Spontaneous breathing and respiratory support of preterm infants at birth

Pas, A.B. de

CHAPTER 12

General discussion

Resuscitation, "bringing back to life", of infants at birth is almost always a matter of establishing effective ventilation (1). Clinicians are guided by professional guidelines (2), but the evidence for the efficacy and relative merits of various approaches to initial respiratory support for infants is limited. This lack of evidence reflects the difficulties encountered in conducting randomized clinical studies in the delivery room. Current recommendations for ventilation are based on relatively few clinical studies and for the greater part extrapolated from small case studies, studies performed in asphyxiated or immature animals and *in vitro* tests (3).

After the start of this thesis a new consensus of the International Liaison Committee on Resuscitation (ILCOR) became available in which little distinction was made between the treatment of preterm and term infants (2). In this consensus the use of a sustained inflation, positive end-expiratory pressure (PEEP) and continuous positive airway pressure (CPAP) in the delivery room are mentioned but not recommended as ventilation strategies for preterm infants immediately after birth (2). Preterm infants need separate recommendations because they are more susceptible to lung injury at birth and therefore ventilation should be performed with care and consideration (4-10). In addition, most preterm infants are born without significant intrapartum asphyxia but are slow in establishing effective spontaneous breathing. Their respiratory efforts may be too weak to adequately pull them through the transition period. It is hotly debated whether the primary aim should be for the clinician to intubate the infants, take over ventilation and provide surfactant, or to avoid intubation and provide support with nasal CPAP. Jobe (11) stated in an editorial that antenatal steroids and inflammation, together with obstetric practices to delay the delivery of preterm infants have contributed to a reduction in the incidence and severity of respiratory distress syndrome (RDS). In contrast, unnecessary intubation and ventilation soon after birth may cause RDS and Jobe claimed to avoid this, if possible, by "Don't just do something, stand there!" (11). A mental change is needed for the realization that most preterm infants don't need "resuscitation", but "stabilization". In many cases a more gentle support for spontaneous breathing might be all that is required to get them through the transitory phase.

We have shown in our randomized controlled trial that for preterm infants who need respiratory support at birth, a sustained inflation directly followed by nasal CPAP, delivered through a nasopharyngeal tube, is a more efficient strategy than the conventional approach of repeated manual inflations with a self-inflating bag and mask followed by nasal CPAP on admission to the NICU (12). With this trial we demonstrated that the search for a more efficient and less injurious approach in preterm infants is worthwhile. This "compound" interventional approach versus the conventional approach has improved outcome among our population of preterm infants. We can only speculate which treatment factor contributed most to the final results. It is possible that a single treatment factor may not dem-

onstrate significant differences, but the strength was in combining these factors in one approach (13). In addition, another possible reason for the success of this trial is that supporting preterm infants with nasal CPAP immediately after birth buys time to differentiate between RDS and transition problems. This may have been an important factor in reducing the number of unnecessarily intubated infants.

We reported the first observations of spontaneous breathing patterns of preterm infants immediately after birth. We described the various patterns in detail and categorized them to be used in further prospective studies. We observed that immediately after birth the breathing pattern of preterm infants is characterized by expiratory braking and that very preterm infants treated with CPAP frequently hold their breath. These patterns are recognized as a method to create and maintain functional residual capacity (FRC) (14-21). We also described the crying patterns in term and preterm infants, which also appear to be a pattern of breathing that uses expiratory braking and facilitates lung volume recruitment. During expiratory braking intrapulmonary pressure is increased and causes the airway pressure to be maintained above atmospheric pressure. This helps clear liquid from the lung, facilitates distribution of gas within the lung, and splints the alveoli and airways open (15;16;18;21-23). The gas flow patterns we observed are completely different from those seen when manual inflations are given during neonatal resuscitation. It seems logical that we should mimic these gas flow patterns as well as possible. The effectiveness of respiratory support in the delivery room may be improved using a similar strategy during initial resuscitation of a preterm infant who is apnoeic or breathes insufficiently. The built-up of intrathoracic pressure during expiration can be mimicked by applying PEEP during positive pressure ventilation or supporting spontaneous breathing with CPAP. The effect of an expiratory hold can be mimicked by giving a sustained inflation at birth.

We mentioned in our review that PEEP is often used but the international guidelines do not stipulate this (3). Animal studies have shown that the use of PEEP immediately after birth protects against lung injury and improves lung compliance and gas exchange (24-29). Oxygenation and an increase in heart rate are dependent on lung aeration and the retention of an FRC to facilitate effective gas exchange. PEEP is generally used in mechanically ventilated preterm infants in the NICU and in ventilated preterm infants FRC is mainly determined by PEEP (30). We have shown, using phase contrast X-ray imaging and plethysmography, that PEEP has an essential role in facilitating lung aeration, accumulating FRC and preventing distal airway collapse at end-expiration in preterm rabbit pups mechanically ventilated from birth. We tested in the same setting the effect of PEEP in combination with sustained inflation and also in this study it was shown very clearly that during ventilation at birth PEEP was needed to create and maintain FRC. In both the presence and absence of a sustained inflation, without PEEP no FRC was maintained.

