Physiological based CPAP for preterm infants at birth

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Chapter 1

Supporting breathing of preterm infants at birth: a narrative review

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Abstract

Most very preterm infants have difficulty aerating their lungs and require respiratory support at birth. Currently in clinical practice, non-invasive ventilation in the form of continuous positive airway pressure (CPAP) and positive pressure ventilation (PPV) is applied via facemask. As most very preterm infants breathe weakly and unnoticed at birth, PPV is often administered. PPV is, however, frequently ineffective due to pressure settings, mask leak and airway obstruction. Meanwhile, high positive inspiratory pressures and spontaneous breathing coinciding with inflations can generate high tidal volumes. Evidence from preclinical studies demonstrates that high tidal volumes can be injurious to the lungs and brains of premature newborns. To reduce the need for PPV in the delivery room, it should be considered to optimise spontaneous breathing with CPAP. CPAP is recommended in guidelines and commonly used in the delivery room after a period of PPV, but little data is available on the ideal CPAP strategy and CPAP delivering devices and interfaces used in the delivery room. This narrative review summarises the currently available evidence for why PPV can be inadequate at birth and what is known about different CPAP strategies, devices and interfaces used the delivery room.

Introduction

Lung aeration at birth plays a key role in initiating the major physiological changes that are required for survival after birth (1-3). Most very preterm infants have difficulty aerating their lungs and establishing functional residual capacity, for which respiratory support is often needed (4, 5). Respiratory support has to be provided with care as preclinical studies in premature lambs have shown that inadequate or improper respiratory support can easily injure the premature lung and brain via haemodynamic instability and activation of inflammatory pathways (6, 7) Previously, all infants were intubated and mechanical ventilation was given; however, clinical trials (8, 9) have shown that nasal continuous positive airway pressure (CPAP) instead lowers the combined risk of death or oxygen requirement at 28 days after birth and reduces the duration of ventilation. The focus has therefore shifted (10) to non-invasive ventilation in the form of CPAP and positive pressure ventilation (PPV).

While most very preterm infants breathe spontaneously at birth, their respiratory drive is insufficient to achieve lung aeration (3, 4) and their spontaneous breathing is often missed (11). PPV is therefore initiated via facemask, however observational clinical studies have shown that PPV is often inadequate to deliver tidal volumes between 4 and 8 mL/kg due to pressure settings, mask leak and obstruction. Meanwhile, PPV can also generate potentially injurious high tidal volumes due to high positive inspiratory pressures (PIP) or when spontaneous breathing coincides with inflations (5, 6) Given the fact that infants often breathe spontaneously, although insufficient, and PPV is often inadequate and/or injurious, optimising respiratory effort of very preterm infants with CPAP may represents an improved approach. While CPAP has been adopted worldwide and several studies have described the technique and equipment to use this technique (12), there is little evidence for the optimal pressure strategy and which devices and interfaces that should be used to best support breathing in very preterm infants (13).

In this review, we summarise the currently available evidence for why PPV can be insufficient and what is known about the effect of different CPAP strategies in very preterm newborns at birth. We searched on PubMed for (pre)clinical studies comparing different pressure support levels, CPAP supplying devices or pressure delivering interfaces specifically used in the delivery room. The reference list of included articles was checked to identify articles not included in the primary search.

CPAP or PPV via facemask when breathing is insufficient in very preterm newborns

PPV is currently initiated at birth when infants are apnoeic or breathe insufficiently (14-16). PPV, however, often fails to support the respiratory need of the infant. In a clinical observational study (5), 36% of all inflations consisted of a tidal volume below 2.5 mL/kg, while healthcare providers aimed to deliver tidal volumes of 4-8 mL/kg. This can be caused by the use of inadequate pressures, incorrect facemask positioning leading to mask leak and by obstruction (Figure 1). Pressing the mask on the face too tight, obstruction of the nose and mouth and overextension or flexion of the neck may obstruct gas flow to the lungs (17, 18).

