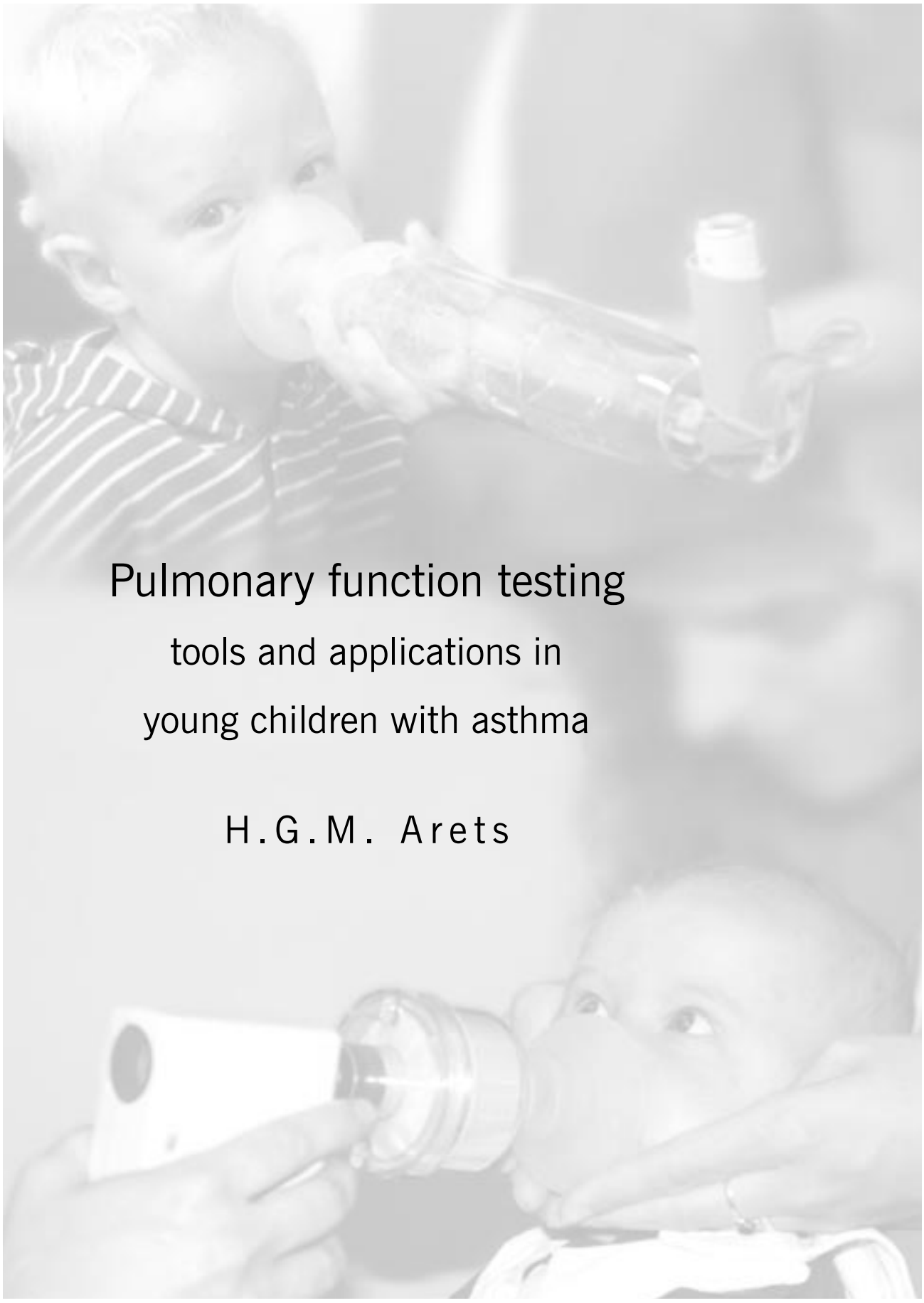

Pulmonary function testing

tools and applications in young children with asthma

H.G.M. Arets

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Pulmonary function testing: tools and applications in young children with asthma

Longfunktie-onderzoek: technieken en toepassingen bij jonge kinderen met astma

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen
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Frontpage:

Even small children are often able to perform simple pulmonary function tests during tidal breathing and inhale from pMDI using holding chambers.

Voor Ingrid, Kors en Amber
Voor mijn ouders

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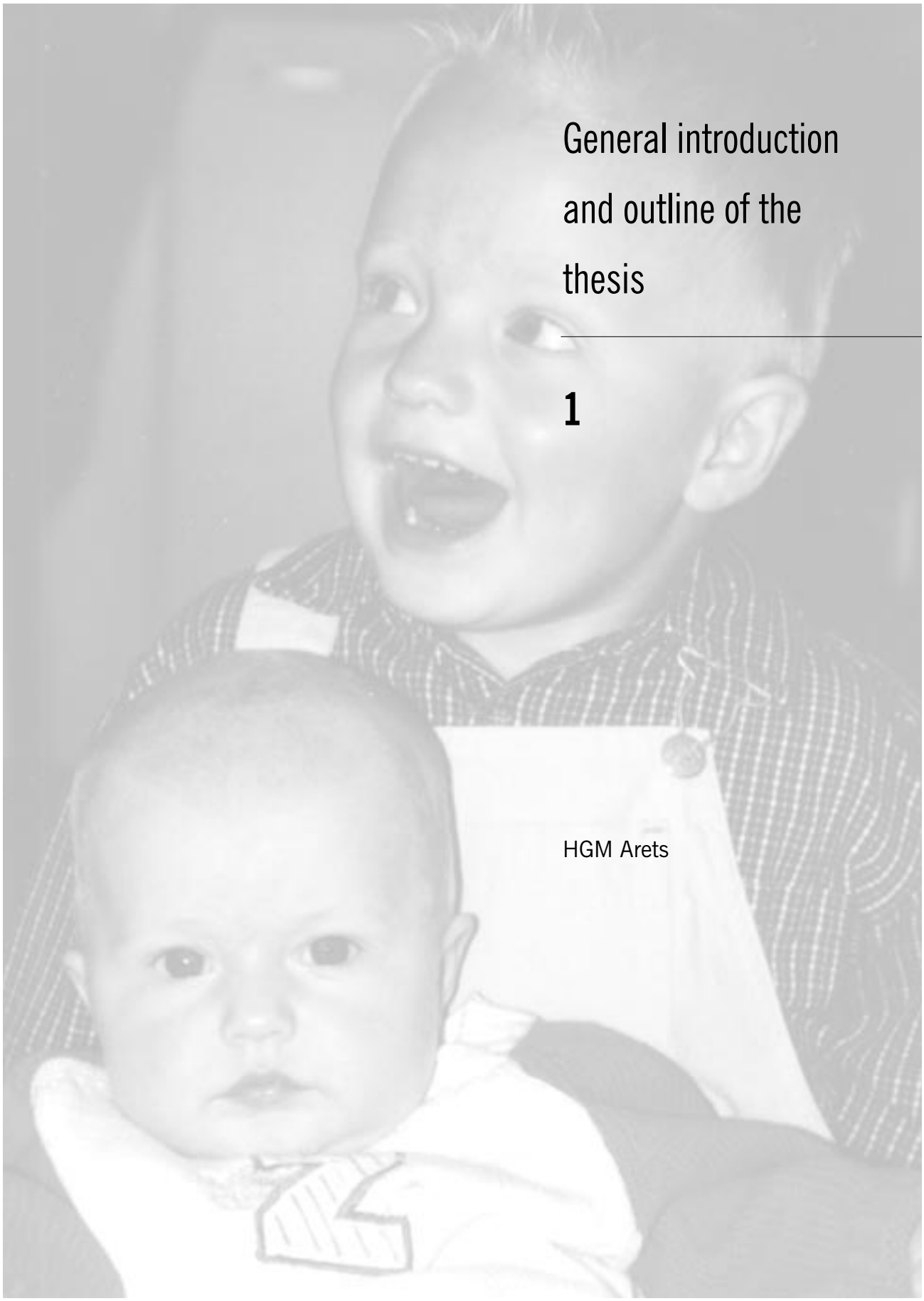

General introduction and outline of the thesis

1

HGM Arets

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[13] found a prevalence of 40%. Although up to 60% of these children are symptom free around the age of 6 years[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[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[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[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[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[21]. 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[22]. 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[23] 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[24]. 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[25].

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

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

1.	Easy performance for children of all ages
2.	Not burdensome or long lasting procedure
3.	Repeatable/reproducible
4.	Cheap
5.	Distinguishing healthy from diseased children
6.	Not invasive
7.	Applicable during spontaneous breathing, not requiring sedation
8.	Quickly available results
9.	Responsive to therapeutic influences
10.	Useful for follow up

most widely accepted and best standardised method to quantify airway obstruction is the maximal expiratory flow-volume measurement[26]. The "gold standard" parameter derived from this test is the forced expiratory volume in the first second of expiration (FEV1). 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[27]. Respiratory system mechanics can also be measured using passive deflation by applying single[28] or multiple occlusions[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[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[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 1980[36]. 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 results[33,37]. 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)**.

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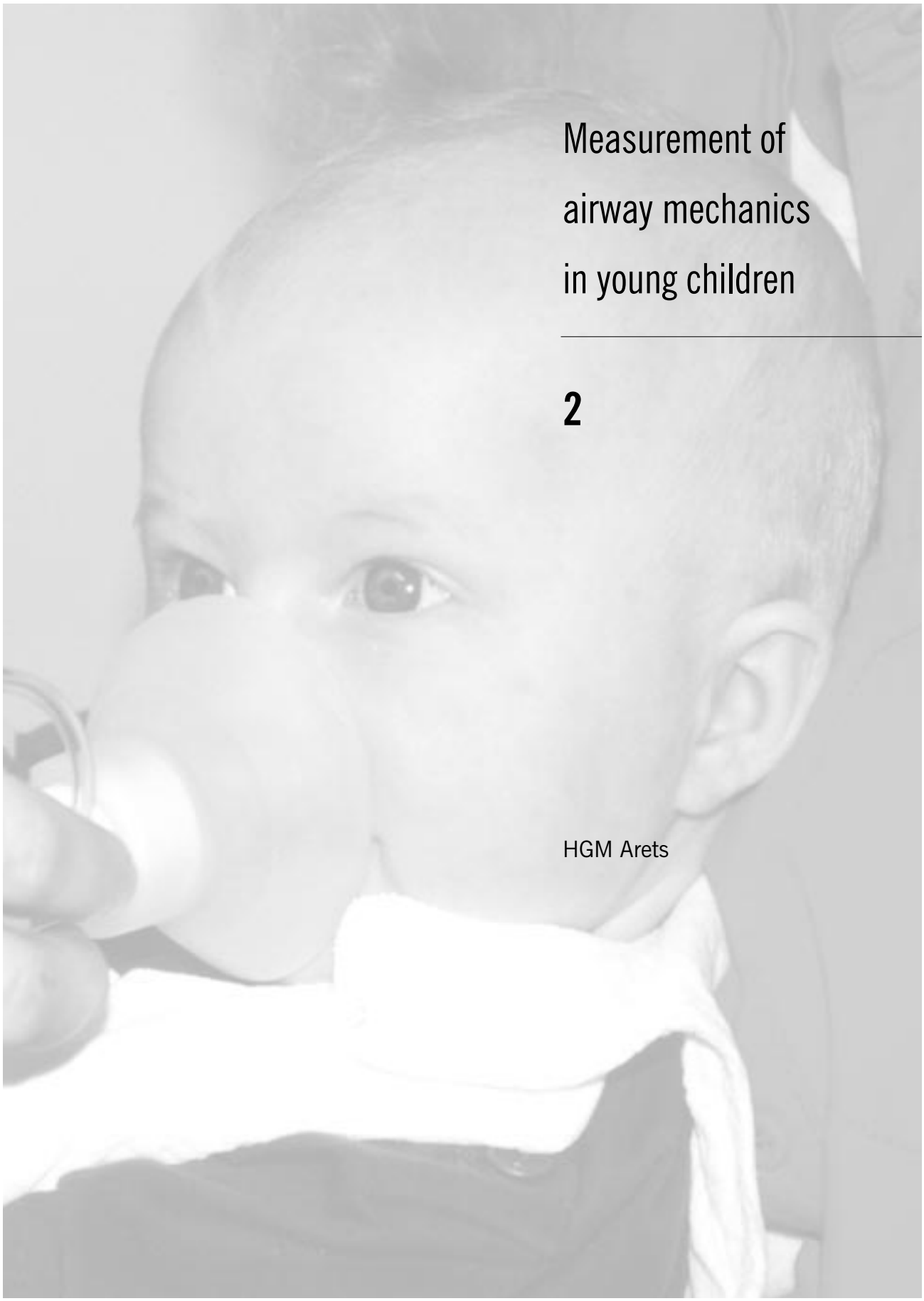

Measurement of airway mechanics in young children

2

HGM Arets

Introduction

Measurement of pulmonary function is an important tool for the diagnosis and monitoring of respiratory diseases. The gold standard of pulmonary function testing (PFT) is the maximal expiratory flow volume (MEFV) curve. However, only children aged 6-8 years and older can be expected to perform reproducible forced respiratory manoeuvres[1,2]. In younger children MEFV measurements are rarely performed, because these children lack co-operation, but also show diminished reproducibility and reliability of results[3].

There are little alternatives in this age group. The clinical evaluation of lung function by auscultation appears to be an extremely insensitive indicator of bronchial obstruction[4-6]. For instance a fall in oxygen tension of 33% may occur in young asthmatic children without audible wheeze[4]. Probably at least 30% fall in FEV1 is necessary before wheezing is heard[5].
Between infancy and school age only methods that do not require sedation (unlike e.g. baby body plethysmography, $V'_{max}FRC$ measurement by the squeeze jacket method) and are not invasive (unlike airway pressure measurement using pitot static probe[7] or oesophageal balloons[8]) are widespread applicable. In small children they should only require passive co-operation. Tidal breathing analysis and resistance measurement by the interrupter technique or (impulse) oscillation technique all appear to fulfil these requirements. The accuracy of these methods, i.e. their relationship to true airway resistance is not well known. These measures may be considered as indices of lung function[3].
In this chapter general principles of pulmonary and especially airway anatomy, development and physiology are discussed, followed by an overview of the different available methods to measure airway mechanics. The tidal breathing technique is comprehensively discussed in the next chapter.

1. General principles of respiratory mechanics

Modelling of the respiratory system

The respiratory system can be considered as a physical model, i.e. a collection of physical components interacting with one another and with the environment. Most real life systems, such as the respiratory system are non linear, but they can be simplified to linear models under certain conditions. A linear model has useful properties that makes analysis easier.
The most simple model of the complex respiratory system is that of a single balloon on a pipe. The relationship between the pressure applied at the opening of the model (P(t)) and the volume in the model (V(t)) during emptying of this balloon can be described as a first order model:

$$P(t) = E.V(t) + R.V'(t)$$

where E = elastance of the balloon, R = resistance of the pipe and V' = flow through the opening. Using regression analysis one can calculate E and R from P(t), V(t) and V'(t).
If this model is applied to the respiratory system, the values of R and E reflect the R of the airways and the E of the respiratory system, whereas V(t) is the volume increase from functional residual capacity (FRC), i.e. where P(t) at mouth opening is zero.
In other words the passive deflation of the respiratory system is characterised by a volume-time profile determined by E and R.
In vivo measurements show that the lungs can not be seen as a single compartment and when one reports a single airway resistance or elastance value, the underlying assumption that this is the one and only value for these parameters is never satisfied in real life, especially in non healthy subjects. Nevertheless, the majority of respiratory mechanics are represented by this simple linear, single compartment model.

Using this model there are three important components:

1. time constant (τ)
2. compliance or elastance
3. resistance

The relationship of these parameters is given by the equation:

$\tau = C \times R, \tau = R/E$

Time constant of lung emptying

The time constant (τ) describes the expiratory airflow generated by the elastic properties of the respiratory system (balloon)[9].
During passive emptying the time to reduce by 63% is known as the time constant of the respiratory system (Figure 1). In healthy adults τ = approximately 0.5 sec. This allows the lung to empty to FRC at each expiration. In infants with normal lungs τ = 0.3 sec and in infants with stiff 'hyaline membrane' lungs 0,1 sec[10]. In obstructive airway disease increasing R (with or without decreasing E) increases τ, leading to a need for longer expiration time.

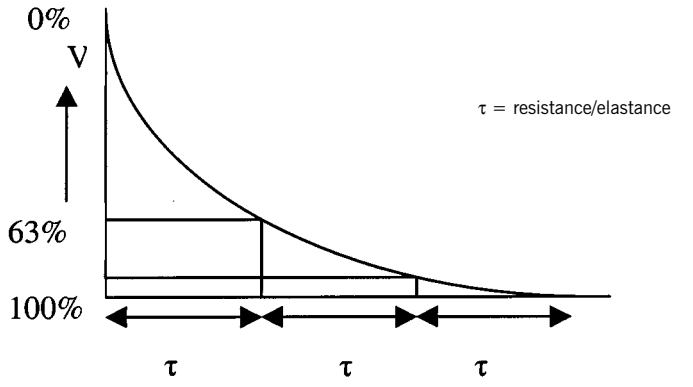

Figure 1. Time constant (τ) of lung emptying. V = lung volume,

Elastance and compliance

When forces are applied to elastic structures such as the lungs, these structures will resist deformation by an opposing force in order to return to their relaxed state. This opposing force is called elastic recoil. The pressure needed to overcome elastic recoil, the elastic recoil pressure (Pel), depends on the lung volume above or below the equilibrium volume. The Pel divided

by the lung volume gives a measure of the elastic properties of the lung tissue and is called elastance (E):

$$E=Pel/V$$

The slope of the volume (V) versus pressure (Pel) gives the reciprocal of elastance, i.e. compliance (C).

$$C = V/P \qquad C = 1/R$$

The phenomenon that elastance and compliance depend on the volume history of the lung is called hysteresis. Expiration and inspiration are represented by different pressure-volume curves. Actually this is the failure of tissue to follow identical paths of response during in- and expiration as shown in Figure 2. Hysteresis depends on visco-elasticity and plasticity of the lung. It is important to know that during tidal breathing hysteresis is negligible, which is functionally desirable because the area of the hysteresis loop represents energy loss from the system. This also means that in all PFTs during tidal breathing hysteresis will hardly influence results.

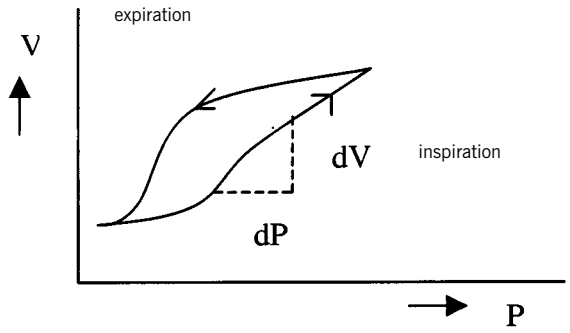

Figure 2. Hysteresis in the pressure volume curve of the lung. The area contained within the curve represents the energy lost in the system. V = volume, P = pulmonary pressure, d = change.

Resistance

Resistance is expressed as changes in pressure divided by changes in flow:

$$R = dP / dV'$$

In other words, the flow (V') measured at the mouth depends on the driving pressure (i.e. the pressure difference between alveoli (P_{alv}) and mouth P_{mo})) and the airway resistance (R_{aw}):

$$V' = (P_{mo}-P_{alv})/ R_{aw}$$

If mouth pressure is 0 (i.e. atmospheric pressure), driving pressure is alveolar pressure.
Alveolar pressure is determined by two components: elastic lung recoil pressure (P_{el}) and intrathoracic or pleural pressure (P_{ith} or P_{pl}).
P_{el} is the pressure caused by the elastic properties of the lung, resulting in volume reduction of the lungs. P_{pl} results from the influence of breathing muscles on the thorax. During inspiration these forces counteract ($P_{alv} = P_{pl} - P_{el}$) during expiration they work together ($P_{alv} = P_{pl} + P_{el}$)

Airway resistance (R_{aw}) can be considered the sum of peripheral airway resistance (peripheral intrathoracic airways < 2 mm diameter; R_{awp}), central airway resistance (large intrathoracic airways > 2 mm diameter; R_{awc}) and extrathoracic airway resistance (especially glottis; R_{ext}).

$$R_{aw} = R_{awp} + R_{awc} + R_{ext}$$

In healthy persons R_{ext} accounts for 50% of total R_{aw} and R_{awp} accounts for about 15% of $R_{aw.}$ R_{awp} and R_{awc} are influenced by lung volume, i.e. by P_{el}. Higher lung volumes give higher P_{el} and therefore increase airway diameter. With increasing volumes during inspiration the increased P_{el} is counteracted by P_{pl}, resulting in increased radial distending force. This distending force is the transmural pressure and is the difference between pressure in (P_{in}) and outside (P_{out}) the airway.

During breathing arrest the pressure inside the airways (P_{in}) equals atmospheric pressure and transmural pressure (P_{tm}) equals P_{el}:

$P_{in} = P_{mo}$

$P_{tm} = P_{el}$

Airway diameter is sigmoidally related to P_{tm} of the intrathoracic airways. This results in volume dependency of R_{aw}. At higher lung volumes R_{awp} decreases. The specific relation between R_{awp} (or its reciprocal conductance G_{aw} (=1/R_{aw}) and volume is mirrored by the specific R_{aw} (sR_{aw}) and specific G_{aw} (sG_{aw}).

$R_{aw} = R_{aw} / V$ and $sG_{aw} = G_{aw} / V$

Dynamics of breathing

The forces produced by respiratory muscles should overcome the elastic, flow resistive and inertial properties of the lungs and chest wall to produce ventilation.
The inertance is the "resistance of the respiratory system to acceleration". During tidal ventilation inertance is negligible. 90% of pressure is required to overcome the elastic forces, only 10% to overcome flow resistant forces.
The elastic properties, compliance and resistance, are the main determinants. Frictional resistance to airflow acceleration to airflow accounts for 1/3 of the work during quiet breathing. The magnitude of pressure loss, due to friction depends on the pattern of flow, which can be laminar (streamlined) and turbulent. This depends on the properties of the gas (viscosity, density), velocity of airflow and the radius of the airway. In general there is laminar flow in small peripheral airways and turbulent flow in larger central airways.