The positive findings of PEEP on gas exchange in these animal studies, could not be confirmed by the only randomized clinical trial available of applying PEEP in the delivery room (31). Finer et al showed that applying PEEP at birth did not decrease the need for intubation in very preterm infants (31). However, this study was designed as a feasibility trial, underpowered to show differences (31). We agree that most evidence obtained from animal models is not directly applicable to preterm infants. However, the rabbit studies in this thesis and other animal studies (24-29) were specifically designed to assess the effects of PEEP immediately after birth. Although it will not be possible to perform such experiments in very preterm infants, we expect similar results. Indeed, in the early seventies similar studies were done using a preterm rabbit model to demonstrate the efficacy of surfactant treatment (32;33). We suggest that it is now time to recommend application of PEEP during ventilation of preterm infants at birth. At this time, a T-piece pressure limited mechanical ventilator as the Neopuff (Neopuff Infant Resuscitator, Fisher and Paykel, New Zealand) is the best available device to deliver PEEP in the delivery room and should be recommended for general use (34-36).

The long time constant of a liquid-filled lung and the observation of a prolonged first breath at birth (15;21;37) made Vyas et al. (38) use a sustained initial inflation in apnoeic infants. The tidal volumes measured were similar to the tidal volumes measured during spontaneous first breaths (38). The use of sustained inflation during resuscitation has since been studied in preterm infants and animals, with conflicting results (39-42). Many clinicians do not use a sustained inflation because they are concerned about volutrauma when large volumes enter the lung. This seems paradoxical considering the general acceptance of recruitment manoeuvres during ventilation in the NICU when lungs have a short time constant (43). In addition, during the spontaneous prolonged first breaths, large inspired tidal volumes have been measured. Moreover, we have shown in our preterm rabbit model that applying a sustained inflation of 20 sec leads to a large first inspiratory volume, but does not cause over-expansion as the gas volumes achieved were not different from the volumes achieved at end-expiration during ventilation with PEEP and a tidal volume of ~ 10 mL/kg.

We demonstrated that a sustained inflation immediately leads to a large FRC and more uniform aerated lung. As a result the complete lung is uniformly used for tidal ventilation. Although the effect of PEEP and SI were additive on creation of FRC, PEEP had the greatest influence. An initial sustained inflation should always be combined with the application of PEEP.

Extrapolating these results to the clinical setting, applying the strategy of SI and PEEP to insufficiently breathing preterm infants leads to fast and effective aeration of the lung. Oxygenation of the myocardium leads to an increase in heart rate and blood pressure, the brain stem recovers and spontaneous breathing starts, with the advantage of a fully recruited

lung. This fast recovery could explain the lower intubation rates in the delivery room among very preterm infants in our trial (12) in which they received a sustained inflation directly followed by PEEP, given as CPAP, to support spontaneous breathing.
Subsequently we investigated the effect of different lengths of a sustained inflation. The best effects of increasing the duration of the initial inflation were noticeable in the 10 and 20 sec groups. A sustained inflation of 10-20 sec led to greater gas volumes entering the lung and a greater FRC, both pivotal determinants of the ability of the lung to exchange gases. Although we calculated that a mean initial sustained inflation of 14.0 $\pm$ 4.1 sec is required to fully aerate the lungs, the time constant varies between individuals and will also be determined by the initial pressure gradient. However, it is likely that using a higher initial pressure, as recommended by current guidelines, instead of a longer inflation, leads to over-expansion in lung regions aerating first. We speculate that using a lower pressure and a longer initial inflation is preferable.

When interpreting the studies of early nasal CPAP as primary strategy for infants with respiratory distress, it is important to realize that in only a few studies nasal CPAP was started in the delivery room during resuscitation and in the presence of signs of respiratory distress (40;44-51). One of the strategies in our RCT was to start nasal CPAP immediately after initiation of ventilation using the Neopuff. The starting time for early nasal CPAP is important because a noncompliant lung collapses and lung volume is not maintained if CPAP is not given immediately to keep the lung open (52). The high success rate in avoiding intubation in the early nasal CPAP cohort studies could be explained by the fact that a high FiO_2 threshold ($\geq$ 0.6 to 1.0) for intubation was maintained (40;44;45;47-50;53-55). Interestingly, some reported favourable outcomes and a low incidence of BPD (40;47;48;50;53;54;56). However, we showed in our cohort study that preterm infants still benefit from selective intubation and early nasal CPAP when combined with a lower FiO_2 threshold ($\geq$ 0.4) for intubation (57).

