Spontaneous breathing and respiratory support of preterm infants at birth

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CHAPTER 5

Ventilation of preterm infants in the delivery room

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Abstract

Adequate functional residual capacity (FRC) is difficult to create with manual ventilation in very preterm infants and carries a high risk for creating lung damage. Peak inspiratory pressures (PIPs) generated with bag and mask ventilation may be insufficient to open up the lung or unintentionally excessive. The long time constant of the fluid filled immature lung can be overcome by delivering a prolonged inflation at a lower PIP, followed by application of positive end-expiratory pressure (PEEP) to maintain FRC after lung recruitment. A mechanical pressure-limited T-piece resuscitator is the only device that can give a consistent PIP, adequate PEEP and sustained inflation. Leakage between mask and face can be avoided by using a nasopharyngeal tube. After resuscitation, FRC can be preserved by starting nasal continuous positive airway pressure (nCPAP) in the delivery room, which will reduce the need for intubation and mechanical ventilation. This review discusses the available data supporting these strategies.

Introduction

Effective neonatal resuscitation is primarily based on adequate ventilation. Neonatal resuscitation has benefited from physiological studies and has come under critical review in recent years. These critical considerations focus especially on resuscitation of the preterm infant. In a preterm infant it is difficult to create adequate lung volume with manual ventilation as immature lungs have low compliance, are surfactant-deficient and at greater risk of complications. The guidelines for the resuscitation of newborn infants issued by the International Liaison Committee on Resuscitation (ILCOR) recommend pressures of 30 to 40 cmH_2O or higher and longer inflation times for the first breaths to establish an adequate lung volume and air breathing. Premature infants receive special consideration and despite the high risk for decreased lung compliance lower initial pressures (20-25 cmH_2O) are recommended. Some experts recommend early elective or prophylactic intubation for surfactant treatment (1; 2-7). New evidence is accumulating for a different approach towards ventilatory support during resuscitation of preterm infants and discussed in this review.

The first breaths of life: establishment of a functional residual capacity

In order to generate adequate ventilation, a newborn infant must clear his lung liquid and create an adequate volume of gas at end-expiration (functional residual capacity, FRC) (8). Whatever the mechanism is for removal of liquid from the airways before birth (catecholamines (9), sodium channels (10;11), birth canal squeeze (12), fetal postural changes by uterine contractions (13) (see review 1), residual lung liquid still fills the airways when the infant takes his first breath. Healthy, term infants start creating FRC during their first breaths (14;15), but a normal FRC of 30ml/kg is usually achieved within a few hours after birth (16;17;18). A recent study using phase contrast X-ray imaging (19) demonstrated that the transpulmonary pressure gradient during inspiration promotes the movement of liquid into the interstitial tissue compartment from which it is gradually cleared (20;21). An "opening" pressure is needed to overcome frictional and the newly surface tension forces (19;22-26). A term neonate spontaneously generates higher mean inspiratory pressures (-52 cmH_2O) during the first breaths than those produced by positive pressure ventilation (12). Surfactant reduces the "opening pressure" needed to aerate the lungs (27). Lung expansion stimulates surfactant release, facilitating further alveolar expansion, preventing their collapse and less pressures are needed for the following breaths (28;29). At expiration, an even higher pressure in the lung will be generated by closing the glottis, contributing to clearance of lung fluid and a better distribution of air throughout the lung (30) .

The information on achieving FRC has been gained from term infants, but how very preterm infants defend their lung gas volumes immediately after birth is poorly understood. There are several reasons why very preterm infants may have difficulty aerating their lungs and need ventilatory support. Poor respiratory muscle strength and surfactant deficiency,

compliant chest walls (31;32) and impaired lung liquid clearance(11;33;34) can lead to reduced tidal volumes and FRC. Retention of lung liquid in the air spaces reduces lung gas volume, promotes non-uniform aeration and impairs the changes in cardio-pulmonary physiology during transition (11;33;34).

Positive pressure ventilation may cause overdistention of the lung (volutrauma) and repeated alveolar collapse and re-expansion (atelectrauma) can initiate an inflammatory process, which may progress to bronchopulmonary dysplasia (BPD) (35-37). This ventilator induced lung injury is a well-known concept among neonatologists (35;37). Animal studies have demonstrated that this inflammatory process can happen with the first manual inflations after birth (38-44). Histologic lung injury is shown in preterm newborn animals within a few minutes at the onset of mechanical ventilation (38). Bjorklund *et al.* showed in preterm lambs that only 6 large insufflations with tidal volumes of 35-40 mL/kg, forced into a surfactant-deficient lung immediately after birth, can compromise the effect of subsequent surfactant rescue treatment. The immature lambs were more difficult to ventilate and had more widespread lung injury in histological sections (39). In a subsequent study, Bjorklund *et al.* showed that the size of inflations had an inverse relation with inspiratory capacity, static compliance and FRC at 4 hours after birth (40). Even administration of prophylactic surfactant provides incomplete protection against the adverse effects of large lung inflations at birth in immature lambs (41). Ikegami *et al.* hyperventilated preterm lambs at birth with tidal volumes of 14 mL/kg and $PaCO_2$ values of 25-30 mmHg, followed by surfactant treatment. Lung edema and injury were associated with an increase in tumor necrosis factor-α (TNF-α) expression, which is associated with the development of BPD (42). Wade *et al.* ventilated preterm lambs with tidal volumes of 20 mL/kg for 30 minutes after birth, which resulted in $PaCO_2$ values of 24 mmHg after 20 minutes and initially high compliance. Compared with lambs receiving tidal volumes of 5 and 10 mL/kg, this group had less compliant lungs, decreased gas exchange, a decreased response to surfactant and their lungs were damaged more, as determined by protein measurements in lung lavage samples (43). Hillman et al also demonstrated that an injurious process in the lung and a hepatic acute-phase response was initiated when preterm lambs at birth were ventilated for 15 minutes with a tidal volume of 15 ml/kg and no PEEP (44).

