 cmH_2O increased the risk of pneumothoraxes (24, 39-42). There were however no adverse effects observed in preterm infants when 6-15 cmH_2O PEEP was used in the DR (33-35). It is possible that CPAP/PEEP levels up to 15 cmH_2O do not cause adverse events during the initial process of establishing aeration, but that maintaining pressures above 8 cmH_2O after aeration has been established may lead to over-expansion of the lungs.

In **Chapter 2** we reported our findings of a retrospective comparison study, in which we compared the CPAP strategies for preterm infants at birth of two neonatal centers. In this study we observed that oxygen saturation (SpO_2) in the first minutes was not different when 12-35 cmH_2O or 5-8 cmH_2O CPAP was used. It is likely that other factors influenced oxygen saturation, such as breathing effort and that the larynx hampered the respiratory support (4-7). Once the fraction of inspired oxygen (FiO_2) levels were increased in the 5-8 cmH_2O group, these infants achieved higher SpO_2 compared to those supported with 12-35 cmH_2O CPAP. Because gas exchange (as reflected by SpO_2/FiO_2 ratios) remained similar between groups and FiO_2 was increased in the 5-8 cmH_2O but not in the 12-35 cmH_2O group, we can assume that higher CPAP levels facilitated the increased in lung aeration that was needed to attain similar SpO_2/FiO_2 ratios.

We did not observe signs of over-expansion of the lungs leading to cardiac output compromise in the 12-35 mH_2O CPAP cohort, as heart rate was similar in both groups the first ten minutes after birth. However, there was a non-significant increase in pneumothoraxes in the 12-35 cmH_2O group (early 4 vs 11%; ns, during admission4 vs 19%; ns). When these pneumothoraxes occurred and the factors that may have contributed remains unclear. This

also could indicate that while initial high CPAP does not over-expand the lungs, reducing CPAP levels following lung aeration may reduce the risk of adverse effects such as pneumothoraxes. It is important to note, while there is much concern centred around the application of high airway pressures at birth, most infants in the 5-8 cmH_2O CPAP cohort received iPPV and as such, were subjected to MAPs of ~15 cmH_2O across the 10 min resuscitation period

The findings in **Chapter 1 and 2** implied that 6-20 cmH_2O CPAP/PEEP may have beneficial effects on lung aeration at birth, but previous studies have shown that continuation of PEEP levels above 8 cmH_2O after lung aeration may cause harm. Taking into account that infants already are subject to a MAP of ~15 mH_2O during iPPV in the DR and that 8 cmH_2O is the upper range of the CPAP levels used on the NICU, we decided to use an initial 15 cmH_2O for our PB-CPAP approach, that is then gradually reduced to 8 cmH_2O once lung aeration has been established and the infant has been stabilized.

Effects of physiological based CPAP

We investigated the effects of PB-CPAP in experimental setting using preterm animals models in **Chapter 3** and 4. We investigated the effect CPAP levels on aeration and breathing rate in preterm animals receiving 0, 5, 8, 12, 15 continuous, 15 to 5 or 15 8 cmH_2O CPAP at birth. In **Chapter 3** we focussed on the ability of PB-CPAP to promote lung aeration in preterm rabbits, whereas in **Chapter 4** we focussed on the potential adverse effects of PB-CPAP on PBF in preterm sheep. In **Chapter 5** we reported the introduction PB-CPAP in the DR and tested the feasibility and effect of PB-CPAP in preterm infants. In this small randomized clinical trial, infants were randomized to receive either CPAP of 5-8 cmH_2O or PB-CPAP starting with 15 cmH_2O that was reduced to 8 cmH_2O.

Lung aeration

The use of phase contrast x-ray imaging allowed us to directly visualise and measure lung aeration, specifically functional residual capacity (FRC), in preterm rabbits (**Chapter 3**). We demonstrated that (initial) 15 cmH_2O CPAP facilitates higher FRCs compared to the currently used CPAP levels and that rabbits supported with 15 cmH_2O more often reached physiological FRCs (≥15 mL/kg). After lung aeration was established, at least 8 cmH_2O CPAP was required to maintain lung aeration.

