Physiological based CPAP for preterm infants at birth

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Summary

Introduction

Most preterm infants require respiratory support at birth, which is currently most commonly applied non-invasively along with a focus on stimulating and supporting spontaneous breathing (1). Recent studies demonstrated that breathing effort can be improved by repetitive tactile stimulation, caffeine administration and adequate oxygenation (2-4). There is, however, little data on the optimal continuous positive airway pressure (CPAP) approach to assist preterm infants in establishing and maintaining lung aeration at birth (5). Lung aeration is driven by the transpulmonary pressure gradient that is generated during inspiration and this gradient can be increased by applying CPAP. Currently, 5-8 cmH_2O is used for CPAP in the delivery room (DR), however this pressure range is extrapolated from CPAP support in the neonatal intensive care unit. As the physiology of a newborn infant at birth is considerably different than it is later on in the unit, it is likely that a different CPAP strategy may also be needed to establish lung aeration at birth.

The underlying principle of physiological based (PB)-CPAP is to tailor the CPAP level to take into account the physiological changes that occur in the infant during the transition at birth. Immediately at birth, the main role of CPAP is assist the infants attempts to move liquid out of the airways into the interstitial tissue and hence promote lung aeration. During this process, the high airway resistance requires (6-8) higher pressure gradients and, therefore, high initial CPAP levels (9, 10). After lung aeration has been established, airway resistance decreases and the role of CPAP converts to maintaining lung aeration. Lower CPAP levels match the lower airway resistance and are likely to be sufficient to prevent alveolar collapse and liquid re-entry in the post aeration period (6-14). When the CPAP titration is guided by real time parameters, PB-CPAP can be individualized and CPAP levels will suit the different phases of lung aeration.

The aim of this thesis was to develop a PB-CPAP strategy and to investigate the effect on cardiopulmonary stabilization of preterm infants at birth. We hypothesized that infants at birth benefit from PB-CPAP, mostly by promoting lung aeration. The potential benefits and harms of PB-CPAP were evaluated in preclinical studies and the feasibility was investigated in a small clinical trial.

Which CPAP levels to use for PB-CPAP?

In **Chapter 1** we evaluated the available literature to determine which CPAP levels to use for our PB-CPAP approach. As the existing literature was limited, the search strategy included articles on CPAP during spontaneous breathing and positive end-expiratory pressures (PEEP) levels during positive pressure ventilation at birth. Studies found that higher CPAP levels could be beneficial, as animal studies showed that 8-20 cmH_2O CPAP/PEEP improves aeration and oxygenation (10, 15-19) and clinical studies found that 6-15 cmH_2O of PEEP reduced intubation and ventilation rates in the DR when compared to 4-5 cmH_2O (20-22). However,

there were also concerns regarding the use of higher pressures. In intubated preterm sheep whose lungs were already aerated, 8 cmH_2O CPAP did not cause pneumothoraxes (15), however 8-12 cmH_2O PEEP reduced pulmonary blood flow (PBF) and increased the risk of pneumothoraxes (23-26). Clinical studies found no indications of adverse events when 6-15 cmH_2O PEEP was implemented in the DR (20-22) and it is possible that 15 cmH_2O CPAP does not over-expand the lungs immediately at birth. However, harm may be caused if pressures remain above 8 cmH_2O after lung aeration.

In **Chapter 2** we report our findings of a retrospective comparison study, in which we evaluated the CPAP strategies of two centers (5-8 cmH_2O vs 12-35 cmH_2O CPAP). We included 27 pairs of infants, who were born before 28 weeks of gestation and were matched based on birthweight and gestational age. We could not detect the effect of different CPAP levels on oxygen saturation (SpO_2), which could be due to the fact that the larynx hampered support from reaching the lungs during apnea. However, the SpO_2/FiO_2 ratio remained similar between groups when FiO_2 was increased in the 5-8 cmH_2O but not in the 12-35 cmH_2O group, which is likely due to the fact that higher CPAP levels facilitated increased aeration that was needed to attain similar SpO_2/FiO_2 ratios. We also found that most infants who were supported with 5-8 cmH_2O CPAP received iPPV and were then subjected to MAPs of ~15 cmH_2O. There were no signs of pulmonary over-expansion and cardiovascular impairment in both groups. Yet, infants in the 12-35 cmH_2O CPAP group developed a higher pneumothorax rate later on and while different factors may have contributed to the development of these pneumothoraxes, it could also emphasize the risks of continuing high CPAP levels after lung aeration has been established.

Proposed physiological based CPAP approach

Based on our findings in **Chapter 1 and 2**, we know that higher pressures are beneficial for promoting lung aeration (15, 17, 18) and that infants commonly receive MAPs of ~15 cmH_2O as a result of iPPV during stabilization. We also know that once lung aeration has been established, continuation of pressures above 8 cmH_2O could cause harm (23-26) (**Chapter 2**). Taking this in consideration and that 8 cmH_2O CPAP is the upper range commonly used in the NICU, we decided that our PB-CPAP approach should commence with 15 cmH_2O and be reduced to 8 cmH_2O once the infant is stabilized.

