Open lung high frequency ventilation in preterm infants with respiratory distress syndrome: practical considerations and recommendations
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Chapter 1

General introduction

Anne De Jaegere
Background

Respiratory failure plays an important role in morbidity and mortality of preterm infants. Lung immaturity, small surfactant pools, altered respiratory mechanics and respiratory drive, each to a variable extent cause respiratory failure. Subsequent inadequate gas exchange results in hypoxia, respiratory acidosis, multi-organ failure and eventually death. Introduction of respiratory support therapies, especially mechanical ventilation, reduced mortality dramatically (1-3). However, as a consequence part of the survivors develop bronchopulmonary dysplasia (BPD), a distinctive lung disease of the preterm infant characterized by chronic pulmonary morbidity and also associated with neurological impairment (4-7). Part of the respiratory failure is directly related to ventilator induced lung injury which induces further deterioration of lung function and results in pulmonary sequelae as seen in BPD (8). After the introduction of adapted ventilation strategies the incidence of BPD decreased in the “more mature” preterm infant above 28 weeks but in the very premature infant the incidence of BPD did not change. In contrast the combined outcome dead or BPD improved significantly in this younger group (9,10). So by now the improved survival of the very preterm infant only seems possible at the cost of BPD (11). The challenge remains to further identify contributing factors whether inherent to the patient, to the applied treatment or both. Strategies to reduce the incidence of pulmonary morbidity and inherent neurodevelopmental consequences could ensue and so result in an improved survival without chronic pulmonary morbidity.

Acute respiratory failure of the Preterm Infant and Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is typically described as the constellation of respiratory symptoms (cyanosis in room air, grunting, tachy-dyspnea), respiratory acidosis, supplemental oxygen need and the presence of radiological signs of diffuse alveolar collapse (12,13). The relationship of RDS to surfactant deficiency was first described by Avery in 1953 (14,15). More then half a century later RDS is still an important cause of respiratory morbidity and mortality in preterm infants (16) but targeted and refined therapeutical approaches significantly transformed patient and disease characteristics. Patients are much younger and not all of them develop classical RDS despite small surfactant pools (17,18).

Diagnosis of RDS as a surfactant deficiency syndrome is difficult and mainly circumstantial as the degree of surfactant deficiency is not established nor quantified. Beside the clinical signs of a low lung volume (cyanosis, grunting and tachypnoe) combined with prematurity (19), the chest radiograph is used as a diagnostic tool to evaluate the degree of alveolar collapse. Radiological characteristics of RDS, first described by Donald and Giedion (20,21) and adjusted by Edwards and Thome (22,23) mainly reflects the degree
of alveolar collapse in 4 increasing stages. Stage 1 represents the mild degree of alveolar collapse and stage 4 the most severe degree. The use of antenatal corticosteroids, exogenous surfactant and positive end expiratory pressure in respiratory care improved lung aeration to various extent. As a consequence radiological characteristics of RDS also changed (24-27).

Clarification of RDS physiology and pathology resulted in current therapeutical approaches that consists of an appropriate cocktail of antenatal steroids, early nasal positive pressure, “gentle” ventilation, reduced oxygen administration and selective early rescue surfactant treatment. From this cocktail endotracheal administration of exogenous surfactant and the application of mechanical respiratory support with oxygen remain the essential cornerstones for postnatal treatment of neonatal RDS (28,29).

**Exogenous surfactant therapy**

Surfactant is a complex mixture of phospholipids, neutral lipids and four proteins and reduces the surface tension of the alveoli. Surfactant has proven to be beneficial in reducing pneumothorax, pulmonary interstitial emphysema and mortality in preterm infants (10,30,31). Synthetic and naturally surfactant products are available (32,33) and used for either prophylaxis or rescue treatment of RDS (34). Synthetic surfactant do not contain surfactant protein in contrast with the natural products. Dosage varies from 100 mg/kg tot 200 mg/kg depending on the product and/or the dosage frequency. Surfactant is administered through an endotracheal tube. Prophylaxis is not superior to rescue surfactant treatment if given early, that is within 2 hours after birth (34). Late rescue surfactant, that is 6 hours and later after birth, is less effective then early rescue treatment (35). So it is crucial to identify the patient with RDS who will need surfactant within 2 hours after birth but no studies on the very early identification of these patients are published.

