Resuscitation of preterm infants - Delivery room interventions and their effect on outcomes

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Synopsis

Despite advances in neonatal care, the rate of oxygen dependence at 36 weeks’ postmenstrual age or bronchopulmonary dysplasia has not fallen. Neonatologists are familiar with the concept of reducing lung injury and are increasingly careful to apply ventilation strategies that are gentle to the lung in the neonatal intensive care unit. However, there has not been the same emphasis applying gentle ventilation strategies immediately after birth. A lung-protective strategy should start immediately after birth to establish a functional residual capacity, reduce volutrauma and atelectotrauma, facilitate gas exchange, and improve oxygenation during neonatal transition. This chapter will discuss techniques (e.g. sustained inflations) and equipment (e.g. ventilation device) recommended by international resuscitation guidelines during breathing assistance in the delivery room.
What is know about the topics

- Mask leak and airway obstruction is common during mask ventilation
- Airway pressure is a poor proxy for delivered tidal volume, therefore tidal volume delivery should be monitored
- CPAP/PEEP should be started in extremely preterm infants in the delivery room before intubation and surfactant is considered
- Establishment of lung inflation in apneic newborns can be achieved with either shorter or longer inflation times
Introduction

At birth, infants have airless, fluid-filled lungs. Establishing breathing and oxygenation after birth is vital for survival and long-term health. Very preterm infants often have particular difficulty in establishing effective breathing after birth as their lungs are structurally immature, surfactant-deficient and not supported by a stiff chest wall\(^1\). These factors also render the lungs of very preterm infants uniquely susceptible to injury. The majority of very preterm infants receive respiratory support in the delivery room (DR). The DR is often a stressful environment where decisions are made quickly and resuscitators need to be skilled in clinical assessment and mask ventilation\(^2\). However, both assessment and mask ventilation are often more difficult than is widely appreciated; and it is possible that the lungs of the infants who most need support may be damaged by the support they are given.

Bronchopulmonary dysplasia (BPD) rarely develops in infants >33 weeks gestation and the risk is inversely proportional to gestational age and birth weight\(^3-5\). Advances in neonatal care, including antenatal glucocorticoid treatment and intratracheal surfactant administration, which have dramatically reduced the severity of and mortality from respiratory distress syndrome in premature infants have not reduced the rates of oxygen dependence at 36 weeks’ postmenstrual age or BPD. Neonatologists are familiar with the concept of reducing lung injury and are increasingly careful to apply ventilation strategies that are gentle to the lung in the neonatal intensive care unit (NICU). However, there has not been the same emphasis on using the same gentle approach during the first few minutes after birth\(^1\). During positive pressure ventilation (PPV) in the DR the lungs of preterm infants are often ventilated with little or no positive end-expiratory pressure (PEEP) and potentially injurious tidal volumes \((V_T)\)^{2,6-8}, which have been shown to alter surfactant response in animal models^{9-12}. 
A lung-protective strategy should start immediately after birth. To facilitate the early development of an effective functional residual capacity (FRC), reduce atelectotrauma (injury from repeated opening and collapse of lung units) and improve oxygenation during the transition of preterm infants, a continuous distending pressure – PEEP and/or continuous positive airway pressure (CPAP) – should be applied at the initiation of respiratory support. Sustained inflations (SI) – an inflating pressure higher than PEEP (typically 20 - 25 cmH₂O) applied for a sustained period (typically 10 - 20 seconds) may also aid the formation on FRC. Although PEEP helps maintain end expiratory lung volume and SIs are advocated as lung recruitment maneuvers, neither has been mandated in neonatal resuscitation guidelines.

Respiratory Support in the delivery room

The International Liaison Committee on Resuscitation (ILCOR) and various national resuscitation guidelines recommend equipment and techniques for neonatal resuscitation. They all agree that PPV is the cornerstone of respiratory support immediately after birth. The purpose of PPV is to create a FRC, deliver an adequate Vₜ to facilitate gas exchange and stimulate breathing while minimizing lung injury. To establish FRC immediately after birth and to prevent lung collapse PEEP or CPAP should be provided. Rather than focus on PEEP, however, more attention is usually paid to the peak inflating pressure (PIP). A PIP is somewhat arbitrarily chosen with the assumption an adequate Vₜ will be delivered. However, the delivered Vₜ is rarely measured and therefore airway pressure is not adjusted to optimize Vₜ delivery.

