Prevention of ventilator induced lung injury in preterm infants with respiratory distress syndrome: PreVILIG
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CHAPTER 1

GENERAL INTRODUCTION
1.1 Respiratory distress syndrome and bronchopulmonary dysplasia in premature infants

Between one and three percent of live born infants are born before 32 weeks of gestation.\textsuperscript{1,2} These premature infants frequently suffer from respiratory distress syndrome (RDS), a disease of the premature lung characterized by a deficiency of surfactant and an insufficient alveolarisation, and thus diminished functional surface area for gas exchange. The majority of infants with RDS need surfactant replacement therapy and mechanical ventilation in the first days to weeks of their life. In a large cohort of infants (1998-2000) born at < 30 weeks gestational age, 90\% received mechanical ventilation and 79\% were treated with exogenous surfactant. The proportion of infants receiving surfactant therapy was highest among the most immature infants: 90\% at 24 weeks and 91\% at 25 weeks gestational age.\textsuperscript{3}

Despite the advances in neonatal respiratory care a considerable number of these infants develop chronic lung disease of prematurity, called bronchopulmonary dysplasia or BPD, characterized by a prolonged need for supplemental oxygen.\textsuperscript{4} Twenty-three percent of infants with a birth weight below 1500 g are oxygen dependent at the postmenstrual age of 36 weeks. This proportion increases with decreasing birth weight: 7\% for infants 1251-1500 g, 15\% for infants 1001-1250 g, 34\% for infants 751-1000 g and 52\% for infants 501-750 g.\textsuperscript{1,5} BPD is associated with prolonged neonatal intensive care and with long term morbidities such as home oxygen use, recurrent respiratory infections often requiring hospitalization,\textsuperscript{6} feeding difficulties with impaired growth,\textsuperscript{7} neurodevelopmental delay\textsuperscript{8-13} and long term pulmonary impairment.\textsuperscript{14,15} Since the recognition of these consequences clinicians have tried to reduce the incidence of BPD in children with RDS.

1.2 Ventilator induced lung injury (VILI)

Although the pathogenesis of BPD is multifactorial,\textsuperscript{16-20} mechanical ventilation is one of the most important causative factors.\textsuperscript{21,22} Mechanical ventilation is associated with interstitial and alveolar oedema, widespread alterations of endothelial and epithelial barriers and diffuse alveolar damage.\textsuperscript{23} Three basic mechanisms of ventilator-induced lung injury are distinguished: 1) volutrauma is caused by alveolar overexpansion secondary to high lung volume; 2) atelectrauma is an alveolar shear-stress injury due to repetitive alveolar recruitment-derecruitment; 3) biotrauma is caused by the release of inflammatory mediators resulting in local and systemic inflammatory responses.\textsuperscript{24,25} All these noxious events occur during conventional mechanical ventilation of atelectasis-prone lungs, such as in premature infants with RDS.

1.3 Prospect of high-frequency ventilation: experimental data

In the late seventies a new ventilation technique was developed, called “high-frequency ventilation” (HFV), using tidal volumes smaller than anatomical dead space delivered at a rate of 600 to 900 per minute, thus avoiding the large volume swings seen with conventional ventilation (CV). High-frequency ventilation can be delivered using different ventilator techniques, i.e. a piston pump oscillator (“true” oscillator), a high-frequency jet flow (HFJV) or a high-frequency flow interrupter (HFFI). HFV not only proved to be an effective way to ventilate both normal and abnormal lungs,\textsuperscript{26,27} animal experiments also clearly showed that in RDS-models HFV resulted in less lung injury compared with CV.\textsuperscript{28,29} Therefore it was thought that HFV, used as the primary mode of ventilation early in the course of RDS, might result in less mortality and BPD compared with CV.
1.4 Merits of high-frequency ventilation: evidence from clinical trials

In clinical trials and clinical practice, piston pump high-frequency oscillators (such as the SensorMedics®, Dufour OHF-1®, Hummingbird®) and high-frequency flow interrupters (such as Dräger Babylog®, Infant Star®) have often been considered as equivalent techniques in delivering high-frequency ventilation and have both been called “high-frequency oscillatory ventilation” or HFOV in literature. This is in contrast with high-frequency jet ventilators (such as Bunnel Life Pulse®) which have always been considered as a separate HFV technique. Therefore, in this thesis HFOV will refer to the use of either a “true” oscillator (piston pump driven) or a high-frequency flow interrupter (HFFI), whereas HFV also includes the use of a high-frequency jet ventilator (HFJV).

Over the past 20 years, 19 randomized controlled trials, involving more than 3800 premature infants, have investigated the efficacy and safety of HFV versus CV in the early management of RDS. The results of the first large randomized trial, the HIFI-trial in 1989, were in sharp contrast with the positive findings from animal studies, showing no decrease in BPD, but an increased risk of brain damage, instead. At that time, the disappointing results were explained by the inadequate ventilation strategy that was used in the HIFI trial, aiming at minimizing ventilation pressures instead of recruiting lung volume. Studies in different animal models of surfactant deficiency had shown that a “high lung volume strategy” using higher distending pressures in order to maximally recruit collapsed alveoli was a prerequisite to prevent lung injury, and hence to see the benefits from HFV. As a result, starting from the early ‘90ies, subsequent randomized controlled trials followed, now applying the “high lung volume strategy” (HLVS).

Nevertheless, the results of these trials with regard to pulmonary outcomes remained inconsistent, with only some trials showing a clear reduction of BPD with the use of HFV. Also, uncertainty remained whether or not HFV was associated with an increased risk of severe intracranial hemorrhage. As a result, and despite the large amount of evidence, the debate continued whether or not HFV should be used as the primary mode of ventilation in premature infants with RDS.