**Mechanical respiratory support**

**Early Nasal Continuous Positive Airway Pressure**

In 1987 Avery published a paper entitled ”Is Chronic Lung Disease in Low Birth Weight Infants Preventable? A Survey of Eight Centres” which described differences in prevalence of BPD among different neonatal intensive care units (14). In this study she speculated that the lower rate of chronic lung disease in one of the 8 centres could partially be explained by avoidance of intubation and liberal use of Early Nasal Continuous Positive Airway Pressure (ENCPAP) in respiratory failure of preterm infants. Several cohort evaluations (36-39) endorsed the findings of Avery. Thereby a debate between the more aggressive intubating and “softy-softy” CPAP neonatologists regarding optimal treatment of RDS arose (40,41). Since then, 4 trials studying about 2800 infants established that ENCPAP
with rescue surfactant therapy is an equal alternative treatment to the combination of surfactant, supplemental oxygen and artificial ventilation in the treatment of respiratory failure in (very) preterm infants (42-45). In summary neither of both strategies is superior to reduce the incidence of death or BPD at 36 weeks corrected gestation. Data on the effect of these 2 approaches on neurodevelopmental and/or motor outcome are unknown yet, but ENCPAP does reduce the need for artificial ventilation and the use of surfactant. However 50 % of the very preterms started on ENCPAP fail and still need intubation for the administration of exogenous surfactant. The ENCPAP attempt resulted in a delay of the administration of surfactant (42,43). As described surfactant administered as rescue therapy is similar to surfactant prophylaxis on the condition that it is given within 2 hours (35). But to allow for surfactant rescue administration within 2 hours after birth, it is of the utmost importance to early identify infants who will fail ENCPAP. Patient characteristics as low gestational age and birth weight and data on oxygenation have been identified to predict ENCPAP failure (46,47) however the very early prediction of this failure was not studied.

**Mechanical ventilation**

After the introduction of artificial ventilation neonatal mortality decreased dramatically. Some of the mechanical ventilated premature infants with RDS developed the new clinical entity BPD. Conventional mechanical ventilation (CMV) consists of repeated application of a positive pressure directly to the lung through an endotracheal tube. It soon became clear that (high) pressures directly applied to the surfactant deficient lung caused pulmonary interstitial emphysema and gross air leaks as pneumothorax, and this phenomenon resulted in the introduction of the term barotrauma. At first oxygen toxicity was considered the most important cause of the pathological findings of BPD (6) but the key role of barotrauma as contributing factor in the process of BPD followed soon (2,48-51).

**Ventilator Induced Lung Injury**

Although mechanical ventilation is meant to guarantee gas exchange, animal experiments have shown that mechanical ventilation itself may inflict damage to the injured lung, the so called ventilator-induced lung injury (VILI) (8,52,53). Several key risk factors for the development of VILI have been identified.

**Volutrauma and barotrauma:** high inflation pressures, leading to high tidal volumes, result in alveolar and perivascular edema, deteriorating lung mechanics and ultimately death in healthy rats (54). High inflation pressures will only damage the lung if volume can enter the lungs. Preventing thorax expansion exposing the lung to only low volume will protect against VILI (54,55). So volutrauma and not barotrauma seems one of the main
determinants in the development of VILI. Volutrauma is often thought to be equivalent to high tidal volume ventilation. But low tidal volumes can also induce volutrauma if superimposed on a high functional residual capacity and exceeding total lung capacity (56).

**Atelectrauma:** Surfactant system dysfunction results in alveolar collapse and roughly three zones can be identified: (1) alveoli which remain open during the entire respiratory cycle; (2) alveoli that are recruitable during the inspiration phase, but collapse during expiration; and (3) non-recruitable alveoli (81). Alveoli in zone (2) will be subjected to repetitive opening and collapse during conventional ventilation with insufficient positive end-expiratory pressure. This condition is injurious in the diseased lung (57,58). As alveoli in zone (3) do not participate in tidal ventilation, the tidal volume is redistributed over the alveoli in the other two zones, which may increase the risk of regional overdistention (volutrauma) (59). Finally, co-existence of atelectatic and open alveoli may result in shear forces that exceed transpulmonary pressures, increasing the risk of structural damage to the alveolar unit (60).