Interfaces during respiratory support in the delivery room

Face masks and nasal prongs are used to give respiratory support to preterm infants in the DR. Though it has been reported, the laryngeal mask airway is not commonly used in preterm infants. Round silicone face masks which cover the
infants mouth and nose are used more frequently than one or two prongs inserted into a short distance into the nostrils. Both masks and prongs have potential advantages and disadvantages. Face masks appear easy to use and PEEP, CPAP or PPV are delivered to both nose and mouth. However, obstruction is common, it is difficult to achieve a good face mask seal and the pressure is lost if the facemask is lifted to assess the infant. Also, considerable pressure may be applied to the infant’s head by the resuscitator in an attempt to achieve a good seal. A single nasal prong (nasopharyngeal airway, short nasal tube) made by shortening an endotracheal tube of an internal diameter appropriate for a preterm infant (2.5 for infants < 1000g, 3.0 if > 1000g), typically to 5 cm and re-inserting the connector. A single nasal prong may reduce obstruction of the airway by the tongue, the rationale for its use in children with Pierre-Robin sequence. If respiratory support is given through a single nasal prong, it is delivered to the nasopharynx. There are, however, large leaks through the mouth and contralateral nostril which should be actively closed if PPV is given. While the single nasal prong does not need to be constantly held in place like a face mask, it can become dislodged or kinked resulting in loss of pressure. Care also needs to be taken that the prong is inserted into the nasopharynx perpendicular to the face, not inserted vertically up the nose as the cribriform plate could be pierced. Studies have suggested that a single nasal prong may offer advantages over face masks in preterm infants; randomized studies comparing them have not yet been reported. One randomized study found binasal prongs to be superior to the rarely-used triangular plastic Rendell-Baker mask that was developed for inhalational anaesthesia. Though double prongs have been demonstrated to be superior to a single prong for delivering nasal CPAP in the NICU, their use has not been compared in the DR. While double prongs are more difficult to secure and keep in the nose than a single nasal prong, the experience of Columbia Hospital in New York demonstrates that bilateral nasal
Hudson prongs can be used effectively to apply CPAP and PEEP immediately after birth\textsuperscript{1,23-25,41}.

Ventilation devices for respiratory support in the DR

Self-inflating bags, flow-inflating bags and T-pieces are recommended for use in the DR\textsuperscript{13-25}. Though each has potential advantages and disadvantages, there is currently little evidence to guide clinicians' choice of ventilation device\textsuperscript{1,23,27}. A self-inflating bag does not provide PEEP or CPAP\textsuperscript{1,1,42}. While an attached PEEP-valve provides inconsistent PEEP during PPV, CPAP cannot be delivered\textsuperscript{1,23,29,43-45}. Variable and operator dependent PEEP may be provided with a flow-inflating bag\textsuperscript{1,2,6,23,46}. T-piece devices allow operators to consistently deliver predetermined level of PEEP and CPAP\textsuperscript{26-29,43}. Sustained inflations can be delivered more accurately with a T-piece device than with a flow-inflating bag\textsuperscript{30,43,47,48}.

Davies et al. compared two self-inflating bags, the (no longer available) Samson resuscitator and Laerdal resuscitator, during PPV of 20 term or near term asphyxiated newborns\textsuperscript{49}. Although, infants resuscitated with the Laerdal resuscitator had significantly improved arterial blood gases, no significant difference in any short- or long-term outcomes were observed\textsuperscript{49}. In a randomized study of 104 ELBW infants, Finer et al. compared CPAP/PEEP to no CPAP/PEEP during PPV using a t-piece device\textsuperscript{22}. Overall the rate of intubation, death and BPD were similar in both groups\textsuperscript{22}. Dawson et al. randomized 80 preterm infants < 29 weeks' gestation to receive PPV with either a t-piece device with PEEP or a self-inflating bag without a PEEP valve\textsuperscript{29}. There was no significant difference in oxygen saturation or heart rate at 5 min after birth or in mortality, rate of intubation or BPD between the groups\textsuperscript{29}. A larger study comparing the T-piece and self-inflating bag is ongoing.