The pressure gradient required to maintain laminar flow through a tube is given by Poiseuille's law:

$P = V' (8l\eta/\pi r^4)$

P = pressure, V' = flow, l = length, r = radius of the tube, η = viscosity of the gas.

Viscosity of air is low (0.000181 poise).
Because resistance = pressure/flow, it is clear that the most important determinant of resistance in small airways is the radius raised to the fourth power in the denominator of the equation.

Flow limitation

Expiratory flows are limited throughout most of the forced expiratory manoeuvre[11-13]. Above a certain expiratory effort expiratory flow is independent of the applied pleural pressure.
During forced expiration, the driving pressure for air flow is determined by the sum of elastic lung recoil pressure and actively applied pleural pressure. As the actively applied pressure is also applied to the airway walls it is only the elastic recoil pressure at any lung volume that allows pressure inside the airways to be higher than that outside the airways. During forced expiration flow-related frictional and convective accelerative intrabronchial pressure losses occur. At some point along the airways from the alveoli to the mouth, the flow-related pressure losses will equal the lung elastic recoil pressure and the difference between the intrabronchial and extrabronchial pressures will be zero. This point is called the equal pressure point (EPP)(Figure 3). Downstream, i.e. mouthward from this point airways are compressed by the pressure surrounding the airway wall which will be greater than the decreasing intrabronchial pressure, thus leading to dynamic compression of the airway lumen.
Following this theory, MEFV measurements can be considered the blue print of the mechanical properties of the lung parenchyma and airways and explains the high reproducibility within one subject of the MEFV curve. The shape of the MEFV curve is determined by the variable site of the flow limiting segment. This site is normally located in the central intrathoracic airways[14-16], especially the lobar and segmental airways[17,18] during forced expiration and does not move beyond the subsegmental airways[19].

2. The influence of anatomy on airway mechanics

The force generated by the respiratory muscles must overcome the total respiratory resistance (R_{rs}), consisting of resistances of the lung (R_L) and chest wall (R_{cw}) and the resistance to gas flow through the airways (R_{aw}).

$$R_{rs} = R_{cw} + R_L + R_{aw} .$$

The contribution of R_{cw} and R_L to R_{rs} is not completely clear. In adults and older children R_{cw} and R_L represent only 10-20% of R_{rs}[20]. Polgar and String reported that in newborns R_L averaged 24% of R_{rs}, almost twice that in adults[21], but other investigators found almost identical values for R_{aw} and R_{rs}, so only small contributions of R_{cw} and R_L[22,23]. Largely because of different techniques of measurement, absolute values for resistance in infants and children remain unsettled and values in different age groups can hardly be compared.

The upper airway

The upper airway consists of the passages between airway opening and larynx. Normally this is the nasal passage (from nostrils to the posterior ending of the nasal septum), the nasopharynx (from end of nasal septum to lower border of the palatum mollle) and the pharynx (from soft palate to glottis). When breathing orally, it also includes the mouth. Breathing through the nose causes much greater resistance than breathing through the mouth. There are important anatomic features that have to be considered in the phase of gas transport through the upper airways. The axis of the nose to that of the trachea is 90%. Cross sectional area of the airways increase from anterior nares, containing hairs to large turbinated airways, than decreases again in the nasopharynx and the rest of the airways. The nose accounts for 50% of total respiratory resistance, although there is marked variation among subjects and the contribution is less in children than in adults. Most of this is accounted for by the first 2 cm of the nasal passage.
Under normal conditions 15-50% of airway resistance is accounted for by oral cavity, pharynx and larynx[24-26]. The individual contribution of these three elements was studied by Schiratzky in 1965. She found that the larynx

accounts for 25% of the total airway resistance and oral cavity for 30%[27]. Similar findings were presented by Pressman and Kelemen[28]. These results show that especially the angulation of the airway results in decreased air transport capacity.
Several studies showed that the orifice between the vocal cords represents an important resistance to air flow and significantly influences total airway resistance[25,29,30]. Vocal cords move apart during inspiration and close somewhat during expiration[31]. During panting the glottis stays wide open[32]. This technique is used when performing body plethysmography.
Stanescu et al. found significant correlations between glottis opening, lung volume and flow rate. The variation of glottis opening with lung volume was larger during expiration. The glottis opening was greater during panting than during tidal breathing. As a result airway resistance (from the glottis) was smaller during panting at comparable lung volumes. This indicates that, to reduce the influence of the glottis during airway resistance measurement, panting is a suitable method[33].
The cricothyroid muscle is especially active during inspiration, contributes to vocal cord abduction and thereby causes the airway to open[34].

Infants are believed to be obligatory nasal breathers[35]. Indeed, when both nose and mouth are open infants, but also most older subjects are exclusively nasal breathers[36]. However research by Rodenstein et al showed that during nasal obstruction tight apposition of the soft palate and tongue occurs, but that after a mean of 8 (range 1-30) seconds oral breathing was initiated. The older and more awake the child, the earlier switch to oral breathing occurred. This switch occurred by detaching the soft palate from the tongue[37]. So, infants, children and adults only prefer nasal breathing but at all ages oral breathing is possible .

When the temperature of inspired air falls below 7° C there is a marked rise in resistance caused by vascular engorgement. Also changes in body posture alter resistance through hydrostatic effects on vasculature. Going from vertical to horizontal position increases resistance. Resistance through both nasal passage is not similar and varies in 3-4 hour cycles.
The pharynx is the most compliant region of the upper airways and negative pressures tend to collapse the airway. This is prevented by the tone of the airway muscles, but can cause tremendous resistance in subjects with anatomic abnormalities or muscle dysfunction or during REM sleep.
Even minimal mucosal thickening in the nose or mild oedema of the larynx

or trachea in infants may cause significant increases in resistance.
Both the measurement and the degree of airflow resistance is influenced by the breathing pattern. During spontaneous breathing 80-90% of breathing of most people is nasal[38,39]. Only during exercise they shift to oral breathing and at maximal exercise about 60% of breathing is orally. However some people show combined oronasal breathing and few people persist nasal breathing even at maximal exercise[40].
During oronasal breathing inspiratory nasal airflow is greater than expiratory nasal airflow. Using a mouth piece will wedge open the mouth and this will influence oral airflow resistance values. Probably respirologists have obtained falsely low oral resistance values using mouthpieces. The opening of the lips and the position of the tongue against the palate will influence airflow obstruction. If nasal airflow increases there is more turbulent flow with exponential increase in airflow resistance[41].

The lower airways

The diameter of the lower airways is caused by a balance of forces distending and forces narrowing the airway.
Narrowing forces are bronchial smooth muscle contraction, mediated by efferent autonomic nerve control. Sympathetic impulses relax, parasympathetic impulses constrict these muscles. Constriction can also develop as a reflex caused by irritants (dust, smoke, cold), hyperventilation, embolisation of vessels and some vaso-active agents (acetylcholine, histamine, bradykinine). Airways dilation may occur as a reflex to increased blood pressure (baroreceptors in carotid sinus) and sympathomimetic agents (epinephrine, isoproterenol).

Airway resistance is lung volume dependent and increases when lung volume decreases from functional residual volume (FRC) and approaches infinity at residual volume. It is especially the decrease in lung elastic recoil that is responsible for this increase. This recoil provides a tethering effect tending to increase airway diameter. Thus older children with bigger lungs have increased elastic recoil and thereby lower airway resistance. That's why the measurement of airway resistance and it's reciprocal airway conductance are normally corrected for lung volume. The resultant is the specific airway resistance (sR_{aw}) or conductance (sG_{aw}), which is remarkably constant regardless of age or height.

An extra narrowing force to airways exists during forced expiration, when there is dynamic airway compression caused by pleural and peribronchial pressures. This effect is counteracted by the intraluminal pressure and the tethering action of the surrounding lung (Figure 3)

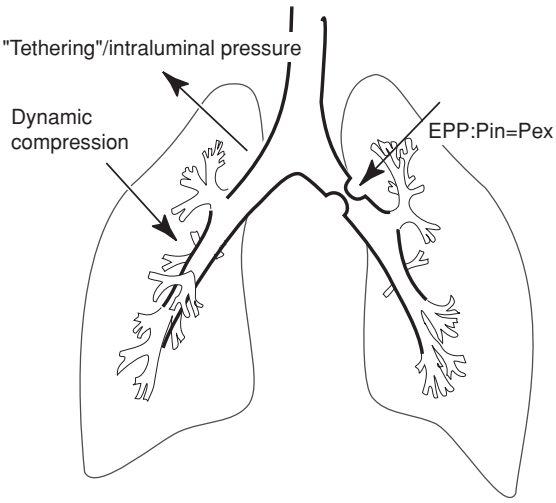

Figure 3. The relation of pressures in- and expanding the airway lumen. P_{in} = intraluminal pressure. P_{ex} = dynamic compression by pleural and peribronchial pressure. EPP = equal pressure point

Small airways

The contribution of small airways (< 2 mm diameter) to total resistance in adults is only some 20%, caused by the very vast number of small peripheral airways, providing a large cross sectional area for flow. That is why small airway disease may severely impair ventilation of distal air spaces but go undetected by total airway resistance measurement. However, in children small peripheral airways may contribute up to 50% of the total airway resistance. This proportion does not decrease until about 5 years of age. This increases the value of resistance measurements in small children, who can be severely affected by small airway diseases (e.g. bronchiolitis).

3. The influence of growth and development on airway mechanics

Developmental anatomy and physiology of the respiratory system

The respiratory system is in a continuous process of development from early embryonic stages to young adulthood. As with height and weight, children show a constant and rapid growth of lung volume and lung function parameters. This growth however shows a wide variety within and between individuals. Therefore normal values of pulmonary function parameters are often presented as referenced by standing height, sex and sometimes weight. However also age, arm-span[42], body composition, sitting height[43] and even ethnicity[44] influence lung function parameters.
Some steps in the development of the lung that bear particularly influence on lung function during (early) childhood and on the pattern of respiratory disease are discussed below.

Respiratory system development

In humans the lungs begin to form at 21-24 days of gestation as a bud of the primitive foregut[45]. During the first, i.e. pseudoglandular phase this process evolves rapidly resulting in complete formation of all the airways through the terminal bronchioles by week 16 of gestation. This branching process of the airways is more or less dichotomous. Only then the first gas-exchanging units are formed (canalicular phase). From 26 weeks, during the final or alveolar (or terminal sac) phase lungs prepare for gas exchange by formation and growth of type II pneumocytes, secreting surfactant. About 50 million alveoli are present at birth in a term infant. After birth new alveolar formation is thought to continue especially until 2, but probably even until 7 years of age[46]. At this stage the number of alveoli has increased to about 300 million. From then alveoli only grow by enlargement.
Airways continue to grow in length and diameter with remodelling of the peripheral airways from week 16 of gestation, but do not increase in number[47-49].
Postnatal growth of the airways has been studied in only a limited number of anatomic investigations. One study describes the infant's airway as a

miniature of the adult one[48], but another study suggests that peripheral airways increase in size relative to the central airways after the fifth year of life[50].

Smooth muscle is present in the airways of the foetus early in development and extends from the trachea to the alveolar ducts in newborns as in adults[51–53]. Smooth muscle content appears to remain relatively constant in airways of a given generation and mechanisms controlling airway tone in the neonate are comparable to the adult[54]. Cartilage is present in the bronchi at about 25 weeks of gestation and its distribution is similar to that of adults[47]. Increased cartilage develops in the first years of life, thereby contributing to the stiffening of the airways observed in the first months of postnatal life[55,56].

Although collagen and elastin are important in airway morphogenesis and branching, the interstitium of the human lung contains little collagen and elastin during late gestation and at birth. From birth elastin and collagen formation increase. The changing ratio of elastin and collagen probably contributes to the change in volume-pressure relationships in the developing lung. However little is known about the organisation and development of these tissues at various stages of lung growth and in various regions of the lung[57].

Considerable structural changes occur in the chest wall, particularly during early postnatal life. The ribs, oriented in a horizontal plane, slant in a progressively caudal direction to the downward slope seen in adults[58]. Also the ossification of ribs, sternum and vertebrae and muscle mass development contribute to changing volume pressure relationships during childhood.

In adults, the functional residual capacity (FRC) is mainly set passively by the balance between elastic recoil of the lungs and chest wall. However in newborns the high compliance of the chest wall would cause nearly complete collapse of the lungs, if not actively counteracted by glottic narrowing or interruption by the onset of inspiration. Probably, the major function of the Hering Breuer reflex in young children might be the termination of the expiratory process before lung volume gets too small. Once the chest wall has become stiff enough to counteract elastic recoil of the lungs, this reflex is reduced and may disappear from the age of 1 year[59]. Then passive characteristics appear to determine end-expiratory lung volumes[60]. The easy collapsibility of the rib cage is advantageous in utero to prevent pleural effusion and during birth, when it allows deformation of the chest during passage of the birth canal and expulsion of fluid before the first breath. After birth it diminishes metabolic demands but a decrease in collapsibility is nec-

essary to decrease the need for outward recoil of the lung, necessary to maintain lung volume.

Respiratory function development

It may not be surprising that the remarkable change of respiratory structures also has significant functional implications. Lung volume and volume-pressure relationships (e.g. pulmonary compliance) reflect parenchymal (air space) development, and airflows and pressure-flow relationships (resistances and conductances) reflect airway development. But the relationships are not as direct as they might seem.

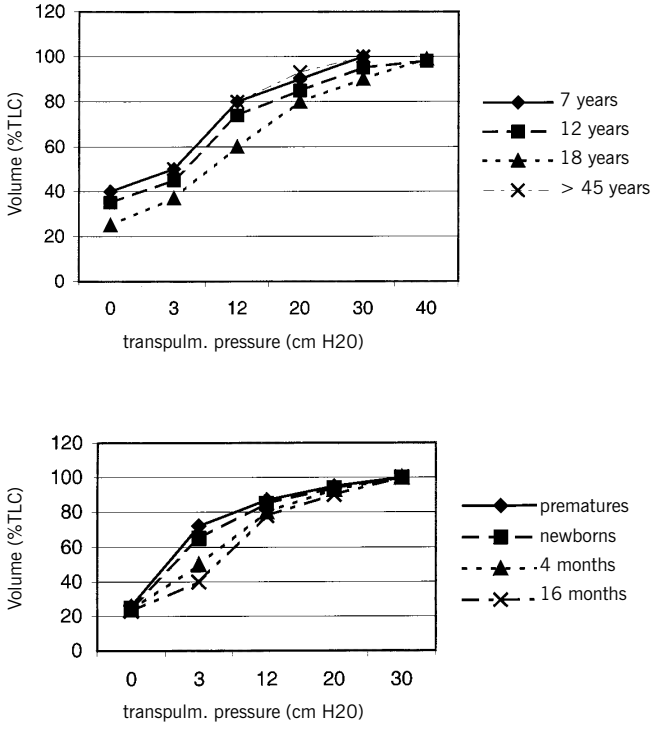

Figure 4. Deflation volume-pressure curves of the lung at different ages (obtained from studies on excised lungs[61]. With increasing age up to young adulthood the curves become straighter and at a given lung volume elastic recoil pressure is greater. The curve from elderly subjects resembles that from a 7 year old.

Pulmonary compliance depends on the number of air spaces expanded, the size and geometry of the air spaces, the characteristics of the surface lining layer and the properties of the lung parenchyma that change with growth and maturation. This is represented by changes in the shape of the volume-pressure curve. These curves, when normalised by expressing volumes as the percentage of the maximal observed lung volume, are more curvilinear in infants than in older children (Figure 4).

This reflects immature air spaces rather than mature alveoli and probably the differences in elastin-collagen ratio with age[61]. The lung volume at which airway closure occurs is higher in younger children (7 years) and elderly adults than in older children and younger adults[62]. In infants higher collapsibility is illustrated by atelectasis in dependent regions.
The configuration of the relationship of maximal expiratory flow and lung volume (maximal expiratory flow-volume (MEFV) curve) is similar in the child and in the elderly; in both age groups there is alinearity of F-V curves compared to younger adults, compatible with decreased elastic recoil[63].
Pressure-volume relationships of the total respiratory system show comparable developments as those of the lung in young children in that they are more curvilinear in infants[64]. However in 2-16 year children the shape of these curves is constant. This means that there is a constant relationship between the increasing elastic recoil of the lung and the increasing recoil of the chest wall. Overall the total respiratory system becomes stiffer with increasing age, especially in children under 5 years of age.
Chest wall compliance corrected for body (i.e. also lung) size is 50% greater in infants under 1 year compared to infants over 1 year of age. In infants chest wall compliance is threefold greater than lung compliance but in older children and adults these values are virtually equal.
The changes in resistance of airways, lungs and total respiratory system are substantially but also variably influenced by the upper airway resistance, notably from the glottis. Although in adults this may comprise over 50% of measured resistance, studies by Hogg et al, who partitioned airway resistance by means of a retrograde catheter technique into central and peripheral components, showed that in children up to 5 years of age the contribution of peripheral airways to respiratory resistance is greater than in adults[50]. This increases the usefulness of resistance measurements in children, especially during small airway disease. On the other hand it diminishes the usability of this parameter to reflect changes during development of normal subjects. This also affirms that the infant's tracheobronchial tree is

not simply a miniature of the adult one[48], but that the contribution of peripheral airways to the total changes with age.
Data on compliance and resistance collected in children 3 weeks to 15 years of age support the relatively greater increase in lung parenchymal growth relative to airway growth throughout childhood[65].
Although the increase in total alveolar content increases the absolute compliance, the changes in shape of the volume pressure curve suggests that to some extent maturation makes the lung relatively stiffer. Indeed with increase of parenchymal volume relative to airways, there is a decrease in specific conductance and rate of lung emptying.
In daily practice, however, individual variability in airway size and lung volume are probably more important indicators of lung disease than maturational changes. Some studies found indications of inter-individual differences in the interaction between parenchyma and airway growth[66,67], which is presumably genetically determined. There is increasing epidemiological evidence that diseases in early childhood, e.g. wheezing with lower respiratory infections, is linked to physiologic indicators of lung and airway size, already established in early infancy[68-70].

4. Techniques for the measurement of resistance in spontaneously breathing young children

It is important to realise that several measures or resistance are used in daily practice. Several techniques measure different kinds of resistance, that are not completely interchangeable. Specific techniques have been developed for measurement of R_{aw}, total pulmonary resistance ($R_{tot} = R_L + R_{aw}$) and active or passive respiratory system resistance ($R_{rs} = R_{aw} + R_L + R_{cw}$) (Table 1).

During measurement of resistance, pressure is measured at the two endings of an open tube, in case of the lungs at the mouth and at the alveoli and corresponding flow is recorded. Measurement of alveolar pressure is difficult. With most techniques pressure and flow are measured at the mouth and alveolar pressure can be measured at the mouth after airway occlusion when equilibration of alveolar and mouth pressure occurs.

Table 1. Measurement of resistance in humans. Techniques that are possible in spontaneously breathing pre-school children are presented in bold, techniques possible in infants in italics.

Respiratory system resistance ($R_{rs}= R_L + R_{aw} + R_{cw}$)	**Total pulmonary resistance** ($R_{tot} = R_L + R_{aw}$)	**Airway resistance** (R_{aw})
Active breathing against occlusion	Intra-oesophageal balloon	*Body plethysmography*
Airway occlusion technique		
Forced oscillation technique (FOT)		
Impulse oscillation technique (IOS)		
Interrupter technique		

A. Respiratory system resistance (R_{rs})

Respiratory system resistance (R_{rs}) can be measured, using active and passive techniques

1. Active measurement: active breathing against occlusion

Measurements of active R_{rs} can be performed in infants during quiet breathing under sedation or spontaneous sleep. Simultaneously airway pressure, volume and air flow are measured. After a normal breath the airway is occluded at end expiration. During the following occluded inspiratory effort, repetitive measurements of pressure can be related to flow and volume measured during the preceding breath. From these relations elastance E, compliance C (i.e. 1/E) and resistance R_{rs} can be calculated. Inspiratory resistance measured in this way represents about 70% of expiratory resistance during infancy[71].

2. Passive measurements: airway occlusion, oscillation and interrupter techniques

2.a. The airway occlusion technique

The basis of the airway occlusion technique is that after airway occlusion at end-inspiration the Hering Breuer reflex causes apnoea, both inspiratory

and expiratory respiratory muscles relax and a passive expiratory flow-volume curve can be analysed after release of the occlusion[72].
Also in children and adults changes in the mechanical properties of the lungs and thorax can be demonstrated by the measurement upon purely passive expiration curves. This, however is only possible under complete apnoea, inflating the lung to a known alveolar pressure and than permitting deflation by elastic recoil only. During this expiration the pressure of recoil is approximately proportional to lung volume added to FRC. Flow will only be retarded by frictional resistance, lung tissue resistance to movement and the pressure required to overcome inertia. Flow decreases with time during expiration. Inertia is negligible[9].

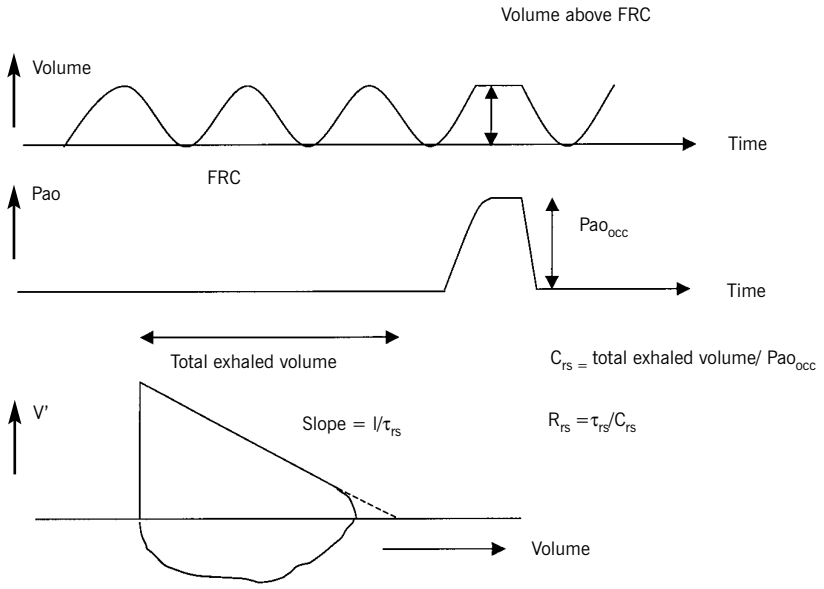

Figure 5. Calculation of the respiratory compliance (C_{rs}) and resistance (R_{rs}) using the single breath occlusion technique. Pao_{occ} airway opening pressure following occlusion; Pao pressure at the airway opening; τ_{rs} expiratory time constant.