The physiology of the very preterm newborn also impacts on the success of non-invasive ventilation in the delivery room: closure of the larynx is a contributing factor for PPV failure (19-21). Before birth, the larynx of the fetus is closed to retain lung liquid in the airways to create a positive expanding pressure that stimulates lung growth and development (22-24). After birth, the larynx transitions to create a patent airway for breathing. Phase contrast (PC) X-ray imaging (21) in preterm rabbit pups immediately after birth showed that the larynx is closed if the pup is apnoeic. During a spontaneous breath, the larynx opens, which allows aeration of the lungs, but closes again if the breathing is intermittent. Unlike previously suggested, opening of the larynx throughout the respiratory cycle is closely associated with a stable breathing pattern (21) rather than the degree of lung aeration (25). Establishing a stable breathing pattern by stimulating spontaneous breathing might be the key to accelerate the laryngeal switch from closed fetal to open newborn state. Very preterm infants could benefit from focussing on spontaneous breathing rather than providing PPV against a closed glottis, especially as PPV triggered closure of the larynx again in rabbit pups who already had a stable breathing pattern (21).

PPV can also be injurious to the premature lungs and brains when high tidal volumes are given. As it is hard to estimate the delivered tidal volume during PPV (26), an observational study showed that in 10% of all inflations, tidal volumes were >10 mL/kg despite target values being 4-8 mL/kg (5). While this could be attributed to a high PIP, it has been observed that spontaneous breathing coincided with inflations also contributes to higher delivered tidal volumes (5, 11). Preclinical studies showed that high tidal volumes adversely affect the cardiopulmonary haemodynamics and even can cause lung (27, 28) and brain injury (6, 29). A recent clinical study (30) confirmed the danger of high tidal volumes, as they found more intraventricular haemorrhages in infants receiving tidal volumes >6 mL/kg.

PPV is often ineffective at aerating the lung or can even be injurious. Optimising spontaneous breathing by CPAP might be a better approach. Most very preterm infants breathe at birth, although weakly, and stimulating spontaneous breathing may be the key to accelerate the switch from closed fetal to open newborn larynx state and CPAP might therefore be less obstructive. Also, during CPAP, less mask leak occurs, as most mask leak occurs during intermittent pressurisation of the mask (5). Most very preterm infants breathe in between inflations and the mean tidal volumes generated by these spontaneous breaths in are commonly at least as large on CPAP as the tidal volumes those generated by PPV (5). Since infants generate their own tidal volume when breathing spontaneously, it is likely that ideally titrated CPAP during the transition at birth will cause less harm.