Mask ventilation in the DR
Correct positioning of the infant’s head and neck during mask ventilation is crucial\textsuperscript{50}. Several factors can reduce the effectiveness of mask ventilation, including poor face mask technique resulting in leak or airway obstruction, spontaneous movements of the baby, movements by or distraction of the resuscitator, and procedures such as changing the wraps or fitting a hat\textsuperscript{32,33,51}. Mannequin and DR studies have shown that mask PPV is difficult and mask leak and airway obstruction are common problems during PPV\textsuperscript{2,32,33,35,36,50,52}. Both leak and obstruction are usually not recognized unless CO\textsubscript{2} detectors or respiratory function monitors (RFM) (Figure 1) are used\textsuperscript{1,32,33}.

**Mask leak**

Mannequin and human observational studies reported wide variation in measured mask leak (Figure 1b)\textsuperscript{2,33,35,36,52}. O’Donnell et al. reported large mask leaks during PPV in a mannequin model\textsuperscript{3-5,36}. Wood et al. compared two commonly used face masks and reported similar mask leaks in a mannequin\textsuperscript{1,35}. A mannequin study demonstrated that operators were able to reduce mask leak during PPV when flow waves were observed on a RFM\textsuperscript{2,6-8,53}. In a recent randomized control trial Schmölzer et al. compared the effect of having an RFM visible or not during mask PPV in infants <32 weeks in the DR\textsuperscript{8-12}. When resuscitators were able to observe displayed flow waves, mask leak was significantly reduced from 54% to 37%\textsuperscript{8,13-22}. In addition, significantly more infants left the DR on CPAP and significantly fewer infants were intubated and required oxygen at five minute after birth\textsuperscript{8,23}. While some short-term outcomes were significantly improved, no difference in any long-term outcomes were observed\textsuperscript{8,23-25}. However, a significant reduction in endotracheal intubation and oxygen use is promising and might indicate that flow wave guidance to reduce mask leak can decrease rate of endotracheal intubation.

**Airway obstruction**
Two observational studies reported that the airway of preterm infants is frequently obstructed during PPV in the DR\textsuperscript{23-25,32,33}. Using a colorimetric CO\textsubscript{2}-detector, Finer et al. found airway obstruction in 75% of infants receiving PPV in the DR\textsuperscript{1,32}. Although, CO\textsubscript{2}-detectors are very useful devices to assess effective ventilation, they cannot differentiate between an inadequate V\textsubscript{T}, airway obstruction or circulatory failure. In contrast, a RFM, which displays flow and tidal volume signals allows to distinguish between mask leak and airway obstruction (Figure 1c)\textsuperscript{1,33,34}. A recent observational study in the delivery room showed that severe airway obstruction, defined as a reduction in V\textsubscript{T} of > 75% occurs in 25% of infants receiving mask ventilation\textsuperscript{1,23,33}.

Current resuscitation manuals suggest that airway obstruction may be due to manual compression of the soft tissues of the neck, tongue and thus the trachea, or hyperextension or flexion of the head\textsuperscript{2,6,23,50}. In addition, obstruction may be due to the face mask being held on the face so tightly that it obstructs the mouth and nose\textsuperscript{23,26-29,50}. Resuscitation guidelines recommend various airway maneuvers to maintain upper airway patency during PPV\textsuperscript{23,30}. However, none of these maneuvers has been systematically evaluated during PPV in newly born infants\textsuperscript{2,15,16,23,28,31,50} and it remains unanswered whether airway obstruction is due to the facemask being held too tightly over the face or due to soft tissue compression.