In the single breath occlusion technique (Figure 5), the airway is occluded at end inspiration, with the subsequent expiration occurring passively. A passive expiratory flow volume curve is then constructed. The slope of the linear part of the passive flow volume curve is equal to the reciprocal of the

time constant of the respiratory system (τ_{rs}) during expiration. Respiratory system resistance (R_{rs}) can be calculated by dividing τ_{rs} by C_{rs}.

In the multiple breath occlusion technique (Figure 6) pressure is measured at the mouth during brief airway occlusions performed on multiple breaths, at different volumes above FRC and the individual measurements are plotted as volume vs. pressure. The slope of the line of "best fit" is the compliance of the respiratory system.

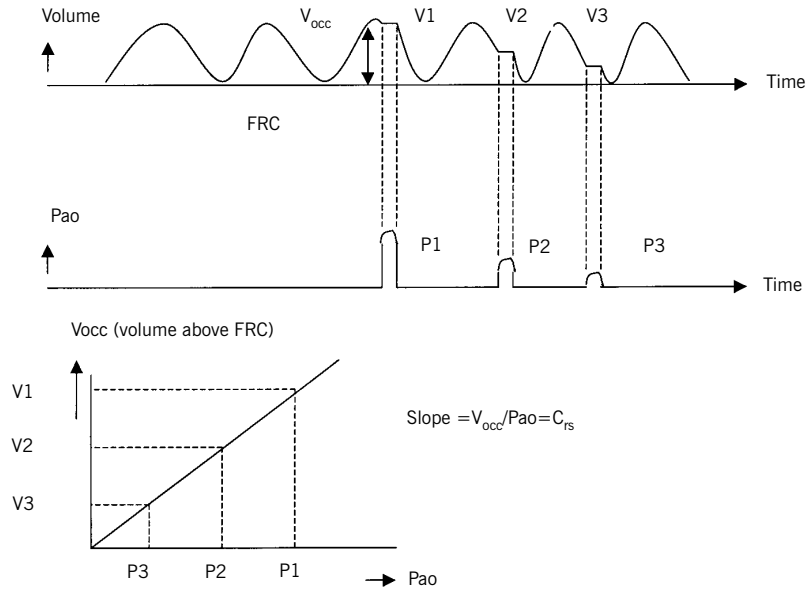

Figure 6. Calculation of compliance of the respiratory system using the multiple-breath occlusion technique. V_{occ} volume at which occlusion is made, P pressure, Pao pressure at the airway opening, C_{rs} compliance of the respiratory system.

2.b. Oscillation techniques

2.b.1. Forced oscillation technique (FOT)

Total pulmonary resistance can be measured in infants and children by the forced oscillation technique. This measurement includes tissue viscous resistance of lungs and chest wall. A sinusoidal pressure applied at the upper airways changes the airflow and resistance can be calculated. When the forced oscillations are applied at the so-called resonance frequency of the

lung (5-7 Hz in children[73]), it is assumed that the force, required to overcome elastic resistance of the lung and the force required to overcome inertia are equal and opposite.
The forced oscillation technique (FOT) was introduced by Dubois et al[74], to characterise respiratory impedance (Z_{rs}) and its two components reactance (X_{rs}) and resistance (R_{rs}) over a wide range of frequencies[75].

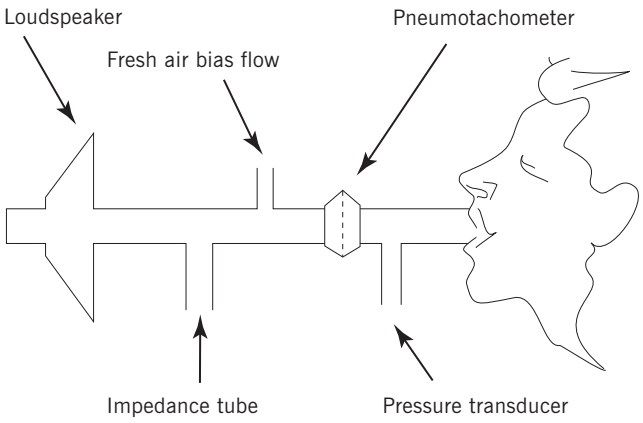

Figure 7. General set up of oscillation system.

The general set up of the oscillation system is shown in figure 7. Flow oscillations, generated by means of a loud speaker are applied at the subject's mouth and superimposed on normal breathing (Figure 8). A large bore impedance tube directs the oscillations to the patient without offering any resistance to spontaneous breathing. Fresh air bias flow prevents rebreathing of the expirate.

The driving pressure, either sinusoidal (single frequency) or composite (multiple frequencies), results in flow oscillations, the magnitude and phase of which are determined by the resistive, elastic and inertial properties of the respiratory system (Figure 9). The resulting pressure and flow signals are recorded at the mouth using a pressure transducer and a pneumotachometer and analysed. These signals are, in general, waveforms containing several frequencies. For each of these frequencies, the ratio of pressure to flow can be considered (i.e. the impedance), which is a complex number of the magnitude of pressure to flow and about the phase shift between these sig-

nals. Most often this complex number is represented by its real part, the respiratory resistance (R_{rs}) and its imaginary part, the respiratory reactance (X_{rs})[76-79].

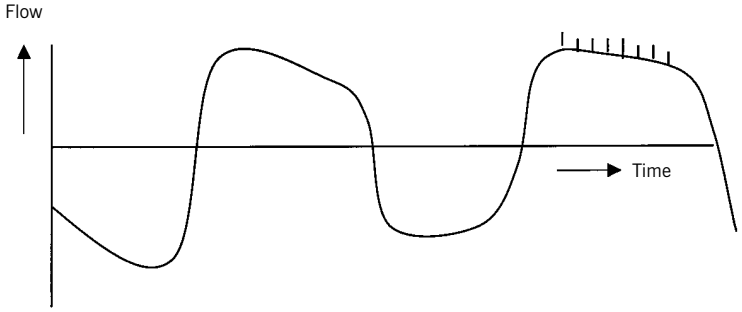

Figure 8. General principle of FOT and IOS. A wave form pressure signal causes flow changes superimposed on the tidal breathing pattern

With the random noise or pseudo random noise method oscillations of different frequencies are analysed and frequency dependency of resistance and reactance can be found[76,80]. Microprocessor techniques allow analysis of the complex signals by Fourier transformation[80-82].

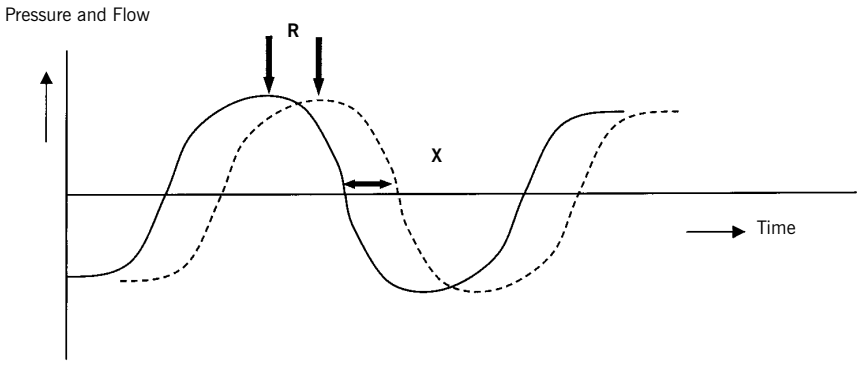

Figure 9. A sinusoidal pressure wave causes a flow wave that is analysed using Fourier analysis. From the relationship of pressure and flow changes resistance (R) and reactance (X) can be calculated.

In children and obstructive patients the resistance is frequency dependent, with higher R_{rs} at lower frequencies. The fact that during inspiration the vocal cords are more open than during expiration[33] makes measurements, obtained during inspiration more appropriate. From clinical studies it appears that R_{rs} at low frequencies allows the best discrimination between healthy subjects and various obstructive conditions[83]. Xrs is mainly determined by the elastic and mass-inertial properties of the airways, lung tissue and chest wall. At low frequencies the elastic properties dominate (negative Xrs), at higher frequencies the mass-inertial forces take over (positive Xrs). The frequency at which Xrs crosses zero is called the resonance frequency (RF). In obstructive airway disease Xrs deviates to more negative values[83,84] and therefore the RF will be reached at higher frequencies. Both the Xrs and RF are useful indices in establishing positive reactions to provocation tests.
The estimation of R_{rs} and X_{rs} can be made in several ways but , in principle the two are determined by the amplitude and the phase of mouth pressure and flow at a given frequency. In the multiple frequency technique the use of Fourier transformation algorithm enables the assessment of the frequency dependency of R_{rs}.

2.b.2. The impulse oscillation technique (IOS)

An alternative method for FOT uses an impulse oscillation system (IOS, 5-35 Hz)[3,85]. In this technique an impulse (a rectangular wave form), rather than a pseudorandom noise signal (a mixture of several sinusoidal wave forms) is applied by a loud speaker. Also the data processing and analysis (the so called Fourier analysis) is different.
There are recommendations for measurement of respiratory input impedance by means of forced oscillations but the IOS technique has not been standardised against the recommendations stated in this publication[86].

2.c The interrupter technique (Rint)

The interrupter technique is a non-invasive method to measure airflow resistance[87]. It was first described by Von Neergaard and Wirz in 1927[88]. During sudden occlusion of the airway pressure changes at the mouth. The interrupter technique is based on the premise that, during this transient interruption of the tidal airflow, alveolar pressure and mouth pressure equilibrate within a few milliseconds. The alveolar pressure can therefore be derived from the measurement at the mouth immediately after interruption. If the flow is measured immediately prior to interruption, the ratio of flow to pressure changes gives the interrupter resistance (Rint). Difficulties

in interpreting the post-occlusion pressure tracing has delayed the further introduction of this technique and until recently the interrupter technique has never been widely accepted as a clinical tool. Also other technical considerations (e.g. the discussion if post-occlusion flows instead of pre-occlusion flows should be used) have delayed general acceptance. However, recent studies have unravelled the factors which influence the post-occlusion mouth pressure tracing and the physiologic basis of this technique[89-93]. Also the introduction of a small portable device to measure interrupter resistance has caused a revival of the interrupter method technique[94].

When the airway is occluded at the mouth airflow ceases and there is an initial large and rapid increase in mouth pressure succeeded by a smaller and more gradual one (Figure 10). Approximately 5 msec after actuation of the valve, closure is complete[94]. The initial change in flow is caused by the rapid equilibration of alveolar and mouth pressure. This is due primarily to mouth pressure jumping to meet pre-occlusion alveolar pressure. However alveolar pressure changes immediately after occlusion due to transference of chest wall pressure[90]. In paralysed subjects the second pressure change is caused by stress relaxation of the lung tissue and chest wall. If this is the case in awake spontaneously breathing humans is not known but the influence of respiratory muscles is probably less during expiration compared to inspiration. However, other authors suggested the use of inspiratory values to minimise the influence of glottic aperture[33].

During brief interruption of airflow the estimate of mouth pressure (Pmo) is more influenced by glottic resistance during expiration than during inspiration[33].

The time course of the post-occlusion pressure tracing is influenced by the compliance of the upper airways (especially cheeks) and gas in the lungs, the resistance of the airways and the inertia of the system[95-97].

Both increased airway resistance and upper airway compliance prolong the equilibration time from about 40 msec in normals up to >100 msec. Most devices use interruption times of 100 msec. Only after 150-250 msec active breathing against the occluded valve occurs. Back-extrapolation of the post-occlusion pressure tracing to the time of valve closing is considered by most authors to be the best method to approximate the resistive pressure drop across the airways at the time of interruption[90,92,98,99]. For this the pressure trace between 40 and 80 msec[87] or 30 and 70 msec[94] are advised (Figure 10). This is late enough to allow equilibration of mouth and alveolar pressure in most patients and early enough to prevent active breathing against the valve.

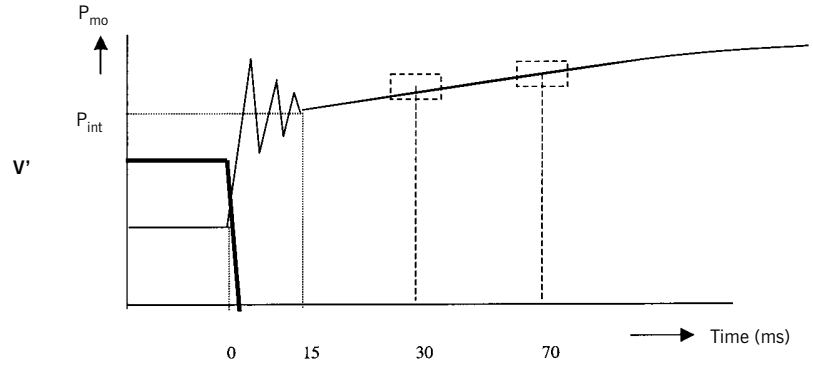

Figure 10. Interrupter resistance. During tidal breathing short interruption of airflow (V') causes changes in respiratory system pressure that can be measured at the mouth (P_{mo}). P_{int} is computed by back-extrapolating a line drawn through two points, centered at 30 and 70 msec (which are blocked averages of pressure during 10 ms) to the point at 15 msec from start of occlusion (t = 0)[94]

B. Total pulmonary resistance(R_{tot})

Oesophageal balloon

Before the introduction of the bodyplethysmograph in 1956 total lung resistance measurement was only performed in specialised centres, using oesophageal balloons to measure transpulmonary pressure. R_{tot} can be measured by placement of an intra-oesophageal balloon or catheter. Oesophageal pressure is related to flow changes at midtidal lung volumes.
A balloon is positioned in the distal part of the oesophagus. During tidal breathing pressure and volume changes can be measured and from these compliance and resistance can be calculated. This technique is of course not useful in general practice, but is frequently used in animal studies.
It is assumed that elastic forces are equal but opposite at points of equal volume during inspiration and expiration. Rtp is conventionally calculated at the midtidal volume points during inspiration and expiration by dividing differences in oesophageal pressure at those points by the corresponding absolute difference between the in- and expiratory flow (Figure 11).

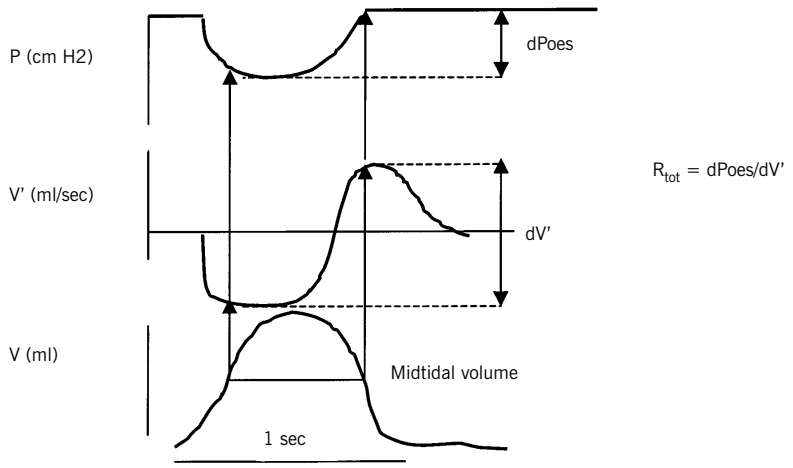

Figure 11. A method for calculating dynamic total pulmonary resistance (R_{tot}). R_{tot} is calculated by dividing changes in elastic oesophageal pressure Poes by flow V' obtained between two isovolume points during inspiration and expiration

C. Airway resistance (R_{aw})

Bodyplethysmography

Airway resistance (R_{aw}) in both adults and older children is most commonly measured using body plethysmography. The method is based on the assumption that when a shutter occludes the tube airflow ceases and the mouth pressure equilibrates to alveolar pressure. At BTPS conditions R_{aw} can be determined from the difference between alveolar pressure (Palv) and airway opening pressure (Pao), divided by airflow (V').

A sitting person in an airtight box breathes spontaneously through a tube connected to a pneumotachometer, measuring airflow (V') and plethysmographic pressure (Pbox). Simultaneous changes in V' and Pbox are recorded on an x-y oscilloscope and the slope of this relationship is recorded (V'/Pbox). After occlusion of the airway changes in volume (recorded from Pbox) and mouth pressure (Pm, which reflects Palv) are monitored. Provided that the ratio of lung volume to plethysmographic gas volume remains constant, the Palv corresponding to a given Pbox remains constant whether or not flow is interrupted. Thus derivation of R_{aw} is obtained by dividing the slope of Pm/Pbox by the slope of V'/Pbox:

$$R_{aw} = dPalv/V' = dPm/V' = (dPm/dPbox)/V'/dPbox)$$

Higher lung volumes show lower resistance. Because this technique measures resistance and volume simultaneously resistance can be related to lung volume and specific airway resistance (sR_{aw}) or its reciprocal conductance (sG_{aw}) can be calculated. Airway conductance (G_{aw}) is linearly correlated to lung volume ($sG_{aw}=G_{aw}/FRC$) and is therefore regularly determined in older children and adults (Figure 12).

Plethysmographic measurements of resistance are dependent on the assumption that pleural pressures are homogeneously applied to all lung fields. If not, the Pmo does not reflect Palv.
The plethysmograph is recording volume changes of intrathoracic gas. In a closed system pressure changes in the airways caused by in- and expiratory movements lead to volume changes in the airways.

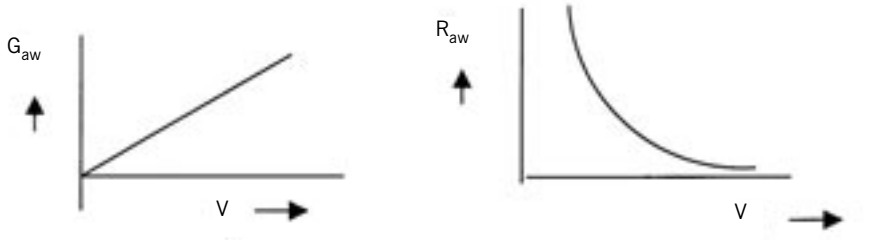

Figure 12. The relationship of airway conductance (G_{aw}) and resistance (R_{aw}) with lung volume (v).

Compared to spontaneous breathing during panting higher frequencies and higher flows are applied. Both methods gave similar values in healthy subjects[100], but in patients with obstructive airway disease higher values were found during spontaneous breathing. However other investigators found slightly increased values during panting[101]. During panting the glottis will open (decreased resistance), there may be turbulent flow during panting in obstructive patients (increased resistance) and there is higher breathing frequency (lower resistance). The total sum of these factors will determine if resistance during panting is higher or lower.
Important issues in the interpretation of airway resistance measured by body plethysmography are:

1. This R_{aw} represents especially resistance of extrathoracic and central airways and hardly peripheral airways.
2. Panting is especially difficult for children and the closing of the flow pressure loop performed to calculate resistance impairs the reliability of results.
3. Laminar versus turbulent flow at different lung volumes impairs the applicability of this technique in patients with high airway resistance.
4. The difference between inspiratory and expiratory flow pressure curves impairs reliability of this technique. Especially in patients with high airway resistance the expiratory loop is irregular.

5. Feasibility of different techniques to measure airway mechanics in children

During pulmonary function measurement in young children no active co-operation nor co-ordination may be expected. Also only testing during spontaneous breathing allows for application of the technique in all day practice. The minimal age above which these measurements are possible depends especially on the ability to passive co-operation. This may vary in individual children.

Obtaining lung function measurements in young children presents a great challenge and very rarely produces reliable results when conventional methods are used. That's why all possible disturbances that influence reliability should be kept to a minimum. Co-operation of the children can only be optimal, not perfect. Instruction to the child has to be made as simple as possible in a positive encouraging atmosphere, because real passive co-operation is essential for reliable and reproducible measurements. The child is sitting upright and, if possible, a mouthpiece and nose clip are used. Only in the smallest children tight fitting face masks should be used.

Several studies evaluated applicability of pulmonary function tests in young children. A summary of these studies is presented, together with important technical considerations.

R_{rs} measurements

1. Active measurement

This technique has only been applied in infants, not in older children. In adults it was only studied under halothane anaesthesia

2. Passive measurement

2.a. Airway occlusion technique

This technique depends on the Hering Breuer reflex. Therefore it is possible in infants but very difficult in older children who lack this reflex and will normally react to airway occlusion with active counteracting by trying to "blow away the occlusion". Considerable training is needed for older children to relax their respiratory muscles, in order to obtain quasi static pressure volume curves.
These methods are only applicable when a linear expiratory flow-volume relation is obtained, i.e. when τ_{rs} is constant. In obstructed airway disease curvilinear flow-volume relations demonstrate significant heterogeneity of τ_{rs}. In these children the interpretation of results is hampered if not impossible.

2.b. Oscillation techniques

This method can be used in children from 3 yrs of age onwards[3,75,102]. The use of forced oscillation in children has been limited by some practical problems encountered when applying this technique and by the lack of user-friendly commercially available equipment. Major technical problems are caused by the interference of applied oscillations with spontaneous breathing, by air leak around the mask or mouthpiece and by upper airway compliance. The breathing frequency causes loss of coherence from the forcing function, which means that no useful data are obtained at frequencies below 4 Hz. Air leak results in overestimation of resistance because mouthpiece or masks acts as an extra resistance parallel with the respiratory system. This air leak occurs especially in obstructed patients. Compliance of the upper airways acts as a shunt compliance in parallel with the respiratory system. Especially at higher frequencies this causes shunting of the applied forces and overestimation of resistance and underestimation of inertance (higher resonance frequency). Here again airway obstruction increases this confounding. The cheeks and floor of the mouth should be supported by an assistant, but variation in this support will enable variable results.

