General introduction and outline of the thesis

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Introduction

Acute and chronic respiratory problems are the most common reasons for parents to visit a physician. Apart from upper and lower airway infections especially recurrent wheezing and asthma are important differential diagnoses in children with respiratory complaints. Serious respiratory disease accounts for 30% of paediatric mortality and thirty percent of hospital admissions is caused by serious respiratory illnesses\(^1\). In infants it is the most common cause of death\(^2\). Several studies report an increasing incidence and prevalence of asthma and asthma-like diseases, especially in young children\(^3,4\).

Additionally, recent advances in neonatal medicine have improved the outcome of very premature and small children\(^5,6\) and better treatment of children with congenital respiratory malformations and cystic fibrosis has prolonged survival as well as quality of life for these patients\(^7,8\). However, a considerable part of these children will develop chronic lung disease in childhood, adolescence and adulthood.

Asthma and asthmatic symptoms

Within Europe the prevalence of asthma has been reported to vary between 5 and 10%\(^9-11\), but the incidence of asthma and atopy is rising in all countries that have improved standards of living. Some studies report a prevalence of 30-40% in many developed countries\(^3\). Part of this is certainly due to better recognition, but there has been a real increase in incidence\(^4\).

Several reasons have been reported for this increase and recent studies indicate that probably environmental changes more than genetic drifts are major determinants. Probably there is not only a real increase in the incidence of atopy and asthma (e.g. caused by lower incidence of early childhood respiratory infections) but also an increased incidence of pulmonary symptoms in children with atopy and asthma (e.g. caused by external air pollution)\(^12\).

During early childhood many children experience recurrent asthmatic symp-
toms such as wheezing, cough or breathlessness. Silverman et al\textsuperscript{13} found a prevalence of 40%. Although up to 60% of these children are symptom free around the age of 6 years\textsuperscript{14}, a substantial proportion remains symptomatic during later childhood and adulthood. Specifically the latter group is eventually labelled as asthma, especially when further diagnostic work up is indicative of asthma and atopy (pulmonary function tests, reaction to therapy, bronchial hyperresponsiveness, skin prick tests or specific IgE, etc.). The treatment of asthma with inhaled corticosteroids has shown to be effective and relatively safe in adults and older children\textsuperscript{15,16}. In the younger age group there is a tendency to treat recurrent asthmatic symptoms in a similar way, although there is uncertainty about the diagnosis and thus uncertainty about the most appropriate treatment. Recent studies indicate that anti-inflammatory treatment for asthma should start as early as possible to prevent the development of irreversible, structural airway remodelling\textsuperscript{17-19}.

Paediatric pulmonology, from pregnancy to adulthood?

Chronic lung disease in childhood and adulthood is determined partially by upper and lower respiratory illnesses during early childhood. Apart from infectious or chemical agents, increasing evidence indicates that significant events in foetal life predispose to abnormal lung function during infancy, predisposing to early childhood respiratory illnesses and chronic airway disease in later life\textsuperscript{20}. Probably not only childhood asthma, chronic lung disease, cystic fibrosis or congenital malformations, but many other respiratory problems, encountered during early life have consequences for pulmonary well being during later life. It is important to recognise the child that is at risk for later respiratory disease as early as possible during infancy or childhood. Only in this way adequate treatment (e.g. inhaled corticosteroids) and prophylaxis (e.g. smoking prevention) might prevent long term morbidity and possibly mortality\textsuperscript{21}. 
Pulmonary function measurement in young children.

The diagnosis of respiratory disease in children is based on medical history and physical examination. In most cases one must rely on clinical assessment without the benefit of objective measures of respiratory function. Sometimes further diagnostic work up contains laboratory and radiological investigation.

The evaluation of pulmonary function is helpful to enable clinicians to objectively measure functional abnormalities in children with (or without) respiratory symptoms (Table 1).

Although lung function studies are increasingly used for the diagnosis and assessment of severity and follow up of asthma and other respiratory problems, objective pulmonary function testing is often only possible for older children. Currently, forced expiratory volume in 1 second (FEV1) is the most widely used parameter of airway obstruction. This parameter cannot be used in children younger than 4 years old. That’s why other lung function methods are needed in this age group.

