The relative impact of respiratory muscle activity on tidal flow and lung volume in infants
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Chapter 1

Introduction
Introduction

1.1 Respiratory diseases in infancy
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. However, it is not possible to recognize asthma among wheezy infants. Population studies have shown that approximately 1 in 3 children will have at least one episode of wheezing prior to their third birthday, and the cumulative prevalence of wheeze is almost 50% at the age of six years.

Many birth cohort studies and phenotype driven studies (lung function, serum markers, broncho-alveolar lavage, biopsy) have tried to recognise phenotypes that can predict which child has, or will develop, asthma. Disappointingly, phenotypes used in epidemiological studies (transient vs. persistent wheeze) can only be applied retrospectively, and all phenotype driven studies who tried to distinguish between different phenotypes show huge overlap between groups. The use of these phenotypes has improved mechanistic understanding, but they are of little use to the clinician.

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 more rare, chronic lung diseases, such as anatomical malformations of the respiratory tract, cystic fibrosis, primary ciliary diskinesia, immunologic diseases, etc.

A second group of wheezing infants is children with wheezing due to problems around birth. Premature birth is associated with asthma and obstructive lung disease at older age. Breathing patterns of premature infants are known to be immature, probably due to an immature neural drive. This is demonstrated by their short quiet sleep state, the occurrence of apnoeic events, and periodic breathing. Furthermore, the resistance of their lungs is higher, and the compliance is lower than their term counterparts. Wheeze occurs also in premature infants with chronic lung disease (CLD) and infants with birth-related group respiratory problems (e.g. meconium aspiration).
CLD represents the final common pathway of a heterogeneous group of pulmonary diseases that start in the neonatal period that usually evolves from acute respiratory disorders experienced by a newborn infant. The pathogenesis of the disease is multifactorial, like oxygen toxicity, baro and volutrauma as a result of neonatal ventilation. Since the advent of a wide range of therapeutic interventions and modes of ventilation, there is an increased survival of premature infants but unfortunately no reduction in the prevalence of CLD.

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. 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. In this chapter we will give a short introduction on infant lung function, with the focus on the methods that we used in our research. Furthermore, we will give an introduction on the EMG of the respiratory muscles. Finally, at the end of this chapter we will describe the aims of the studies.

### 1.2 Infant lung function

At present, infant lung function is increasingly applied in research and tertiary clinical centers. Infant lung function can be used for:

1. Early diagnosis of respiratory diseases
2. Monitoring of disease progression
3. Effect of therapeutic interventions
4. Assessment of disease outcome.

Infants are unable to cooperate with specific breathing maneuvers. Measurements in this young age group are particularly based on tidal breathing parameters obtained from measurements of the flow and volume changes at the airway opening. It is the most
performed lung function measurement and provides information pertaining to a number of processes related to respiratory control and pulmonary mechanical function \textsuperscript{10,11}. The most common meaningful parameters are tidal volume (TV), respiratory frequency (f), minute ventilation (MV), inspiratory time (t\textsubscript{i}), expiratory time (t\textsubscript{e}), t\textsubscript{i} as a proportion of total cycle time (t\textsubscript{i}/t\textsubscript{TOT}), time to peak tidal expiratory flow as a ratio of expiratory time (t\textsubscript{PTEF}/t\textsubscript{e}).

The functional residual capacity (FRC) and lung clearance index (LCI) can be calculated from multiple breath washout curves. This technique is ideally suited to assess lung volume and ventilation inhomogeneity in non-cooperating subjects like infants \textsuperscript{12} and measure the volume of the lung regions that communicate readily with the central airways during tidal breathing \textsuperscript{13}. A gas is washed into the lung and breath-by-breath measurements of gas composition are made in the expired gas. The more homogenous the lung, the more rapidly the washout procedure takes place.

Recently, a task force of the combined societies of the European Respiratory Society/American Thoracic Society published standards in which is described what currently is seen as good laboratory practice, and they provided recommendations for users of infant lung function equipment \textsuperscript{11,14-17}. These standards ensure consensus about how the different techniques should be applied, and are a quality label for lung function studies.

Accurate assessment of lung function in infants is difficult to perform, time and manpower consuming and often sedation is needed in older infants \textsuperscript{18}. Another difficulty is the absence of reference data and predicted values. “Normative values” have been reported, but these are based on relatively few observations. Furthermore, these values are only applicable to a specific population, specific equipment, software and respiratory function test that were used \textsuperscript{19}.

Parameters (e.g. t\textsubscript{PTEF}/t\textsubscript{e}) that are influenced by lung mechanics, and control of breathing should be interpreted with care. There is a need to provide more insight into the afferent and efferent functions of the neuroregulatory control of breathing \textsuperscript{10}. 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.

1.3. Electromyography of the respiratory muscles

There is general agreement that the principal inspiratory muscle in men is the diaphragm 20. Other important respiratory pump muscles are the ribcage muscles. Diaphragm and rib cage musculature have to contract rhythmically, and generate the required force to maintain ventilation throughout life 21. These contractions are influenced by autonomic and voluntary respiratory inputs. The electrical impulses originate in the respiratory neurons of the brainstem 22.

The bio-electric source of the muscular activity is found in the sarcolemma of the muscle fiber 23. A group of muscle fibers are, together with an axon, part of the motor unit. The raw EMG signal is a result of the electrical activity of many motor units. In 1960 Taylor was the first who recognized that it was possible to record diaphragmatic EMG activity, using surface electrodes 24.