The retrospective nature of these clinical studies is an important limitation and the antithesis is that meta-analyses have demonstrated that prophylactic or early surfactant treatment is more effective than late rescue treatment (58-60). Although the studies in these meta-analyses were performed at a time when early nasal CPAP was not used as an alternative approach, many clinicians still electively intubated all very preterm infants to administer prophylactic surfactant therapy. The disadvantage of this strategy is intubation and surfactant treatment of infants who may not develop serious RDS. Signs of respiratory distress at birth in preterm infants may not be due to RDS, but due to their efforts to clear liquid from their lungs. Intubation and ventilation of these infants, while in a transitory phase, could injure the lungs (5-9;29;61). In our case-control study (62) and randomized trial (12) we have shown that a trial of early nasal CPAP is not detrimental and buys time to make a better differentiation between RDS and transition problems. Interestingly, in the intervention group less RDS was diagnosed and the incidence of BPD was lower (12).

Morley et al. have also shown that a trial of early nasal CPAP is feasible (63). They compared in a large international randomized controlled trial (COIN-trial) nasal CPAP with elective intubation in the delivery room and reported a reduced need for oxygen at 28 days in the nasal CPAP group, but no significant differences in death or BPD at 36 weeks (63). Many differences in the design of their trial make it difficult to compare and explain the differences in outcome with our trial. Interestingly, Morley et al. reported a higher incidence of pneumothoraces in the nasal CPAP group (63), whereas we found a lower incidence in our trial (12). This could be explained by the different thresholds for intubation maintained in the trials (FiO_2 of 0.6 in the COIN-trial and 0.4 in our randomized controlled trial) (64).

Conclusions

Although we have made progress in the past decade, current recommendations for respiratory support of preterm infants at birth are based on a few case series (level of evidence 5) and accepted common practices (level of evidence 8, common sense). Animal studies (level of evidence 6) show that preterm lungs are more prone to lung injury and it may be argued that the current interventions are of dubious efficacy and can be harmful. Most preterm infants breathe at birth and the focus of the recommendations should be shifted from "resuscitation" towards "stabilization" or support during the transitory phase. Clinical randomized trials (level of evidence 1-2) in the delivery room are feasible and should be encouraged to provide evidence-based guidelines for the clinicians. Although the level of evidence from observational and experimental studies is lower (level of evidence 3-6), data from these studies are accumulating and support a different approach towards respiratory support of preterm infants at birth. This thesis has contributed to these data.

We have learned from observing spontaneous breathing patterns of preterm infants at birth that they use specific mechanisms to defend their FRC. It is possible to mimic these strategies when respiratory support is needed (level of evidence 3). Our studies have contributed to the available data that applying PEEP is essential for creating and maintaining FRC during ventilation of preterm infants at birth (level of evidence 3-6). This should be recommended and a manual device that delivers adequate and consistent PEEP should be used. Applying PEEP in the form of nasal CPAP and allowing preterm infants to breathe spontaneous is feasible and not detrimental, providing early surfactant is given (level of evidence 4). A sustained inflation at birth creates an immediate FRC and more uniform lung aeration (level of evidence 6). The length of the initial inflation should be 10-20 sec to overcome the long time constant and aerate the lung (level of evidence 6). Further evaluation of the risks of sustained inflation is needed. Combining these strategies has led to a more efficient approach than the current recommended repeated manual inflations with a self-inflating bag and mask (level of evidence 1)

Future Directions

Stabilization of preterm infants in the delivery room is common practice for neonatologists and more basic information about the optimal respiratory support strategies is needed. Research in this area should be encouraged and with the current emphasis towards practice of evidence-based medicine, we need more randomized controlled trials.

Concerning respiratory support of preterm infants the following relevant clinical questions will be addressed in the future:

1. What are the risks of a sustained initial inflation?
2. Which approach is better: a higher initial pressure or a sustained inflation using a lower pressure?
3. Which interface should be used during manual positive pressure support: mask or nasopharyngeal tube?
4. Which FiO_2 threshold for primary intubation is better in preterm infants with RDS: 0.4 or 0.6? What effect does this have on the rate of pneumothoraces?

These questions could be answered by performing large clinical randomized controlled trials.

5. The knowledge gathered from our basic observation of breathing patterns of preterm infants can be used to perform prospective studies: does the frequent appearance of breath holds in preterm infant indicate that more respiratory support is needed, does it disappear if the level of nasal CPAP is increased, and does it correlate with other known clinical signs? What is the optimal range of pressures to be delivered during the use of nasal CPAP?

6. The combination of simultaneous phase contrast X-ray imaging and plethysmography in experimental animal models has enabled us to observe and measure the rate and pattern of lung aeration at birth and the critical role it plays in regulating the physiological changes at birth. We expect to perform more studies using the synchotron: What effect does surfactant have on lung aeration at birth, endotracheally given or pharyngeal? Is it possible to aerate the lung when sodium channels are blocked? Is applying PEEP still needed when surfactant has been given at birth?

We started this thesis with the statement of Milner in 1982 that it was unlikely that answers will be provided by further studies on newborn babies. We are convinced that answers and evidence will be obtained from the combined strength of randomized clinical trials, clinical observational and animal studies.

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