Table 1. Contribution of pulmonary function testing to diagnosis and treatment in paediatric pulmonology

Pulmonary function tests can be used to:
1. detect the presence of pulmonary functional abnormalities
2. quantify the degree of abnormality
3. differentiate between obstructive, restrictive and mixed obstructive/restrictive pathology
4. differentiate between fixed from variable airway obstruction
5. differentiate between central (intra- or extrathoracic) and peripheral obstruction
6. follow the time course of disease
7. evaluate the effect of therapy
8. evaluate the presence and degree of increased airway responsiveness
9. evaluate the risk of therapeutic or diagnostic interventions
10. monitor pulmonary side effects of therapy (chemotherapy/radiation)
11. enable prognosis of disease and disability
12. evaluate effects of disease or intervention on lung growth
For infants and pre school children several alternative methods to measure pulmonary function have been developed. However, most cannot be implemented for use in daily clinical practice. Standardisation of these techniques is a developing science in paediatric pulmonary medicine. Many of these tests are currently available only in specialised centres and development of these methods is a growing area of interest and will add greatly to understanding the growth and development of the respiratory system. Pulmonary function testing is not only useful in clinical diagnosis and assessment of disease severity, but may also help to monitor progression of disease and evaluate response to therapeutic intervention.

Lung volumes can be measured by body plethysmography or gas dilution techniques. Whole body plethysmography has been used to determine thoracic gas volume since 1956 and is also possible in infants. With the infant’s body in a sealed box and breathing through a shutter which is closed at a predetermined point in the respiratory cycle, changes in alveolar pressure can be measured at the mouth piece and related to the simultaneous change in pulmonary volume of gas in the lungs. Airway conductance can be measured simultaneously. However, several technical difficulties and the necessity of sedation impairs widespread application.

During the gas dilution method the patient breathes a known concentration of helium from a reservoir. After some time a new equilibrium of helium concentration is reached and the functional residual volume can be calculated from the additional volume into which the helium has diffused.

In the evaluation of bronchus obstructive disease, especially asthma, the

Table 2. Requirements for pulmonary function tests in infants and young children

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<td>1. Easy performance for children of all ages</td>
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<td>2. Not burdensome or long lasting procedure</td>
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<td>3. Repeatable/reproducible</td>
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<td>4. Cheap</td>
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<td>5. Distinguishing healthy from diseased children</td>
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<td>6. Not invasive</td>
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<td>7. Applicable during spontaneous breathing, not requiring sedation</td>
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<td>8. Quickly available results</td>
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<td>9. Responsive to therapeutic influences</td>
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<td>10. Useful for follow up</td>
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most widely accepted and best standardised method to quantify airway obstruction is the maximal expiratory flow-volume measurement\textsuperscript{26}. The “gold standard” parameter derived from this test is the forced expiratory volume in the first second of expiration (FEV\textsubscript{1}). This parameter is obtained from flow-volume measurements during forced expiratory manoeuvres. The technique, necessary to perform these manoeuvres requires optimal co-ordination and co-operation and these premises impair the applicability, not only in infants, pre school children and geriatric patients but even in older children and adults.

Compliance and resistance of the lung can be measured during active breathing using an oesophageal balloon or a weighted spirometer method\textsuperscript{27}. Respiratory system mechanics can also be measured using passive deflation by applying single\textsuperscript{28} or multiple occlusions\textsuperscript{29}. The static compliance of the respiratory system $C_{rs}$ is calculated from the exhaled volume, related to mouth pressure at end-inspiration. Forced expiratory flow-volume measurements can be obtained from partial expiratory flow-volume loops by applying rapid thoracic compression with an inflatable plastic jacket\textsuperscript{30}. However all these tests require difficult technical procedures, allowing only application in well equipped research laboratories. Most techniques are only useful at specific ages. Also in many children sedation is required to perform reliable tests.

Clinical application of new or alternative pulmonary function tests in young children is only possible for techniques that show characteristics as described in Table 2. Indeed no co-operation can be expected from toddlers and infants and non invasive methods are of paramount importance to avoid disturbing the physiology being studied and to ensure patient and parent acceptance\textsuperscript{21}.

