The relative impact of respiratory muscle activity on tidal flow and lung volume in infants
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Chapter 8

Summary
Chapter one describes a general introduction about respiratory diseases in infancy, infant lung function and electromyography (EMG) of the respiratory muscles. Much of the burden of respiratory diseases in childhood and later life has his origins in infancy and childhood. The largest group of infants with respiratory problems are infants with wheezing disorders. The aetiology of wheeze in infancy is diverse. Wheeze is associated with environmental agents, such as viral upper and lower respiratory tract infections, environmental tobacco smoke exposure during and after pregnancy, and even rarer, chronic lung diseases, such as anatomical malformations of the respiratory tract, cystic fibrosis, primary ciliary dyskinesia, immunologic diseases, etc. Second groups of wheezing infants are children that wheeze due to problems around birth, such as prematurity or infants who are small for gestational age.

Lung function measurements can be used to monitor the clinical progression of the different wheezing phenotypes, and may be used to monitor the effect of therapeutic interventions, such as treatment with inhaled corticosteroids or bronchodilators. In addition to lung function, measuring the electrical activity of the respiratory muscles may help to assess temporal dynamic interaction of intercostal and diaphragmatic muscle activity with the resulting flow pattern as well as the lung volume. This may provide a more complete picture of the control of breathing and, in addition, respiratory mechanics.

Finally in this chapter the aims of the studies described in this thesis are discussed in detail. The overall goal of this thesis is to gain insight into control of breathing by describing the relation between air flow, lung volume and respiratory muscle activity in healthy infants, infants with bronchopulmonary disease (BPD) and wheezing infants. This thesis is divided in a methodological part and a clinical part.

**Methodological part**

Chapter 2 reviews the literature regarding the available literature on the methodology of transcutaneous respiratory EMG (tc-rEMG) and transesophageal rEMG (te-rEMG). We reviewed the literature on human studies using EMG to measure respiratory muscle activity. We aimed to summarize the literature of the different applications of rEMG and
assessed whether the measurement techniques used adhere to earlier defined standards, concerning practical aspects of measurement and rated the available literature by category of evidence. We excluded the literature on the intramuscular method (im-rEMG), in which the needle or wire sensors are introduced in the muscle tissue, because of the invasiveness of this method and the limited usefulness in clinical paediatric care. The outcomes were the type of method of the rEMG measurement, the description of the technique that was being used, and the quality of evidence that supports the use of the different techniques. Papers containing a description of the technique were subjected to different criteria: feasibility, repeatability, signal disturbance, ECG-gating and the quantity and description of the participants. The category of evidence was graded according to the Centre for Evidence Based Medicine Oxford scale (www.cebm.net/levels_of_evidence.asp). Furthermore, we aimed to propose recommendations for future studies.

We found that many studies showed neither a description of the technique nor a validation of the technique that was used. Other papers referred to other studies that describe a measurement technique. We propose for further validation of the different rEMG techniques to validate the different methods in clinical trials and cohort studies. There is a need for future studies that recognize clinically significant changes as a result of disease progression or response to treatment in individual patients. The clinical usefulness of the different techniques not only depends on its ability to measure parameters that discriminate between health and disease and clarifies underlying pathophysiology, but depends also on within-subject reproducibility both within and between test occasions. Furthermore, it is necessary to come to a consensus on how to reduce the contamination of rEMG signal.

In chapter 3 we respond to a paper from Nobre and colleagues that was published in Respiratory Physiology & Neurobiology. In their paper the authors described a study in which they have analyzed regional pulmonary ventilation and EMG activity of respiratory muscles during an inspiratory muscle endurance test in 10 young women. Regional pulmonary ventilation was measured with a radioaerosol (99mTc-DTPA) and was compared with EMG activity from the muscles of the lower rib cage. The findings of
the authors suggest that the inspiratory muscle endurance test is associated with a greater radioaerosol deposition in the medium third and intermediate and central segments of the lower rib cage and with increase in respiratory EMG activity of the lower rib cage.

Unfortunately, it is not clear from this paper what the authors exactly mean by “EMG activity of the lower rib cage”. EMG activity of the lower rib cage contains activity of intercostal muscles, diaphragm activity (frontal and dorsal) and, last but not least, electrical activity of the abdominal muscles. For many investigators it appears to be difficult to distinguish the separate signals from these three different muscle groups. Some authors have expressed concern that EMG tracings can be contaminated by activity of other muscles. This phenomenon is referred to as cross talk of the respiratory and abdominal muscles 5-6. With two cases we clearly and elegantly illustrate that it is well possible with the transcutaneous rEMG method, to distinguish between EMG activity of abdominal muscles and the diaphragm.