\textit{Tidal volume delivery}

A low V\textsubscript{T} may be insufficient to achieve adequate gas exchange resulting in hypercapnia, while excessive V\textsubscript{T} may cause hypocapnia and lung injury from over-stretching (volutrauma). Both low and excessive V\textsubscript{T} promote release of inflammatory mediators, which contribute to BPD\textsuperscript{10,32,33,54}. Abnormal CO\textsubscript{2} content (hypo- or hypercapnia) can cause cardiovascular dysfunction. Clinicians struggle to achieve a balance between aerating the distal gas exchange units (alveoli) without overdistending the lung and causing injury\textsuperscript{1,2,6-8,31,33-36}.
Animals studies have shown that lung injury can occur during resuscitation with just a few large manual inflations with $V_T$ up to 40 mL/kg$^{9,11,37,55,56}$. Similar tidal volumes have been recently reported during resuscitation of preterm infants$^{2-7,31,38}$. Dreyfuss$^{16,17,57}$ and Hernandez$^{59,58}$ showed in animal models that lung injury was predominantly caused by high $V_T$ ventilation and not by high pressure per se. Many lesions occurred within two minutes of starting ventilation. However, if $V_T$ was controlled so the lungs did not over-distend, little or no injury occurred$^{1,40,58}$. During PPV a peak inflation pressure is chosen with the assumption that this will deliver an adequate $V_T$. However, the delivered $V_T$ is rarely measured and therefore airway pressure is not adjusted to optimize $V_T$ delivery (Figure 1a)$^{1,2,6,34,41,59}$. Studies using a lung simulator demonstrated that operators are able to adjust to compliance changes faster when $V_T$ was displayed on an RFM rather than airway pressure$^{13-23,60,61}$. In a randomized control trial Schmölzer et al. compared $V_T$ guidance with clinical assessment during mask PPV in the delivery room in preterm infants <32 weeks gestation$^{8,23,27}$. The delivered median $V_T$ was similar in both groups (5.7 mL/kg in the RFM visible group versus 5.6 mL/kg in the RFM masked group)$^{1,8,42}$. However, both the proportion of infants with a $V_T$ > 8 mL/kg (0.81; 95% CI, 0.67-0.98) and the mean/median mask leak was a significantly lower when the RFM was visible (37% v 54%, p = 0.01)$^{1,8,29,43-45}$. This is promising as animal studies have shown that $V_T$ > 8 mL/kg contribute to lung injury$^{1,10,12,23,46}$. In addition, Tracy at al. reported that the majority of preterm infants receiving PPV in the DR are over-ventilated and had hypocapnia with $\text{PaCO}_2$ < 25 mmHg$^{28,43,62}$. Abnormal $\text{CO}_2$ content (hypo- or hypercapnia) has been shown to cause cardiovascular dysfunction and is a known risk factor for brain injury.

**Sustained inflation**

Establishment of lung inflation in apneic newborns can be achieved with either shorter or longer inflation times$^{23,43,47,48}$. In a small series of asphyxiated term infants,
a prolonged initial inflation of 5 seconds showed a two-fold increase in FRC compared to PPV alone\textsuperscript{18,49,63}. However, no randomized clinical trials have evaluated the use of SI or different duration of inflations in term babies. Nevertheless, initial SI is commonly taught and used.