In **Chapter 4 and 5**, we demonstrated that PB-CPAP, which commenced with 15 cmH_2O CPAP, accelerates and/or elevates the physiological increase in heart rate and PBF. While lung aeration was not measured, the elevated physiological increase in PBF and heart rate likely reflected a higher degree of lung aeration than those supported with the currently used CPAP levels of 5-8 cmH_2O. When infants are born, lung aeration is known to trigger a large increase in PBF. Recent studies suggest that the movement of lung liquid into the interstitial tissue, triggers the J-receptors located in the alveolar wall (12, 21). The stimulation of these receptors

then initiates a vagal reflex that facilitates a global pulmonary vasodilation and a subsequent increase in PBF and heart rate (43, 44).

The finding that PB-CPAP improves lung aeration is in line with previous studies (18, 24-28). However, it remains difficult to compare spontaneous breathing animal models with intubated animals. When intubated, pressures were immediately transmitted to the lungs, which is substantially different from non-invasive CPAP wherein the larynx and upper airway is included in the respiratory circuit. Indeed, in preterm sheep (**Chapter 4**) we observed that 15 cmH_2O CPAP was partially (~75%) transmitted below the trachea, whereas 5-8 cmH_2O CPAP was fully transmitted to the lungs. This suggest that the larynx regulates pressure transmission to the lungs during spontaneous breathing. We suspect that higher CPAP levels may provoke volume receptors in the lung that initiate a Hering-Breuer reflex (45, 46) that prevents over-expansion of the lung.

Oxygenation

We hypothesized that the increase in lung aeration would occur concomitantly with an increase in oxygenation and decrease in oxygen requirement, as oxygenation depends on the lung's surface area available for gas exchange and the oxygen gradient for O_2. In preterm lambs (**Chapter 4**), a static 15 cmH_2O CPAP tended to increase SaO_2 and reduce FiO_2 when compared to 5 cmH_2O. The decrease in CPAP levels always caused an increase in FiO_2 requirement, which indicates that the timing when to decrease the CPAP level is crucial and in this experiment we may have decreased the CPAP level too soon. In our study in preterm infants (**Chapter 5**), it remains difficult to test whether CPAP affect SpO_2, as the high FiO_2 given to most preterm infants has a dominating effect on SpO_2. However, it was possible to decrease FiO_2 sooner in the BP-CPAP. While aeration is likely to positively affect SpO_2, the relative contribution of lung aeration versus the gradient for oxygen diffusion is complex and influenced by other factors e.g. PBF, cardiac output. We speculate that in the clinical trial examining the benefits of PB-CPAP (**Chapter 5**), the use of high FiO_2 levels may have masked the effect of PB-CPAP on SpO_2.

Breathing effort

We evaluated the effect of CPAP levels on breathing effort, i.e. apnea, minute volume and/or rate of breathing. While we evaluated the occurrence of apnea (indicated by iPPV), the studies in this thesis were powered to detect differences in continuous outcomes and groups were too small to detect statistical differences in binary outcomes. In preterm rabbits (**Chapter 3**) we observed that higher CPAP levels reduce the incidence of apnoea, as this was more present in rabbits supported with initial CPAP pressures ≤ 8 cmH_2O (36-46%) compared to those receiving 12-15 cmH_2O (16-20%). Similarly, in our preterm lamb study the incidence of apnoea was higher with 5 cmH_2O (83%) as compared to 15 (17%) cmH_2O CPAP (**Chapter 4**). We concluded that initial higher CPAP levels decrease the risk of apnea. The limited number of included infants and unbalanced occurrence of hypoxia immediately at birth did not allow

us to confirm or refute this in our clinical trial (**Chapter 5**). Larger clinical trials are needed to determine the effect of PB-CPAP on apnea in preterm infants.

