Electrical impedance tomography in high frequency ventilated preterm infants: the search for the Holy Grail
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Summary, conclusions and future perspectives
Summary

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure in preterm infants. RDS is characterized by primary surfactant deficiency which leads to a loss of lung volume due to alveolar collapse. End-expiratory lung volumes below functional residual capacity (FRC) can compromise lung function and lead to acute respiratory failure. The basic goal of respiratory support is to restore and maintain lung volume at a normal FRC in preterm infants with RDS, resulting in adequate gas exchange and minimal ventilator-induced lung injury. So far, measuring lung volume non-invasively at the bedside has been cumbersome in (ventilated) preterm infants. This has now changed with the introduction of electrical impedance tomography (EIT), a bedside tool measuring changes in lung impedance in a cross-sectional slice of the lung, which have a high correlation with changes in aeration. In this thesis we used EIT to investigate the effect of open lung high-frequency oscillatory ventilation (HFOV) and several standardized respiratory interventions on lung volume in ventilated preterm infants with RDS.

Chapter 1 identifies a high chest wall compliance, surfactant deficiency, and intensive care interventions such as endotracheal intubation and suctioning as the most important causes of low lung volume in preterm infants with RDS. The presence of low lung volume will compromise lung function and increase work of breathing, all of which may lead to respiratory failure. In case of mechanical ventilation, low lung volume or atelectasis (atelectrauma) and alveolar overdistension (volutrauma) will also contribute to so-called ventilator-induced lung injury (VILI) which is considered an important risk factor for bronchopulmonary dysplasia (BPD). Studies in animal models and adults also showed that VILI is often not homogeneously distributed across the lung, partly due to the gravitational effects on the lung.

It has been suggested that HFOV, which uses by design very small tidal volumes, can attenuate VILI in preterm infants with RDS, but only if combined with an optimal lung volume or open lung ventilation (OLV) strategy. Such an OLV strategy aims to recruit collapsed lung tissue and stabilize ventilation on the deflation limb of the pressure volume relationship of the lung. Ideally, such a recruitment procedure should be guided by a bedside non-invasive lung volume monitoring tool. However, the available lung volume assessment techniques such as CXR, whole-body-plethysmography, nitrogen-washout and helium or sulphur hexafluoride dilution and respiratory inductive plethysmography have serious practical limitations and do not provide regional information on lung volume changes. The latter is imperative in case of a heterogeneous lung disease. Because of these limitations, lung recruitment in daily clinical practice is most often guided by changes in oxygenation, which only provides indirect information on lung volume changes.
EIT, a non-invasive, radiation-free and bedside tool, might solve this problem as it is capable of continuously measuring regionally changes in lung volume. The basis principles of EIT measurements, analyses and validation as well as its limitation are discussed. Based on its characteristics and possibilities, EIT seems the ideal tool to answer some of the unresolved issues concerning HFOV preterm infants with RDS, which are listed in the aims and outline of this thesis (Chapter 2).

Chapter 3 illustrates the importance of regional information provided by EIT as we present a case report of a preterm infant with an unilateral pneumothorax during HFOV. We show, for the first time, that EIT is capable of identifying regional loss in both oscillatory and spontaneous ventilation in case of a pneumothorax. Based on this report, EIT seems a promising tool to detect at the bedside acute changes in regional lung ventilation which can, in case of a pneumothorax, potentially reduce the delay in diagnosis and treatment.

Chapter 4 describes the effect of a standardized closed endotracheal tube suction (ETT) procedure in HFOV preterm infants with RDS, on regional lung volume changes monitored by EIT. In 11 preterm infants ETT resulted in an acute loss of lung volume followed by a gradual spontaneous recovery. After a stabilization time of 8 seconds the median functional residual capacity loss was 3.3% of the maximum volume loss. However, regional analysis shows that this loss is heterogeneous in nature. So despite the fact that the overall loss in lung volume after ETT is low, a recruitment manoeuvre might be beneficial as a means to restore homogenous aeration after ETT suction.