The results of these experimental studies advocate that to reduce lung injury during the first few minutes of life, existing knowledge about the causes and prevention of lung injury during ventilation (45) must be applied from birth in preterm infants instead of waiting until the infant has been admitted to the NICU.

Peak Inspiratory Pressure: how much and how long?

It is difficult to advise a standard peak inspiratory pressure (PIP) to open up the lung at birth. The pressure needed is dependent on various factors: the degree of lung compliance (severity of RDS in preterm infants), amount of lung fluid, the length of inspiration and the amount of spontaneous breathing activity of the infant. Physiological measurements in asphyxiated neonates have shown that pressures of 30-40 cmH_2O, maintained for 1 second, resulted in mean inflation volumes of 5 mL/kg. These inflation volumes were less than half of the volumes reached in spontaneously breathing newborns and indicates that more inflations are necessary to establish a FRC (46) due to the viscous force in the fluid-filled lungs (47). A PIP exceeding the opening pressure is necessary in the first manual inflations to expand the lungs. Upton and Milner resuscitated asphyxiated neonates endotracheally with an anaesthetic rebreathing bag and found a median mean pressure of 40 cm H_2O (range 28-60 cmH_2O) over the first 10 breaths was needed to elicit chest rise and to develop FRC in a stepwise fashion. Two-thirds of the patients were preterm infants (median gestational age 33 weeks) but half of them failed to establish any FRC (48).

The pressure needed to resuscitate preterm infants is even more controversial. Resuscitation guidelines recommend 20 to 25 cmH_2O for initial PIP in preterm infants, but higher pressures may be needed (1;2;2-7). Hoskyns et al, reported that endotracheal resuscitation of preterm infants with inflation pressures of 25-30 cmH_2O rarely leads to tidal volumes of more than 4 mL/kg. Higher pressures were sometimes needed for optimal resuscitation (49). In contrast, Hird et al found that a median inflation pressure of 22.8 cmH_2O was necessary to achieve observable chest wall expansion in preterm infants; no infant required a PIP >30 cmH_2O (50).

"Adequate" chest rise has been used as criterion in clinical studies (48;50) and is widely accepted as clinical sign to evaluate the response of ventilation technique given in the delivery room. However, chest rise is a very subjective measure of lung expansion but not a very accurate and may even lead to delivery of excessive tidal volumes (51) In addition, pressure is a very crude proxy for volume and clinicians are not aware which tidal volume is delivered as this is rarely measured. It has been shown in mature animals, that lung injury was predominantly caused by high tidal volume ventilation and not by high pressure (52;53). Tidal volume changes in the minutes after birth when the lung expands and compliance improves. Immediately after birth it is not possible to deliver an appropriate tidal volume using ventilation with a set pressure because the compliance of the lung varies from infant to infant and during the course of lung aeration. Clinicians should be aware of the tidal volume used during PPV and deliver less than 8 ml/kg, particularly with very preterm infants (54). Tidal volumes normally targeted in the NICU (4-5 ml/kg) may represent a good starting point (55).

At birth a lung has a long time constant due to the high resistance to flow associated with the fluid filled lung and large airway secretions. Once the lung clears the fluid, the low compliance of preterm infants results in a very short time constant. A prolonged inflation time may overcome the long time constant of a fluid-filled lung and prevent the use of potentially dangerous, high pressures. Hird et al used an initial inflation time of 2-3 seconds during resuscitation at birth and needed less pressure to create FRC (50). Boon noted that during the first inspirations, gas was still entering the lung after one second (56). When an inflation of 30 cm H_2O was prolonged for 5 seconds, FRC was formed during the initial inflation. There was a twofold increase in inspired volume compared to normal inflation and similar to that achieved by spontaneously breathing infants (47). When the inflation pressure was increased slowly over three to five seconds, lower opening pressures were required compared with standard inflations (10 to 25 cm H_2O) (47).

