The relative impact of respiratory muscle activity on tidal flow and lung volume in infants
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Chapter 9

General discussion and perspectives
General discussion

In the next paragraphs, the most relevant findings of this thesis are discussed. In addition, suggestions for future research are provided.

Much of the burden of respiratory diseases in childhood and later life has its origins in infancy and early childhood. The largest group of infants with respiratory problems are infants with wheezing disorders. Lung function measurements can be used to monitor the progression of the different wheezing phenotypes, and may be used to monitor the effect of possible therapeutic interventions, such as bronchodilators. Accurate assessment of lung function in infants is difficult to perform, time and manpower consuming and often sedation is needed in older infants. 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 provides a more complete picture of the control of breathing and respiratory mechanics.

Despite earlier standards defined by the ATS/ERS, such as description of interference of the EMG signal by movements of the subjects, cross-talk between the QRS complex with the EMG, and description of ECG gating, a substantial amount of reviewed studies, who use the EMG technique for measuring respiratory muscle activity, failed to adhere to these standard.

Crosstalk of the respiratory muscles by abdominal muscle or the heart is a famous phenomenon. We showed in two cases that it is possible in infants to distinguish clearly and elegantly the EMG activity of abdominal muscles and respiratory muscles. Furthermore, we have found good feasibility and repeatability of rEMG measurements in matched comparison to flow and lung volume in infants. Combining non-invasive rEMG and lung function measurements may help to provide a more comprehensive picture of lung mechanics and its adaptive reaction in disease. In infants with BPD, the temporal dynamic interaction between respiratory muscle activity, resulting flow and lung volume is altered in comparison with healthy counterparts. In infants with wheeze the dynamic interaction changes after administration of β2-agonist, although
tidal volumes and FRC were similar. The temporal relationship of rEMG to flow and the increase of decrease of adaptive variability provide additional information on coping mechanism in infants with impaired lung mechanics which not is obvious in tidal breathing and lung volume measurements alone.

**Methodological part**

A critical point in the analysis of the rEMG signal is the gating and filtering process, which may lead to problems of measuring the exact time indices of the breathing cycle. To make the time indices of the rEMG parameters meaningful and applicable to clinical practice and the interpretation of the results reliable, the reader must critically appraise this filtering and gating process. For this reason, it is important to describe the validation of the used technique or use reference to the validation, based on the earlier defined standards. The strongest evidence that the described rEMG time indices in this thesis are reliable is the excellent correlation of the time indices in flow and rEMG and the good repeatability. Furthermore, this new method of cone filtering is fairly robust against time delays.

Transcutaneous recordings of the electrical activity of the respiratory muscles have been criticized, especially because of contamination of the signals by electrical activity of other muscles like the abdominal muscles. We demonstrated clearly the absence of contamination of abdominal muscle activity during the measurements during quiet sleep. The argumentation of the absence of cross talk of the abdominal muscle is based on two cases. The evidence would be stronger if we had the opportunity to measure more infants, but infants with a dysfunction of the diaphragm are rare. The absence of abdominal muscle activity during quiet sleep is also reported by Praud et al. Therefore it is likely that our measurements are reliable.

Transcutaneous rEMG is favorable in spontaneously breathing infants, because it is a non-invasive way to obtain information about the electrical activity of the respiratory muscles, and correspondingly to obtain indirect information about the respiratory
neural drive. This measurement technique is easy to handle and the described validation adhere to the standards of the ATS/ERS concerning respiratory muscle function testing. The feasibility and reproducibility of this technique in infants is good. We recognized the electrical interference to the EMG signals, caused by contact between the conducting parts of the electrodes and this problem was easily solved by avoiding the contact with electrodes. During all measurements, there was no line frequency caused by the surrounding power lines and the ultra sonic flow meter. Altogether, transcutaneous rEMG in matched comparison to airflow and lung volume measurements can be used in the future. The bases for this combination is that the infant lung function testing, as both the rEMG measurements adhere to standards and are well validated.

At present, infant lung function is increasingly applied in research and tertiary clinical centers. A difficulty in the infants lung function is the absence of reference data and predicted values. Furthermore, parameters (e.g. $t_{PTEF}/t_{E}$) that are influenced by lung mechanics, and control of breathing should be interpreted with care. In this thesis we have shown that also interpretation of lung volumes alone is not enough. The temporal relationship between of the rEMG to flow and adaptive variability of respiratory muscles provide additional information on coping mechanism in infants with impaired lung mechanics which is not obvious in tidal breathing and lung volume measurements alone.