In Chapter 5 we investigated the effect of oxygenation guided lung recruitment on lung volume and oscillatory ventilation distribution measured by EIT in open lung HFOV preterm infants with RDS. By mapping the pressure/impedance and pressure/oxygenation relationships we were able to show, for the first time, that lung hysteresis is present in preterm infants with RDS. This hysteresis is more pronounced in the pressure/oxygenation curve as indicated by the decreased upper inflection point (10.9 ± 1.9 cmH₂O) of the deflation limb compared with the pressure/impedance curve (14.7 ± 2.6 cmH₂O). This difference is best explained by the fact that oxygenation, in contrast to impedance, will only detect a loss in lung volume based on alveolar collapse and not reduced alveolar distension. Regional analysis for the ventral and dorsal lung regions showed similar findings with no significant differences. Compared with the pre-recruitment phase, the oscillation volume increased significantly at optimal lung volumes. However, the distribution of the oscillation volume was homogenously and unchanged by the recruitment procedure. Based on these results we concluded that EIT is feasible in monitoring lung volume changes in HFOV preterm infants. The presence of lung hysteresis emphasizes the
importance of backing down with the CDP once the lung is recruited. The fact that FRC changes and oscillation volumes are homogeneously distributed seems to suggest that RDS, in the first 72 hours of life, is a relatively homogeneous lung disease without gravity-dependency.

**Chapter 6** focussed on the immediate effect of surfactant administration on lung mechanics and ventilation distribution during open lung HFOV preterm infants. Continuous EIT monitoring showed that surfactant resulted in an immediate increase in lung volume within a median time of 241 s. Besides this increase, alveoli stabilized after surfactant resulting in an upwards and left-sided shift of the deflation limb of the pressure/impedance curve. Maximal compliance increased after surfactant treatment, but this increase was reached at lower airway pressures. Regional EIT data showed that the increase in lung volume was most dominant in the dependent (dorsal) lung region, supporting previous findings that gravity plays an important role in the distribution of exogenous surfactant. In line with the findings described in Chapter 4, oscillation volume distribution showed no change after surfactant treatment, supporting the hypothesis that RDS is a relatively homogenous disease. These findings clearly indicated that clinicians should attempt to lower the CDP shortly (5 minutes) after surfactant treatment in order to prevent lung overdistension.

In **Chapter 7** we measured the actual time for lung volume to stabilize after each pressure step during the recruitment procedure. Continuous EIT registration made it possible to establish the time constants of the respiratory system during both incremental and decremental pressure steps before and after surfactant treatment using a one phase exponential decay fitting curve. These time constants were significantly longer for the incremental pressure steps (median 27.3 s) compared to the decremental steps (median 16.1 s) before surfactant with no clear regional difference. Surfactant administration almost tripled these time constants with a longer stabilization period in dorsal- compared to the ventral lung regions. Based on these results we were able to determine that the stabilization time (= 3 times the time constant) during oxygenation guided open lung HFOV preterm infants with RDS is approximately 40 seconds to 3 minutes before and 2 to 6 minutes after surfactant treatment. This information has important implications for clinicians performing open lung recruitment in preterm infants with RDS.

In **Chapter 8** we explored the hypothesis that changes in CDP or pressure amplitude independently control, respectively, oxygenation and ventilation during HFOV. First, the effect of CDP changes (i.e. FRC changes) during an open lung recruitment procedure on oscillation volumes and TcPCO₂ levels was assessed. Despite the constant delta pressure, ventilation clearly changed during the stepwise increase in CDP, following a parabolic pattern: ventilation increased during the initial CDP steps and decrease during
the final CDP steps. During deflation the oscillation volume increased. TcPCO\textsubscript{2} levels were strongly, but inversely, related to the changes in oscillation volumes. The pressure at maximal compliance, maximal oscillation volume and minimal TcPCO\textsubscript{2} levels during inflation were similar and significantly correlated, indicating that ventilation was probably dependent on the position of ventilation on the pressure/volume relationship of the lung. Second, the effect of an increase (5 cmH\textsubscript{2}O) in pressure amplitude at a constant CDP on ventilation was assessed. We showed that higher pressure amplitudes resulted in an increased oscillation volume with a concomitant decrease in TcPCO\textsubscript{2} levels and a decrease in the spontaneous breathing frequency. The FRC remained stable during this increase in pressure amplitude. Based on these results we can refute the hypothesis that CDP and pressure amplitude control oxygenation and ventilation independently. Our results also show that not only oxygenation but also TcPCO\textsubscript{2} can help clinicians to assess lung volume during lung recruitment.