In infants the usefulness of this technique is further reduced by the fact that there is considerable variation of R_{aw} during the respiratory cycle and there is no international standardisation of the technique as is in older children and adults, in whom measurements are standardised to a flow rate of 0,5 L/sec.
Therefore it is not unexpected that Phagoo et al, but also other investigators, found that the forced oscillation technique is a rather unreliable method to find bronchial responsiveness to challenge with methacholine. This method combines great baseline variability with low sensitivity and unsustained increase in R_{rs} with rising obstruction[4,103-106]. This is especially caused by the need to breath against the oscillating column of air, the mandatory length of quiet breathing, consistent breathing required to obtain a measurement and the importance of maintaining a consistently patent upper airway.

2.c. Interrupter technique

Feasibility studies were performed recently and reported in several publications. Our study on feasibility is discussed in chapter 6 of this thesis. The resistance measurements obtained in awake spontaneously breathing children are only a gross approximation of airway resistance. There are many variables that can affect the final value obtained with the interrupter technique, e.g. air leak around mask or mouth piece, compliance of the cheeks, airflow rate at interruption, lung volume at the time of interruption, the time and point in the respiratory cycle of flow interruption, the type of interrupter device and especially criteria for selecting and back-extrapolating the post-occlusion pressure tracing to the time of valve closing. The ideal interrupter device should have a solid state piezoresistive pressure transducer. Shutter closure must be as rapid as possible to prevent air leak during closure[107]. Most young children prefer the face mask[108]. Dead space of the device should be as small as possible and the compliance of the upper airways must be minimised by applying gentle support to the cheeks. This decreases equilibration time significantly. The effect of uncontrolled tongue position and mouth movements, variation in glottic aperture, head or neck movements should be prevented as much as possible.

After comparison of several different ways of back extrapolation of post-occlusion mouth pressure tracings, a linear back extrapolation was the least variable and most sensitive in children and is recommended for standard use[103] although a comparable study by the same authors in adults showed that a smooth curvilinear back extrapolation was the most sensitive in

adults[109]. Also the number of interruptions averaged, the criteria for rejecting individual post-occlusion pressure curves and software used for analysis are not yet standardised. It should be possible to define the precise flow at which valve closure occurs. There is hardly any quality control for interrupter devices. There should be a possibility to store and display pressure and flow curves. Acceptance criteria for these curves should be defined and standardised.
Carter stated in 1997 that, after standardisation, evaluation of normal values, reproducibility and standard differences we will really know the Rint its ultimate clinical potentials[110]. Technical considerations as mentioned above and the moment of airway occlusion in the respiratory cycle were recently studied by an ERS working group. Only after standardisation of these factors application in daily practice can be advised.
A studie by Sly et al. showed the applicability in infants[111]. Several studies have evaluated the applicability in (pre) school children[85,112-114]. In 3-12 year old children, both normal and diseased, the technique proved to be applicable[87]. Both children and parents prefer this technique to the forced expiration technique. Changes in airway obstruction could be assessed, caused both by disease and by pharmaceutical intervention[85,112-115]. Feasibility defined as the ability to complete two measurements 15 minutes apart, before and after bronchodilation was found in 53%, 71% and 91% of 2, 3 and 4 year old wheezy children respectively. The total session took about 25 minutes[112]. The same authors also found that inter observer variability was rather low, indicating that training of the pulmonary function technician should not be difficult.
Merkus et al. found no problems in applying the interrupter technique in school children with asthma and CF[116].
Phagoo applied the technique without problems in 3 year old children after some practice[117], but in infants with a history of wheeze Chavasse et al. could only apply the technique in 15 out of 26 patients, partly because of low flows that failed to trigger the interrupter valve[118].

Total pulmonary resistance (R_{tot})

Oesophageal balloon

For the measurement of pulmonary resistance using oesophageal balloons subjects should voluntarily undergo balloon introduction through nose and

throat. Active co-operation is required unless the procedure is performed under anaesthesia. These premises do not allow wide spread use of the technique, especially not in children. Therefore this technique is not used in daily practice

Airway resistance (R_{aw})

Bodyplethysmography

Body plethysmography is routinely possible in most pulmonary function laboratories. This method requires a complex equipment and is time consuming[119]. The specific technical requirements and the expensive equipment limit the use of this technique to specialised laboratories. This technique can be used in younger children but requires sedation. Recently bodyplethysmographic measurements were also applied and validated in children accompanied by an adult during bodybox measurements[120]. Nowadays, after many years of clinical experience this technique has been technically adapted, so that the actual measurement has become relatively easy for the pulmonary function technician.
Bodyplethysmography has several limitations when applied in young children. Young children have a tendency not to blow against a closed valve, restricting volume measurement and thereby resulting in unreliable measurements with increased intra-individual variability[121].

6. Reference values

Respiratory system resistance (R_{rs})

1. Active measurements

This approach has only been applied to infants. The mean (+SD)value of R_{rs} in a group of healthy neonates averaged 45 + 21.6 cm H_2O/(L/s). These values are comparable to the estimated passive inspiratory R_{rs} in the same infants[122].

Table 2. Reference values of R_{aw} and R_{rs}.

Technique	Ref.	sex	age	Regression equation	r
plethysmography	122	M/F	4-18	$R_{aw} = 1{,}660\text{-}8{,}772.\ 10^{-3.H}$	-0,8
				$sG_{aw} = 2{,}029$	
	121	M/F	3-17	$R_{aw} = 5{,}15^{e\text{-}0{,}01473.H}$	-0,7
				$sG_{aw} = 1{,}0$	
	124	M/F	0-5	$sR_{aw} = (68{,}205 + 4{,}109.H).\ 10^{-3}$	
oscillometry	125	M/F	3-17	$R_{rs} = 10^{0{,}868\text{-}0{,}0089.H}$	
	126	M/F	3-14	$LogR_{rs}4{,}9 = 2{,}42\text{-}1{,}27.H^{\star}$	-0,74
	127	M		$R_{rs}3\text{-}10 = 6{,}79x10^{3}.H^{-1{,}93}$	-0,9
		F		$R_{rs}3\text{-}10 = 2{,}22x10^{5}.H^{-2{,}17}$	-0,9
	127	M/F	2-18	$LogR_{rs}4 = 1{,}053 - 2{,}18 \log H^{\star}$	
				$LogR_{rs}12 = 0{,}997 - 1{,}97 \log H^{\star}$	
	128	M/F	2-16	$R_{rs}6 = 9{,}2s.H^{\star 2}\text{-}34{,}1.H^{\star}+35{,}2$	
	129	M/F	3-18	$R_{rs} = 13{,}92\text{-}0{,}0635.H$	-0,89
	130,131	M/F	2,25-12,5	For abundant equation see references	
	132	M/F	3-17	$LogR_{rs}8 = 11{,}122\text{-}2{,}759 \log S$	-0,84
		M/F	3-17	$LogR_{rs}12 = 10{,}380 - 2{,}608 \log S$	-0,83
		M/F	3-17	$LogR_{rs}12 = 6{,}221 - 1{,}547 \log S - 0{,}040A$	-0,84
		M/F	3-17	$LogR_{rs}16 = 8{,}867 - 2{,}278 \log S$	-0,81
		M/F	3-17	$LogR_{rs}8 = 110{,}990\text{-}2{,}370 \log H$	-0,82
		M/F	3-17	$LogR_{rs}12 = 10{,}357 - 2{,}259 \log H$	-0,84
		M/F	3-17	$LogR_{rs}12 = 6{,}225 - 1{,}349 \log H - 0{,}040A$	-0,85
		M/F	3-17	$LogR_{rs}16 = 8{,}705 - 1{,}945 \log H$	-0,81

R_{rsx} = kPa/L/s, measured at frequency x; R_{aw} = kPa/L/s; sG_{aw} =1/(kPa.s); sR_{aw} = kPa.s, H = standing height in cm; $H^{\star}$ = standing height in m; S = sitting height in cm; A = age in years.

2. Passive measurements

2.a. Airway occlusion technique

The mean (+SD) values of R_{rs} reported in a group of healthy newborns amounted to 58,7 + 27,0 cm H_2O/(L/s) (121). It is assumed that inspiratory resistance represents approximately 70% of expiratory resistance during infancy[71].

No normal values for older children are available. In adulthood, as in infants, similarity between active and passive measurements exists.

2.b. Oscillation techniques and body plethysmography

Several authors have studied FOT and IOS parameters in healthy subjects. Most authors use regression equations for resistance versus height (Table 2). Ducharme among others found that height is the best predictor for total respiratory resistance in children at 8, 12 and 16 Hz[131]. Because standing height is easier measured than sitting height and the latter does not add anything extra, standing height should be considered as the main predictor. In- and expiratory R_{rs} have been shown to be equal[133]. R_{rs} decreases with growth[127].

2.c. Interrupter technique

Until recently no reference values were reported in literature for Rint. Reference values are subject of chapter 6 of this thesis. In this chapter other recent publications of reference values are discussed.

Reference values have only recently been established for specific age groups. The range is wide and therefore a single measurement in any individual is of limited value.

McKenzie et al presented reference values based on measurements in 48 healthy pre-school children. For the age group 2-5 years they found: logRint = -0.078 x age(yrs) + 0.24. Because height did not better predict Rint the authors preferred age, which is simpler to determine[115].

Klug and Bisgaard presented reference data for 2-7 year old healthy children, using a face mask[113]. Merkus presented reference values in pre school children using a mouth piece[134]. Lombardi et al presented reference values in pre school children[135]. They used a card board mouth piece and nose clip, valve closure occurred at peak expiratory and peak inspiratory flow, but they did not support the cheeks. Although the latter is generally accepted as essential to minimise the influence of upper airway compliance using this technique[136], they found no differences between supporting and not supporting the cheeks. Also in contrast to other studies they found no differences between inspiratory and expiratory values. Significant correlations with age, height and weight were found for inspiratory Rint but only height was independently correlated with expiratory Rint[135].

Total pulmonary resistance (R_{tot})

Using the approach as described earlier R_{tot} was found to average 21 (SD 4) to 29 (SD 13 cm H2O/L/sec in healthy newborns[71], with similar values found during the first 2 years. When corrected for lung size the specific expiratory conductance was reported to be relatively high in newborns compared to older infants and children[137]. Conductance values were significantly linearly correlated with height:

G_{tot} = 0,000475 x height - 0,0079 (r = 0,937).

(G_{tot} in L/(cm H2O.sec), height in cms)

However, despite numerous reports of dynamic lung mechanics in healthy infants and children, none are based on large enough populations of subjects either studied longitudinally or cross sectionally to be considered as reference values.

Airway resistance (R_{aw})

Reference values derived from bodyplethysmographic measurements of airway resistance are presented in Table 2. Best correlations are found between R_{aw} and height.

7. Comparison of different techniques

Different techniques to measure resistance consider different aspects of anatomy and physiology of the respiratory system. Therefore direct and perfect correlation between individual techniques can not be expected.
Correlations with other measures of pulmonary function such as FEV_1 may be expected to be even worse, because not only other physiology but also other parameters are concerned. The relation of resistance measurements with FEV1 is discussed in the next paragraph of this chapter. Here several techniques for resistance measurement are compared.

Comparison of oscillation techniques, Rint and body plethysmography

Methodological considerations

With all techniques considering resistance measurement, flow is measured at the mouth, but the location of pressure measurements varies. With bodyplethysmography the difference between alveolar pressure and mouth pressure is the driving pressure for flow. Thus the measured resistance represents only airway resistance (R_{aw}).
With the oesophageal balloon the pressure difference between mouth and pleura is measured. The measured resistance therefore gives the total lung resistance (R_{tot}), composed of both airway resistance (R_{aw}) and resistance of lung tissue (R_L) ($R_{tot} = R_{aw} + R_L$)
Both forced oscillation and interrupter technique measure pressure change over airways, lungs and chest wall, i.e. they measure the resistance of the total respiratory system (R_{rs}) ($R_{rs} = R_{aw} + R_L + R_{cw}$). The indices derived from IOS and FOT are, in principle , comparable[81].
R_{rs} is expected to be higher than R_{tot} and R_{aw}. Rint and R5 are expected to be comparable.

Studies comparing values in healthy subjects.

In animal studies values of Rint were higher than those measured with bodyplethysmography, probably due to a contribution of chest wall rigidity and the glottis to airway resistance[90,138]. The latter is reduced by the panting manoeuvres performed during bodyplethysmography.
Both interrupter and oscillation techniques measure total respiratory system resistance but the oscillation method can show frequency dependency. With lower frequencies the tissue deformation factor can be distinguished and with higher frequencies the gas inertia factor. In healthy persons the most representative resistance values are found with frequencies around 10 Hz. These values correlate well with those found with the interrupter method[139]. Hellinckx et al. found resistance and reactance measured by IOS similar but not identical to those provided by the FOT[140].
Phagoo et al. showed in their study that the method of back extrapolating post interrupter pressure changes considerately influences the correlation between R_{aw} and Rint values. When back extrapolation of the post occlusion pressure was performed from 100 msec post occlusion to mid occlu-

sion pressure, Rint showed good correlation with R_{aw}, with other methods Rint significantly exceeded R_{aw} measured with bodyplethysmography[109].
R_{rs} determined by the oscillation technique correlates well with airway resistance[73,81] and with total lung resistance[141,142]
R_{rs} measurements reveal significant frequency dependency especially in young children and in subjects with airway obstruction, probably reflecting inequality of the distribution of ventilation. In young children this is probably not an indicator of abnormal airway function, supported by the finding of frequency dependency in healthy young children[130]. Klug and Bisgaard also presented normal values for IOS, Rint and sR_{aw} in 2-7 year old children. Mean values of sR_{aw}, Rint, $R_{rs}5$, $X_{rs}5$ and Z_{rs} in children were 1.09, 1.04, 1.38, -0.5, 1.48 kPa/L/s in the under 5 group and 1.13, 0.9, 1.18, -0.37 and 1.23 in the over 5 group. Surprisingly the best correlations were found for all parameters with weight compared to age or height (although not significant). As could be expected there was no correlation between sR_{aw} and either age, height or weight. The authors presented linear regression equations for all techniques[113].

Studies comparing values in diseased subjects.

In a recent study evaluating the agreement between Rint and R_{aw} in children with asthma and cystic fibrosis (CF) Rint was found to underestimate R_{aw}, especially in children with severe airway obstruction[143]. In these patients equilibration times are probably longer than 70-80 msec, and in these patients the extrapolation method underestimates true resistive pressure drop across the airways and thus airflow resistance[87]. Substantial differences between Rint and R_{aw} have also been found in individual patients[94]. In obstructed patients longer equilibration times may be required to prevent underestimation of resistance.
In a recent study IOS was validated against the FOT and body plethysmography in children. Klug and Bisgaard found good correlations of IOS with both whole body plethysmography[85] and also the correlation with results of FOT is acceptable[144]. These results were recently confirmed in adults.
Klug and Bisgaard found that both Rint and IOS techniques revealed abnormal results in 44% (Rint) and 8% ($R_{rs}5$) of asymptomatic asthmatic 2-5 year old children but the outcome after 1.6 to 4.5 years was unrelated to baseline pulmonary function. Hence lung function measurement using IOS or Rint is not helpful in identifying children with a poor prognosis[145].

Studies comparing feasibility.

In a study by Klug and Bisgaard, IOS, Rint and sR_{aw} values could be obtained in 80% of all children, and almost 100% of children above 5 years of age[113].

Studies comparing reproducibility

Most studies on the reproducibility of different techniques applicable in (young) children were recently performed in research centres in Great Britain and Danmark.

In a study in school children Bridge et al. found that the coefficient of variation (CV) of Rint was 11%, higher than R_{rs} (9%), FEV_1 (5%) and PEF (5%)[146]. From the same centre results were presented describing repeatability of Rint in 3 year old children with an intra subject CV of 13% (ranging from 4-35%) compared to 1,6% (0,4-3,2%) for PtcO2[117].

In a Danish study in 4-6 year old children reproducibility was much better for FEV1 (CV =5%) compared to sR_{aw} (CV =13%), $R_{rs}5$ (CV = 10%), $X_{rs}5$ (CV = 17%) and Rint (CV = 12%)[3].

In 2-4 year old asthmatics the reproducibility findings were more or less comparable to the former study: better for Rint (8%), sR_{aw} (9%) and $R_{rs}5$ (10%) than for $X_{rs}5$ (16%)[85].

The same authors also compared IOS, interrupter technique and whole body plethysmography in healthy 2-7 year old children and found that the repeatability was age independent and best for Rint (CV = 8.1%) compared to $R_{rs}5$ (10.2%), Z_{rs} (10.8%) and sR_{aw} (11.1%). For all parameters no significant sex differences were found and frequency dependency was confirmed[113].

In a recent study Klug et al. compared within observer and between observer variability of the interrupter technique (Rint), impulse oscillation ($R_{rs}5$ and $X_{rs}5$) and whole body plethysmography (sR_{aw}) in 2-6 year old children and found that the within subject standard deviation (SD) was not significantly different in observers but the between observer variability was greater for Rint than for the other parameters[147].

Reproducibility of the oscillation technique has shown to be dependent on the support of cheeks and mouth floor, is strongly related to the patience of the investigator and can vary from 5-20%[73,78,128,129].

Phagoo et al. compared the interrupter technique with forced oscillation and transcutaneous oxygen tension (PtcO2) measurement in 5 year old

asthmatic children during methacholine challenge. The lowest variability was found for PtcO2 (CV = 1.2%) compared to Rint (12-15%) and R_{rs} (12%)[103]. The CV for inspiratory and expiratory Rint values are similar in children[146].
Bridge and McKenzie evaluated the Rint in expiration and inspiration in 2.5-5 year old children and found that expiratory Rint was significantly higher (mean 4%), but no significant differences were found for the CV of inspiratory and expiratory values, nor for bronchodilator response. Mean and median of 5-10 values contributing to a measurement were similar. The authors recommend to use the median[148].
Of course these findings on reproducibility should be taken into account when judging changes in the parameters in disease or after interventions of any kind.
Several confounders that have been discussed before may be responsible for the relative lack of reproducibility of resistance measurements in general, e.g. a switch from nasal to oral breathing or vice versa in young children using a face mask, changes in breathing patterns, respiratory muscle activity, tongue movements, glottic aperture etc.[116].
The use of a face mask with inner mouthpiece versus mouth piece with nose clip in 4-7 year old children resulted in comparable repeatability (CV = 11% for both) but in higher Rint values (p = 0.0002). This might be due to another breathing pattern, more rapidly and with greater tidal volumes. Maybe also a more turbulent flow in the mask because of a small ridge at the connection with the mask mouthpiece added to this higher value[3].

Studies comparing sensitivity

The sensitivity to detect changes in airway resistance (e.g. after intervention) can be expressed as the sensitivity index (SI):

SI = (R after intervention - baseline R)/ within subject SD of baseline R

or:

SI = (Rpost - Rpre)/ SDRpre

In adults the SI for measurement of the response to bronchial challenge is significantly smaller for Rint(1.9-3.1) than for R_{aw} (10.5) [109].

Bisgaard and Klug found in 21 4-6 years old children that the order of sensitivity of different techniques to assess airway obstruction was Z_{ios} > sR_{aw} > FEV_1 > Rint. Parallel changes in all parameters were found but Z_{ios} was significantly more sensitive than FEV_1[3]. It should be stated that they performed interruptions using a pneumotachometer and they measured mouth pressure during the last part of interruption during inspiration and measured flow directly after occlusion. This is another technique than used during later studies[3].

In another study in school children SI was not significantly different for Rint (3.5), R_{rs} (3.6), PEF (3.0) and FEV_1 (2.4)[146]. Phagoo et al found a SI for Rint of 3 in 3 year old children compared to 16 for PtcO2. They found better sensitivity for detecting bronchodilator response (SI = 4.9%) than for detecting induced bronchoconstriction in asthmatic children. In up to half of the children a significant decrease in PtcO2 was not detected by Rint, in only 1 of 12 subjects bronchodilation was not found[117].

In a recent study Rint was measured to distinguish pre school children with recurrent wheeze from those with recurrent cough and healthy peers. Rint was significantly higher in wheezers and coughers did not differ significantly from normals. The bronchodilator response defined as the ratio between pre bronchodilator Rint and post bronchodilator Rint differed significantly between all three groups (wheezers 1,40, coughers 1,27 and normals 1,07). A bronchodilator response of >1,22 had a specificity and sensitivity for wheeze of 80% and 76% respectively[115].

In a study by Klug and Bisgaard $X_{rs}5$ was significantly more sensitive to induced bronchoconstriction than sR_{aw}, FEV1, $R_{rs}5$ and Rint. In patients with subclinical bronchoconstriction after provocation, this subclinical increase in muscle tone was detected by IOS, Rint and sR_{aw} but not by FEV1 or PtcO2[3]. In another study the same authors compared IOS and interrupter technique with body plethysmography in 2-4 year old asthmatic children at baseline, during bronchoprovocation and after bronchodilation. In this study the sensitivity was best for sR_{aw} and $X_{rs}5$. Both were significantly more sensitive than Rint and $R_{rs}5$ (4%). Measurements during an asthma exacerbation yielded comparable results. In the latter study improvement after bronchodilation was best determined with PtcO2[85]. Both studies indicate that both Rint and $R_{rs}5$ are less useful for determination of reversible airway obstruction than $X_{rs}5$ (unless worse reproducibility) and sR_{aw}. The usefulness of $X_{rs}5$ was supported by results of Buhr et al[149] and Duiverman et al[83].

Phagoo et al. compared the interrupter technique with forced oscillation

and transcutaneous oxygen tension (PtcO2) measurement in 5 year old asthmatic children during methacholine challenge. PtcO2 was significantly more sensitive than the other methods to find airway responsiveness (SI = 18.9 compared to 4.2 (Rint) and 4.6 (R_{rs})[117]. Important possible causes for the relative lack of sensitivity of Rint are retarded pressure equilibration in the presence of airway obstruction (underestimation of Rint), inhomogeneity of airway patency and extrathoracic airway compliance (underestimation of Rint). Their conclusion was that because of its simplicity the interrupter method provides a better method for assessing airway obstruction in this age group compared to the oscillation method[117]. Buhr and colleagues found comparable sensitivities for FOT and sR_{aw} (SI = 8.2 and 12.0 respectively) to detect bronchial responsiveness in school children induced by carbachol[149]. In adults, Rint shows a close correlation to airway resistance (R_{aw}) measured by whole body plethysmography (r = 0,86). The methods were equally sensitive in detecting changes in airway resistance following bronchodilation[94].