Clinical studies of sustained inflations in preterm infants at birth produced conflicting results (57-59). Harling et al compared, in a small trial, an initial inflation of 2 s versus 5 s, given before standard ventilation was commenced, and identified no differences in terms of gas exchange and lung injury (57). However, in Ulm, Germany, the intubation rate of preterm infants in the delivery room decreased from 80 to 40% when they used an initial pressure of 20-25 cmH_2O for 15-20 seconds, followed by a positive end-expiratory pressure (PEEP) of 4-6 cmH_2O (58). A small randomised trial using the same strategy showed no difference in need for intubation and ventilation within two days after birth (59).

Caution should be taken with a sustained inflation when the lungs are not liquid-filled. This could lead to a large volume entering the lung and it is theoretically possible to promote air leak in a spontaneously breathing infant.

In summary, there is very little data about how much inflation pressure should be given initially and most are based on inaccurate clinical signs as chest rise. Ideally inflation pressure should be adjusted to a measured tidal volume, especially in preterm infants. Until then a pressure of 20-25 cmH2O seems appropriate for most preterm infants and initially a sustained inflation of 5-10 seconds could be helpful to overcome the long time constant of the liquid filled lung at birth.

Use of PEEP: keep it open

While PEEP is often used during ventilation in the neonatal unit, the ILCOR guidelines do not stipulate the use of PEEP during positive pressure ventilation of preterm infants at birth (1;2;2-7). A survey by Graham and Finer demonstrated that 59% of neonatologists in the USA use PEEP during neonatal resuscitation (60). The lungs of preterm infants are immature, surfactant deficient, partially liquid-filled and prone to collapse at end-expiration. After an

inflation without subsequent PEEP, the lung will collapse and "atelectrauma" can develop during the next inflation (61). To successfully establish and maintain FRC, many preterm infants need either PEEP (48) or prophylactic surfactant treatment (see later). In mechanically ventilated preterm infants FRC is mainly determined by PEEP (62).

Studies using animal models of resuscitation support the use of PEEP in the delivery room (63-68). Increasing PEEP preserves surfactant (63) and reduces alveolar collapse, expression of pro-inflammatory mediators (67) and the formation of hyaline membranes (64). In preterm lambs 4-8 cm H_2O PEEP improves arterial oxygenation and decreases pulmonary vascular blood flow with no adverse effects on the cardiovascular system (69). Crossley et al, showed the same effect of PEEP after antenatal betamethasone and postnatal Curosurf (70). Probyn et al, ventilated preterm lambs at PEEP levels of 0, 4, 8, and 12 cm H_2O. All lambs ventilated with a PEEP above zero showed an improvement in oxygenation, but increasing the PEEP to 12 cm H_2O resulted in pneumothoraces (65).

It is difficult to predict the right PEEP-level for an infant (71-73), although infants with the highest oxygen requirements have the lowest FRC (73). Studies of surfactant-treated preterm infants showed that increasing PEEP to 4-6 cm H_2O increased FRC and improved oxygenation, but also $PaCO_2$ increased due to overdistention (71;74). However, no increase of PaCO2 was noted in animal studies (65;69;70). PEEP levels up to 8 cm H_2O should be considered for resuscitation of preterm infants.

The data on the positive effects of PEEP on FRC are compelling. To facilitate the early development of an effective FRC, reduce atelectrauma, and improve oxygenation during the transition of infants, PEEP should be applied during ventilation of preterm infants at birth at levels up to 8 cm H_2O. Randomised controlled trials of different levels of PEEP during resuscitation of human infants at birth are required (75).

Which device? The tools to work with

Ventilation of preterm infants is ideally done with a device that delivers a consistent PIP and consistent PEEP. O' Donnell et al performed a survey in 40 neonatal centers in 19 countries to determine the equipment used to resuscitate newborns at birth. Most centers used self-inflating bags and masks (33 centers, 83%), 10 centers (25%) used flow-inflating bags and 12 centers (30%) used the Neopuff Infant Resuscitator® (Fischer-Paykel, Auckland, New Zealand), a mechanical pressure-limited device (76).

Self-inflating bags

A self-inflating bag re-expands, after compression, by elastic recoil and no gas source or flow is needed. Commonly a self-inflating bag of 240 mL is used and this should be large

enough to deliver the tidal volume of a neonate. If the tidal volume delivered is inadequate, a large proportion of the inflation is lost through a leak around the mask (77). Kain et al also described non-registrable tidal volumes given with self-inflating bags (78). It is also impossible to deliver a consistent PIP as this depends on the strength and speed of compression of the bag, the degree of leak and the compliance of the lungs (77). Finer et al showed that the pressure relief valves were activated throughout a wide and inconsistent range of pressure (the Laerdal range 41 to 72 cm H_2O) and cannot be trusted as a mechanism to limit the inflation pressure (79). It is difficult to deliver PEEP with a self-inflating bag as there is no continuous gas-flow and the mask seal can break very easily. Hussey et al showed that self-inflating bags may deliver excessively high PIP and minimal PEEP and they advised that a manometer and a PEEP device should be incorporated, particularly when used for resuscitation of preterm infants (80). However, a recent comparative study showed no difference in mean PIP and leakage in the presence or absence of a manometer (81). Field et al compared different self inflating bags and reported it was difficult to deliver a prolonged inflation-time with a self-inflating bag of 240 ml(82).