Volutrauma and atelectrauma reflect lung injury at both ends of the lung volume, with volutrauma occurring in the high lung volume zone and atelectrauma in the low lung volume zone (52).

**Endotrauma:** The relatively high chest wall and low lung compliance of the neonate result in a lower functional residual capacity, which is counteracted by an adaptation in the breathing pattern with a crucial role for the coordination between the laryngeal and diaphragmatic muscles. This breathing pattern results in an elevation of the end-expiratory lung volume above the relaxation lung volume. With the use of an endotracheal tube coordinated laryngeal and diaphragmatic control of the respiratory pattern and so the end-expiratory lung volume, is disrupted (61). The laryngeal bypass and subsequent loss of lung volume control results in a physical insult of invasive artificial ventilation called endotrauma (62).

**Biotrauma:** Volutrauma and atelectrauma also induce an inflammatory response in the lung which can further aggravate VILI. During recent years, numerous cytokines have been identified as players in the inflammatory process. The production of inflammatory mediators recruits polymorphonuclear cells in the lung (63,64) and these cells can inflict tissue damage through proteases, reactive oxygen species and cytokines (65). Several observational studies in ventilated preterm infants showed an enhanced inflammatory response after birth in those developing BPD. The response seen in the lung consists of a persisting neutrophil influx and upregulation of inflammatory mediators (66-68).

**Oxygen toxicity:** High fractions of inspired oxygen can result in excessive production of oxygen radicals overwhelming the normal antioxidant-detoxifying capacity of the cell. Beside a direct cytotoxic effect with pulmonary edema and hemorrhage (69-71), an inactivation and decreased synthesis of pulmonary surfactant and an enhanced
inflammatory cytokine response (71-73), there is an inhibitory effect on lung development resulting in decreased alveolarization (74,75). Premature infants are extremely vulnerable to oxidative stress as the ability to increase antioxidant enzymes in response to hyperoxia is impaired (76,77).

**Surfactant system dysfunction:** Secondary to the biotrauma surfactant function declines as it is inactivated by the proteins involved in the inflammatory process (78,79). Ventilation can enhance the secretion of endogenous surfactant pulmonary (80,81). Subsequently the surfactant can be squeezed out in the small airways especially with large tidal breaths which induces a loss of surfactant (82). Net result is a further decrease of an already small surfactant pool due to prematurity (83). Combined inflammation and changing alveolar surface result in a deterioration of the surfactant system function (84).

The combination of all these “traumatic” key factors often induces a vicious circle with different factors enhancing each other and results in an increasingly injured lung. The variety of mechanical and biological traumas described in VILI are present at all ages, although premature infants are more susceptible with less buffer at both the low volume injury zone and the high volume injury zone (52,85). Less or even scarce alveolarization and a smaller ratio between total lung capacity and body weight explain this increased vulnerability of the lung tissue in the premature infant compared to the pediatric and adult population (86).

**Bronchopulmonary Dysplasia**

Bronchopulmonary dysplasia is the most common serious pulmonary morbidity of premature infants (16,87-89). The costs of the disorder are both social as well as economic, and are measured in impaired childhood health, family stress and increased healthcare costs. BPD is a complex and multifactorial disease that already can be initiated before birth and continues during the neonatal period (18). With improved prenatal and neonatal respiratory care a change in the disease arose. Originally as described by Northway (6), the disease occurred during the alveolar stage of lung development and was mainly characterized by scarification secondary to VILI with diffuse interstitial fibroplasia, airway injury and emphysema. Nowadays the so called “new BPD” is a clinical syndrome at the end of a continuum of lung developmental abnormalities when the lung is in the saccular stage (90). Pathological characteristics consist of a simplified lung architecture with fewer but larger alveoli and a concomitant lower number of vessels (18,91-94). Beside the aforementioned VILI with its mechanical and biological components, other risk factors for BPD are antenatal fetal vascular and/or inflammatory hits and infection (95-97), prematurity (18,98), poor nutritional condition (99,100) and patent ductus arteriosus (101). Despite a better insight into the pathogenesis of RDS, VILI
and BPD, and modulation of different therapeutical approaches no significant change in the prevalence of BPD occurred (102). In contrast, a decrease in mortality with a shift towards lower gestational age survivors, less need for artificial ventilation and a diminished use of exogenous surfactant was seen (42-45). Yet it is unknown whether BPD is the inevitable result from very preterm birth and if medical practice, in particular respiratory support, can further decrease the incidence of BPD. As a consequence for those preterm infants who need to be ventilated, it is crucial that the application of ventilation strategies reducing VILI should be performed and documented accurately and precisely (103).