While breathing effort was also evaluated by minute volume and breathing rate, the true effect is hard to determine as these are the results of a complex integration of several competing factors. In the rabbit study (**Chapter 3**), breathing rate was higher when kittens were supported with CPAP compared to no CPAP but there seemed to be little difference in breathing rate between CPAP levels. Kittens were able to maintain breathing rates when CPAP was gradually reduced to 8 cmH_2O but not when CPAP was lowered to 5 cmH_2O. In preterm lambs (**Chapter 4**), breathing rates were higher in those supported with 15 cmH_2O CPAP as compared to 5 cmH_2O and when CPAP levels were gradually reduced to 8 cmH_2O lambs were still able to maintain their breathing rate. In a previous study, lambs achieved similar breathing rates when supported by invasive CPAP in the first hours after birth (24).

In preterm infants (**Chapter 5**), PB-CPAP and CPAP levels of 5-8 cmH_2O resulted in statistically similar breathing rates and tidal volumes, however infants supported with PB-CPAP achieved a breathing rate that was ~10 breaths/min higher and tidal volumes seemed to stabilize sooner and at lower volumes. As previous preterm rabbit studies (12, 25) have demonstrated that with each breath tidal volumes decrease while lung aeration increases, we speculate that the time course of changes in breathing rate and tidal volumes may indicate that infants in the PB-CPAP group were breathing more effectively and aeration was established sooner. Increased breathing rates could also result in a Heads paradoxical reflex (47, 48). Lung inflation would then stimulate irritant receptors that provoke the respiratory centre to enhance breathing, which is a common phenomenon in preterm infants who start to breathe during sustained inflations (46, 49-51). However, as tactile stimulation can stimulate breathing (8) this could have led to bias between groups which minimized differences. Tactile stimulation was not standardized and difference in the frequency and method of tactile stimulation in the animal and human infant studies could have occurred, which could explain why CPAP had an effect on breathing rates in preterm infants and sheep but not in preterm rabbits. The CPAP levels may affect breathing effort but there are other factors which can have a larger impact.

Potential adverse effects of physiological based CPAP

Using higher CPAP levels could potentially over-expand the lungs and thereby negatively affect the cardiovascular system. We assessed this in preterm rabbits using PCXI (**Chapter 3**), where we did not find a difference in the occurrence of bulging (visual over-expansion of the non-dependent lung in between the ribs and pneumothoraxes did not occur.

In preterm sheep (**Chapter 4**), we assumed that lung over-expansion would adversely affect the cardiovascular system, which would be reflected by lower heart rates and pulmonary blood flow (40). Instead, lambs supported with 15 cmH_2O CPAP showed an higher PBF, heart rate and blood pressure when compared to 5 cmH_2O, while cerebral blood flow and jugular

venous pressure were left unaffected. 15 cmH_2O clearly provided more cardiovascular stability and all lambs in this group reached the 30 minute end point as opposed to 50% in the 5 cmH_2O group. Post-mortem examinations showed no increase in the risk of pneumothoraxes. From the animal data we conclude that 15 cmH_2O CPAP does not lead to lung over-expansion and provides more cardiovascular stability as compared to lower CPAP levels.

Expansion of the lungs could not be measured in our clinical study (**Chapter 5**), but we did not observe cardiovascular signs of over-expanded lungs. On the contrary, infants receiving PB-CPAP showed an earlier and higher increase in heart rate when compared to 5-8 cmH_2O CPAP. Although this was a small study, none of the infants (n=8) in the PB-CPAP group developed pneumothoraxes during NICU admission and short-term respiratory outcomes were similar between groups.

Once lung aeration has been established, the role of CPAP in supporting the respiratory effort of the infant likely changes. Previous studies (39-42) demonstrated that 8-12 cmH_2O of PEEP during positive pressure ventilation reduces PBF and increases the risk of pneumothoraxes in intubated preterm lambs with already aerated lungs. These findings are not conflicting but emphasize the difference between CPAP during spontaneous breathing and PEEP during positive pressure ventilation as well as the importance of timing the reduction in CPAP. When 15 cmH_2O CPAP is given immediately at birth to facilitate lung aeration, the activation of a neural reflex in response to lung aeration presumably overwhelms the increase in alveolar pressure associated with high CPAP to prevent the reduction in PBF (43, 44). This has also been shown in a previous lamb study whereby 30 second sustained inflations using pressures of 35 cmH_2O did not adversely affect the increase PBF (52). In **Chapter 4**, we found that after lung aeration, a sudden increase in CPAP from 5 to 15 cmH_2O, led to a ~10% reduction in PBF. This is in line with a previous study with intubated preterm lambs where increasing PEEP from 4 to 12 cmH_2O resulted in a ~40% decrease in PBF (40). This again demonstrates that high CPAP levels can be beneficial, but decreases in CPAP levels are needed and the timing of this is essential.