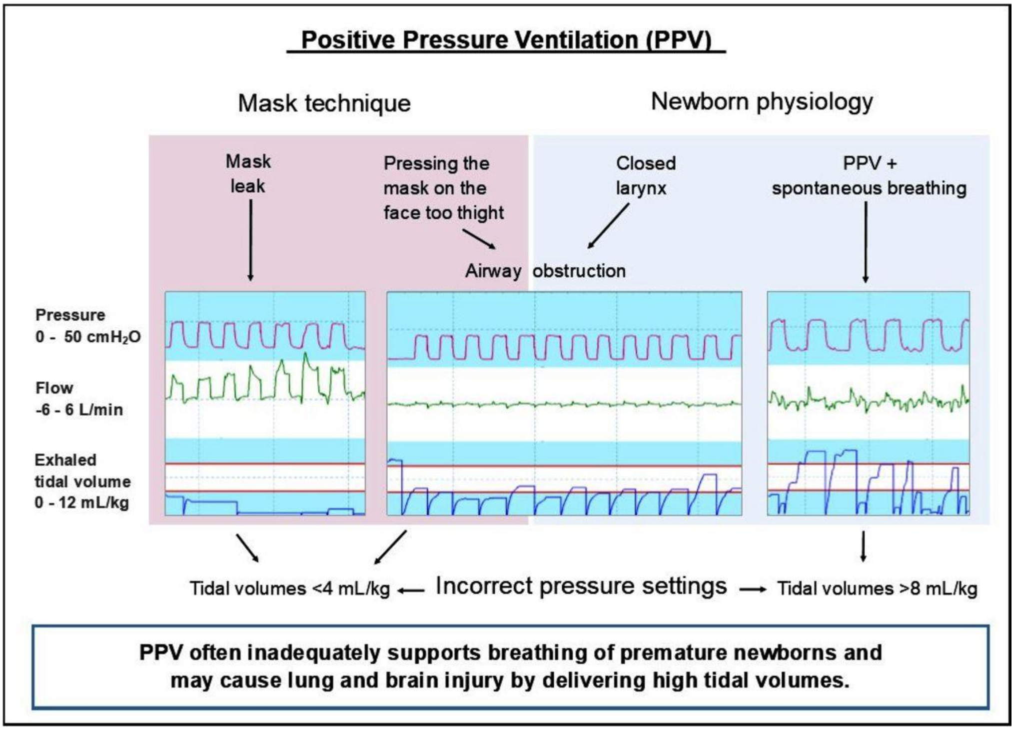

Figure 1. Why is positive pressure ventilation (PPV) often inadequate and/or injurious? The success of PPV is determined by pressure settings, mask technique and newborn physiology. During mask leak, the flow escapes and the baseline shifts up and the infant only generates small tidal volumes. When the mask is pressurised too tight to the face or when the larynx is closed gas flow is obstructed; the flattened flow line shows the air is unable to enter the lungs and small tidal volumes are generated. When the infant breaths coinciding with PPV inflations the tidal volumes rise unexpectedly above safety ranges (4-8 mL/kg; red lines). Inadequate and high tidal volumes can cause injury to the premature lungs and brain.

Which CPAP strategy?

Although CPAP levels of 5-6 cmH_2O are commonly used in the delivery room, CPAP levels and titration strategies vary widely between neonatal centres (13, 14) To date, no clinical trials have been performed assessing different CPAP strategies in very preterm infants at birth. Preclinical studies (Table 1) have provided fundamental evidence comparing the use of different CPAP (31) and positive-end expiratory pressure (PEEP) strategies (32-36) in preterm newborns in the delivery room. During mechanical ventilation (MV), both PEEP and PIP are used to ventilate the infant via an endotracheal tube, whereas PPV is applied non-invasively via facemask or prongs. On CPAP, infants breathe spontaneously on a continuous pressure to prevent the alveoli from collapse. In this review, we distinct PEEP (as part of PPV or MV) and CPAP. The preclinical studies investigated (changing) CPAP and PEEP levels of 0-12 cmH_2O, and some studies (31, 32, 34, 36) were performed after the lungs were aerated as part of the ventilation strategy.

Mulrooney et al. (31) compared bubble CPAP in preterm lambs, whereas other studies (32-34, 36) compared various PEEP strategies as part of MV (Table 1). All studies concluded that increasing and/or initiating with higher PEEP levels improved oxygenation and was more effective at supporting the respiratory transition at birth.

A PC X-ray imaging study (35) in premature rabbit pups found that the initial levels of PEEP also influence the distribution of air throughout the lungs, and this effect even remains after pressure levels are adjusted over time. The study highlighted that when initial PEEP levels of 10 cmH_2O were used in preterm rabbits during MV, the air distributed uniformly across the lungs. When the PEEP level was reduced, the uniformity of lung aeration deteriorated but could easily be restored by increasing the PEEP pressure. When MV was initiated with 0 or 5 cmH_2O PEEP, lungs were not uniformly aerated, and this could not be improved by increasing the PEEP. This finding suggests that uniform lung aeration is best achieved by starting respiratory support with higher PEEP levels.