Open Lung Ventilation
The basic goal of open lung ventilation (OLV) is to establish an acceptable level of gas exchange while minimizing VILI, that is prevent overdistention and atelectasis. Together with advances in unraveling the pathophysiology of lung injury in adult acute respiratory distress, the findings in the newborn baboon animal model resulted in better understanding of the crucial role of using low tidal volumes, and the application of a recruitment procedure followed by stabilization of the recruited lung (51,55,56,85,104-108). Applying this triad with the lowest possible pressure results in a ventilation in which overdistention and lung collapse are minimized as much as possible.

The importance of recruitment
It was demonstrated that low tidal volumes applied during high frequency ventilation (HFV) are not sufficient to attenuate VILI (109-111). As hysteresis represents the main characteristic of the lung, the recruited volume can be maintained at lower airway pressures. Therefore, during OLV recruitment is applied to reverse atelectasis but subsequently the recruited alveoli have to be stabilized with sufficient distending pressure (111,112). This allows to avoid repetitive alveolar overdistention and collapse. Keeping the lung recruited at this lower pressure will both reduce intrapulmonary shunting which improves oxygenation, and place the tidal ventilation on the steepest part of the deflation limb of the pressure volume loop which optimizes ventilation and minimizes lung injury (112-114).

Establish lung volume at the bedside
Although the importance of an open lung during mechanical ventilation is well recognized, there is currently no validated, easy to use, bedside tool to measure changes in lung volume in newborn infants. A compilation of several suggested definitions for optimal lung volume could be the volume resulting in optimal dynamic compliance and gas exchange at the lowest possible pressure level and FiO2, without compromising hemodynamics (110,114-116). Although both dynamic compliance and oxygenation can
be measured bedside most clinicians have adopted oxygenation as the indirect tool to measure changes in lung volume (117-123). Increases in airway pressure that result in alveolar recruitment will reduce intrapulmonary shunt and improve oxygenation. In theory in absence of pulmonary vasoconstriction, optimal recruitment will reduce intrapulmonary shunt fraction < 0.10, allowing for adequate oxygenation without supplemental oxygen. Most clinicians use FIO2 ≤ 0.30 to define optimal recruitment both in adult and neonatal patients. No “dose”-finding studies on the relationship of fraction of inspired oxygen (FIO2)/ oxygen saturation measured by pulse oximetry (SpO2) ratio targets and lung volume were performed. In newborn infants the use of oxygenation to assess lung volume could be hampered by pulmonary vasoconstriction and/or pulmonary hypertension, especially during transition of the circulation in the first days after delivery. The increased extra-pulmonary right to left shunt across the patent ductus arteriosus or open foramen ovale, will cause changes in oxygenation that are independent of lung aeration. Three of the 4 randomized controlled trials (RCT’s) with protocolized optimal (or high) lung volume strategy in terms of oxygenation managed to reach a target FIO2 ≤ 0.3 (16,87-89,118,119,124). No data are published on the feasibility and safety of the use of oxygenation as an indirect bedside tool during the recruitment procedure.

Ventilator
In the human pediatric and adult population the OLV strategy is mostly applied with a “conventional” mechanical ventilator using positive pressure ventilation in the pressure controlled mode (125-127), since the use of HFV in adults has its own challenges (128). All studies in newborns on the use of the OLV strategy were performed with a HFV (117,118,120,121). It is not known whether the OLV strategy can be applied using positive pressure ventilation with a conventional ventilator in the newborn.