8. Comparison of resistance measurements with MEFV curves

Evaluation of airway calibre can be performed either by measuring airway resistance during spontaneous breathing or by indices obtained from a forced expiration. Tests of forced expiration, such as PEF and FEV1 are widely used especially because of their simplicity and reproducibility. However there are several disadvantages of forced expiratory manoeuvres.
They require full co-operation and co-ordination of the patient, which can not be expected from young children. Forced expiration parameters appear to be less sensitive to changes in airway calibre than are resistance measurements. Also the deep inspiration necessary for these tests is known to influence bronchial tone[119,150,151].

Forced expiration manoeuvres and resistance measurements during tidal breathing represent different physiologic parameters. Therefore the relationship between resistance and maximal expiratory flow volume (MEFV) parameters is expected to be not very significant.
In the first place, it is important to realise that FEV_1 is not a measure of air-

ways resistance but of airway patency. Resistance is especially determined by the patency of (upper (large)) airways, both intra and extrathoracic. Maximal expiratory flow is especially influenced by patency of lower (smaller) airways and also by lung compliance. Lower airway obstructive disease can present with normal airway resistance and severely reduced FEV_1. Spirometry assesses the combined interaction of lung recoil and airway resistance and can not distinguish which of these has caused a specific change in lung function. That's why specific measurement of airway resistance is required to assess what change in spirometry is due to changes in airway resistance, and not to changes in elastance.
Secondly, it should be stated that FEV_1 is a useful measure of airway obstruction, not because it represent a specific physiologic entity, but rather because it correlates with changes in airway calibre.

Nevertheless comparison of both methods gives significant correlations[152], probably caused by an important common mechanism, namely the airway obstruction.
In a study by Duiverman et al they found favourable sensitivity of the oscillation technique compared to FEV_1 in revealing short term changes in the bronchial status either during bronchial provocation tests or after administration of bronchodilators[83].
Mijnsbergen et al. found the correlation of Rint with FEV_1 to be somewhat higher in asthmatic than in CF patients ($r = -0,74$ versus $-0,58$)[152]. As in adults, also in children changes in Rint (and its reciprocal Gint) correlated with changes in FEV_1 and R_{aw} measured by body plethysmography. The linear correlation of Gint and FEV1 showed a r=0,77 (p,0,001), The curvilinear correlation of Rint and R_{aw} showed a r=0,91 (p<0,001), but Rint was higher than R_{aw}[87].
In their study Bridge et al. found significant correlations of interrupter conductance (Gint), the reciprocal of Rint, with FEV_1 ($r = 0,837$, $p < 0,001$ and peak expiratory flow (PEF) ($r = 0,773$, $p < 0,001$), as well as with Rrs ($r = 0,942$, $p < 0,001$)[146].

9. Final considerations

Although the functional evaluation of patients with lower airway obstruction is probably best performed using FEV_1, resistance measurement can be applied when MEFV measurements are impossible (e.g. infants and pre school children, geriatric patients, myopathic or mentally retarded patients). The development of simple and easily available techniques to measure airway and respiratory system resistance might open new doors for diagnosis and follow up of these patient groups[76,80,88].

Different techniques measure different aspects of resistance. Only with bodyplethysmography the measured pressure causes hardly anything else but flow, so their relationship really gives resistance (only the inertia of gas should be overcome by alveolar pressure, but this is minimal and can be denied at breathing frequencies not exceeding 120/min).
Also with the interrupter technique no correction for volume is necessary because no volume changes occur during this technique, so all pressure is applied to overcome respiratory system resistance. Interrupter resistance measurements are considered as only estimations of the resistance of the total respiratory system. Especially due to confounding variables and arbitrary choices that have to be made prior to the calculation of Rint, absolute Rint values have no general acceptance. With all other techniques only indirect resistances are measured[3,154].
Interrupter and oscillation technique, applied during tidal breathing, are not very burdensome. Therefore these techniques are suitable in both daily practice and in a laboratory setting or for research purposes. The availability of these techniques has come with devices, that are currently tested and presented by commercial manufacturers. Although this does encourage more widespread use of these techniques, it does not imply that standardisation of these techniques has been performed and e.g. reference values and a good relation to pathophysiology are available.
Several drawbacks of resistance measurements in young children can be mentioned. The paediatric lung is not a miniature of the adult lung and developmental changes significantly influence pulmonary function test results. Especially in infants with airway obstruction, airway occlusion does probably not lead to even distribution of airway pressure between mouth and alveoli. This might lead to inaccurate estimation or airway resistance.

Because specific techniques are only possible at specific ages or in specific patients (e.g. baby body box, squeeze jacket technique, airway occlusion technique) follow up studies using the same technique throughout life are nearly impossible. Until now no single pulmonary function test is applicable in spontaneously breathing children and adults of all ages. This impairs longitudinal studies on pulmonary function development from early infancy to late adulthood (i.e. "cradle to grave"). Many techniques are not yet standardised (interrupter technique, tidal breathing technique) and normal values are not available (for all patient/age groups). Comparison to the "gold standard" shows that the reproducibility is worse which impairs clinical applicability.

However, there are several aspects that make resistance measurements preferable.
In the first place, resistance parameters are measured during spontaneous quiet breathing, so without forced respiratory manoeuvres. Therefore these values might be more representative of normal breathing, i.e. daily life situations. Forced expiratory manoeuvres are hardly applied during all day activities, not even during exercise.
Secondly, resistance measurements and tidal breathing analysis require only passive co-operation and each measurement may be accomplished within short time. The methods are non-invasive, apart from a closely fitting mask, eventually equipped with a mouth piece. The general acceptance of these methods is therefore good among young children in whom the methods are used.
Thirdly, during childhood the most important pulmonary diseases have an obstructive character and especially peripheral airway resistance is better mirrored by resistance measurements in children than in adults. Also, changes after intervention or in disease are at least similarly reflected by these techniques compared to "gold standards".
Finally, most criteria for pulmonary function tests as mentioned in Chapter 1 are met by the interrupter resistance, forced and impulse oscillometry (and tidal breathing analysis). Therefore these are useful alternatives for objective evaluation of obstructive airway disease in children.

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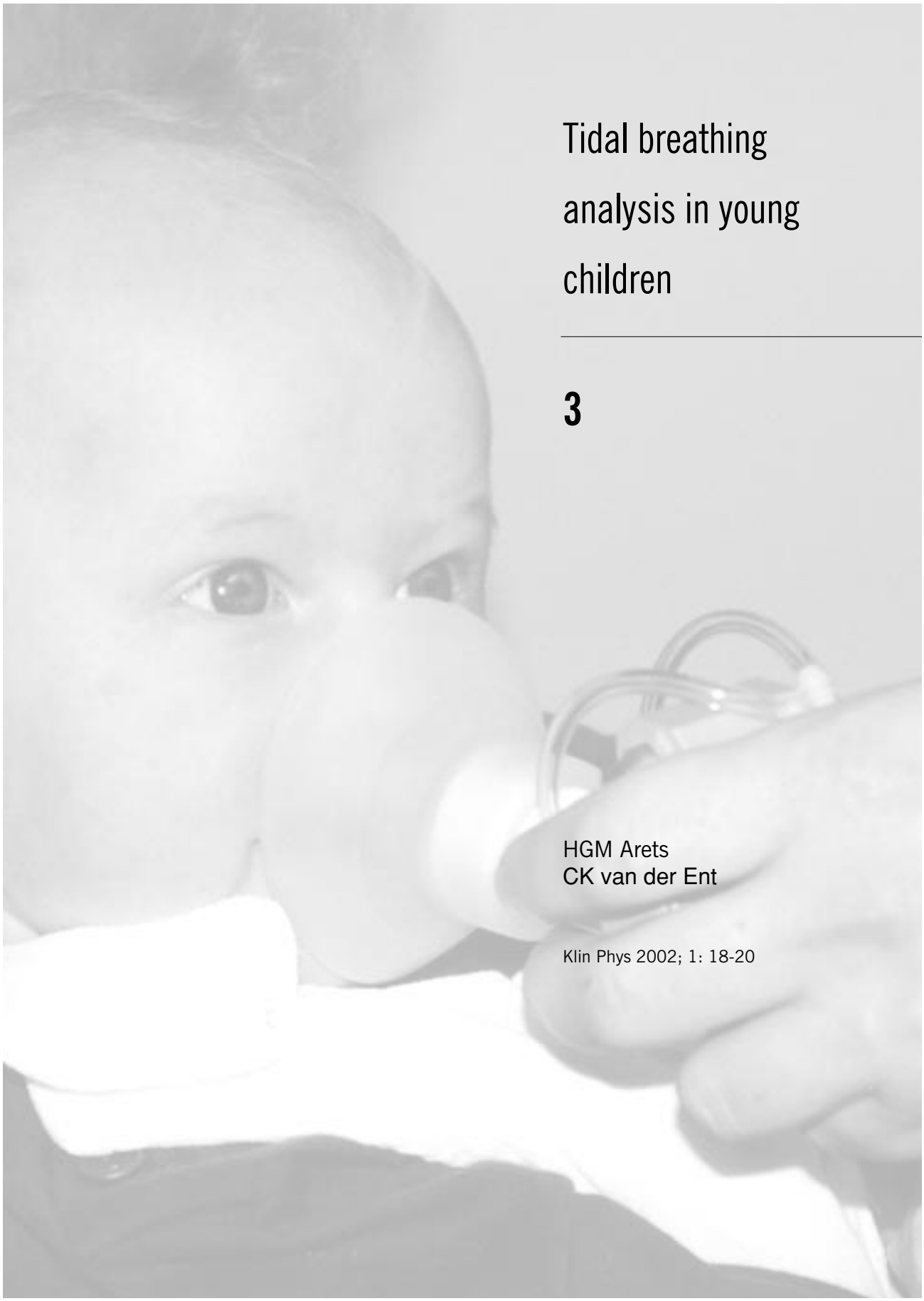

Tidal breathing analysis in young children

3

HGM Arets
CK van der Ent

Klin Phys 2002; 1: 18-20

Abstract

The shape of flow pattern during tidal expiration is influenced by peripheral airway obstruction. The time from the start of expiration to peak expiratory flow (*t*PTEF) divided by the total expiratory time (*t*E) is significantly decreased in children with asthma. Experimental studies in the cat have shown that the expiratory flow pattern is the result of mechanical properties of the respiratory system (resistance and compliance) and of post-inspiratory activity of inspiratory muscles. Computerised modelling of these mechanical and muscular properties during tidal breathing allows to derive the resistance and compliance of the respiratory system from the expiratory flow pattern.

Pulmonary function in young children

The increasing incidence of lower respiratory illnesses and wheezing in young children and the diverse aetiology of these complaints are a challenge to the clinician. Diagnosis and treatment of these children are often largely based on medical history and physical examination. Assessment and quantification of airflow obstruction can be helpful in the formulation of proper therapeutic strategies and follow-up of these patients. Several objective methods are available to evaluate pulmonary function in these young children. Lung volume can be measured with body plethysmography or with gas dilution techniques. Resistance and compliance of the respiratory system can be measured both non-invasively (passive deflation or oscillation techniques) and invasively (e.g. with an oesophageal balloon). Partial expiratory flow-volume curves can be obtained in young children using rapid chest compression techniques. All these techniques, however, are hard to apply in daily practice, because they require fully equipped research laboratories, are often only applicable under sedation and are (more or less) invasive.

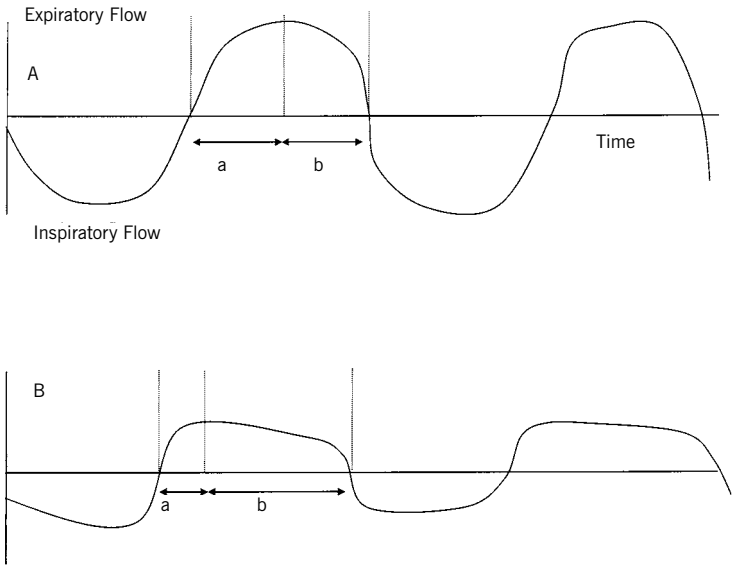

Figure 1. Representative recordings of tidal breathing flow over time in (A) a normal subject and (B) a patient with moderate airway obstruction. The ratio tPTEF/tE can be calculated as a/(a+b) x 100%. The ratio is decreased in patients with airway obstruction.

Tidal breathing analysis - historical perspective

The need for simple, objective methods to measure pulmonary function in young children led to several studies on the evaluation of tidal breathing patterns. In 1905 Ten Have was the first to describe differences in expiratory flow patterns between healthy persons and patients with obstructive lung disease: "The expiratory flow-curve in patients with asthma is particularly different from normal. At first flow increases rapidly, afterwards it decreases rapidly and eventually slowly reaches zero flow"[1] (Figure 1).
Later, in 1956, Bouhuys (in his thesis "Pneumotachography, the Clinical Significance of Respiratory Airflow Recording") was the first to describe the parameter *t*PTEF/*t*E, which was decreased in patients with asthma[2]. In this ratio, *t*PTEF is the time to peak tidal expiratory flow and *t*E is the total expiratory time. It was not until 1981 that Morris and Lane[3] showed renewed interest in the changes in expiratory flow patterns in patients with airway disease. They found significantly decreased values of *t*PTEF/*t*E in 51 adult patients with obstructive airway disease compared to 24 healthy controls. They also described a significant correlation between the parameter *t*PTEF/*t*E and FEV_1, the gold standard of airway obstruction[3].

Analysis of flow pattern in children

In 1980 the parameter *t*PTEF/*t*E as a measure of airway obstruction was also investigated in young children. The recording of flow patterns is easily performed in young children, using a mouthpiece or facemask and pneumotachograph. These measurements do not require active co-operation or co-ordination and children are allowed to breathe quietly while laying in bed or sitting upright.

In 1996 a study was performed in our centre to evaluate the validity of the ratio *t*PTEF/*t*E as a measure of airway obstruction in children[4]. In a group of 226 healthy schoolchildren (age 3-11 years) *t*PTEF/*t*E was measured. The mean value (43.0 ± 7.6%) was significantly higher compared to a group of 64 asthmatic children (30.0 ± 8.2%, $p<0.001$) (Figure 2). Moreover *t*PTEF/*t*E in children with asthma increased after bronchodilation and was

significantly correlated to other parameters of airway obstruction including FEV_1, MEF50 and MEF25[4]. These findings demonstrated that *t*PTEF/*t*E is related to airway obstruction not only in adults, but also in children.

Practical application of tidal breathing analysis

Although these findings were very promising, the application of tidal breathing analyses in daily practice was not easy. Although group analysis showed significant differences in mean *t*PTEF/*t*E values between healthy and asthmatic children there was a huge overlap of values in these groups, caused by a wide variation in normal values. That is why a single measurement in the individual patient does not allow to discriminate between healthy children and those with obstructive airway disease (Figure 2). Another disadvantage is the wide intra-subject variability of *t*PTEF/*t*E. The development of special software for on-line automatic data processing improved analysis of the tidal breathing pattern in children. Using this software a fast measurement of mean *t*PTEF/*t*E can be obtained from 20 breaths, thereby decreasing the intra-subject variability[5].
However, using the same software, it was difficult to record the tidal breathing pattern in each individual child for almost 1 minute. In daily practice this method appeared to be possible in infants using a facemask, and in children from the age of 2-3 years using a mouthpiece. In these children *t*PTEF/*t*E can be used as a measure of airway obstruction, especially when studying groups rather than individual children.

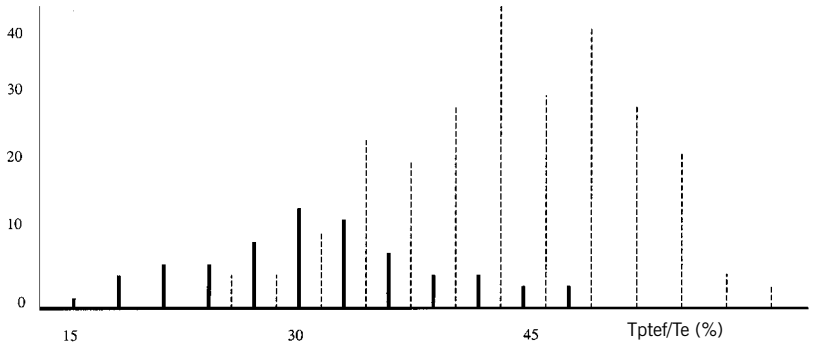

Figure 2. tPTEF/tE values in 226 healthy volunteer children (interrupted bars) and 64 patients with asthma (closed bars).

Physiological background of *t*PTEF/*t*E

The physiological background of *t*PTEF/*t*E was also studied[6]. It was assumed that the expiratory flow follows the laws of elasticity from the end of inspiration. This "lung-emptying curve" is characterised by the time-constant of the respiratory system (τ_{rs}), the product of flow resistance and compliance. At the start of expiration the expiratory flow during tidal breathing is decreased by the post-inspiratory activity of inspiratory muscles (especially the diaphragm). This muscle activity decreases exponentially, characterised by the time-constant of the muscle (τ_{muscle}). The expiratory flow can be considered the result of the elastic recoil pressure of the lung and the post-inspiratory muscle activity of the diaphragm. In this way the parameter *t*PTEF follows the equation[6]

$$tPTEF = (1/\tau_{muscle} - 1/\tau_{rs})^{-1} \ln (\tau_{rs}/\tau_{muscle})$$

In studies on cats, simultaneous measurement of flow patterns and muscle activity showed that real-life *t*PTEF-values significantly correlated with the values predicted by the above model[6].
Based on these observations it then was postulated that *t*PTEF/*t*E is not a direct representation of airway obstruction but especially a reflection of breathing control, expressing both the mechanics of airway and lungs (τ_{rs}) and the inspiratory muscle activity (τ_{muscle}). This explains why the relationship between *t*PTEF/*t*E and other parameters of airway obstruction is not always unequivocal.

Tidal breathing analysis, the future

The important disadvantages, described above, explain the diminished interest in the parameter *t*PTEF/*t*E in recent literature. However latest studies (unpublished data) have shown that this model can describe and analyse not only the single *t*PTEF/*t*E value in the expiratory flow volume curve but the complete expiratory flow pattern. The most important

parameters of this model are still the mechanics of airway and lungs (τ_{rs}) and the inspiratory muscle activity (τ_{muscle}). Therefore, very accurate recording of both τ_{rs} and τ_{muscle} can be obtained by recording the patient's flow pattern followed by computerised fitting of these data to the above-described model. Because τ_{rs} is the product of resistance and compliance of the respiratory system, this parameter can provide important information to the physician. When this technique is followed by expiration through an external known resistance, both resistance and compliance of the respiratory system can be calculated.

Summary

Tidal breathing analysis has been studied for almost 100 years. After a simple phenomenological description both animal and human studies have evaluated the parameter *t*PTEF/*t*E. The availability of a computerised lung model enables accurate description of the mechanics of the respiratory system. Although several disadvantages still exist, this technique has contributed significantly to our understanding of airway mechanics.