Although not achieving adequate tidal volume exchange, many neonates respond well to inefficient mask and bag resuscitation because inflation pressures stimulate the infant to inspire via the Head's paradoxical reflex (83;84). In the Head's paradoxical reflex a neonate responds to an inflation by making an inspiratory effort, which is often responsible for the first effective inspiratory volume during resuscitation and the first appearance of an FRC (85;86).

Clinical experience indicates that use of bag and mask during resuscitation leads to gastric distension, which splints the diaphragm and adversely affects lung expansion. Vyas et al showed that neonates do not swallow during resuscitation since not more than 2 mL of air could be withdrawn from the stomach. However, gastric distension develops when pressures higher than 35 cmH_2O are used during resuscitation (87).

Flow-inflating bag

In 1979, Cole et al described a resuscitation device that combined a flow-inflating bag with an adjustable underwater pressure limiting system (88). A flow-inflating bag needs gas flow to inflate it. The user needs to control the rate of gas escaping from the bag with thumb and index finger or a control valve, enough to squeeze the bag and to maintain a positive pressure during expiration. Compared with a self-inflating bag, the technique of a flow-inflating bag is difficult and use should be avoided to ventilate a preterm infant, unless the operator is experienced and skilled with this technique (89;90). Inexperience and inefficient technique can lead to the delivery of dangerously high pressures (77). A comparative study demonstrated that it was not possible to deliver a constant pressure during a sustained inflation of 5 seconds with a flow-inflating bag and that the pressures delivered could reach up to 15 cmH_2O above the target-pressure (90).

Neopuff Infant Resuscitator

Hoskyns et al showed in 1987 that T-piece resuscitators are effective and convenient to use (91). A single center observational study of 17,890 infants provided further evidence for the safety and efficacy of T-piece ventilation. Prolonged inflations can easily be applied with a T-piece system (90;91).

Although there are more T-piece devices available, the Neopuff Infant Resuscitator® is one of the most commonly used flow-controlled and pressure-limited mechanical devices, delivering gas flow through a T-piece to a mask, ETT or nasopharyngeal tube. It is a purpose-built mechanical device, which is easy to use, even by inexperienced operators (80). The T-piece has a valve that controls the rate of gas escape and can be adjusted to set a PEEP for a given gas flow. PIP is generated by occlusion of the valve with a finger and PIP and PEEP are consistent and constant for every breath. Studies comparing the self- inflating bag, flow-inflating bag with the Neopuff® device using a intubated mannequin showed more precisely and consistent PIP and PEEP (80;90;92), even during sustained inflation (90;93), and more consistent breaths per minute (80;94). It is also possible to use any pressure-limited mechanical ventilator to deliver the same controlled and consistent pressures (95). The Neopuff is the only device which allows PEEP to be maintained between inflations and can give continuous positive airway pressure (CPAP) when it is not used as a ventilator.

The interface: mask or nasal route?

Both round and anatomically shaped facemasks are available. O'Donnell showed, in an *in vitro* neonatal resuscitation model, large leaks between mask and face (92). There is limited evidence that leakage is less with a round mask (96), but O'Donnell et al showed no difference between face masks (92). Segedin et al examined whether the nasal or oral airway was the better route for resuscitation using a Laerdal infant mask in infants and observing chest expansion and capnography. They demonstrated that manual ventilation was more often successful when given via nasal route (100% vs 40%) (97). Capasso et al compared in a randomized trial nasal prongs and facial masks during neonatal resuscitation of infants with moderate asphyxia. Neonates resuscitated with nasal prongs needed significantly less intubation (0.6% versus 6.3%; $p<0.001$) and chest compressions (1.65% versus 8.28%; $p<0.001$) (98).

Using nasal prongs or a nasopharyngeal tube to deliver PIP and PEEP during resuscitation alleviates dependence on sufficient sealing by a facemask, providing both the mouth and the other nostril are closed. Another advantage is that CPAP can be continued immediately after positive pressure ventilation to prevent lung deflation.

100% Oxygen, air or somewhere in between?

Concerning the use of supplemental oxygen ILCOR recommends that "there is currently insufficient evidence to specify the concentration of oxygen to be used at initiation of resuscitation"(1). Although we concentrate in this review on the ventilation methods during resuscitation, the use of air instead of 100% oxygen during resuscitation deserves attention. Biochemical studies demonstrated that exposure to high level of oxygen can trigger oxidative tissue injury (99-102). Meta-analyses of air versus oxygen for resuscitation of infants at birth showed a significant reduction in mortality for infants resuscitated with air, although the effects on long-term development could not be reliably determined (103;104). Although the available evidence was insufficient to recommend one or the other (103), authors proposed air should be used initially, with oxygen as backup if initial resuscitation fails (104;105). However, other experts think it is too early to change practice (106).

The studies in these meta-analyses included only small numbers of preterm infants, which made subgroup analysis not possible (107-109). There is increasing concern about hyperoxia levels in very preterm infants and their contribution to retinopathy of prematurity and chronic lung disease (110;111). Preterm infants are particularly susceptible to oxygen-induced toxicity due to an underdeveloped antioxidant defence system (112). More large clinical trials in preterm infants are needed to address the necessity of changing current protocols that may lead to hyperoxia in these infants.