**Clinical part**

Transcutaneous rEMG has been used in the past to study breathing pattern in neonates and has been validated as an estimate of lung function changes in older children with asthma. This thesis described for the first time the feasibility and repeatability of rEMG measurements and compared rEMG measurements with flow and independently measured lung volume in infants where by the measurement conditions adhere to the recently defined standards of infant lung function testing. The thesis showed that to monitor lung disease in infants with CLD or recurrent wheeze it may not enough to measure tidal flow and lung volume alone. So, the combination of rEMG measurements, tidal breathing measurements and FRC measurement helps to provide a more
comprehensive picture of lung mechanics and its adaptive reaction in disease or its reaction to medication, since it is important to describe underlying mechanism in impaired lung function and respiratory morbidity.

For the analysis of the EMG signals we calculated the EMG-activity ratio (log EMGAR), the variability of the relative contribution of the diaphragm and intercostals muscles expressed as CV, and $t_{\text{ris}}/t_{\text{tot,EMG}}$ and $t_{\text{pia}}/t_{\text{tot,rEMG}}$.

The advantage of the logEMGAR is the possibility to calculate individual increase or decrease of the EMG activity of the diaphragm and intercostals muscles. It is also possible to compare group means logEMGAR of age matched infants, like healthy infants in comparison to infants with CLD. The logEMGAR is a sensitive measure for calculating changes in the electrical activity of the respiratory muscles 15;16. Although we did not find a significant difference in the logEMGAR before and after administration of $\beta_2$-agonist in infants with recurrent wheeze, we determined that the rEMG amplitude appeared to be significantly dependent on the resistive load of the face mask. In the future, the logEMGAR can be a ratio-measure in dyspneic infants who are admitted to the hospital.

Lung mechanics in infants is a dynamic equilibrium of the complex interaction between control of breathing, respiratory muscle activity and respiratory mechanics. Such a system may show large fluctuations and behaves like a dynamical non-linear system 20;21. We have shown that the contribution of the respiratory muscles activity to flow changes on a breath-to-breath basis. Furthermore, we have shown that the contribution of the respiratory muscles activity to flow significantly differs between age matched healthy infants and infants with CLD. The contribution changes after inhalation of $\beta_2$-agonist in infants with recurrent wheeze and in all infants as response on the onset of the elastic and compliant face mask load. We propose that the breath-by-breath fluctuations are an expression of a rapid adaptive process to maintain optimal ventilation. A possible drawback of calculating the coefficient of variation (CV) of the respiratory muscle activity cycle is the center of maximal muscle activation relative to
the electrode position. In dyspneic and tachypneic infants the CV of the intercostals muscle can be affected by the electrical activity of the heart because the center of maximal heart activation relative to the electrode position decreases. So, larger proportions of the rEMG must be gated with an increasing of the heart rate. The variability of respiratory muscle activity may be an important parameter for the estimation of the severity of wheezing and possibly also an indicator to predict the prognosis of wheezing attacks. Further research in this field is necessary to elucidate the diagnostic possibilities of this parameter.

A third possibility of this outcome measure may be the monitoring of the effectiveness of a β2-agonist at home. An increase of the CV of the diaphragm after administration of a β2-agonist indicates that breathing becomes easier after inhalation of salbutamol. The literature contains different definitions of a response to a β2-agonist. Kraemer et al defined a treatment response if pulmonary function changed more than two standard deviations. Chavasse used a clinical outcome by a parent defined measure of response. The increase of the CV after inhalation of a β2-agonist is physiological response. Measuring the CV at home makes it also possible to investigate the change of the CV to salbutamol compared to placebo.

Other efforts need to be addressed to develop reference data and predicted values of the variability of the relative contribution of the respiratory muscles, specially the diaphragm in healthy infants.

The outcome measures \( t_{\text{ris}}/t_{\text{tot,EMG}} \) and \( t_{\text{pia}}/t_{\text{tot,EMG}} \) depend on the flow signal, so it is not possible to measure this ratios alone with the EMG equipment. The outcome measures are in younger infants related to the end-expiratory volume, but in older infants we found no relation. Furthermore we found significant differences between the relation \( t_{\text{ris}}/t_{\text{tot,EMG}} \) and \( t_{\text{pia}}/t_{\text{tot,EMG}} \) to FRC in healthy infants and infants with CLD. The parameters change after administration of a bronchodilator in infants with recurrent wheeze. Further research in this field is necessary to elucidate the predictive value of this parameter and to develop reference data.
Conclusions
Transcutaneous rEMG measurements are feasible and repeatable in infants. This measurement combined with lung tidal breathing and lung volume measurements provide additional information on lung mechanics which is not obvious in tidal breathing and lung volume measurements alone. In the future further extension of rEMG parameters should be aimed in infants. Specially, efforts need to be addressed to develop reference data and predicted values
References