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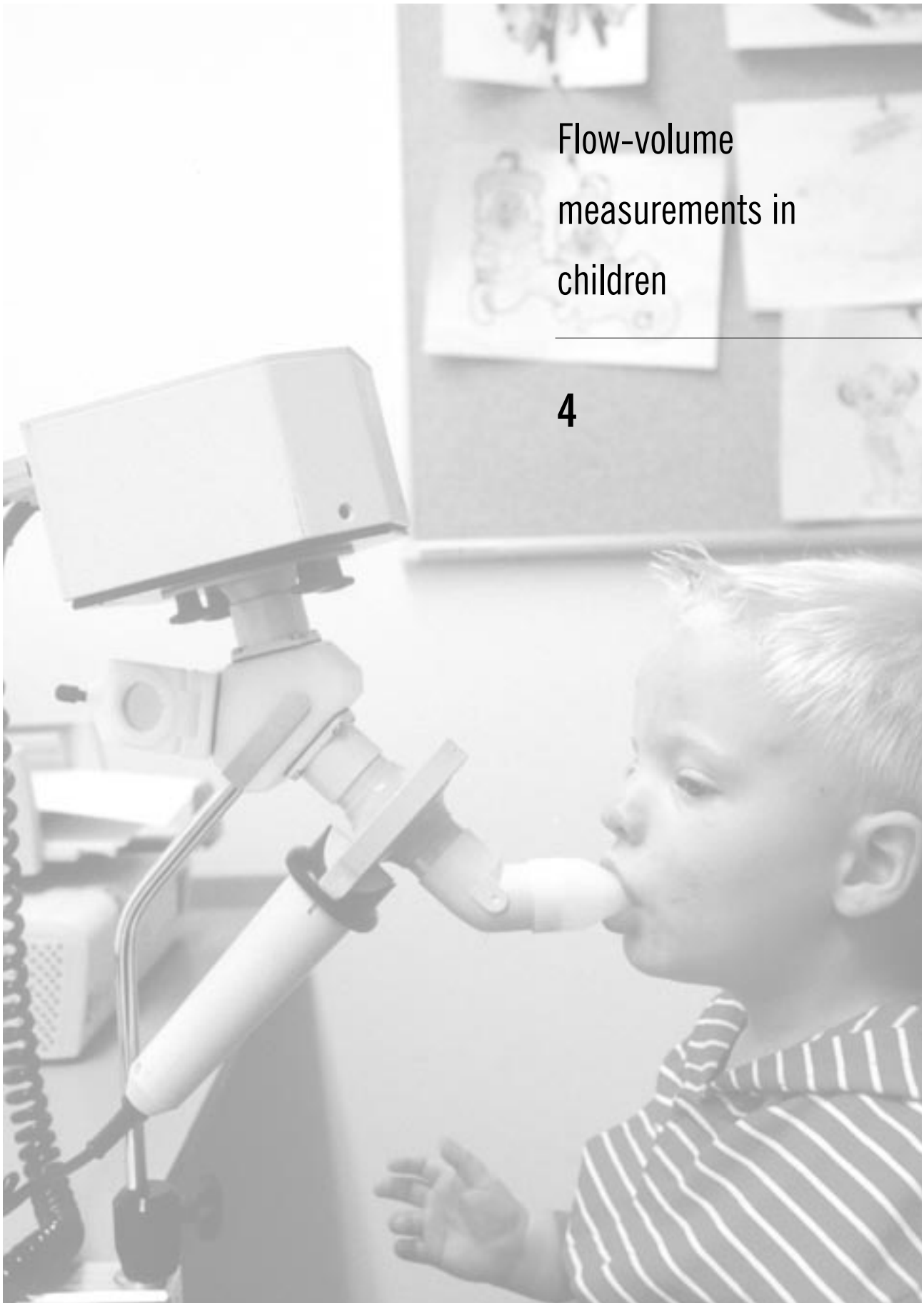
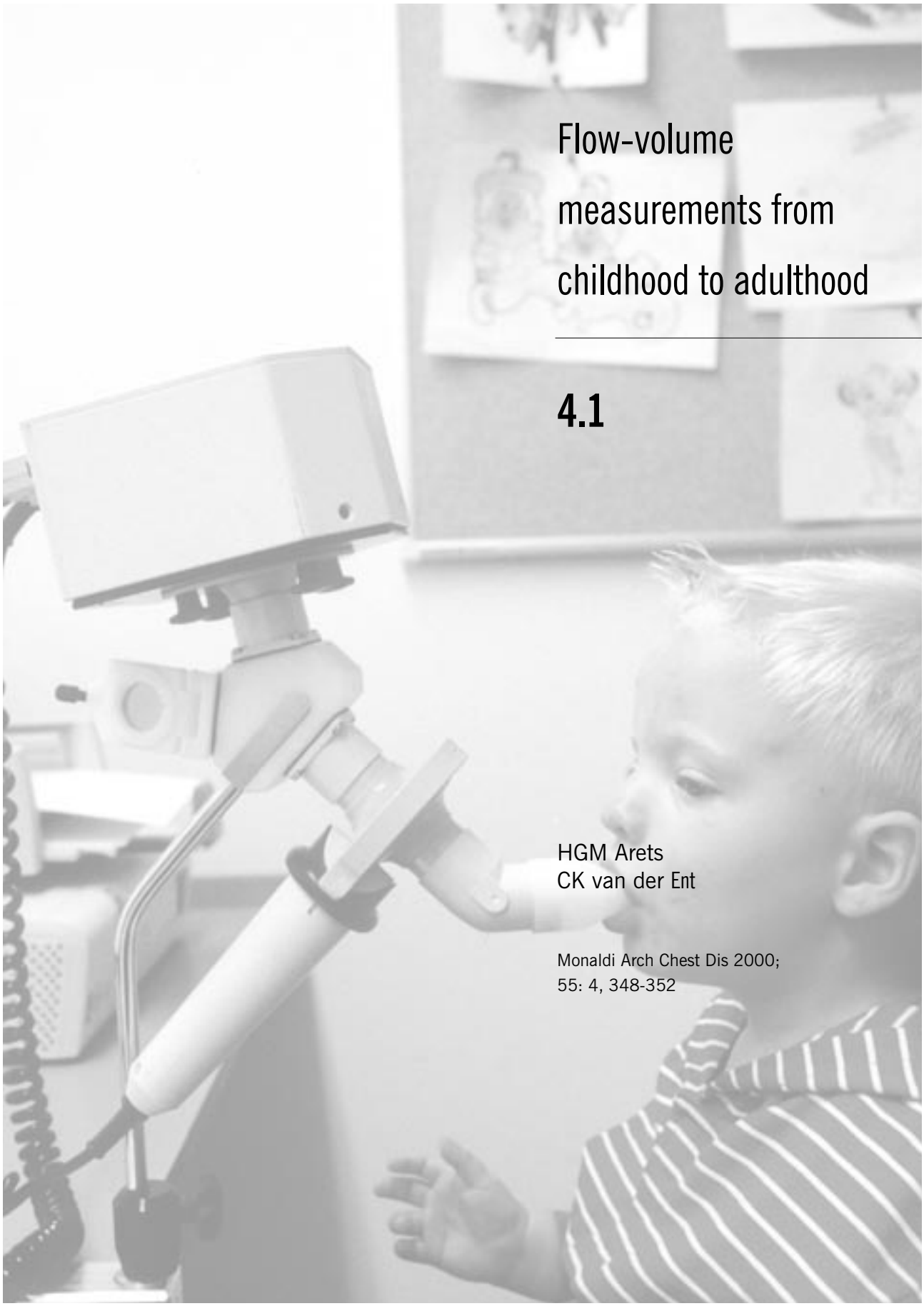


Flow-volume measurements in children

4



Flow-volume measurements from childhood to adulthood

4.1

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Monaldi Arch Chest Dis 2000;
55: 4, 348-352

Abstract

Flow-volume curves are the most frequently used pulmonary function test during childhood. Even pre school children are sometimes able to perform the maximal effort breathing techniques, required for this pulmonary function test. We report on the most important conditions for reliable measurement of flow-volume curves at all ages. Especially testing atmosphere and equipment, pulmonary function technician requirements, testing procedure, reliability criteria, report making and interpretation are discussed.

Introduction

Pulmonary function testing (PFT) provides an objective method to place a disease into physiologic proportions. The combination of medical history, physical examination and PFT can elicit a clinical diagnosis. In this way PFT does not make, but can confirm a clinical diagnosis, monitor response to therapy and follow progression of disease. The most commonly used test to objectivate lung disease is the flow-volume curve[1]. Results of flow-volume measurements can be presented graphically as flow-volume curves and as corresponding parameters of flows and volumes. More than hundred years after Hutchinson described spirometry, which still is the most basic PFT, the well-known flow-volume curve was described by Hyatt who plotted flow and volume on the y- and x-axes, respectively, of an oscilloscope[2]. This graphic display of results has advantages over the use of spirometry. Simple visual inspection of the flow-volume curve is very useful as a screening method for peripheral airflow obstruction (e.g. asthma), upper airway obstruction (e.g. vascular rings), or restrictive lung disease, although especially restrictive lung disease can not definitely be proven by flow-volume curves . Interpretation of the numeric data of flow-volume measurements, as described in Table 1 takes more time, is less convenient and is less informative compared to interpretation of the graphic flow volume curves of the same patients, as presented in Figure 1. International guidelines for this technique have been developed, in order to guarantee standardised performance and interpretation world-wide[3].

Table 1. Lung function test results (expressed as percentage of predicted values) in patients with various conditions: a patient with peripheral airway obstruction (A), with central airway obstruction (B), and restrictive lung disease (C).

	PEF	FEV_1	MEF50	MEF25	FVC
A	90%	60%	35%	25%	100%
B	65%	100%	95%	100%	100%
C	95%	60%	100%	100%	65%

Flow-volume curves of these three patients and a normal subject are shown in Figure 1.

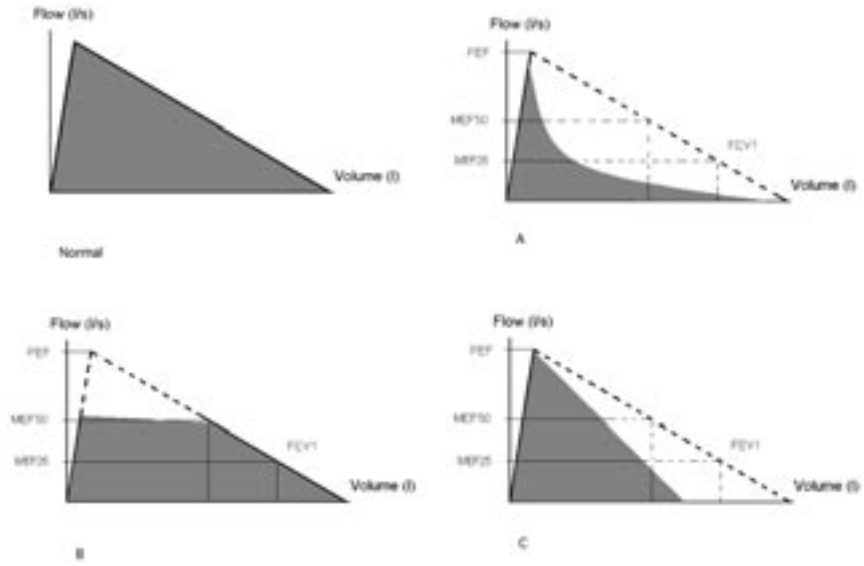

Figure 1. Artificial presentation of flow-volume curves in a normal subject and in a patient with peripheral airway obstruction (A), central airway obstruction (B), and restrictive lung disease (C). Numeric lung function test results of these patients are shown in Table 1.

Because of the relative simplicity to perform and to interpret flow-volume curves, this technique has widely entered paediatric practise. Respiratory diseases represent the most common cause of morbidity in childhood[4]. In the Netherlands every paediatrician treats some 500-600 asthmatic children each year, for general practitioners this is about 170 children per year[5]. Nowadays, the flow-volume curve is considered as 'gold standard' measurement for airway obstruction in children and many paediatric patients are tested in adult lung function labs. However, children are not small adults and a lot of child-specific items in the performance and interpretation of flow-volume curves can be overlooked, resulting in errors in diagnosis and treatment. This article reviews the most important differences in flow-volume measurement between children and adults.

Atmosphere

For many children the first visit to a pulmonary function laboratory can be considered as the beginning of a long (if not ever) lasting PFT career and "well begun is half done". At this stage many things in the lung function lab can cause anxiety or distract the child. That's why the testing area should be child-friendly and safe. No unpleasant experiences should be related to this area, so to test a child in the same area in which blood is drawn or painful examinations are performed will reduce the amount of co-operation and effort. The first contact with the lung function lab in children aged 5 to 7 years should be no more than a first acquaintance.

Working with children puts several requirements on the investigator. Pulmonary function technicians are often used to stress their adult patients to an utmost performance in a direct way. With children they should take time and pay special attention to welcome the child and to draw its attention from the beginning. They should be able to judge the developmental level of the patient and to explain and instruct the procedure in a catching way. A formal period of instruction and practice can enhance performance[6]. Not every technician is able to work with children. Therefore, it is advisable to have a special lab for children, or to have a limited number of technicians who are specifically trained for children in the adult lab. The importance of a calm, success-oriented environment with an experienced tester cannot be overemphasised.

Most young children have a short span of concentration which can interfere with good results. The technicians' custom to measure the next patient while the first is waiting for his bronchodilator effect can destroy the child's motivation to do it's best. Flow-volume measurements in children take much more time than in adults. For a routine flow-volume measurement with reversibility testing at least 30 minutes should be scheduled. When the management of the laboratory is not willing to take this time, children should not be measured.

Equipment

The lung function equipment should fit to children of several ages. This requires mouthpieces of different sizes to be available, permitting convenient closure of mouth and lips to every child. Improper mouthpieces can result in air leakage and can influence lung function results by changes in upper airway resistance[7] and by trigeminal nerve stimulation[8]. In adults most times a nose-clip is used. However, for flow-volume measurements this is not necessary and it can better be withheld from some children. The equipment should be height adjustable, to prevent flexion or extension of the neck because this can influence maximal expiratory flows[9]. It has been advised to keep the child's torso and head erect throughout testing in either sitting or standing posture[10]. When measuring in sitting position often a footstool to support the feet is necessary to facilitate maximal expiratory manoeuvres.

Paediatric pulmonary function test equipment should have low inertia, be responsive to small changes in volume and flow. Also it must provide reproducible results. This "technical reproducibility" is a conditio sine qua non. One of, if not the, most important reason to require optimal equipment reproducibility is the fact that in all day clinical practice each patient is his or her own reference for future measurements (e.g. after bronchodilation, challenge or treatment)

Most flow-volume equipment uses commercial software. Software programmes should be explicitly developed for use in children. Apart from the routine requirements for adults (e.g. for flow range, calibration and BTPS corrections) the software should be provided with child specific options. An on-line presentation of flow-volume curves improves co-operation and endurance. Also artefacts (e.g. coughing) can easily be discovered.

The user must have the ability to introduce data on gender, height and weight and should be able to choose the right reference values (see below). Reports of lung function tests must show a flow-volume curve with appropriate scaling of the axes (see below).

When children are measured in a lung function lab, devices for adequate measurement of weight and height have to be available. The growth velocity in children ranges between 5 an 12 cm per year. Important deviations in lung function test results can emerge when recent growth data are not implemented in the measurement. For example, a healthy 12 years old boy who showed a FEV_1 of 100% predicted at the age of 11, can show FEV_1 of

125% predicted when the technician fails to take and implement a current measurement of body height.

Children's performance of flow-volume measurements

The performance of a flow-volume curve implies an, especially for young children, relatively complicated manoeuvre, that requires maximal and forced expiratory and/or inspiratory efforts. In most cases of obstructive airway disease especially forced expiration parameters are desired. After a few tidal breaths the child is asked to inspire maximally from functional residual capacity to maximal inspiration, followed by a rapid, forced and complete expiration to residual volume. For detection of upper airway obstruction rapid, forced and complete inspiration follows maximal expiration. Pulmonary function technicians should support these maximal manoeuvres subjectively and control the child's effort with each testing.

Reliability criteria

For adults reliability criteria have been defined by the ATS and ERS societies[3]. Flow-volume measurements can be interpreted when the curve is technically acceptable and when it is reproducible (Figure 2). Criteria for technical acceptability and reproducibility are summarised in Table 2.
Although many authors state that children can perform reliable flow-volume measurements from the age of about 5 years[11], most children can not reach the above mentioned criteria. Kanengiser and Dozor reported that even most children aged 3 to 5 years of age are able to co-operate and perform forced expiratory manoeuvres, but they failed to test for reliability criteria[12].
Recent data from our own lung function lab showed that more than 90% of children aged 5 - 19 years can perform "technician accepted" flow-volume curves that reach the start-of-test criterion[13]. A flow-volume curve with a rapid rise to peak flow and a sharp peak, nearly always has a back extrapolated volume (Vbe, (see Chapter 4.2, Figure 1)) of less than 5% of FVC as defined by the ATS-ERS (Table 2). However, the end-of-test cri-

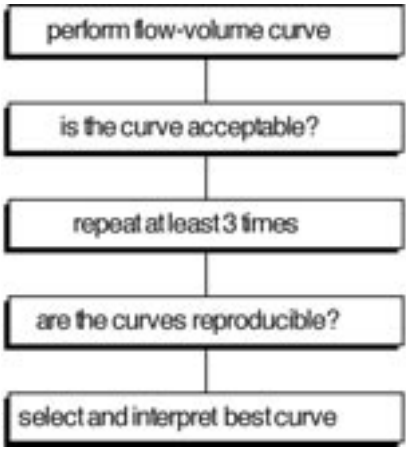

Figure 2. Algorithm for getting a reliable flow-volume curve according to ATS-ERS statement.

terion (exhalation time of more than 6 sec) was reached in only a small minority of patients. We suggested to lower the minimally required exhalation time to 1 second in children below 8 years of age and to 2 sec in older children[13].

A minimum of three technically acceptable manoeuvres should be repeated in order to judge reproducibility of the measurement (Figure 2). We have shown that the ATS-ERS reproducibility criteria (i.e. a difference between

Table 2. Criteria for acceptability and reproducibility of flow-volume curves as defined by ATS-ERS.

Curve is acceptable if:
- Vbe is less than 5% of FVC *or* less than 0.15 l
- Exhalation time is more than 6 sec
- No more volume change during 1 sec
Curve is reproducible if:
- difference between highest and next highest FVC < 200 ml
- difference between highest and next highest FEV_1 < 200 ml

the highest FVC/FEV_1 and the next highest FVC/FEV_1 less than 200 ml) is not suitable for children. Especially in young children with small lung volumes, this criterion can easily be met despite considerable variability. A difference between highest and next highest FVC or FEV_1 values of less than 5% would be a more appropriate criterion for reproducibility in children[13].
After assessing technical acceptability and reproducibility the best flow-volume curve is defined as the curve with the highest sum of FEV_1 and FVC. This best curve can be used for interpretation (Figure 2).

Reference values

In general numeric results of flow-volume measurements are compared with reference values and are expressed as percentage of reference value, also called percentage of predicted. To be able to judge to what extent the reference values are acceptable in a particular situation, information is required about the population from which they are derived, and the circumstances during the measurement. Lung function results largely depend on height, gender and race of the patient.
During childhood, especially during puberty, lung growth is not linearly related to height. It is definitely incorrect to extrapolate reference values form adult populations to paediatric values. Figure 3 shows that important differences exist between different reference value data sets. The figure shows that a healthy boy with a height of 130 cm and a FEV_1 value of 1,5 l has a predicted value ranging from 68 - 107 %, depending which reference data set is used. These findings show that it is extremely important to use an adequate reference value data set. Reference value data sets are most often obtained from relatively small groups of children and/or adults who are considered to be free from disease or circumstances, that influence testing (pulmonary disease, smoke (or other irritant) exposure, viral infections, etc.). These value sets are reduced to simple regression equations with standing height as the only independent variable.
The reference population should match the patient with regard to sex, age, weight and height, genetic, ethnic and social background, and geographical location[17].
Unfortunately such reference values are not available in all countries and one should use the 'best fitting' population. In most modern lung function

measurement software a panel of reference value data sets is available.
In lung function laboratories for adults, the risk for the use of wrong reference values for children is more than imaginary when the lab is visited by children only incidentally. Measurement of current height and selection of the most adequate reference value data set should be a standard operating procedure in every lung flow-volume measurement in children. Ideally paediatric normal values are included in the software.

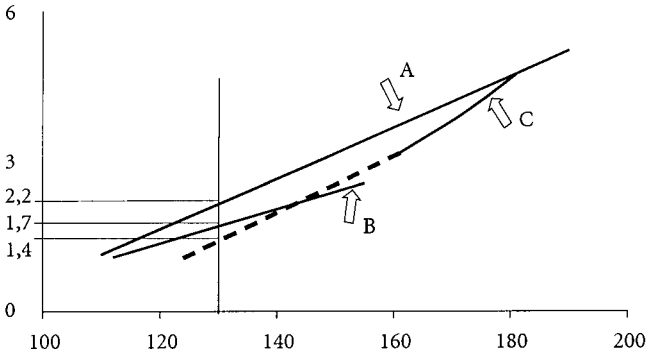

Figure 3. Regression curves of 3 different sets of predicted values for FEV_1 in boys. A healthy boy with a height of 130 cm and a FEV_1 value of 1,5 l has a predicted value of 68% according to set A[14] (100% =2.2 L), of 88% according to set B[15] (100% =1,7 L) or of 107% according to the extrapolated set of values in adolescents in regression line C[16] (100% =1,4 L).

Report making

Reports of paediatric flow-volume measurements should not be printed at adult settings. Because, as stated above, the visual inspection of the curves is the most important part of the interpretation of the test, curves should be printed in a standardised way. The optimal way is to print the flow-volume curve as large as possible, with the smallest possible scaling of the flow- and volume axes in a 2 to 1 ratio (Figure 4). Discrete bronchial obstruction can be easily overlooked when the flow-volume curve is printed too small, or when the axis scales are too large (adult sizes in young children). When the

axes are changed in the computer software, the 2 to 1 ratio for flow and volume should be maintained in order to prevent changes in the shape of the curve which can lead to misinterpretations (Figure 4).
In most young children it is very difficult to perform both inspiratory and expiratory flow-volume curves in the same manoeuvre. Because most times the lung function technician will focus on the expiratory manoeuvre, it is advisable to print only the expiratory curves in order to prevent the interpretation of non-informative inspiratory curves.
The numeric data on the paediatric lung function report should be relevant and concise. In young children it is sometimes more relevant to print out $FEV_{0.5}$ values in stead of FEV_1 values. A main restriction is that, to our knowledge no normal values for $FEV_{0.5}$ are available. With the increasing use of flow-volume curves in pre school children this should be a main objective of further research. Inspiratory parameters should be left out if the inspiratory manoeuvre was not explicitly performed. Adequate reference value data for the different parameters should be given together with the parameters as percentage of predicted. For lung function parameter ratios

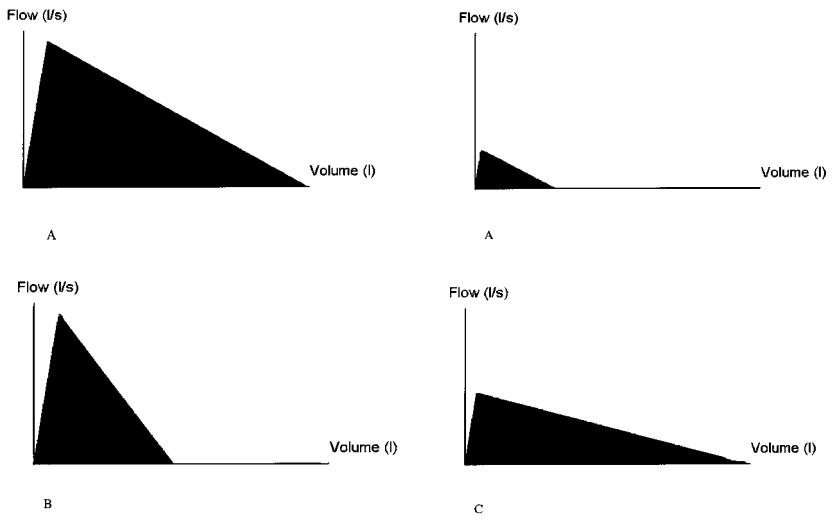

Figure 4. Flow-volume curves of a healthy child printed with wrong axis-scaling. Discrete abnormalities can be overlooked when scales are too large (A) or misinterpretation can occur as restrictive lung disease (B) or upper airway obstruction (C) when scales are not printed in the standard 2 to 1 ratio for flow and volume.

(e.g. FEV_1/FVC) no percentage of the reference value should be calculated, because a percentage of a percentage is most often not informative.