The optimal concentration of gas may be neither air nor 100% oxygen but somewhere in-between, depending on the condition of the infant. Now that pulse oximetry readings can be obtained within 90 s of birth the FIO_2 should be individually adjusted according to SpO2 and HR values until stabilization (51;113). Wang et al compared in very preterm infants the use of room air versus 100% oxygen and showed that room air failed to achieve their target oxygen saturation by 3 minutes of life (114). In our neonatal intensive care unit we currently ventilate preterm infants initially with 100% oxygen when manual ventilation is needed and wean down as quickly as possible depending on the infant's response, SpO_2 and heart rate.

CPAP in the delivery room, the gentle way

After initial ventilation the surfactant-deficient lung of a spontaneously breathing preterm infant can easily deflate again and continuous respiratory support is needed. To avoid intubation starting CPAP directly after resuscitation is a gentle, non-invasive attempt to keep the lung open. CPAP is commonly used in the neonatal intensive care unit to maintain lung volume, prevent atelelectasis and stimulate respiration. Experimental studies have shown that CPAP immediately after preterm birth minimized lung injury (68;115), did not cause arrest in alveolar development in contrast to mechanical ventilation (115) and enhanced gas exchange (116).

Various non-randomized retrospective studies, with or without historical controls, from Neonatal Units all over the world, using early CPAP in preterm infants with respiratory distress syndrome (RDS) showed a reduction in FiO_2 and a lower incidence of mechanical ventilation (58;117-134). Some reported favourable outcomes and a lower incidence of BPD (58;122;123;125;126;129-132). Many differences exist among these studies, including gestational age of the preterm infants, methods used to deliver CPAP and the levels of CPAP used.

The interpretation of "early" CPAP is rather broad and only in a few studies CPAP was started in the delivery room during resuscitation when signs of respiratory distress were present (58;124;126-129;131;134;135). In Denmark a philosophy of less intensive and aggressive therapy emerged in the 1990s. Retrospective cohort studies of this "minitouch regimen", which started in the delivery room, reported favorable survival and lower BPD rates at 28 days when preterm infants were treated with early CPAP in combination with permissive hypercapnia (124;136;137). A prospective national study (ETFOL) evaluating early CPAP in preterm infants reported a low incidence of mechanical ventilation and BPD (129). Follow-up showed similar proportions of adverse effects on the brain compared to published follow-up studies of preterm neonates treated with mechanical ventilation (138). Narendran et al compared in extremely low birth-weight infants the use of early bubble CPAP in the delivery room with a historical control where mask and bag was used but no CPAP. The introduction of CPAP in the delivery room resulted in a reduced need for intubation in the delivery room (32% versus 60%, $p<0.05$), fewer days on mechanical ventilation (mean 13 versus 28, $p<0.05$) and a lower rate of postnatal steroid use (14% versus 42%, $p<0.05$), but was not associated with a difference in mortality (34% versus 38%) or BPD at 36 weeks (34% versus 40%) (134). Also, in a recent retrospective study Aly et al studied the effect of CPAP as initial airway management on outcome of extremely low birth weight (ELBW) infants (<1,000 g). Over a 4-year period as the frequency of use of CPAP increased and its success improved, the incidence of intubation during the first week after birth decreased from 38% to 7%. Over time, the incidence of BPD decreased significantly from 33% to 11% and average weight gain increased (126). They also compared outcome of early CPAP, early CPAP-failure and delivery room intubation in very preterm infants but found, after controlling for basic characteristics, no difference in outcome, except for more NEC in the early CPAP-failure group (127).

In a retrospective study with historical controls performed in Ulm, Germany, by Lindner et al, early CPAP at birth was combined with a sustained inflation using a Neopuff®. In 1996 the resuscitation guidelines for respiratory support were changed in their unit to include placement of a nasopharyngeal tube and delivery of continuous (15-20 seconds) controlled pressure (20-25 cmH_2O), followed by CPAP (4-6 cmH_2O). Before this change was made, neonates were intubated soon after birth if they presented with the slightest signs of respi-

ratory distress or asphyxia after initial resuscitation using a face mask and a handbag. Comparison of the outcome of ELBW infants during two periods, 1994 and 1996, showed that in the second period significantly more infants did not need mechanical ventilation (25% versus 7%; p<0.01), BPD and IVH decreased significantly (BPD 12% versus 32%, p<0.05; IVH 16% versus 38%, p<0.01) and hospital stay was reduced (mean 79 days versus 105 days) without a significant increase in mortality (27% versus 22%) (58).

Meta-analyses of studies performed in the presurfactant/pre-antenatal steroids era concerning continuous distending pressure for RDS in preterm infants showed a reduction in mortality of preterm infants >1,500 g with CPAP and a greater benefit from early application (139;140). However, a meta-analysis evaluating prophylactic (= early) CPAP concluded that the information is insufficient and further large randomised controlled trials are needed (141). Neither of the two included studies comparing early CPAP with rescue treatment showed evidence of benefit in reducing the use of mechanical ventilation or BPD (142;143).