Evaluating physiological based CPAP

In **Chapter 3** we examined the potential benefits of PB-CPAP, as we measured the effects of CPAP on lung aeration. Spontaneously breathing preterm rabbits (~26-28 weeks human gestation) received 0, 5, 8, 12, 15 cmH_2O of CPAP or variable CPAP of 15 to 5 or 15 to 8 cmH_2O (decreasing ~2 cmH_2O/min) for up to 10 min after birth. Lung function was measured using phase contrast x-ray imaging. We demonstrated that 15 cmH_2O indeed improved lung aeration and reduced the occurrence of apnea when compared to the currently used CPAP

levels but that there was no effect on breathing rate. Once lung aeration was established, at least 8 cmH_2O CPAP was required to maintain aeration and breathing rate. We also observed that the use of 15 cmH_2O did not increase the risk of lung over-expansion, pneumothorax or CPAP belly, which were rare in this study.

In **Chapter 4** we investigated the potential adverse effects of PB-CPAP on pulmonary and cerebral blood flow (PBF). We hypothesized that 15 cmH_2O may over-expand the lungs, which may reduce physiological increase in PBF caused by lung aeration at birth. Preterm lambs received 5, 15 continuous or 15 to 8 cmH_2O CPAP while we measured cardiovascular parameters. In this study, we demonstrated that 15 cmH_2O CPAP improved the physiological increase in PBF and heart rate at birth, which reflects improved lung aeration. The increase in PBF, as well as higher arterial pressures and normal jugular venous pressures, indicates that PB-CPAP does not cause pulmonary over-expansion or impede cardiovascular function. Similarly, as cerebral blood flow and jugular venous pressure were not affected, B-CPAP did not increase the risk for intraventricular hemorrhage. Furthermore, 15 cmH_2O seemed to positively benefit oxygenation and better support spontaneous breathing as lambs achieved higher SpO_2, required lower FiO_2, lower apnea incidences, higher breathing rates and lower intubation rates. We found that the decrease of CPAP levels caused an increase in FiO_2 requirement, which may indicate that CPAP levels were decreased too soon. There were no indications of increased risk on pneumothoraxes, as these were not found in the lambs receiving 15 cmH_2O CPAP during post-mortem examination. Because we observed that 15 cmH_2O CPAP was only partially (~75%) transmitted below the trachea and 5-8 cmH_2O CPAP was fully transmitted to the lungs, we suggest that the larynx regulates pressure transmission to the lungs and functions as a preventive mechanism to protect the infant from possible harm.

Finally, in **Chapter 5** we describe a small randomized controlled trial where we tested the feasibility and effects of PB-CPAP in infants born between 24-30 weeks gestation. Infants were randomized to PB-CPAP or 5-8 cmH_2O CPAP for the first 10 min after birth. PB-CPAP involved applying an initial CPAP level of 15 cmH_2O, which was decreased stepwise until 8 cmH_2O once infants were stabilized (defined as: spontaneous breathing and heart rate ≥100 bpm, SpO_2 ≥85% with FiO_2 ≤0.4). Planned enrollment was 42 infants, however the study was halted prematurely due to a low inclusion rate and recent changes in the local resuscitation guideline that conflicted with the study protocol. We evaluated the feasibility of our PB-CPAP approach by checking protocol adherence and via post-trial evaluations. We found that there were only few minor protocol deviations, which occurred in both groups. Yet, the PB-CPAP protocol was too complex for caregivers and requires simplification. This was due to the need to make many CPAP changes and evaluations. We measured the effects of PB-CPAP in 28 infants (PB-CPAP n=8, 5-8 cmH_2O n=20). We found evidence to indicate that PB-CPAP improves lung aeration, which was reflected by improved heart rate and the course of change in breathing rates and tidal volumes. While improved lung aeration may explain the shortened duration of mask ventilation and faster stabilization of infants supported with PB-CPAP, there were no

statistical differences in SpO_2 or FiO_2. In this study, there were no indications for increased risk of adverse events, however the low number of included infants prevented us from making appropriate conclusions on short-term outcomes.

Conclusion

In the **General discussion** we discuss the beneficial effect of PB-CPAP on establishing and maintaining lung aeration, as demonstrated in our experimental studies. In addition, no cardiopulmonary adverse effect could be demonstrated in the experimental setting. We demonstrated in our clinical study that infants reached cardiovascular stability sooner, shortening the duration of mask ventilation. While improved aeration positively affects oxygenation in preterm lambs, we found no effect of CPAP on SpO_2 and FiO_2 in our clinical trial, which apart from a small sample size, can likely be attributed to the use of high FiO_2 levels. Our findings of the effect of PB-CPAP on breathing effort were conflicting. As spontaneous breathing depends on various competing factors and can be influenced by oxygenation or tactile stimulation, for example, the true effect of CPAP levels on breathing effort remains unclear.

In this thesis, we also found that the timing of reducing CPAP levels following stabilization is essential. Decreasing CPAP levels too soon leads to an increase the FiO_2 requirement, but decreasing CPAP levels too late may increase the risk of adverse events. To ensure the optimal CPAP decrease in our clinical trial, the PB-CPAP approach involved several predefined evaluations and changes in CPAP levels. This has shown to be too complex for caregivers and hard to combine with standard delivery room care. While a more pragmatic approach with a less complicated algorithm would increase feasibility, this should be balanced against the importance of optimal timing of the CPAP level reduction. Future studies are needed to test the feasibility and effectiveness of this improved BP-CPAP approach before it can be implemented in daily practice.

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