Scope and outline of this thesis.

During the past decades several new alternatives for measurement of pulmonary function in pre-school children have been developed. The studies described in this thesis addressed several aspects, both methodological and clinical, of pulmonary function tests in school and pre-school children.

An overview of literature on relevant anatomy and physiology, followed by
an overview of currently available methods to measure airway mechanics in non-sedated, spontaneously breathing children is presented in Chapter 2. One of the pulmonary function techniques that has been subject of several studies in the University Medical Centre Utrecht is the tidal breathing analysis. In Chapter 3 a short overview of this technique is presented. The gold standard of pulmonary function testing at all ages is the maximal expiratory flow volume (MEFV) curve. Prior to attempting to interpret any MEFV curve (or whatever other pulmonary function test) result in physiologic terms the quality of the tests should be assessed. Patient effort, co-ordination, co-operation, artefacts and reproducibility should be evaluated and less than optimal procedures should be judged with caution. General standards for pulmonary function technicians, equipment and recommendations for testing procedure were published and subsequently adapted by both the American Thoracic Society (ATS)31-33 and European Respiratory Society (ERS)34-35. Specific guidelines for children were published by Taussig in 198036. An adaptation and overview of these guidelines are presented in Chapter 4.1. The performance of a maximal effort expiratory manoeuvre is not easy, as was discussed before. Especially young children lack the co-ordination and co-operation to perform the difficult breathing techniques necessary for acceptable and reproducible measurements. The American Thoracic Society and the European Respiratory Society have developed specific criteria for this procedure, especially concerning acceptability and reproducibility of performance and results33,37. In a retrospective study the flow volume curves, performed by children of all ages were evaluated for their capability to meet these international criteria. The results are described in Chapter 4.2. Recently an old technique, the interrupter technique, for assessment of airway resistance showed a revival after introduction of a small handheld device, the MicroRint. In Chapter 5.1 the feasibility of this method is described in both healthy children and children with asthmatic symptoms. Values in healthy children in Utrecht were combined with the findings in healthy children in a study, performed in the Sophia Children’s Hospital in Rotterdam. These enabled the publication of reference values for children of 3-13 years old, presented in Chapter 5.2. One of the methods to measure resistance and reactance of the respiratory system which is applicable in young children is the impulse oscillation tech-
nique (IOS). To study the clinical applicability of this method to measure airway responsiveness a study was performed in school children in whom results of IOS and MEFV were compared (Chapter 6).

The maintenance treatment of asthmatic children with inhaled corticosteroids has evolved during the last decennia. There is a tendency to treat not only severely affected subjects, but also children with less frequent and (mild to) moderate symptoms. The availability of preparations for inhalation, with few important side effects, the increasing knowledge of airway remodelling and the presence of asthma-like airway inflammation in children during early childhood has supported this concept. The effect of ICS in children with infrequent symptoms, quite normal lung function and less specific symptoms is difficult to measure.

The effect of prophylactic treatment with inhaled corticosteroids in 5-10 year old children with mild to moderate asthma was studied in a prospective, randomised, placebo controlled, double blind, multi-centre study. This study was called the SJOKOLA 1 study, short for “Steroiden bij Jonge Kinderen als Onderhoudsbehandeling van Astma” (Chapter 7.1). The effect of ICS in children with mild asthma was evaluated using both subjective and objective effect parameters.

As in older children and adults, there is a tendency to treat recurrent asthmatic symptoms in the younger age group in a similar way, although there is uncertainty about the diagnosis and thus uncertainty about the best ways of treatment. There is no consensus on this treatment modality and there are no studies on the effect of ICS on tidal breathing parameters, impulse oscillometry and interrupter resistance in pre school asthmatic children. In a prospective study the effect of ICS in this age group was evaluated with both subjective and objective parameters (Chapter 7.2). Also the possibilities of these and other parameters to predict a possible beneficial effect of ICS and the correlation of changes in lung function parameters and subjective parameters are described.

Conclusions from these studies and suggestions for further research are presented in Chapter 8, followed by a summary of the thesis in English and Dutch (Chapter 9).
References