High frequency ventilation
History
During the 1970’s HFV was uncovered as a new ventilation mode with powerful carbon dioxide clearance capacities by oscillating very small tidal volumes at high frequencies in animal models (129-132). Very soon recruitment appeared to be crucial to achieve proper oxygenation. Bryan and deLemos, two important investigators on the role and the use of HFV in the preterm newborn, cautioned the clinical users for the use of a correct ventilation strategy (133,134). Nevertheless the quest for reducing ventilator related barotrauma resulted in the consideration of the quite new ventilation technique HFV as a possible solution (135,136). The ability to guarantee gas exchange at lower pressures generated the concept of lowering barotrauma, but by a lack of insight the importance of the concept of recruitment disappeared. Thus, the urge to use HFV at the beside in
stead of further exploration at the bench resulted in the performance of the prematurely stopped National Institute of Health granted HIFI trial (137). The disappointing effect on the incidence of pulmonary morbidity but more, the hazardous effect on neurological outcome are well known and history by now (137). As a consequence the HIFI trial resulted in an important setback of the use of HFV in newborns. Subsequently the methodological flaws of the ventilatory strategy and the misuse of HFV were published (134,138,139). The critical findings of the HIFI trial were also apprehended to reinforce the quest for the pathophysiology of respiratory dysfunction in neonatal RDS, its relationship with VILI (104,112) and the proper application of the HFV strategy. Indeed, in neonatal intensive care the application of the OLV strategy to reduce VILI is most frequently applied with HFV.

Different types of high frequency ventilators were developed and studied in both animals and humans studies. High frequency oscillation (HFO) or high frequency flow interruption (HFFI) are the most commonly used. Other modalities are HF jet ventilation or HF percussion ventilation. In following text HFV refers to HFO or HFFI.

**Principle**

To guarantee gas exchange a constant pressure, often referred to as mean airway pressure or continuous distending pressure (CDP), is applied to the lungs. This pressure stabilizes airways and alveoli/sacculi. On this CDP small pressure swings are imposed in a frequency of 600 to 900 cycles/min, resulting in small volume changes of approximately 1–3 ml/kg. The mechanisms responsible for adequate gas exchange during HFV are coaxial flow, asymmetric velocity profiles, the pendelluft effect and “enhanced” molecular diffusion. The oscillated tidal volumes guarantee the wash out of carbon dioxide. The small tidal breaths that are intrinsic to the HFV principle entails that HFV applies by design a low tidal volume strategy. Oxygenation relies on an adequate alveolar recruitment without overinflation, that is at functional residual capacity volume level. As bedside lung volume measurements are difficult and cumbersome to perform, the lung volume is determined indirectly using oxygenation and aiming at an intrapulmonary shunt fraction of 0.1, i.e. a FIO2 ≤ 0.3 with normal SpO2 (114). Alternatively some clinicians combine oxygenation with frequent radiological evaluation of the lung aeration to determine lung volume (117,118).

**Clinical studies**

As mentioned the disappointing result of the HIFI trial (137) resulted in an important setback of the use of HFV in clinical practice. In 1991 Bryan and Froese highlighted important methodological flaws of the HIFI trial: 1) the absence of recruitment maneuvers, 2) the absence of maintaining the pressure above the closing pressure, 3) the substantial use of conventional tidal ventilation before starting HFV and the 4) the liberal
use of cross-over between conventional and HFV (139). They also emphasized that there were still trials applying the high volume philosophy during HFV. However 20 years later we are not there yet. Human RCT’s (119-121,124,137,140-148) and their systematic reviews (149-152) comparing HFV to CMV have not provided convincing evidence that HFV is superior to CMV in reducing mortality and/or the incidence of BPD in preterm infants. An important finding in most of the studies is that although the intention to apply an open lung strategy is described, clear targets (e.g. FiO2) to define optimal recruitment are not mentioned. Trials that did define the FiO2 targets showed considerable variations in defining optimal lung volumes by oxygenation targets, and a minority set the FiO2 target ≤ 0.3 (118-120,124) and from these just three managed to reach the FiO2 target ≤ 0.3 (118,119,124). Interpretation of these finding should be done cautiously but one could conclude that most RCT’s on HFV failed to obtain the optimal lung volume, which could, in part, explain the disappointing results on the incidence of BPD (103).

As experiments in preterm lambs have shown that only a few large breaths during CMV are sufficient to trigger the cascade of VILI (153), delayed randomization and cross-over may have confounded a possible treatment effect of HFV on the incidence of BPD. Cross over from HFV to CMV is another important issue in the occurrence of VILI in the preterm infant with RDS. Not only at the start of the disease but also during the weaning period patients are prone to tidal volume induced VILI. As Bryan suggested and Stark confirmed, maintenance of the patient on HFV could be another important factor that could reduce VILI and so BPD (139,154). However some clinicians switch from HFV to CMV once the acute lung disease has improved and subsequently wean and extubate from this ventilation mode (120). Others wean and extubate infants directly from HFV, using a CDP below 8 cm H2O and an FIO2 below 0.30 as extubation criteria (121,147). The validity of these extubation criteria are not established yet.