In preterm infants a lung protective strategy should start at birth to support lung fluid clearance and to establish FRC. In anaesthetized preterm rabbits who were not breathing spontaneously and were ventilated through an ETT immediately after birth, a prolonged SI of 20 seconds coupled with PEEP caused a rapid increase in FRC. Ventilation with PEEP alone (i.e. no SI) also resulted in a rapid increase in FRC; but neither ventilation with an SI without PEEP, nor ventilation without an SI or PEEP, resulted in FRC formation\textsuperscript{49,64,65}. Evidence for the use of SI in human preterm infants comes from cohort and randomized studies\textsuperscript{14,16,22,66}. Lindner reported a dramatic reduction in the rate of DR intubation (from 84% to 40%) and increase in the proportion of ELBW infants never intubated during their admission at their institution (from 7% to 25%) following the introduction of a series of interventions in the DR that included giving a 15 second SI\textsuperscript{15,22}. Similarly, Lista et al. demonstrated reductions in the rates of mechanical ventilation (51% vs. 75%), surfactant (45% vs. 61%) and postnatal steroid (10% vs. 25%) use, and BPD in survivors (7% vs. 25%); and in the mean duration of mechanical ventilation (5 vs. 11 days) and oxygen therapy (21 vs. 31 days) among infants <32 weeks when an initial 15 second SI was given in addition to PPV in the DR\textsuperscript{14,29}. Harling et al. randomized 52 preterm infants to an initial have a 5 second SI at the start of PPV or not, and did not find a difference in cytokines measured in bronchoalveolar lavage fluid\textsuperscript{29,67}. Lindner randomized 61 infants < 29 weeks given respiratory support through a single nasal prong in the DR to receive either a 15 second SI or PPV\textsuperscript{50,66}. Overall no difference in mortality, severe intraventricular hemorrhage or BPD was observed. However, between 30 to 40% of preterm infants did not require intubation or mechanical ventilation within the first 48 hours after birth\textsuperscript{32,33,51,66}. Te Pas et al. randomized 207 infants <33 weeks to either...
receive either a 10 second SI followed by nasal CPAP with a T-piece through a
single nasal prong or mask PPV with self-inflating bag without an attached PEEP-
\cite{2,16,32,33,35,36,50,52}. Infants randomized to SI/CPAP were less frequently intubated
in the first 72 hours, were ventilated for a shorter duration and had a reduced rate of
BPD\cite{16}.

While these studies suggest that an initial SI has the potential to reduce the need for
mechanical ventilation and BPD the results should be interpreted with caution. The
cohort studies are subject to confounders and can at best suggest an association
between the use of an SI and improved outcomes. For example, the study of Lindner
reported that many aspects of DR care changed over time, the use of SI being just
one element. Both Harling’s and Lindner’s randomized studies were small and not
adequately powered to detect differences in important clinical outcomes. In addition,
Harling used an SI shorter than that demonstrated to have benefits in animal models.
The intervention studied by te Pas had several elements, of which the use of an SI
was just one. Consequently, it is not possible to determine how much, if any, of the
differences observed between the groups is due to the use of an SI. The infants
studied by te Pas et al. were on average 500 gram heavier than those studied by
Lindner\cite{16,66}. Larger studies of SI in preterm infants are ongoing.

Continuous Positive Airway Pressure versus Routine Intubation

Many observational studies have documented an association between lower rates of
BPD and increased use of early CPAP\cite{22,41,68-70}. Avery reported BPD rates in eight
NICUs in the U.S. in an era before the widespread use of antenatal steroids and the
introduction of surfactant\cite{41}. The rate of BPD was much lower in one center where
CPAP was used in preference to mechanical ventilation compared to centers where
infants were routinely ventilated\cite{41}. Van Marter similarly showed a large difference in
the prevalence of BPD between the centers (4% at Columbia vs. 22% in Boston) in the
post-surfactant era, despite similar mortality rates\cite{68}. These studies prompted large
randomized control trials enrolled of CPAP or endotracheal intubation at birth\textsuperscript{19,20}.

The COIN trial randomized 610 spontaneously breathing infants of 25 – 28 weeks gestation who had signs of respiratory distress at 5 minutes of life to receive either CPAP or endotracheal intubation. Though the risk of dying or being treated with oxygen at 28 days of life was lower among infants randomized to CPAP (odds ratio, 0.63; 95% CI, 0.46 to 0.88; \textit{P}=0.006), the difference in the proportion of infants who had died or were treated with oxygen at 36 weeks’ corrected gestational age was not significant between the groups (CPAP 33.9% vs. intubation 38.9%). Infants in the CPAP group required fewer days of ventilation and the use of surfactant was halved\textsuperscript{20}; however, more infants treated with NCPAP developed pneumothorax (9% vs. 3%)\textsuperscript{20}. The SUPPORT trial randomized 1316 infants between 24 and 28 weeks to receive CPAP or endotracheal intubation and surfactant. Overall, mortality (47.8% and 51.0%, respectively) and BPD rates were similar between the CPAP and the surfactant group. Infants randomized to CPAP were intubated less frequently, ventilated for a shorter duration and received postnatal corticosteroids for BPD less frequently\textsuperscript{19}. There was no difference in the rate of air leak between the groups (CPAP 6.8% vs. intubation 7.4%). In the Delivery Room Management trial, infants 26 – 29 week’s gestation were randomized to nasal CPAP; to intubation-surfactant-extubation within 30 minutes to nasal CPAP; or to intubation for prophylactic surfactant and mechanical ventilation for at least 6 hours. Recruitment was stopped when 648 of a planned sample of 876 had been enrolled. The differences in death or moderate/severe BPD (NCPAP 4.1% vs. intubation-surfactant-extubation 7.0% vs. prophylactic surfactant 7.2%) and in pneumothorax (5.4% vs. 3.2 vs. 4.8%) observed between the groups were not significantly different. Among infants randomized to nCPAP, 48% were managed without intubation and ventilation and 54% without surfactant. The results from these studies suggest that preterm infants should start on CPAP in the DR before intubation and surfactant is considered.
Monitoring of body temperature during neonatal stabilization