The reasons for this ongoing debate are obvious, as several important questions have remained unanswered. They are: 1) whether certain types of premature infants benefit more from HFV than others, depending e.g. on the degree of prematurity or the severity of lung disease; 2) whether the effects of HFV depend on the ventilator technique (i.e. the use of true oscillators versus high-frequency flow interrupters); 3) whether the ventilation strategy, i.e. the method of lung volume recruitment or the timing after birth of initiation of HFV, modifies the effects. Given these uncertainties, with the existing published evidence being unable to guide clinical practice, the application of HFV in clinical practice varies greatly between neonatal intensive care units, depending on whether or not the neonatologist is a “HFV believer”.

1.5 Neuromuscular paralysis during mechanical ventilation

Other interventions may potentially prevent ventilator-induced lung injury or BPD in premature infants, such as neuromuscular paralysis. A common problem during mechanical ventilation in newborn infants is asynchronous spontaneous respiratory efforts of the ventilated infant. These infants, “fighting” the ventilator, are at risk for complications during mechanical ventilation which, as a consequence, could impair their clinical outcome. In 1983 Greenough showed that asynchronous spontaneous breathing during mechanical ventilation was associated with a high risk for pneumothorax. In a prospective study of preterm infants Perlman showed that fluctuating cerebral blood-flow velocity during the first day of life was associated with an increased risk for intraventricular haemorrhage, this pattern of cerebral blood-flow is likely to be present in struggling infants. Spontaneous breathing during mechanical ventilation is also associated with higher peak transpulmonary pressures, which may put the infant at higher risk for chronic lung disease due to barotrauma.
Neuromuscular paralysis, which eliminates spontaneous breathing efforts of the infant during mechanical ventilation, has potential advantages in this respect. Neuromuscular paralysis could reduce the risk of acute complications such as pneumothorax, hence improving short term outcome and mortality, and it could lead to more efficient ventilation and a shorter duration of mechanical ventilation, hence reducing the risk for lung injury and BPD. On the other hand, a number of complications have been reported with neuromuscular paralysis in infants, such as hypotension, hypoxemia, prolonged muscle weakness, and, more recently, sensorineural hearing loss. Some clinical studies show benefit, whereas other studies show no difference or marked adverse effects of paralysis. As a result, with the existing published evidence being unable to guide clinical practice, the use of neuromuscular paralysis varies greatly between neonatal intensive care units.

1.6 Aim of this thesis

The aim of this thesis is to answer the following questions:

1. Does high-frequency ventilation, as compared to conventional ventilation, offer a clinically important benefit in terms of more survival without BPD, without increasing the risk of adverse neurological events such as severe intracranial hemorrhage of periventricular leukomalacia, when it is used as the primary mode of ventilation in premature infants with respiratory distress syndrome?

2. Do the effects of HFV differ according to the risk profile of the patient in terms of lung immaturity, fetal growth, severity of initial lung disease or delayed start of HFV?

3. How do intervention-related factors such as the HFV-device or the ventilation strategy used, and co-interventions such as exogenous surfactant therapy or postnatal corticosteroids, modify the overall treatment effect?

4. Does neuromuscular paralysis offer a clinically relevant benefit in terms of reduced risk of lung injury without causing adverse effects?

1.7 Outline of this thesis

In Chapter 2 the systematic literature reviews and aggregate data-based meta-analyses of randomized controlled trials comparing the elective use of HFV with CV in premature infants with respiratory failure are presented. In 1998 we performed a systematic review and meta-analysis of randomized controlled trials comparing the early use of high-frequency ventilation – defined as both high-frequency oscillatory ventilation (true oscillators or HFFIV) as well as high-frequency jet ventilation (HFJV) – in premature infants with respiratory distress syndrome (Chapter 2a). In 2000 we started collaborating with the authors of the Cochrane systematic review addressing the more focused question regarding the efficacy and safety of elective high-frequency oscillatory ventilation (HFOV) versus conventional ventilation for acute pulmonary dysfunction in premature infants (Chapter 2b). At the time the review contained 4 trials with 955 premature infants. We updated this Cochrane review in 2001, 2003 and 2007. The most recent update of the Cochrane review, performed in April 2009 and published in July 2009, is presented as Chapter 2c.

Chapter 3 describes the limitations of the existing meta-analyses in addressing a number of clinically important, unanswered questions. These limitations are largely related to the fact that the existing meta-analyses are based on summary data extracted from trial reports. To overcome these limitations, we formed a Collaborative Group in 2006 with all the investigators of the original trials (PreVILIG Collaboration). The aim of the group was to address the clinically important, unanswered questions using the new technique of meta-
analysis based on the individual patient data from the original trial datasets. To this aim a prospective data analytic protocol was developed through several Collaborative Group Meetings since 2006. It is presented in Chapter 4.

In Chapter 5 we describe the results of the individual patient data meta-analysis exploring the modifying effect of several patient-level characteristics as well as trial-level intervention related factors.

In Chapter 6 we analyze and compare, based again on the individual patient data of the original trials, the ventilation strategies which were actually used in these trials both for HFDV and CV, and describe the variation which exists between trials.

In Chapter 7 a systematic review and meta-analysis is presented addressing the question whether neuromuscular paralysis in newborn infants receiving mechanical ventilation has any benefits in terms of decreased risk of lung injury without having adverse effects.

The thesis concludes with a general discussion in Chapter 8. Finally, this thesis contains a summary in English and in Dutch.

1.8 References


33. Clark RH, Gerstmann DR, Null DM, Jr., deLemos RA: Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992; 89:5-12