As high CPAP levels would be expected to increase intrathoracic pressure, this could also increase jugular venous pressure and thereby reduce or increase fluctuations in cerebral blood flow (53), which would then increase the risk of IVH. However, in our preterm lamb study (**Chapter 4**) high CPAP did not affect jugular venous pressure or cerebral blood flow. We speculate that this was because the intrathoracic pressure did not exceed the jugular venous pressure due to selective closure of the larynx and the mechanics of spontaneous breathing. During spontaneous breathing, the pressure transmitted to the lungs is effectively the highest intrathoracic pressure but with every inspiration this pressure decreases allowing air to flow into the lungs and thereby phasically decreases below the JVP. Our clinical trial (**Chapter 5**) was too small to make appropriate conclusions on the risk of IVH.

There were also concerns that during CPAP support, air escapes into the intestinal tract and causes gastro-intestinal distention ("CPAP belly") or spontaneous intestinal perforations. However, we did not observe this in the animal studies (**Chapter 3**) nor did we find spontaneous intestinal perforations in our clinical study (**Chapter 5**).

The feasibility of physiological based CPAP in clinical setting

We tested the feasibility of our current PB-CPAP approach in a small clinical trial (**Chapter 5**), wherein we examined protocol adherence and performed post-trial evaluations with neonatologists. Overall, protocol adherence was good, taking into account that a dedicated researcher was present who focussed on the algorithm. There were a few minor protocol deviations in both the PB-CPAP and 5-8 cmH_2O CPAP group. In the post-trial evaluation caregivers indicated that they support the concept of PB-CPAP, but few felt comfortable in performing our current protocol due to its complexity with many predefined actions and evaluation moments. Caregivers found that following the protocol was hard to combine with routine care. While more regular use of PB-CPAP will likely increase the dexterity and confidence among caregivers, the approach requires simplification before the efficacy of PB-CPAP will be tested in a larger trial. Although it has become clear in this thesis that the timing of the CPAP level reduction is essential, the most pragmatic option for simplifying the approach would be to use a consistent CPAP level until the infant is stable and breathing. CPAP can then be decreased when the infant is transferred to the NICU.

Limitations

The main limitation of this study was the use of additional interventions that were used stimulate spontaneous breathing. These include, tactile stimulation, caffeine, FiO_2, which likely influenced the outcome parameters used in this thesis. In animal experiments (**Chapter 3, 4**) these were needed to continue the experiment, whereas in the clinical trial (**Chapter 5**) these interventions were given as part of the standard DR care. These interventions improve oxygenation and breathing effort (11-14) and by using these interventions, we may have introduced bias and have sacrificed our capacity to detect differences in oxygenation and spontaneous breathing. Because the physiological increase in lung aeration is not dependent on oxygenation and breathing effort (despite some breathing being essential), we were still able to demonstrate the evident effect of PB-CPAP on lung aeration.

Our preclinical studies (**Chapter 3, 4**) provided the scientific basis of PB-CPAP and as the approach was feasible in our animal studies, we assumed that this approach would also be feasible to use in the DR. The approach however, appeared too complex for the clinical setting and a more pragmatic protocol is needed (**Chapter 5**). In the experimental setting, everything was controlled and the focus of the study was centred on determining the effect of CPAP. However, in the DR the study intervention was secondary to the infants well-being and is only a part of the total delivery room care. Although the small number of inclusions limits us to draw hard conclusions, the observed effect looks promising and the study (**Chapter 5**),

provided insight in how the PB-CPAP approach can be improved when studied in future studies.

Future perspectives

This thesis provided the scientific rationale to base the CPAP strategy following the physiological changes at birth. We also provided the first steps in clinical use but more studies are needed before PB-CPAP can be recommended for standard care during resuscitation at birth.