Use of incentives

During the last years several computerised visual incentives have been developed to stimulate young children to perform maximal forced breathing manoeuvres. For example, children are stimulated to blow out burning candles on the computer screen[18] or to ring the bell by blowing up a balloon in the hands of a clown. Such programmes can be very helpful in the instruction of young children. The use of a programme with burning candles was proven to be helpful in 4 to 6 years old children[18].
When visual incentives are used, it is important to realise what is the trigger of the incentive. Incentives can be triggered by PEF, FVC or both. When incentives are triggered by e.g. PEF alone this can have unfavourable effects on other parameters, because children tend to stop their manoeuvre as soon as they have triggered the incentive[19]. In general, incentives are useful to instruct the manoeuvre, but they do not improve the results. Therefore, they should not be used in children who can perform forced breathing manoeuvres without these tools.

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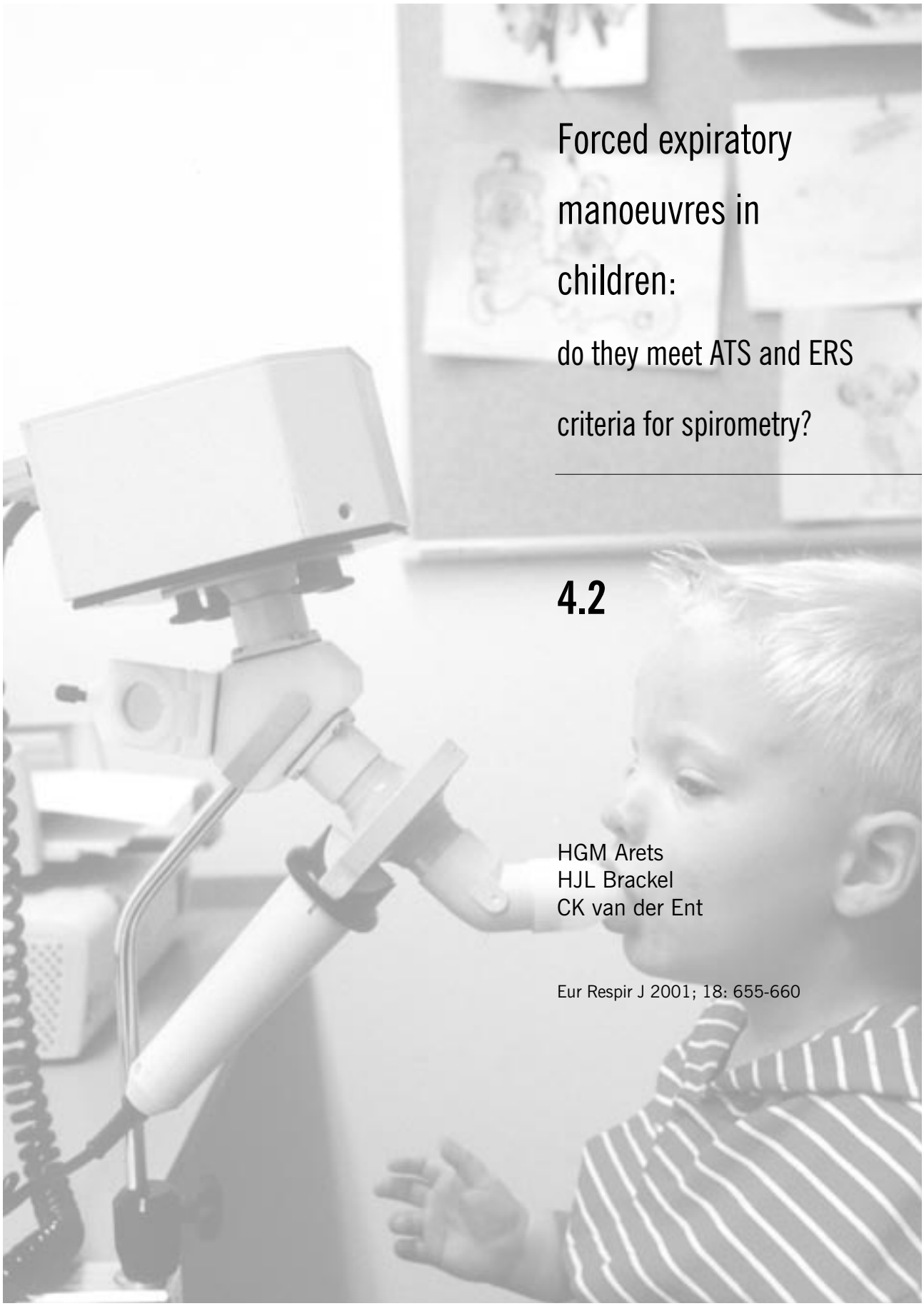

Forced expiratory manoeuvres in children:

do they meet ATS and ERS criteria for spirometry?

4.2

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Abstract

The aim of this study was to evaluate the applicability of ATS and ERS criteria for spirometry in children.

Methods: We studied maximal expiratory flow volume (MEFV) measurements of 446 school-age-children, experienced in performing MEFV manoeuvres and applied to these manoeuvres acceptability criteria (start-of-test (backward extrapolated volume as a percentage of FVC (Vbe%FVC) or as absolute value (Vbe)) and end-of-test (forced expiratory time (FET)) and reproducibility criteria (absolute and percentual difference between best and second best FVC and FEV_1 (dFVCabs, dFVC%, $dFEV_1$abs and $dFEV_1$%)).

Results: The Vbe%FVC criterion was met by 91.5%, the Vbe <0.15L criterion by 94.8% and the Vbe<0.10L by 60.1% of children. Vbe <0.15L appeared to be a more useful parameter than Vbe%FVC. The FET criterion was met by only 15.3% of children. dFVCabs<0.2L and $dFEV_1$abs<0.2L were met by 97.1% and 98.4% and dFVCabs<0,1L and $dFEV_1$abs<0,1L by 79.8% and 84.3% of the children respectively. These criteria appeared to be less useful compared to percentual criteria (dFVC% and $dFEV_1$%).

Conclusions: Even experienced children do not meet all international criteria for spirometry. However, most of their MEFV curves are useful for interpretation. Based on the performance of these children, we propose a re-evaluation of criteria for MEFV measurements in children.

Introduction

Maximal expiratory flow volume (MEFV) measurements were introduced as a valuable tool in the assessment of respiratory disease in 1947[1]. Since then MEFV measurement has become the cornerstone of pulmonary function testing (PFT) and the most widely used tool in diagnosis and follow up of both adults and children with respiratory illness.
However, for young children, the technique of MEFV measurement is often more complicated, because they may lack co-ordination and co-operation. For these children, especially those under the age of 7 years, the instruction and performance of MEFV manoeuvres can be facilitated by the use of computerised visual incentives[2]. In everyday practice MEFV curves are judged to be acceptable when they show a rapid rise to peak flow at the start and a subsequent gradual decrease of flow during the rest of the maximally prolonged expiratory manoeuvre. However, criteria as described by the ATS[3] and ERS[4] for acceptability and reproducibility of MEFV manoeuvres are lacking for (young) children. A summary of these criteria is

Table 1. Criteria for acceptability and reproducibility of MEFV curves as stated by the ATS[3] and ERS[4].

Acceptability

Start of test criteria:

- Vbe%FVC < 5% or Vbe < 0.15 L (whichever is greater) (ATS)
- Vbe%FVC < 5% or Vbe < 0.10 L, (whichever is greater) (ERS)

End of test criteria:

- FET > 6 seconds (ATS)
- Exhaustion of patient or plateau in volume-time curve (no volume change during 1 second) (ATS and ERS)

No coughing, Valsalva manoeuvre or hesitation (ATS and ERS).

Reproducibility

- dFVCabs < 200 ml and $dFEV_1$abs <200 ml (ATS)
- dFVC% <5% or dFVCabs <100 ml (whichever is greater) and $dFEV_1$% <5% or $dFEV_1$% <100 ml (whichever is greater) (ERS)

shown in Table 1. In daily practice, when children perform computer controlled MEFV manoeuvres, the ATS or ERS criteria will be indicated most times as being not reached.
We investigated whether children with experience in lung function testing meet acceptability and reproducibility criteria for MEFV manoeuvres as defined by the ATS and ERS, during routine PFT. For criteria that were not met by these children, new criteria are proposed.

Patients and methods

All MEFV measurements were performed using a pneumotachometer system with a heated Lilly head (MasterScreen Pneumo and Jaeger Masterlab, Erich Jaeger, Würzburg, Germany). Equipment calibration was performed conform ECSC (European Community for Steel and Coal) guidelines[4]. All measurements were BTPS corrected. Measurements were performed with the child sitting straight and wearing a nose clip. Only pre-bronchodilator manoeuvres were evaluated.
Most patients were known with recurrent respiratory symptoms, mostly due to obstructive pulmonary disease such as asthma and cystic fibrosis or recurrent pulmonary infections. A minority of patients were seen preoperatively (e.g. for scoliosis, pectus excavatum) or after chemotherapy.
In the period between January 1997 and January 1999 852 children (436 boys) performed 8388 MEFV tests at the PFT laboratory. We selected all children who were experienced in performing MEFV measurements, i.e. they had previously performed MEFV manoeuvres on at least two earlier occasions. The children were optimally encouraged and performed, after full inspiration, a maximally forced and prolonged expiration. Their MEFV manoeuvres were acceptable, according to our trained and experienced pulmonary function technicians, when the flow-volume curves showed: 1) a rapid rise to peak flow and 2) a full, maximally prolonged expiratory curve, shown by a gradual, asymptotic approach of the curve to the volume axis. If necessary, especially for the first MEFV tests in young children, a computerised visual incentive was used to stimulate this manoeuvre. This consisted of a peakflow triggered series of burning candles on the computerscreen[2]. All MEFV curves with a gradual rise to peak flow, with blunt peaks and/or with sudden end expiratory drop of flow to the volume axis

Table 2. Patient characteristics: mean values (SD, range).

Male/female	234/212
Age (years)	12.1 (3.5, 5-19)
Weight (kg)	43.3 (15.8, 17-83)
Height (cm)	151.2 (17.9, 107-188.5)
FEV_1%pred	95.5 (25.0, 26.5-155.0)
FVC%pred	95.6 (20.1, 28.4-142.6)
FEV_1%FVC	83.6 (11.1, 44.5-100)

were not accepted for further evaluation. All children performed at least three technician-accepted curves and for each child the two curves with the highest sum of FVC and FEV_1 during the last PFT were used for final analysis[5].

Finally, we could evaluate 446 children (age range 5-19 years) who had performed MEFV manoeuvres on an average of 16.7 occasions. Patient characteristics are given in Table 2.

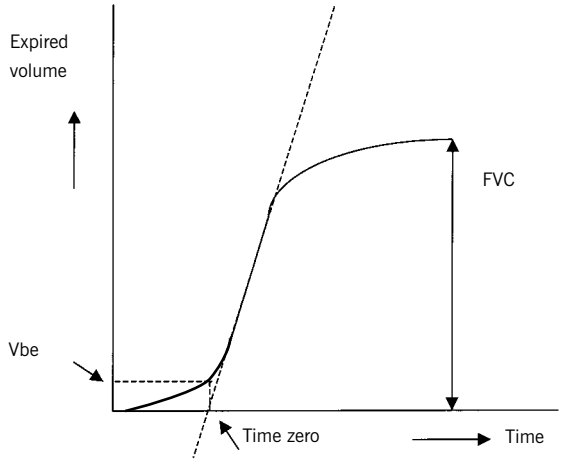

Figure 1. Method to determine the backextrapolated volume (Vbe) from a volume-time curve. Vbe should be <5% of the FVC to represent an acceptable start of forced expiration.

We evaluated whether these technician-accepted curves met the ATS and ERS criteria[3,4] for acceptability and reproducibility (Table 1): backward extrapolated volume (Vbe) as an absolute value and as percentage of FVC (Vbe%FVC) (Figure 1) for the start of test and the forced expiratory time (FET) for the end of test. The best value of the two curves of each patient was used for evaluation of acceptability criteria. Reproducibility was evaluated by the absolute and percentual difference between forced vital capacities (dFVCabs and dFVC%) and the absolute and percentual difference between forced expiratory volumes in 1 sec ($dFEV_1$abs and $dFEV_1$%) of the two best curves out of a minimum of three curves per individual.
Time to peak flow (tPEF) as start of test criterion, mentioned in earlier standardisation reports[6] but not accepted in later consensus reports[3], was also analysed.
All values of ATS and ERS criteria were also related to age, height, gender and pulmonary function results. In order to be able to propose new criteria we calculated the values that could be achieved by 90% of the children studied.

Statistical analysis

Mean values (SD, range) were calculated for all criteria. Correlations between criterion values and age, height and pulmonary function were studied with Pearson's correlation coefficients.
Differences between separate groups were analysed using unpaired t-tests. A p-value < 0.05 was considered statistically significant.

Results

Results for the different criteria are given in Tables 3 and 4.

Acceptability criteria: start of test

Vbe%FVC

The Vbe%FVC was < 5% in 91.5% of all patients. The mean best Vbe%FVC was 3.3 (+1.7, 0.7-9.5)% (Table 3 and 4). The Vbe%FVC was weakly though significantly related to height, age and pulmonary function (Table 4). 77.2% of children under the age of 8 years was able to reach this criterion (Table 3 and 4).

Table 3. Percentages of 'technician-accepted' MEFV curves that meet the ATS and/or ERS acceptability and reproducibility criteria.

Criterion	<8yr. (n=36)	8-11yr. (n=175)	12-15yr. (n=146)	>15 yr. (n=89)	Total (n=446)
Vbe%FVC < 5%	77.2	80.6	91.7	96.5	91.5
Vbe < 0.15L	97.5	95.6	94.5	85.4	94.8
Vbe < 0,10 L	77.8	61.7	59.6	50.6	60.1
tPEF < 0.1sec	75.3	77.8	89.9	92.0	84.7
FET > 6sec	8.6	13.3	15.6	36.0	15.3
dFVCabs < 200ml	100	99.5	94.5	95.5	97.1
dFVCabs < 100ml	91.7	85.7	74.7	70.8	79.8
dFVC% < 5%	82.7	89.8	85.6	89.5	87.9
$dFEV_1$abs < 200ml	100	99.0	98.2	97.5	98.4
$dFEV_1$abs < 100ml	91.7	90.9	78.1	79.8	84.3
$dFEV_1$% < 5%	91.4	85.7	87.2	88.5	87.2

Table 4. Mean values (SD, range) of ATS and ERS acceptability and reproducibility criteria, gender differences and Pearson's correlation coefficients (R) for age, height and pulmonary function.

Criterion	Mean(SD, range)	Age	Height	Gender	FEV_1%pred	FVC%pred	FEV_1%FVC
Vbe%FVC(%)	3.3 (1.7, 0.7-9.5)	-0.30**	-0.45**	n.s.	0.15*	0.23**	0.14*
Vbe(l)	0.09 (0.03, 0.04-0,24)	0.14*	0.27**	n.s.	n.s.	n.s.	n.s.
tPEF(sec)	0.07 (0.03, 0.01-0.22)	-0.28**	-0.28**	n.s.	n.s.	n.s.	0.17*
FET(sec)	4.3 (2.5, 0.5-18.7)	0.30**	0.20**	n.s.	0.50**	0.20	0.72**
dFVCabs(ml)	58 (50, 0-280)	0.19**	0.30**	n.s.	n.s.	n.s.	0.14*
dFVC%(%)	2.3 (2.1, 0-10.7)	n.s.	n.s.	n.s.	0.29**	0.24**	0.19**
$dFEV_1$abs(ml)	51 (50, 0-330)	0.20**	0.28**	n.s.	n.s.	n.s.	n.s.
$dFEV_1$%(%)	2.5 (2.7, 0-14.6)	n.s.	n.s.	n.s.	0.31**	0.28**	0.18**

*n.s. = not statistically significant; * = $P < 0.01$; ** = $P < 0.001$*

Vbe

The Vbe was < 0.15 L in 94.8% of the children. The mean best Vbe was 0.09 (0.03, 0.04-0.24)L. The Vbe was significantly related to height and age (Table 4).

tPEF

A tPEF < 0,10 sec was seen in 84.7% of all children. Mean tPEF was 0.07 (0.03, 0.01-0.22) sec. tPEF was significantly inversely related to height and age, with better results in older children (Table 3 and 4).

Acceptability criteria: end of test

FET

During maximal stimulation the maximal forced expiratory time (FET) was < 6 sec in 84.7% of all children. Mean FET was 4.3 (2.5, 0.5-18.7) sec. There was a significant relationship of FET with age and height, but especially with parameters of airway patency (Table 4).

Reproducibility criteria

dFVCabs

The absolute difference between the two highest FVCs (dFVCabs) was < 200 ml in 97.1% of children. The mean dFVCabs was 58 (50, 0-280) ml. dFVCabs was significantly related to age and height, but not to gender (Table 4).
All patients in the youngest age group and 95.5% in the oldest age group met this criterion (Table 3).

dFVC%

dFVC% < 5% as a criterion for reproducibility was met by 87.9% (Table 3) of children. Mean dFVC% was 2.3 (2.1, 0-10.7)%. In the older age group a higher proportion of the children reached the criterion, but correlation with both height and age was not statistically significant. There was a weak, although significant correlation between pulmonary function and dFVC% (Table 4).

$dFEV_1abs$

Differences between the two highest FEV_1's ($dFEV_1abs$) were < 200 ml in 98.4% of all children. All patients in the youngest age group and 97.5% in the oldest age group met this criterion (Table 3). The mean $dFEV_1abs$ was 51 (50, 0-330) ml. The $dFEV_1abs$ was significantly related to age and height (Table 4).

$dFEV_1\%$

The percentual differences between the two highest FEV_1s ($dFEV_1\%$) were < 5% in 87.2% of the children (Table 3). The mean $dFEV_1\%$ was 2.5 (2.7, 0-14.6)% and there was no significant correlation with height or age, but a weak, although significant, correlation with pulmonary function (Table 4).

Feasibility

Table 5 gives the values of the different criteria, achievable by 90% of the children. The end of test criterion of FET > 6 sec is the least feasible criterion, especially in the younger age group (Table 3).

Table 5. Cut-off points for acceptability and reproducibility criteria for values which can be achieved by 90% of the study population.

Criterion	<8 yr. (n=36)	8-11 yr. (n=175)	12-15 yr (n=146)	>15 yr. (n=89)	Total (n=446)
Vbe%FVC (%)	6.4	5.8	4.6	4.2	5.4
Vbe (L)	0.11	0.12	0.12	0.16	0.13
tPEF (sec)	0.11	0.12	0.10	0.09	0.11
FET (sec)	1.3	2.1	1.8	2.1	1.8
dFVCabs (ml)	83	101	159	150	127
dFVC% (%)	5.0	4.9	5.6	4.7	5.3
$dFEV_1abs$ (ml)	60	92	128	136	110
$dFEV_1\%$ (%)	4.7	6.3	6.7	5.4	6.2

Discussion

The majority of the children studied could perform acceptable flow-volume manoeuvres according to the ATS and ERS start-of-test criteria, but only a minority of the children exhaled as long as required by the ATS, notwithstanding the curves were judged to be acceptably performed. When the absolute difference in FVC or in FEV_1, as proposed by the ATS, was taken as a criterion of reproducibility, this was easily met by the majority of children. Despite these findings, most of the criteria showed dependency of age and height, which precludes the applicability of these criteria for children of all ages. In children we consider absolute criteria to be less suitable, especially when they are age dependent and designed for adults. The focus should be on the applicability of relative criteria which are designed to control for changes in the absolute magnitudes of measurements with (pulmonary) growth. Apart from growth, in childhood many other factors may influence the results of pulmonary function testing, such as time and patience of the PFT technician, equipment, use of incentives and disease state. To perform acceptable and reproducible MEFV manoeuvres the child should be able to blow out forcefully, immediately after maximal inhalation, and to continue forced expiration until no further air can be expired. The instruction and control of technique, combined with sufficient patience requires a well-trained pulmonary function technician, able to cope with and to encourage children and able to judge the expiratory process[7]. Several groups reported successful MEFV measurements in young children. Kanengiser and Dozor reported that many 3-5 year old children are able to co-operate and perform rudimentary forced expiratory manoeuvres that are reproducible, but reliability could not be assumed and hardly any MEFV curve met the ATS criteria for acceptability[8]. Le Soeuf and colleagues found that children can perform adequate forced expiratory manoeuvres from the age of 4-5 years[9].

The present study investigates the applicability of the currently officially accepted reliability criteria, as defined by the ATS[3,5] and the ERS working groups[4].

Start of test criteria

In young children the initial efforts to produce a sharp peak flow are often not very rapid in onset. The present study shows that with guidance of a well-trained technician the majority of experienced children can reach the current start-of-test criteria.
In earlier reports on spirometry criteria, tPEF was described as a start of test parameter[6]. If applicated, a good start of the forced expiratory manoeuvre (i.e. tPEF < 0.10 sec) was seen in 84.7% of children. For PEF meters the use of dwell and rise time for PEF as recently described by Miller et al. needs further study and has not been used in MEFV manoeuvres in children[10]. Their results showed that especially males and asthmatics have shorter "start times" compared to women and non-asthmatics. In the present study the percentage of children who reached a peak flow within 0.1 second was rather low compared to the current ATS and ERS start of test criteria and therefore would exclude MEFV measurements in a considerable number of children. Therefore, our study supports the former recommendation not to use tPEF as a criterion of acceptability.
Our study indicates that the subjective criterion of a 'rapid rise to peak flow', often estimated by eye by pulmonary function technicians, is sufficient to select acceptable curves. Optimally, criteria for acceptability should be independent from age or height. However, our data show that none of the ATS start-of-test criteria are independent from growth. Age and height are negatively correlated with Vbe%FVC and positively correlated with Vbe. This can be explained by the rise in FVC during growth.
The parameter Vbe, although an "absolute" parameter, is most independent from age and height and therefore this parameter seems to be the most appropriate start-of-test criterion. The Vbe < 0.15 L criterion was met by over 94.5% of children under the age of 15 years and 85.4% of children aged 15 years and older (Table 3). The ERS criterion of Vbe < 0,10 L excludes up to 50% of MEFV curves in older children. We suggest to adjust the advised minimal Vbe to 0.12 L in children aged < 15 years; in that case 90% of children would be able to reach the acceptability standard (Table 5).