Two randomised controlled trial with CPAP in the delivery room were performed later and not included in meta-analyses (144;145). Finer et al investigated in a small study the feasibility of randomizing ELBW infants < 28 weeks of gestation to CPAP/PEEP or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration and initiating CPAP on admission to the neonatal unit. In this trial the Neopuff® Infant Resuscitator was used. In the first group CPAP of 5 cmH_2O or IPPV (if necessary) with PIP 15-25 cmH_2O was given, in the second group no CPAP and no PEEP during IPPV were used. CPAP/PEEP in the delivery room did not affect the need for intubation at birth or during the subsequent week, although this preliminary study was underpowered for detecting such a difference (144) .

Most recently Morley et al published the results of a large international multi-centre trial. Spontaneously breathing infants born at 25-28 weeks were randomly assigned to CPAP or intubation and ventilation at 5 minutes after birth. In the CPAP group 46% were intubated during the first 5 days and the use of surfactant was halved. At 28 days, there was a lower risk of death or need of oxygen therapy in the CPAP group than in the intubation group (53.7 % vs 64.7 %; P = 0.006). However, no differences were found in primary outcome (death or BPD at 36 weeks) with 33.9% in the CPAP group vs 38.8 % in the intubation group (P = 0.19). There were no differences in adverse outcome except a higher incidence of pneumothorax in the CPAP group (9% vs 3%; P < 0.001) (145). One can only speculate what caused this increase in air leak: the high level of CPAP (8 cmH_2O) used in the trial, the surfactant defiency or even the high threshold of oxygen (FiO_2 > 0.6) for intubation. Interestingly, Stevens et al suggested in a Cochrane review that a lower FiO_2 threshold (FiO_2 < 0.45) for intubation and surfactant administration was associated with significant reductions of air leak syndromes and BPD (146).

In summary, there are a large number of studies available showing that using early CPAP reduces the need for mechanical ventilation and is more beneficial when it is started as early as possible when signs of distress are present. The most ideal moment would be during initial resuscitation. Using early CPAP has not affected the rate of BPD and death and there is concern about adverse events. It may be possible that early CPAP has to be combined with a low threshold for intubation or early surfactant treatment.

Surfactant in the delivery room

Various systematic reviews have concluded that prophylactic or early surfactant treatment of infants requiring mechanical ventilation is more effective than late rescue treatment (147-151). If a preterm infant with RDS receives CPAP and is not intubated, potential improvement of lung function by early surfactant treatment may be missed. There are a few randomized trials investigating the combination of surfactant and early CPAP (152-154). Verder et al compared in a small trial a single dose surfactant administered during short intubation followed by CPAP with treatment of CPAP alone in preterm infants with moderate-to-severe RDS. The need for subsequent mechanical ventilation was reduced with surfactant therapy (43% versus 85 %, p= 0.003), but there was no difference in mortality, BPD at 28 days and IVH (152). Interestingly, their intubation rate of 85 % in the CPAP group was rather high, considering the fact that the median birth weight of the included infants was 1300 g. In a subsequent small study, Verder et al compared early and late surfactant treatment in very preterm newborn infants with RDS who were primarily supported with CPAP. The early surfactant group received significantly less ventilatory support (25% versus 68%, p=0.005), but the incidence of BPD (1 infant in both groups) and IVH was similar(153). The Infant Flow Driver And Surfactant (IFDAS) trial randomized premature infants of 27-29 weeks of gestation to one of 4 treatment groups: early CPAP with prophylactic surfactant, early CPAP with rescue surfactant treatment if needed, early IPPV with prophylactic surfactant, conventional management with rescue IPPV and surfactant treatment if needed. The requirement for mechanical ventilation in the first 5 days of life was highest in the early IPPV with prophylactic surfactant group and lowest in the early CPAP with prophylactic surfactant group (all not significant), but no reduction in BPD was seen (154).

To obtain the benefits of exogenous surfactant while avoiding the risks of intubation, alternative administration methods have been investigated. Kattwinkel et al prophylactically administered surfactant into the nasopharynx, permitting the infant to aspirate the solution. Directly after birth CPAP was started. This technique appeared to be safe and feasible, but a large RCT is needed to determine the efficacy (155). Kribs et al described an interesting alternative technique of administering surfactant without intubation and mechanical ventilation. They reported it was feasible to administer surfactant in very preterm infants (23-27 weeks) with RDS via an endotracheally placed nasogastric tube while receiving CPAP (156).