In chapter 4, we investigated the feasibility, repeatability and variability of the rEMG technique in comparison to standardized tidal flow and volume in healthy infants. Secondly, we aimed to determine the quantitative temporal correlation on intercostals and diaphragm EMG with tidal flow and we aimed to study the impact on lung volume in the same, spontaneously breathing infants during quiet natural sleep. The interaction between respiratory muscles, flow and lung volume had never been studied according the recently defined standards of infant lung function testing 7-9. We found good feasibility and repeatability of intercostals and diaphragm rEMG in spontaneously sleeping healthy infants. Diaphragmatic activity showed a breath-to-breath variability twice as large as the variability of the intercostal activity. A longer activity time of the diaphragm during expiration resulted in a higher end-expiratory volume. Combining non-invasive rEMG and lung function measurements appeared to help to provide a more comprehensive picture of lung mechanics and its adaptive reaction in disease.
Clinical part
Chapter 5 describes the comparison of tidal breathing parameters, lung volume and ventilation inhomogeneity in preterm infants (mean gestational age at study date 44.6 ± 3 wks) with and without bronchopulmonary disease (BPD) with age-matched healthy infants (mean gestational age at study date 44.8 ± 1.3 wks). We aimed to assess which clinical factors were associated with the respective lung function parameters in infants with BPD. We showed in this chapter that end-expiratory volume and ventilation inhomogeneity are comparable in term-born and preterm infants and in infants with different stages of CLD. Parameters describing the shape of the tidal breathing flow-volume loop (TBFVL) \( (t_{\text{TPEF}}/t_{\text{E}}) \) tidal rate constant described by Tepper et al \(^{10}\) show a change with increasing BPD severity, indicating that infants need to alter breathing strategies in order to maintain FRC. Parameters describing the TBFVL were strongest associated with duration of supplementary oxygen. Using relatively simple tidal breathing analysis, it is possible to obtain clinical data. However, in order to obtain additional information on the underlying pathophysiology of the observed mechanisms, other techniques such as electromyography or bodyplethysmography are needed.

In chapter 6, we aim to assess whether inspiratory muscle activity before inspiration or respiratory muscle activity during expiration in relation to flow and volume are different and/or less variable in infants with CLD (median gestational age at study 44.6 (43.4 – 51.0) weeks) compared to age-matched healthy infants (median gestational age at study date 44.4 (41.9 – 48.1) weeks). Comparison of tidal breathing parameters and rEMG parameters between the two groups showed a significantly longer delay between start of inspiratory muscle activity and resulting flow corrected for the respiratory cycle time and a significantly shorter \( t_i \) and \( t_{\text{TPEF}}/t_{\text{E}} \) in the CLD group. The variability in relative contribution of the diaphragm in infants with CLD was significantly lower than in age matched healthy infants. Although FRC was similar in both groups, we determined different correlations between FRC and respiratory muscle activity. The temporal relationship of rEMG to flow and the loss of adaptive variability provide additional information on coping mechanism in infants with impaired lung mechanics, which is not obvious in tidal breathing and lung volume measurements alone. The lower
variability in the relative contribution of the diaphragm in infants with CLD may explain why these infants are more prone to become respiratory distressed when the regulatory process is disturbed by external influence like respiratory infections 11.

In chapter 7 we investigated in infants with recurrent wheezy episodes (median age 11.7 months (6.2 – 23.0) whether inhalation of β2-agonist resulted in improvement of lung function, and/or an improved relation between lung function and respiratory muscle time indices. We hypothesised that a positive effect of β2-agonist may not become obvious in lung function measurements alone, but can be reflected by a change in rEMG-parameters. We aimed to assess whether inspiratory muscle activity or respiratory muscle activity during expiration in relation to flow and volume are different and/or more variable before and after inhalation of a bronchodilator (salbutamol) in infants with recurrent wheeze. Using lung function measurements according the recently defined standards 7-9, we observed a significant reduction in $t_{PTF}/t_E$ and $t_{ria}/t_{tot,EMG}$ and a significant increase of the $T_V$ and $t_{pia}/t_{tot,EMG}$ after administration of β2-agonist. Furthermore, we found a significant increase in the variability of the relative contribution of the diaphragm after bronchodilation. FRC was similar for and after inhalation of β2-agonist and we found no relation between FRC and $t_{ria}/t_{tot,EMG}$ or $t_{pia}/t_{tot,EMG}$.

Although FRC was similar in infants with recurrent wheeze before and after administration of β2-agonist, the temporal dynamic interaction between respiratory muscle activity, resulting flow and lung volume was significantly altered. The temporal relationship of the rEMG to flow and the increase of adaptive variability provide additional information on coping mechanism in infants with recurrent wheeze treated with β2-agonist which is not obvious in lung volume measurements alone.
References