Pressure levels also affect essential markers of the cardiorespiratory transition at birth to establish an independent circulation: the pulmonary vascular resistance and pulmonary blood flow (PBF). As initial high PEEP levels improve lung aeration, it is likely to promote the increase in PBF. Due to the non-compliant nature of the liquid-filled lung at birth, high PEEP levels will not compress the perialveolar capillaries initially (33, 37). As lung compliance increases as the lung aerates, maintaining high PEEP levels will eventually compress the intra-alveolar capillaries and reduce PBF (32, 34, 36). Other cardiovascular haemodynamic components, that is, ductus arteriosus shunting and heart rate, are affected by the PEEP level and can reduce the PBF. Decreasing the PEEP, however, will not restore PBF to initial values due to volume hysteresis within the lungs (32, 36).

Increasing to higher pressure levels after lung aeration also affect the breathing rate. Crawshaw et al. (21) showed that increasing CPAP levels after lung aeration decreases the breathing rate in very premature rabbit pups. In pups who already established a stable breathing pattern, the respiratory rate was reduced as CPAP levels were increased above 7 cmH_2O.

High PEEP levels could also overexpand the lungs. However, it is unknown at what level overexpansion occurs. Probyn et al. (33) reported optimal lung compliance at 8 cmH_2O and Crossley et al. (34) found no difference comparing different PEEP levels. Both studies started their intervention after the lungs were aerated (Table 1). As they observed pneumothoraxes when ventilating premature lambs with 12 cmH_2O PEEP, it could be too high to use in human infants once the lungs are aerated.

While these studies highlight the fundamental physiology underpinning the newborn transition, the results cannot directly be translated into the clinical setting where we aim to support spontaneous breathing by CPAP and PPV via prongs or facemask. During the experiments, animals were sedated and intubated to provide PEEP as part of MV. During intubation, the larynx is bypassed resulting in less leak and obstruction. In addition, most studies were performed after the lungs were aerated and therefore have not characterised the effect of CPAP during the respiratory transition. The animal experiments are, however, a unique opportunity to investigate the underlying physiology and factors that cannot be measured in humans. The experiments provide a basis for further (pre)clinical trials investigating different CPAP levels. We expect that high CPAP levels improve (the uniformity of) lung aeration, oxygenation and subsequent PBF. Maintaining high CPAP levels after lung aeration can reduce the PBF and respiratory rate and can increase the risk of overexpansion and pneumothoraxes in preterm sheep. Very preterm infants therefore might benefit initial higher PEEP levels that are titrated after lung aeration

Table 1. Preterm animal models using CPAP or MV to investigate PEEP strategies in newborn physiology

Study characteristics				PEEP strategy			Outcome Measure	Summary results focussing on CPAP levels (high levels vs low levels)
Study	Model	Mean age (d)	Pressure support	Lung aeration prior to the experiment	Intervention	Duration (min)		
Mulrooney et al. (31)	Lambs n=21	130-136*	CPAP	10 min 8 cmH_2O	5 cmH_2O vs 8 cmH_2O	360	Blood gas, ventilation parameters	Using 8 cmH_2O oxygenation and lung gas volumes were higher. At 8 cmH_2O the animals had a lower breathing rate while generating similar tidal volumes
Probyn et al. (33)	Lambs n=19	125	MV	No	0 cmH_2O vs 4 cmH_2O vs 8 cmH_2O vs 12 cmH_2O	135	Blood gas, arterial pressure, ventilation and physiological parameters.	Oxygenation improved mostly using PEEP ≥8 cmH_2O. Lambs receiving 12cmH_2O developed pneumothoraxes
Polglase et al. (36)	Lambs n=13	129 +/- 1	MV	20 min 4 cmH_2O	4-6-8-10-8-6-4 cmH_2O vs 4 cmH_2O	70 min; each level held for 10 min	Oxygenation, PBF, shunting through the ductus arteriosus	At PEEP 10 cmH_2O PBF lowered due to an increase in pulmonary vascular resistance and increased R-L shunting. High PEEP also impaired cardiovascular function e.g. reduction in heart rate