Conclusions

In conclusion, the studies in this thesis demonstrate that lung volume monitoring by EIT is feasible and useful in unsedated preterm infants with RDS treated with open lung HFOV. EIT provided the following (patho)physiological information: 1) the lung of preterm infants with RDS shows clear lung hysteresis which allows stabilization of recruited alveoli at lower airway pressures; 2) surfactant treatment in neonatal RDS results in a rapid increase in lung volume and a clear stabilization of lung volume at lower airway pressures; 3) stabilization of lung volume after a pressure increase during a recruitment procedure is a matter of minutes; 4) ventilation during HFOV is affected by both changes in CDP and pressure amplitude, refuting the hypothesis that these two parameters work independently. Furthermore, the ability of EIT to assess regional changes in lung volume provided important additional information: 5) EIT is able to rapidly detect regional changes in ventilation as present during a unilateral pneumothorax; 6) surfactant distribution favours the dependent lung regions, which are most affected by gravity; 7) based on the regional changes in FRC and oscillation volume during lung recruitment and surfactant treatment, RDS seems to be a relatively homogenous lung disease during the first 72 hours after birth.
Future Perspectives

Although this thesis clearly shows that EIT is a promising bedside tool to monitor changes in lung volume in (preterm) infants, several practical difficulties still need to be solved before EIT can be implemented in neonatal intensive care:

1. **Electrode placement:**
   Placement of the 16 electrodes is cumbersome for medical doctors and NICU nurses, especially in the extremely low birth weight infants. More practical solutions like an electrode belt or jacket could solve this problem.

2. **Electrical noise interference**
   Electrical noise generated by the equipment present in the NICU environment can potentially interfere with EIT signal. More optimal isolation of the wires and EIT box might reduce this interference.

3. **Online imaging**
   For EIT to be useful for clinicians who are unfamiliar with EIT basics, EIT analysis should shift from off-line to on-line data interpretation. Newer detection algorithms should be developed and tested, resulting in online imaging of changes in lung volume and ventilation.

In addition to these practical improvements, there are also several research questions remaining that can hopefully be answered with EIT:

1. **Are the changes in lung volume and ventilation different during lung recruitment in other causes of respiratory failure?**
   The results from this thesis can only be applied to preterm infants with RDS during the first 72 hours after birth. It is unknown if these results are different in older infants and other causes of respiratory failure such as, sepsis, pneumonia, aspiration syndromes and pulmonary hypertension. The fact that some of these diseases are probably more heterogeneous might lead different results. This has to be addressed in future studies.

2. **How will lung volume and ventilation be affected by open lung positive pressure ventilation?**
   In this thesis we only explored open lung ventilation during HFOV. It has been shown in animal models and adults that open lung ventilation is also feasible during positive pressure ventilation. EIT can be very useful in future studies exploring this modality in preterm infants with respiratory failure.
3 What are the (regional) changes in lung volume and ventilation during non-invasive modes of respiratory?

During the last decade non-invasive modalities such as nasal continuous positive airway pressure and nasal positive pressure ventilation are increasingly used as a primary mode of respiratory support. Although these non-invasive modalities have clear benefits when it comes to preventing intubation and treatment of apnoea in preterm infants, it is unclear how they work and in what way they affect (regional) lung volume and lung function. EIT could very useful in clarifying these mechanisms.