Clinical practice

OLV procedure with HFV

The clinical application of OLV during HFV has mainly been studied in preterm infants with RDS. One of the difficulties of the practical implementation of OLV is the lack of a standardized definition of an optimal lung volume and as mentioned most clinicians use FiO2 as bedside tool.

In the Emma Children’s Hospital in Amsterdam preterm infants are unsedated, unparalyzed and ventilated in supine position. The individual OLV procedure is applied and can be described as follows (Figure):

1) Recruitment stage (inflation limb)

Immediately after intubation, HFOV is started at a low CDP (CDPst) of 6-8 cm H2O. The pressure amplitude is set at a level that results in visible oscillation of the chest,
with a frequency of 10 Hz and inspiration time of 33%. The FiO2 is dynamically adjusted to keep the SpO2 between 86 - 94%. Subsequently the CDP is increased stepwise with 1-2 cm H2O and if SpO2 exceeds the upper target limit FiO2 will be reduced in steps of 0.05-0.10. After each pressure steps the clinician waits at least 2 – 3 minutes to ascertain any change in oxygenation. The CDP increase is stopped once the FiO2 is ≤ 0.25 or if oxygenation no longer improves after three consecutive pressure steps. The CDP reached at that point is called the opening pressure or CDPo.

2) Derecruitment phase (deflation limb)
Assuming the presence of lung hysteresis, the CDP is decreased with similar 1-2 cm H2O steps, while keeping the FiO2 constant. Again, the clinician will wait at least 2-3 minutes to detect any deterioration in oxygenation indicating alveolar/saccular collapse. The pressure at which this occurs is called the closing pressure or CDPc.

3) Re-Opening and optimizing lung volume
Following derecruitment, the lung is once more opened with the know CDPO for 5 minutes and then stabilized at an optimal CDP (CDPopt) which is set 2 cm H2O above CDPc.

This OLV procedure is time consuming as between the different steps of recruitment and derecruitment an equilibration time for stabilization of the oxygenation (SpO2/ FiO2) is needed. However detailed data on the implications of the performance of the individualized OLV procedure on medical staff resources are not available.

In the presented recruitment procedure some assumptions are made which were not validated nor verified. First, OLV is based on is the presence of lung hysteresis (155,156). It is not known if hysteresis is present in preterm infants with RDS. Second, in daily clinical practice changes in lung volume are guided by changes in oxygenation. However, oxygenation (SpO2) is not only affected by lung aeration but also pulmonary perfusion. Finally, it is unclear how quickly lung volume stabilizes after each pressure step in preterm infants with RDS. This information is important when optimizing the time and the applied pressure during lung recruitment.

Surfactant treatment
The endotracheal administration of exogenous surfactant induces acute changes in alveolar stability and, to less extend, in dynamic lung compliance (157-160). Accordingly, the optimal CDP applied before surfactant therapy will mostly be too high and a risk of overdistention arises. Therefore it is important to tailor the CDP to the new lung condition. In patients with mild RDS this means a decrease of the CDPot at an extubation level. In patients with more severe RDS a new OLV procedure with determination of the new CDPO, CDPc and CDPopt should be performed.
Figure: schematic representation of the 4 successive steps of the individual OLV procedure: panel A recruitment stage, panel B de-recruitment stage, panel C re-opening stage and panel D optimization stage.

* $\text{FiO}_2$ is $\leq 0.25$ or if oxygenation no longer improves after three consecutive pressure steps.

Upper and lower part of the panels represent the pressure (P)-volume (V) loop and the pressure (P)-time course respectively.

Black solid line = progression of the actual pressure steps; black dotted line = past pressure steps; grey solid line = coming pressure. Black solid oval = oscillations.
Weaning and extubation with HFV

Weaning from HFV consists of lowering the CDP till 8 cm H2O with FIO2 0.3 and the oscillatory delta pressure is decreased to barely perceptible thoracic vibrations. These pressure reductions intend to increase the patient spontaneous breathing. At the end of the weaning procedure the infant is thought to be at pressure levels that matches the level at which nasal CPAP is sufficient to support spontaneous breathing. Yet little is known about the feasibility and effectiveness of the suggested pressure variables at which patients should be sufficiently weaned to be extubated.