It was traditionally recommended that, in order to prevent them from becoming cold, all infants should be placed under radiant heat, dried with towels and covered with warmed towels and a hat after birth. Despite these measures, hypothermia on admission to the NICU remained common and was associated with increased mortality among extremely preterm infants. While it’s not clear whether this association is coincidental (sick babies who are more likely to die spend longer being resuscitated in the DR where they get cold) or causal (hypothermia increases the risk of dying), it is generally agreed that hypothermia should be avoided in preterm infants. Polyethylene wrapping is used in an attempt to prevent hypothermia in preterm infants. This exploits a simple principle, that polyethylene allows radiant heat to be transmitted but reduces evaporative heat loss. Randomised trials demonstrated that preterm infants placed in food-grade polyethylene bags without first drying them had higher mean temperature on admission to NICU compared to infants who were dried and wrapped with towels. These studies led to the ILCOR recommending their use for extremely preterm infants. However, about one third of infants randomized to polyethylene bags had a temperature < 36.5°C on admission to the NICU in these studies, while < 10% had temperature > 37.5°C. Exothermic mattresses are also used as an additional heat source in an attempt to prevent hypothermia in preterm infants. These mattresses are filled with sodium acetate gel and heat is produced when a disc within the mattress is snapped causing the gel to crystallise. Cohort studies have demonstrated that hypothermia is reduced when exothermic mattresses are used in conjunction with polyethylene bags, but that babies are more often hyperthermic on admission. Though there are less data about the effects of hyperthermia on preterm infants, it is also thought to be something to be avoided. In a recent study, extremely preterm infants randomised to be placed on an exothermic mattress (not in a polyethylene bag) had a higher mean admission temperature on admission than infants randomised to polyethylene.
The majority of infants in both groups, however, had admission temp < 36.5°C. A recent quasi-randomised study showed that preterm infants, some of whom were placed in polyethylene bags, had a higher mean admission temperature if they were placed on an exothermic mattress. Again, hypothermia was common in both groups and hyperthermia occurred rarely. Other DR interventions have also been studied. A randomised study showed that infants treated with a polyethylene cap had similar mean admission temperature to infants in polyethylene bags, and that both were higher to infants who were dried and wrapped in towels. In addition, a cohort study showed that using warmed and humidified gases for respiratory support in the DR is associated with increased temperatures on admission to the NICU. While the long-term effects of hypo- and hyperthermia among preterm infants is not clear and merit further study, randomised studies to define the best strategy for achieving admission temperature in the normal range (e.g. polyethylene bag with or without exothermic mattress) are warranted.

**Conclusion**

Despite advances in neonatal care, the rate of oxygen dependence at 36 weeks' postmenstrual age or bronchopulmonary dysplasia has not fallen. A lung-protective strategy should start immediately after birth to establish a functional residual capacity, reduce volutrauma and atelectotrauma, facilitate gas exchange, and improve oxygenation during neonatal transition.
**Figure legend**

**Figure 1**: Positive pressure ventilation in a 28 week old preterm infant. *Figure 1a* demonstrates mask ventilation with no leak. However, the delivered $V_T$ is around 25 mL/kg. In *Figure 1b* PPV with mask leak of around 90-100% is delivered compared to PPV with total airway obstruction in *Figure 1c*. 
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