Three methods are currently used to detect the electrical signal, and each type is useful in specific situations; the transcutaneous method (tc-rEMG) in which the sensors are placed on the skin, the transesophageal method (te-rEMG) in which the sensors are mounted on a catheter, which is positioned in the oesophagus and the intramuscular method (im-rEMG), in which the needle or wire sensors are introduced in the muscle tissue.

The tc-rEMG method of measuring the electrical activity of the diaphragm and intercostals muscles is preferred in infants, because it is non-invasive.

During the last years a new device has been developed, that enables on line to measure the electrical activity of the diaphragm and intercostal muscles transcutaneously, and in a non-invasive way. In earlier studies the EMG signal appears to be reproducible in infants, school children, and in adults 25. In school children with asthma was found that this surface electrical signal was reproducible at different levels of airflow limitation and correlated very well with changes in lung function 26,27. In infants and pre-school children the electrical respiratory muscle signal correlated well with the Clinical Asthma Severity score and was able to monitor the clinical course of children during
admission in hospital. Moreover, results in pre-school asthmatic children showed a linear association between the histamine dose and the increase in surface diaphragmatic and intercostal respiratory EMG activity during bronchial challenge testing. All these data suggest that tc-rEMG activity of the respiratory muscles on it self, is associated with changes in lung function and give the physician the opportunity to estimate lung function changes in pre-schoolers and older children in an in-direct way.

However, the combination of synchronised measurements of rEMG activity and measurements of flows and volumes may help to assess the 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 and integrated picture of the control of breathing and respiratory mechanics.

1.4 Aims of the studies
The main goal of this thesis is to gain insight in to control of breathing by describing the relation between air flow, lung volume and respiratory muscle activity. The thesis is divided into two parts:

1. Methodological part: First, we aimed to summarize the literature of the current available literature on rEMG and tried to formulate quality criteria for future studies. Secondly, we tried to solve the ongoing discussion about the so-called crosstalk of electrical respiratory and abdominal muscle activity. Crosstalk is the interference of electrical abdominal muscle activity with the electrical signal of the diaphragmatic muscle activity. Thirdly, we aimed to investigate and describe the feasibility and repeatability of the tc-rEMG measurements of the respiratory muscles with matched measurements of flow and volume at airway opening in healthy, term infants in order to continue the validation process of the tc-rEMG. In this study we relate tidal breathing parameters and lung volume with tc-rEMG parameters.

2. Clinical part: We aimed to compare tidal breathing parameters, lung volume and tc-rEMG parameters of healthy infants with infants with CLD.
Furthermore, we aimed to describe changes in tidal breathing parameters, lung volume and tc-rEMG parameters in infants with recurrent wheeze before and after inhalation of salbutamol, a β₂ agonist.

In Chapter 2, a review of the literature is given, which summarizes the literature of the different applications of rEMG and we hypothesise that most of the studies that have been performed up to now do not adhere to earlier defined standards. We aimed to address the available literature to the following issues: Which methods of rEMG measurement have been used, to what extent adhere the measurement techniques to the earlier defined standards, concerning practical aspects of measurement. In addition, we aimed to rate the available literature by category of evidence. Finally, based on these observations, we aimed to propose recommendations for future studies.

In Chapter 3, we responded to a paper from Nobre and colleagues that was published in Respiratory Physiology & Neurobiology. We wondered 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 (frontal and dorsal) and, last but not least, abdominal muscles. For many investigators it appeared to be difficult to distinguish the separate signals from these three different muscle groups. This phenomenon is referred to as cross talk of the respiratory and abdominal muscles. We aimed to illustrate that it is well possible with surface rEMG measurement to distinguish between electrical abdominal muscle activity and electrical activity of the diaphragm.

In Chapter 4 of this thesis we investigated the feasibility and repeatability of rEMG measurements according to the standards for data acquisition in infant lung function testing. We aimed to determine the quantitative temporal relation of intercostal and diaphragmatic EMG activity with tidal breathing parameters and to study their impact on lung volume in spontaneously breathing healthy term infants during natural quiet sleep.
The aim of Chapter 5 to compare lung volume, ventilation inhomogeneity and tidal breathing parameters in preterm infants with and without BPD with term-born infants matched for gestational age at study date. In addition, we assessed which clinical factors are associated with the respective lung function parameters in BPD infants.

In Chapter 6 we aimed to compare tidal breathing parameters, lung volume and rEMG parameters in infants with CLD with age-matched term born infants. We hypothesized that active neuro-respiratory control mechanisms during natural sleep may lead to maintenance of normal tidal volume and lung volume in infants with CLD.

In chapter 7 we investigated in infants with recurrent wheezy episodes whether inhalation of salbutamol resulted in improvement of lung function, and / or an improved relation between lung function and respiratory muscle time indices. We compared tidal breathing parameters, lung volume, ventilation inhomogeneity, and rEMG parameters before and after inhalation of β2-agonist. We hypothesized, based on the literature, that inhaled salbutamol would not result in improvement of tidal breathing parameters, lung volume and ventilation inhomogeneity, but the possible efficacy could be the result of an improved interaction between lung function and respiratory muscle time indices.

In the general discussion (Chapter 8), the studies are being discussed against the background of the international literature. Concluding remarks are made and suggestions for further steps in the validation process of synchronized measurements of lung function and tc-rEMG measurements are given.
References