Preclinical studies may further expose the underlying mechanisms and indicate if more changes are needed to improve PB-CPAP. These studies may explore the effect of CPAP levels on laryngeal function, how this changes throughout the transition and which reflexes can be triggered during PB-CPAP.

Future studies could also focus on an optimal approach to decrease CPAP levels during PB-CPAP. In this thesis we found that decreasing CPAP too soon increases the FiO_2 requirement (**Chapter 4**) but decreasing CPAP levels too late may increase the risk of adverse events (**Chapter 1**, **2**). In our clinical trial (**Chapter 5**), the PB-CPAP approach involved many predefined evaluations and changes in CPAP levels that were needed to ensure the optimal trajectory for CPAP decrease. As caregivers indicated that the approach was too difficult to execute (when combined with standard delivery room care), we learned that PB-CPAP should also consider feasibility. Future studies may find the optimal PB-CPAP approach and decrease in CPAP levels that considers both effectiveness and feasibility.

Automatization of respiratory support would be a good alternative instead of simplifying the PB-CPAP approach. Algorithms could be developed and based on parameters 1) iPPV would be applied instead of CPAP, automatically decreasing the CPAP/PEEP level and 2) CPAP would be decreased after lung aeration.

Clinical trials may meanwhile investigate our proposed simplified PB-CPAP approach. Larger trials could further explore the potential benefits and allow us to make appropriate conclusions on the potential adverse events. In these future trials, we should reconsider measuring heart rate using pulse oximetry. This measuring technique is only accurate if sufficient cardiac output is established to facilitate adequate peripheral tissue perfusion. As the increase in cardiac output at birth is dependent on the establishment of aeration (43) and PB-CPAP improve aeration and subsequent cardiac output, groups may have an unbalanced timeframe wherein heart rate is underestimated. Therefore, we should consider devices that monitor heart rate more accurately.

In recent years, small clinical trials have studied interventions that stimulate and support spontaneous breathing e.g. repetitive tactile stimulation (8), caffeine (9), FiO_2 levels (10) and now PB-CPAP (**Chapter 5**). While these studies demonstrated potential benefits, all interventions require further evaluation in a larger trial. Because of the low incidence of

extreme prematurity and the high vulnerability of these infants, interventions that stimulate and support spontaneous breathing could be packaged together and studied as a bundle of care. This will reduce the number of patients needed to test the effects (54).

Conclusion

Since the focus of respiratory support at birth has shifted to stimulating and supporting spontaneous breathing, CPAP support at birth should be reconsidered and adjusted to meet the physiological changes at birth. Preterm lamb and rabbit studies demonstrated that an initial 15 cmH_2O CPAP improves lung aeration and provides cardiovascular stability. Once lung aeration has been established, CPAP levels should be decreased. We showed that the timing of the CPAP decrease is essential, but that at least 8 cmH_2O is needed to maintain breathing rate and lung aeration in very immature newborns. In these preclinical studies, we found no indications that PB-CPAP increases the risk of adverse events e.g. pneumothoraxes. When PB-CPAP was introduced in the delivery room, it increased heart rate and shortened the duration of mask ventilation, which is consistent with the proposition that PB-CPAP lead to a better lung aeration. Despite the potential benefits, we found that our current PB-CPAP strategy is considered to be too complex for caregivers and requires simplification. Future studies may i) further explore potential benefits and adverse events of PB-CPAP and ii) explore how to simplify the decrease in CPAP levels while still being effective in maintaining aeration and oxygenation.