A retrospective comparison with a historical control showed a decrease in need for intubation, mortality and BPD when this technique was used (157). Aerosolized surfactant has been studied (158), but it is questionable if it enters the lung and degradation of surfactant can occur in an aequeous solution (159). These techniques are worthy of further investigation and merit large randomised controlled trials

Another approach towards avoiding a period of mechanical ventilation in infants at high risk of RDS is to intubate, treat with surfactant, and immediately extubate to CPAP (the INSURE approach), as the major problem is surfactant deficiency (160). The question is whether exogenous surfactant treatment is necessary or endogenous surfactant production can be awaited. In preterm lambs a surfactant pool size of less than 3 mg/kg, i.e. approximately 3 % of the pool size at term, resulted in CPAP failure and the percent of secreted saturated phosphatidylcholine was higher after 2 hours of CPAP than after 6 hours, suggesting that secretory stimuli are maximal after preterm birth and activation of recycling and catabolic pathways is delayed (161). Rapid changes in surfactant pools just before and after birth have been reported (162;163). In a preterm rabbit model ventilated from birth, the dose-response of exogenous surfactant is decreased after delayed administration after ventilation at birth (164).

The disadvantage of prophylactic surfactant treatment of respiratory distress in the delivery room is putting many infants, who wouldn't develop RDS, at risk for the potential hazards of intubation (165;166). Symptoms of respiratory distress at birth in preterm infants may not be due to RDS, but due to their efforts to clear fluid from their lungs. Early CPAP aids lung expansion and fluid clearance and also allows time to differentiate between RDS and transition problems.

Conclusion

Current guidelines of ventilation of preterm infants at birth are based on limited data and the common practice of intubating and ventilating preterm infants is not based on data obtained from prospective, randomized trials. The limited data reflect the difficulties of performing studies in infants at birth and more well-designed trials like the COIN-trial are needed. The lungs of preterm infants are very vulnerable to injury caused by intubation and ventilation, especially directly after birth, and these modalities should be avoided whenever possible. Inappropriate ventilator support during resuscitation can provoke lung damage very easily. Future investigation should focus on the best strategy to open up the lung and minimize lung injury in a preterm infant. Until then the following recommendations for ventilation of the preterm infant at birth are extrapolated from animal data, observational studies, historical cohort data and a few randomized controlled trials.

1. Positive pressure ventilation with a PIP of 20-25 cm H_2O is advised in preterm infants and initially higher pressures may be needed. Ideally the pressure should be adjusted to a measured tidal volume.
2. A sustained initial inflation seems to be advantageous for physiological reasons and a good alternative for using initially higher pressures. Creating an early FRC with this technique may reduce the need for intubation.
3. PEEP during resuscitation is necessary to keep the lung open and create an adequate FRC. PEEP levels up to 8 cm H_2O should be considered for resuscitation of preterm infants.
4. A pressure limited T-piece ventilator (e.g. Neopuff) is the best and easiest way to deliver a consistent and sustained PIP and adequate PEEP (level of evidence 6). It is the only device which can give CPAP immediately after ventilation.
5. When using a face mask during positive pressure ventilation, one should be aware that leakage occurs and can lead to insufficient ventilation. This may be avoided by using nasal prongs as interface.
6. Awaiting further clinical trials, resuscitation starting with 100% oxygen is still recommended in preterm infants. There is an increasing concern about hyperoxic lung injury, which can be addressed by weaning down the oxygen concentration as quickly as clinically possible.
7. Early CPAP can be used as initial treatment for very preterm infants. To prevent collapse of the lung this should be started directly in the delivery room.
8. Surfactant should be administered early, i.e. as soon as the preterm infant is intubated for RDS. Prophylactic surfactant in the delivery room could lead to overtreatment and should be avoided.

We recently started a randomized controlled trial (EFURCI-trial, Early Functional Residual Capacity Intervention) to investigate whether sustained inflation with a mechanical device (Neopuff®) and early nasal continuous positive airway pressure (Figure 1) will be a more effective management strategy in preterm infants than conventional intervention (Figure 2) and will reduce the requirement for mechanical ventilation and surfactant treatment. Both regimens are depicted in Figures 1 and 2 as they probably present the current choices of ventilation strategies for preterm infants at birth.