Polglase et al. (32)	Lambs n=11	127	MV	20 min 4 cmH_2O	0, 8, 10, 12 cmH_2O in random order, returning to 4 cmH_2O in between vs 4 cmH_2O	120 min; each level held for 20 min	Pulmonary vascular resistance, oxygenation, PBF and its' waveform	PEEP of 8 and 12 cmH_2O improved oxygenation, however increased pulmonary vascular resistance leading to lower PBF, adversely affecting the pulmonary hemodynamic
Crossley et al. (34)	Lambs n=23	126	MV	20 min 4 cmH_2O	0, 8, 10, 12 cmH_2O in random order, returning to 4 cmH_2O in between vs4 cmH_2O	120 min; each level held for 20 min	Blood gases, PBF	Oxygenation improved with increasing PEEP levels ≥8 cmH_2O, however these levels reduced PBF
Kitchen et al. (35)	Rabbits n=16	28	MV	No	0-5-10-5-0 cmH_2O vs 5-10-0-5-0 cmH_2O vs 10-5-0-10-0 cmH_2O	50 min; each level held for 10 min	Distribution of ventilation within the lung	PEEP of 10 cmH_2O accelerates (uniform) lung aeration. Starting PEEP level determines air distribution, even after changing PEEP strategy

Lambs term GA ~147+/-3 days. Rabbits term gestational age ~32 days. *Age is presented as range.

Which CPAP delivering device?

Several pressure delivering devices are currently used to apply CPAP in the delivery room. It is not possible to apply CPAP with a self-inflating mask and bag. The Neopuff T-piece creates PEEP by supplying a constant flow against an adjustable resistor, whereas the Benveniste valve creates PEEP by flow opposition (38, 39). Mechanical ventilators have a microprocessor controlled expiratory valve at the end of the expiratory limb that detect pressure changes and adjust the valve to maintain the target pressure level. Bubble CPAP devices have an expiratory limb placed at fixed depths under water to create pressure with bias gas flow forming bubbles that cause oscillations in the delivered CPAP (40-42).

Although most healthcare providers prefer to use a device that is capable to deliver PPV, it is currently unclear which device is most effective for applying CPAP at birth. Bench tests (40-42) found the lowest pressure stability and highest expiratory resistance with the Neopuff when compared with bubble CPAP, ventilator and the Benveniste valve. The authors stated that these factors combined could lead to a high work of breathing (WOB) (40-42). To reduce WOB, Donaldsson et al. (43) developed a novel ventilator system that reduced the WOB during expiration. In a bench test, they reported higher pressure stability and lower WOB when using the novel device with masks or nasal prongs compared with the Neopuff. We find these findings are difficult to extrapolate to the clinical setting. The sinusoidal pump was used to simulate breathing, leading to an active and forced expiration, whereas the infants' expiration is passive.

Pillow et al. (44) argued that the oscillation of bubble CPAP may promote opening of the airways, hence, improving alveolar recruitment. Comparing bubble CPAP and the Neopuff in newborn lambs showed that bubble CPAP improved arterial oxygen levels 3 hours after birth (45). Although the WOB is dependent on the level of gas flow, no physiological or clinical benefits were found when increasing the flow from 8 to 12 L/min.

There is no further clinical data comparing CPAP devices in the delivery room, except that Donaldson et al. (43) compared the novel resuscitation device using facemask and nasal prongs with the Neopuff in a randomised feasibility trial including 36 infants 27-34 weeks of gestation. There were no differences in study outcomes; the results were difficult to interpret given the large differences in gestational age (231±9.9 vs 228±10.7 vs 215±16.9 days) between groups. Following this feasibility trial, Jonsson et al. (46) are now comparing both devices in a large (n=250) randomised clinical trial, the CORSAD (NCT02563717), including infants<28 weeks of gestation.