References

1. Morley CJ, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7):700-8.
2. Finer NN, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970-9.
3. Trevisanuto D, et al. Changes over time in delivery room management of extremely low birth weight infants in Italy. Resuscitation. 2014;85(8):1072-6.
4. Harding R, et al. Upper airway resistances in fetal sheep: the influence of breathing activity. Journal of Applied Physiology. 1986;60:160-5.
5. Crawshaw JR, et al. Laryngeal closure impedes non-invasive ventilation at birth. Arch Dis Child Fetal Neonatal Ed. 2018;103(2):F112-F9.
6. Renolleau S, et al. Thyroarytenoid muscle electrical activity during spontaneous apneas in preterm lambs. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1396-404.
7. Moreau-Bussiere F, et al. Laryngeal response to nasal ventilation in nonsedated newborn lambs. J Appl Physiol (1985). 2007;102(6):2149-57.
8. Dekker J, et al. Repetitive versus standard tactile stimulation of preterm infants at birth - A randomized controlled trial. Resuscitation. 2018;127:37-43.
9. Dekker J, et al. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. Pediatr Res. 2017;82(2):290-6.
10. Dekker J, et al. The Effect of Initial High vs. Low FiO2 on Breathing Effort in Preterm Infants at Birth: A Randomized Controlled Trial. Front Pediatr. 2019;7:504.
11. Hooper SB, et al. Imaging lung aeration and lung liquid clearance at birth. FASEB J. 2007;21(12):3329-37.
12. Siew ML, et al. Inspiration regulates the rate and temporal pattern of lung liquid clearance and lung aeration at birth. J Appl Physiol (1985). 2009;106(6):1888-95.
13. Siew ML, et al. The role of lung inflation and sodium transport in airway liquid clearance during lung aeration in newborn rabbits. Pediatr Res. 2013;73(4 Pt 1):443-9.
14. Dekker J, et al. Increasing Respiratory Effort With 100% Oxygen During Resuscitation of Preterm Rabbits at Birth. Front Pediatr. 2019;7:427.
15. Wyllie J et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 7. Resuscitation and support of transition of babies at birth. Resuscitation. 2015;95:249-63.
16. Wyckoff MH, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):S543-60.
17. te Pas AB, et al. Effect of sustained inflation length on establishing functional residual capacity at birth in ventilated premature rabbits. Pediatr Res. 2009;66(3):295-300.

18. te Pas AB, et al. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res. 2009;65(5):537-41.
19. Siew ML, et al. Surfactant increases the uniformity of lung aeration at birth in ventilated preterm rabbits. Pediatr Res. 2011;70(1):50-5.
20. Miserocchi G, et a;. Pulmonary interstitial pressure in anesthetized paralyzed newborn rabbits. J Appl Physiol (1985). 1994;77(5):2260-8.
21. Bland RD, et al. Clearance of liquid from lungs of newborn rabbits. J Appl Physiol Respir Environ Exerc Physiol. 1980;49(2):171-7.
22. Hooper SB, et al. Respiratory transition in the newborn: a three-phase process. Arch Dis Child Fetal Neonatal Ed. 2016;101(3):F266-71.
23. Madar J, et al. European Resuscitation Council Guidelines 2021: Newborn resuscitation and support of transition of infants at birth. Resuscitation. 2021;161:291-326.
24. Mulrooney N, et al. Surfactant and physiologic responses of preterm lambs to continuous positive airway pressure. Am J Respir Crit Care Med. 2005;171(5):488-93.
25. Siew ML, et al. Positive end-expiratory pressure enhances development of a functional residual capacity in preterm rabbits ventilated from birth. J Appl Physiol (1985). 2009;106(5):1487-93.
26. te Pas AB, et al. Optimizing lung aeration at birth using a sustained inflation and positive pressure ventilation in preterm rabbits. Pediatr Res. 2016;80(1):85-91.
27. Kitchen MJ, et al. Changes in positive end-expiratory pressure alter the distribution of ventilation within the lung immediately after birth in newborn rabbits. PLoS One. 2014;9(4):e93391.
28. Tingay DG, et al. Effect of sustained inflation vs. stepwise PEEP strategy at birth on gas exchange and lung mechanics in preterm lambs. Pediatric research. 2014;75(2):288-94.
29. Miedema M, et al. Effect of nasal continuous and biphasic positive airway pressure on lung volume in preterm infants. The Journal of pediatrics. 2013;162(4):691-7.
30. Magnenant E, et al. Dynamic behavior of respiratory system during nasal continuous positive airway pressure in spontaneously breathing premature newborn infants. Pediatr Pulmonol. 2004;37(6):485-91.
31. Richardson CP, et al. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. Pediatric research. 1978;12(7):771-4.
32. Bhatia R, et al. Regional Volume Characteristics of the Preterm Infant Receiving First Intention Continuous Positive Airway Pressure. The Journal of pediatrics. 2017;187:80-8 e2.
33. Templin L, et al. A Quality Improvement Initiative to Reduce the Need for Mechanical Ventilation in Extremely Low Gestational Age Neonates. Am J Perinatol. 2017;34(8):759-64.