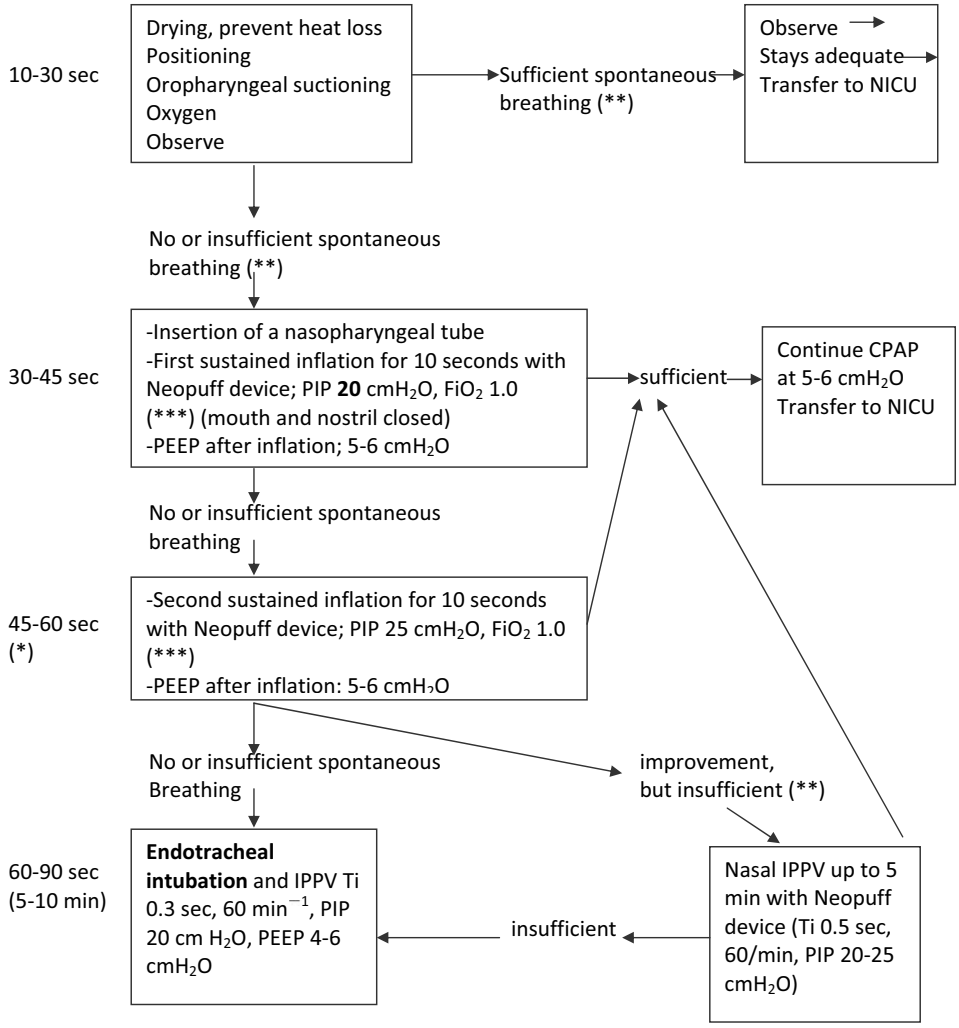

Figure 1. EFURCI (Early Functional Residual Capacity Intervention).

(*) After third phase: if heart rate< 60/min after positive pressure ventilation, start thorax compression and consider epinephrine;

(**) Spontaneous breathing with: good chest movements, skin colour and heart rate>100/min? YES=**sufficient**, NO=**insufficient**, good skin colour and heart>100/min, but apnea or dyspnea = **improvement, but insufficient.**

(***) Start with FiO_2 1.0 and wean down as soon as possible, depending on skin colour and heart rate.

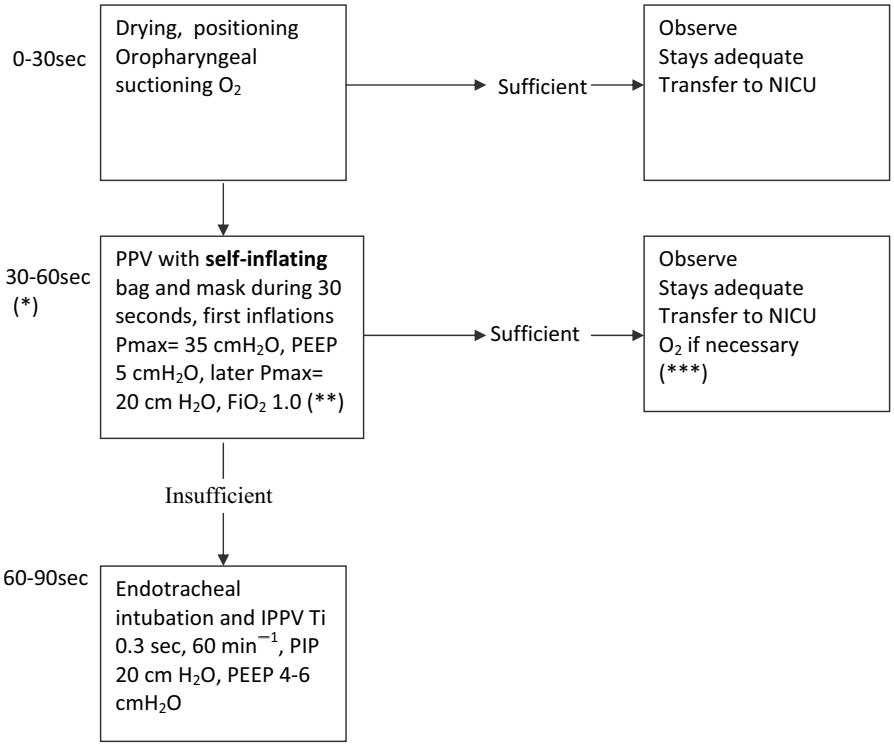

Figure 2. Conventional intervention of preterm infant

(*) After second phase: if heart rate < 60/min after positive pressure ventilation, start thorax compression and consider epinephrine

(**) Start with FiO_2 1.0 and wean down as soon as possible, depending on skin colour and heart rate.

(***) CPAP is started on the NICU depending on the clinical judgment of the neonatologist and severity of RDS.

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