Respiratory support strategies other than CPAP have also been tried in the delivery room. Non-invasive high frequency oscillation has been tested and is anecdotally used in the delivery room, although no published studies are available. Furthermore, an observational cohort study (47) in infants between 23 and 29 weeks of gestation examined nasal high flow at 6-8 L/min to support spontaneous breathing. This study stated that nasal high flow can create

CPAP and is feasible to use in the delivery room. The CPAP levels generated by nasal high flow are, however, dependent on fluctuating factors, for example, mouth opening and cannula size in relation to the infants' anatomy, therefore it is hard to predict and measure the generated CPAP level.

Currently, there are several CPAP devices used in the delivery room. Bench test implicate that the WOB that they produce can significantly differ and novel devices are designed to reduce WOB. The bench test setting is not completely comparable to clinical practice, but the new device is now tested in the delivery room for safety and efficiency.

Interfaces for non-invasive respiratory support

The facemask is currently the most commonly used interface for delivering CPAP in the delivery room (13-16), but sometimes we observe a change in breathing pattern when applying too much pressure on the facemask. As the facemask is placed on the nasotrigeminal area, it could influence the breathing pattern via the trigeminal nerve. Stimulation of this area is well known to cause a cessation of breathing pattern bradycardia, peripheral vasoconstriction and closure of the larynx (48-51). This may provide explanation for failure of CPAP in a number of infants. Observational studies in human adults (52, 53) and infants (54, 55), however, described an initial increase in tidal volume after positioning a facemask. The increase could have been due to an increase in dead space volume as tidal volume and respiratory rate were restored after removal of mask (51, 55). Although healthcare providers should be aware of the possibility of mask leak, it seems prudent to place the mask as gently as possible to prevent any inhibition of breathing.

To avoid mask leak and/or potential reflexes of the facial nerves inhibiting breathing, alternative interfaces for delivering CPAP could be used. Kamlin et al. (56) reported no difference in intubation rate or any other outcome when the nasal tube was compared with the facemask for providing PPV to preterm infants at birth and concluded that the nasal tube would be a good alternative to the facemask. Hereafter, van Vonderen et al. (57) performed a subgroup analysis on the physiological parameters. Forty-three of 363 infants, whose resuscitation was recorded by a respiratory function monitor, were included in the analysis. This analysis showed more leak and obstruction when using the nasal tube, leading to lower tidal volumes and oxygen saturations and higher requirement for supplemental oxygen.

McCarthy et al. (58) compared single nasal prongs with facemasks in preterm infants requiring CPAP in the delivery room. No difference in intubation rate was observed between groups, but higher oxygen saturations and lower supplemental oxygen levels were reported when using prongs. The clinical relevance of this primary outcome was questioned by the authors, as all other clinical outcomes, in both the delivery room and at the ward, were similar between groups. The authors suggested binasal prongs as these are superior to single nasal prongs after extubation at the clinical unit (59).

Although the facemask is the commonly used in the delivery room, it might influence the breathing pattern by stimulating the trigeminal nerve. All studies investigating interfaces were predominantly focused on PPV, it is unclear whether these results are also applicable during CPAP support for spontaneous breathing. Further research investigating the interaction between the interface and infant's physiology during the transition to spontaneous breathing is warranted to improve the success of non-invasive ventilation in the delivery room.

Conclusion

Non-invasive PPV is often administered to very premature infants who breathe insufficiently at birth, however this is often inadequate and can be injurious to the immature lung and brains. The need for PPV could be avoided by optimising spontaneous breathing with CPAP. Currently, there is heterogeneity in its use in clinical practice and to date available data on physiology underpinning non-invasive respiratory support has been generated in preclinical settings. These experiments highlight that starting with initial high level CPAP promote lung aeration but should be decreased hereafter to support spontaneous breathing and minimise risk of lung and brain injury. New preclinical studies focussing on CPAP strategies enlarge the knowledge of the underlying physiology and provide a fundamental base for clinical CPAP studies in the delivery room. The most effective way to apply CPAP also remains unclear: the clinical relevance of performed bench tests are not known and interfaces have only been compared when delivering PPV. Studies are currently focused on novel devices reducing the WOB, but future studies should also compare the effect of different CPAP delivering devices and interfaces that are already in use in the delivery room.

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