34. Petrillo F, et al. Pulmonary Recruitment Strategy in Preterm Neonates <29 Weeks of Gestational Age to Reduce the Need for Intubation in the Delivery Room. Am J Perinatol. 2019;36(S 02):S115-S9.
35. Kanaan Z, et al. Feasibility of combining two individualized lung recruitment maneuvers at birth for very low gestational age infants: a retrospective cohort study. BMC Pediatr. 2020;20(1):144.
36. Hausdorf G, et al. Influence of positive end-expiratory pressure on cardiac performance in premature infants: a Doppler-echocardiographic study. Crit Care Med. 1987;15(7):661-4.
37. Maayan C, et al. Effect of mechanical ventilation and volume loading on left ventricular performance in premature infants with respiratory distress syndrome. Crit Care Med. 1986;14(10):858-60.
38. Trang TT, et al. Optimization of oxygen transport in mechanically ventilated newborns using oximetry and pulsed Doppler-derived cardiac output. Crit Care Med. 1988;16(11):1094-7.
39. Probyn ME, et al. Positive end expiratory pressure during resuscitation of premature lambs rapidly improves blood gases without adversely affecting arterial pressure. Pediatr Res. 2004;56(2):198-204.
40. Polglase GR, et al. Positive end-expiratory pressure differentially alters pulmonary hemodynamics and oxygenation in ventilated, very premature lambs. J Appl Physiol (1985). 2005;99(4):1453-61.
41. Polglase GR, et al. Cardiovascular and pulmonary consequences of airway recruitment in preterm lambs. J Appl Physiol (1985). 2009;106(4):1347-55.
42. Crossley KJ, et al. Blood gases and pulmonary blood flow during resuscitation of very preterm lambs treated with antenatal betamethasone and/or Curosurf: effect of positive end-expiratory pressure. Pediatr Res. 2007;62(1):37-42.
43. Lang JA, et al. Increase in pulmonary blood flow at birth: role of oxygen and lung aeration. J Physiol. 2016;594(5):1389-98.
44. Lang JA, et al. Vagal denervation inhibits the increase in pulmonary blood flow during partial lung aeration at birth. J Physiol. 2017;595(5):1593-606.
45. Haddad GG, et al. The role of airway receptors in the control of respiration in infants: a review. The Journal of pediatrics. 1977;91(2):281-6.
46. Kuypers K, et al. Reflexes that impact spontaneous breathing of preterm infants at birth: a narrative review. Archives of disease in childhood Fetal and neonatal edition. 2020;105(6):675-9.
47. Widdicombe JG, et al. Vagal deflation and inflation reflexes mediated by lung irritant receptors. Q J Exp Physiol Cogn Med Sci. 1970;55(2):153-63.
48. Knill R, et al. An intercostal-phrenic inhibitory reflex in human newborn infants. J Appl Physiol. 1976;40(3):352-6.
49. Kuypers K, et al. The effect of a face mask for respiratory support on breathing in preterm infants at birth. Resuscitation. 2019.

50. van Vonderen JJ, et al. Effects of a sustained inflation in preterm infants at birth. J Pediatr. 2014;165(5):903-8 e1.
51. Lista G, et al. Effects of Breathing and Apnoea during Sustained Inflations in Resuscitation of Preterm Infants. Neonatology. 2017;111(4):360-6.
52. Sobotka KS, et al. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res. 2011;70(1):56-60.
53. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatric research. 2010;67(1):1-8.
54. Dekker J, et al. Stimulating and maintaining spontaneous breathing during transition of preterm infants. Pediatr Res. 2019.