Conclusion

Decreasing the incidence of BPD remains an important challenge in the care of the preterm infant. As VILI plays an important role in the pathogenesis of BPD, preventing and minimizing VILI could further improve survival of preterms without BPD. In animal studies OLV was shown to reduce VILI compared to CV if the triad of the correct strategy, immediately started, for the duration of the ventilation episode is warranted. The correct OLV strategy aims to guarantee gas exchange with low tidal volumes applied on the steepest part of the expiratory limb of the lung with the lowest possible pressures. Thorough analysis of the RCT’s comparing different ventilator strategies reveals that the application of the OLV strategy can be questioned. In particular the recruitment of the lung without inducing overdistention or atelectasis and the uninterrupted application of the OLV strategy remain important challenges, especially in daily clinical care.

Aim of the thesis

The general aim of this thesis is to gain more detailed insight into all aspects of the practical application of the OLV strategy using HFV in preterm infants with RDS during the daily clinical care process. This includes the exploration of the feasibility and safety of the OLV strategy during HFV, the continuous use of HFV without cross over to CMV, and the early prediction of the need for ventilation.

Outline of the thesis

Non invasive ventilation with the use of ENCPAP is increasingly applied and effective in almost half of the patients but does not reduce BPD. Moreover approximately 50% of the patients need surfactant therapy one of the cornerstones for the treatment of RDS. Late rescue surfactant therapy is less effective and, could in part explain the failing effect of ENCPAP on the incidence of BPD. Predicting which infant will fail ENCPAP in the first hours after birth could prevent the delay in surfactant administration and
perhaps contribute to a further decrease of BPD. In chapter 2 retrospective patient and respiratory data of preterms < 30 weeks gestational age treated with ENCPAP were used to develop a prediction model of ENCPAP failure.

From animal and human data it became clear that not the ventilator mode (high frequency ventilator in stead of a conventional ventilator) but the ventilation strategy determines the reduction of VILI. Ventilators to apply HFV are especially manufactured or additional software and hardware has to be built out in a standard ventilator. The question whether the application of OLV with a conventional ventilator reduces VILI in a piglet animal model is explored in chapter 3. The OLV strategy of stepwise recruitment – derecruitment during pressure controlled conventional ventilation is compared to the OLV strategy during HFV and to the standard strategy during conventional mandatory ventilation.

Exact data on the use of oxygenation as an indirect bedside tool to guide the OLV procedure are scarce. No information on changes in circulatory parameters during the actual recruitment procedure is available. Therefore a prospective cohort of preterm infants with RDS, ventilated with primary HFV, using a standardized and individualized OLV strategy and in which oxygenation guided airway pressure changes during the recruitment procedure, was studied as shown in chapter 4.

Chest radiography is one of the tools used for the diagnosis of RDS in preterms with respiratory symptoms. The OLV strategy aims to recruit and to keep recruited all alveoli. High pressures can be necessary during the recruitment procedure. Limited data are available on the radiological characteristics of RDS and the prevalence of air leaks and hyperinflation in preterm infants with the application of the OLV strategy and its recruitment pressures during HFV. Chapter 5 describes the radiological characteristics in terms of lung radiolucency, hyperinflation and air leaks during the application of an individualized and standardized OLV strategy using HFV.

Individualized OLV with HFV needs more steps to set up ventilator parameters than conventional ventilation, but actual data on timing are currently lacking and it is unknown if time needed to perform a lung recruitment procedure is dependent on the level of experience of the health care professional responsible for the ventilation. In chapter 6 these questions are studied to further explore the best approach and resources to apply open lung HFOV in preterm infants during daily clinical practice.

Cross over from the HFV mode to the CMV mode after the acute stage of RDS is one of the possible factors playing a role in the occurrence of VILI. Weaning and extubation criteria on HFV have been proposed but never were studied in detail. In chapter 7 the feasibility of the weaning and extubation process is studied in detail in a retrospective cohort of all preterm infants treated with primary OLV HFV.
References


85. Cheifetz IM. Management of acute lung injury: sharing data between adults and children. Respir Care 2011 Sep;56(9):1258-68.


110. Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 2001 Jan;163(1):69-78.