End of test criteria

The second part of the MEFV manoeuvre was far more difficult to perform for children. The ATS criterion for acceptability demands a minimal FET

of 6 sec, unless there is an obvious plateau in the volume time curve display. The ATS recommendations state that in children shorter exhalation times are acceptable, but fail to be more specific[3]. The ERS working group does not present numeric criteria for maximally prolonged expiration[4]. In this study all children had extensive experience with lung function testing and were maximally encouraged to reach complete exhalation. Nevertheless only 36% of the oldest age group in our study exhaled for over 6 seconds. Although mean FET rises with age, even adolescents not always exhaled (forcefully) during more than 6 seconds, making this criterion unsuitable for use in paediatric practice.

Desmond et al found comparable results. In their study a minimal FET of 6 seconds was reached by 28% and 7% of children over and under the age of 7 years respectively[11]. In contrast a recent study by Enright et al. showed that display of a real time tracing of exhaled volume versus time, used to stimulate subjects and PFT technicians, allowed higher FETs in children over the age of 9 years. However, start-of-test criteria were less easily reached, compared to our group of children. These results show that the use of a particular device will enable more children to satisfy specific criteria but probably not all criteria. In our study we considered a complete expiration and not an exhalation time of 6 seconds as the goal of MEFV measurement. We endorse the statement of Enright and co-workers that underestimation of the FVC is not clinically very important when monitoring children with obstructive pulmonary disease[12]. Therefore, when necessary, especially in inexperienced and young children, we recommend the use of computerized visual incentives that visually stimulate especially a rapid and forced start of maximal expiration such as images of burning candles[2].

Warwick et al. described that young children may empty their lungs within 1 sec because of small lung volumes[13]. This causes the FEV_1 to be equal to FVC and could reduce the usefulness of FEV_1 and FEV_1%FVC as an index of airway obstruction. Kanengiser stated that for this age group the $FEV_{0.5}$ could be more appropriate for determination of airway obstruction[8].

As could be expected the degree of airway obstruction was positively related to the FET. The correlation of FET with age was more evident than with height (Table 4), which suggests that apart from lung volume also ageing, and therefore probably effort and co-operation, influences FET.

Although Enright et al. found better results[12] using specific stimulation one may question how many adults can reach this FET criterion during routine pulmonary function testing.

In our study we defined time criteria which were reached by 90% of children. Assuming that the flow volume curve shows no abrupt termination of expiratory flow and/or the volume time curve shows a plateau (Table 5) we propose to decrease the minimal FET to 2 seconds for children over the age of 8 years and to 1 second for children under the age of 8 years. Other researchers suggested to take 3 sec[11] or 4 sec as goals for exhalation times. Our data show that when children reach a FET of at least 2 seconds, this confirms a maximal effort in more than 90 percent of children.

Reproducibility

In our study the children, especially the younger ones, had no problems in meeting the "absolute volume" criteria for reproducibility (Table 3). This is to be expected because of small lung volumes in children, but does not guarantee reproducibility. Reproducibility criteria using absolute differences for both FVC and FEV_1 are significantly influenced by age and height (Table 4). Criteria using the relative difference as mentioned by the ERS[4] are not correlated with either age or height and therefore seem to be more appropriate in paediatric practice. The 5% difference criteria was reached by 87.9% and 87.2% of children for FVC and FEV_1, respectively (table 3). Increasing these numbers to 90% would require a cut-off point of 5.3% for FVC and 6.2% for FEV_1 (Table 5). The current 5% criteria seems to be more useful in childhood than the absolute criterion of 100 or 200 ml.
It should be stressed that all children in our study were experienced with MEFV manoeuvres. Most children underwent regular PFT during visits to the outpatient clinic. The mean number of PFTs performed by the children before the study was rather high. This means that for inexperienced children several attempts may be necessary to reach the same skills and results. As it could be the start of a "pulmonary testing career" that may last for many decades in children with chronic respiratory symptoms it is important for inexperienced children to become familiar with the procedure and especially use the first laboratory visits to adapt to the situation and get a positive experience. If the first "PFT battle" is lost one may loose a good compliance and performance in later visits.

Conclusion

Even MEFV manoeuvres of experienced children do not reach the goals of all ERS and ATS criteria. However, most of their MEFV curves are useful for interpretation. We propose a re-evaluation of international criteria for MEFV measurements in children. Based on evaluation of MEFV measurements in 446 experienced children we propose as minimum criteria:
Start of test: Vbe<0.12 L (<15 years) and <0.15 L (>15 years); end of test: FET>2 sec (>8 years) and FET>1 sec (<8 years), provided that complete exhalation with a gradual, asymptotic approach of the flow volume curve to the volume axis is seen; reproducibility: $dFEV_1$ and dFVC <5%.

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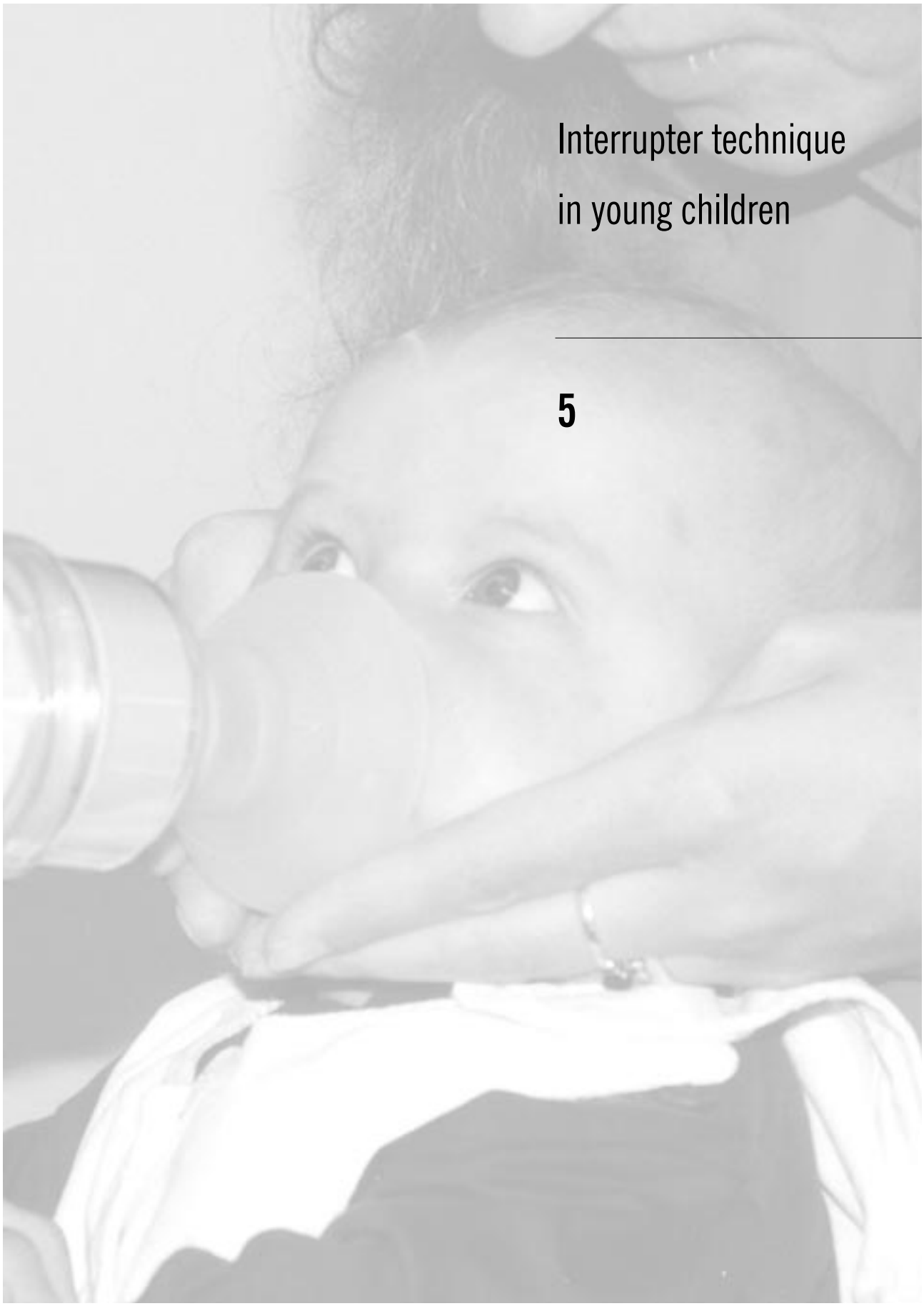

Interrupter technique in young children

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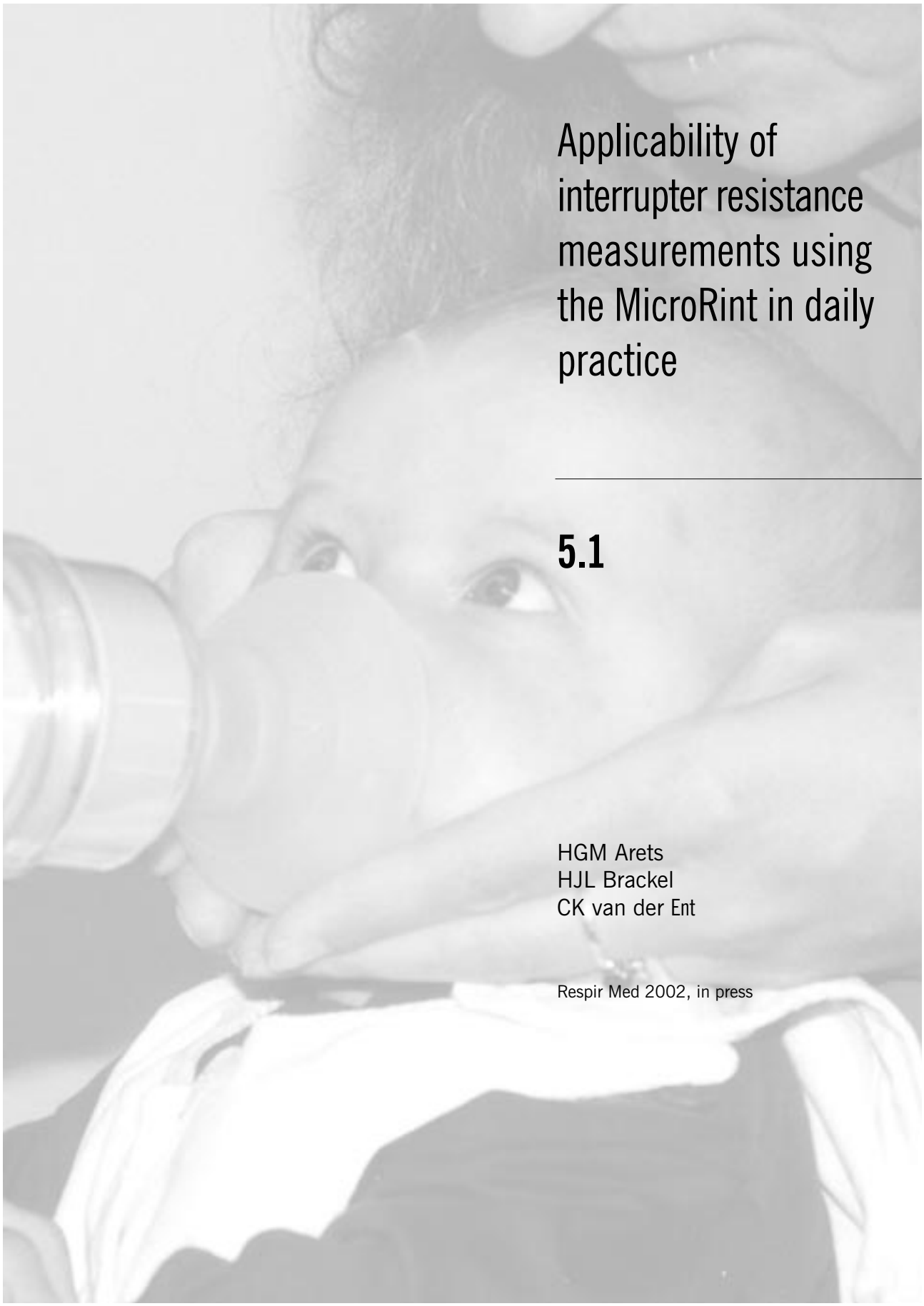

Applicability of interrupter resistance measurements using the MicroRint in daily practice

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Abstract

This study was performed to evaluate the applicability of a simple device (MicroRint®) for measuring airway resistance, to derive normal values and to compare values with maximal expiratory flow volume (MEFV) parameters in asthmatic and healthy children.

Repetitive Rint measurements were performed in 125 healthy children and 107 asthmatic children (age range 0.8-16.8 years). In 42 asthmatic patients Rint and MEFV values were compared and in 29 asthmatic children bronchodilator testing was performed.

Successful Rint measurements were possible in 91% of the children. The mean coefficient of variation of repeated measurements was 7.1(SD6.1)%. Rint values of healthy children showed a significant curvilinear correlation with age ($r = -0.80$, $p<0.001$) and height ($r = -0.81$, $p<0.001$). In asthmatic and healthy children Rint values were comparable. A significant inverse correlation was found between Rint and MEFV values (for FEV_1 and Rint $r = -0,80$, $p<0.001$). After bronchodilation there was a significant increase in FEV_1 and decrease in Rint, but changes between the two parameters did not correlate.

In conclusion, the interrupter technique is feasible and repeatable in children and has a significant correlation with other parameters of airway caliber. Baseline values do not discriminate healthy from asthmatic children.

Introduction

Medical history and physical examination are the most important parameters for diagnosis and treatment of recurrent respiratory problems in young children, because objective parameters of lung function can not always be obtained.
During the last decade several pulmonary function devices for young children have been developed, but most are only applicable in a research setting. Moreover, application of these devices often requires sedation of the child, special equipment and a laboratory setting.
One of the techniques, used for measuring resistance of the respiratory system is the interrupter technique, which was first described by Von Neergaard and Wirz in 1927[1].
The MicroRint® is a small portable data recording airway resistance meter, using the interrupter technique. It measures airway resistance during quiet breathing, requires minimal subject co-operation and can be used during spontaneous breathing and without sedation. Theoretically this makes it applicable even in very young children and in patients unable to co-operate with normal (forced) breathing techniques.
The basis of the interrupter technique is that, during transient interruption of the tidal airflow, alveolar pressure and mouth pressure equilibrate within a few milliseconds. The alveolar pressure can therefore be derived from the measurement at the mouth immediately after interruption. If the flow is measured immediately prior to interruption, the ratio of pressure to flow gives the interrupter resistance (Rint). It should be stated that pressure equilibration is incomplete in case of severe airway obstruction and that this is a limitation of the model on which Rint is based.
In adults, Rint shows a close correlation to airway resistance (R_{aw}) measured by whole body plethysmography. In asthmatic subjects the methods were equally sensitive in detecting changes in airway resistance following bronchodilation[2,3], but Rint tended to measure higher resistances, probably due to a contribution of chest wall rigidity, lung tissue resistance and the glottis to airway resistance[4,5]. Only recently studies have also evaluated the applicability of the Rint technique in children[6-12].
The purpose of the present study was to evaluate the applicability of the MicroRint© in children with and without asthmatic symptoms in daily practice, to establish normal values and to compare Rint values with maxi-

mal expiratory flow volume (MEFV) parameters as measures of airway patency.

Subjects and methods

Subjects

Interrupter resistance was measured during spontaneous breathing in 232 children (112 male, 120 female). 107 children were known with doctor's diagnosed asthma according to the British Thoracic Society (BTS) definition[13]. These children were tested in a clinically stable situation. The other 125 children were recruited from two primary schools and two day care centers. For the latter group parents had completed a modified International Study of Asthma and Allergies in Childhood (ISAAC)[14] questionnaire. Patients with a history of asthma, asthma treatment, dyspnoea, eczema, wheezing or recurrent coughing were not included into the study. Measurements in these children were performed during a visit to the schools. Informed consent was obtained from the parents of all children. Subject characteristics of 107 asthmatic and 125 healthy children are shown in Table 1. There were no significant differences between asthmatic and healthy children.
In 42 asthmatic children (mean age 8.7(3.4) years, FEV_1 107.0(13.3) %pred.) MEFV curves were performed and MEFV parameters were compared with Rint values. In 35 of these children Rint and MEFV measurements were repeated, 15 minutes after inhalation of 800 micrograms salbutamol (pMDI through spacer). Because 6 children could not perform Rint measurements before bronchodilation, comparison of MEFV and Rint values could only be made in 29 children. Prior to pulmonary function testing no bronchodilators had been used for at least 6 hours.

Methods

Airway resistance was measured using the MicroRint® (Micro Medical Limited, Kent, UK). Flow was measured with a pneumotachometer consisting of a steel resistive element and a high frequency solid-state pressure

Table 1. Patient characteristics of the asthmatic and healthy children who performed baseline MicroRint measurements.

	asthma	healthy
number of children	107	125
male/female	52/55	60/65
age (years (SD))	7.6 (3.3)	8.2 (2.8)
height (cm (SD))	125.8 (19.6)	132.2 (18.2)
weight (kg (SD))	27.4 (11.5)	29.8 (10.4)
no successful measurements	10 (9%)	10 (8%)
one successful measurement	17 (16%)	19 (15%)
two successful measurements	80 (75%)	96 (77%)
total successful measurements	97 (91%)	115 (92%)

transducer. The same pressure transducer was used to measure the mouth pressure post-occlusion. Measurements were performed in a sitting position. Children were entertained and attention was diverted to reduce their anxiety and to prevent abnormal breathing. Measurements were made using a cardboard mouthpiece (>10 years: 2.7 cm diameter, <10 years 2.0 cm) and the subjects were instructed to wear a nose clip, seal their lips around the mouthpiece and to lay their tongue on the floor of the mouth to prevent obstruction of air flow. Cheeks and mouth floor were supported by the hands of the investigator to prevent energy loss and to reduce the effect of mouth compliance. During spontaneous normal and quiet breathing the interrupter valve was operated manually twice to accustom the child to the shutter action. Thereafter, 10 airflow interruptions were made on the peak flow of an expiration; these occurred at random frequency and automatically so that they could not be anticipated, thus independent of the investigator's timing. After 10 interruptions the median Rint value was displayed as were the flow and pressure curves. A single interruption resistance value was (automatically) rejected when an artifact on the pressure curve occurred. Manual rejection was performed in case of tachypnoea, usage of vocal cords, extreme neck flexion or extension or leakage of the mouth piece. Tracings not showing the timing of interruption on the flow tracing, or tracings with a horizontal or declining pressure signal suggesting leakage at the mouth, or with an altered ventilation pattern were discarded as well.

Before a Rint measurement was considered successful, a median Rint value had to be obtained from a minimum of 5 out of 10 interruptions. Reasons for failure were recorded. The number of successful measurements and the number of acceptable interruptions per measurement were recorded. All Rint measurements were attempted twice in order to evaluate inter-measurement variability. Rint measurements always preceded MEFV maneuvers.

We evaluated the validity of Rint measurements by measuring the inter-measurement repeatability of two tests 30-60 seconds apart and the intra-measurement variability for every individual measurement consisting of 5-10 acceptable interruptions. Normal values were calculated for healthy subjects and these were compared with those for asthmatic children (according to age, height and gender).

MEFV curves were measured using a pneumotachometer system with a heated Lilly head (MasterScreen Pneumo or Jaeger Masterlab, Erich Jaeger, Würzburg, Germany). Equipment calibration conformed to ECSC (European Community for Steel and Coal) instructions[15]. All measurements were BTPS corrected.

Values for the following parameters were obtained: FEV_1, FVC, PEF, MEF75 and MEF50. All parameter values were described both as absolute values and as percentage of predicted values, described by the summary equations of Zapletal et al.[16].

Statistical analysis

Data are reported as mean (SD), unless indicated otherwise.

The repeatability of Rint measurements was evaluated by inter-measurement and intra-measurement coefficients of variation (CV=SD/n). Bland Altman plots were constructed to find limits of agreement between two repeated measurements[17].

The reliability coefficient (RC), also called the intra class correlation coefficient, was used to describe the within-subject stability of average Rint values. In children with "n" successful interruptions the subject's true Rint value was estimated by taking the average over n interruptions. The RC of this average calculated Rint was defined as:

$$RC = \sigma^2_{inter} / (\sigma^2_{inter} + \sigma^2_{intra}/n)$$

in which σ^2_{inter} is the between-subject variance of true Rint mean, σ^2_{intra} is the within subject variance of single Rint values within one subject, and n is the number of interruptions used to calculate the average Rint within a subject. The nearer RC is to 1, the more stable the average ratio.
A student's t-test was used for comparison of data. Correlation between two parameters was evaluated by Pearson correlation coefficients. Correlation between age and number of successful measurements was analyzed using logistic regression with the number of successful measurements as the dependent variable

Results

A. Feasibility

Results are shown in Table 1 and 2. At least one (out of two) acceptable baseline Rint measurement could be performed in 212 of the 232 children (91%) (Table 1); this percentage was similar in asthmatic (97/107 = 91%) and healthy children (115/125 = 92%). In 5 asthmatic children measurement was possible after, but not before bronchodilation (Table 2). Age distribution is shown in Figure 1.
Of all children, 76% were able to produce two successive measurements. A significant although weak correlation was found between age and number of successful measurements ($r = 0.18$, $p < 0.01$). Of 20 preschool children (15 in kindergarten, 5 in outpatient clinic) in whom two repetitive efforts were made at least one succesfull measurement was possible in 15 (75%) of children. Results for pre school children are presented in Table 3. The main reasons for failure were blowing into or sucking on the device, or refusal to take the device into the mouth.
The mean number of successful interruptions per measurement was not significantly different between healthy (7.6 (2.2)) and asthmatic (8.0 (2.1)) children. There was a significant correlation between age and the number of successful interruptions (i.e. during 1 measurement), ($r = 0.17$, $p = 0.012$).

Table 2. Feasibility of Rint measurements in the different subject groups (n = number, meas = measurements). ⋆ Because 5 children in the bronchodilator group were only able to produce values after B2, only 212 usable baseline measurements were evaluated.

	n	meas.	Number of successful measurements					≥1 good test	All good tests
			0	1	2	3	4		
A	15	2	3	5	7			80%	47%
B	158	2	8	21	129			95%	82%
C (no B2)	24	2	3	4	17			88%	71%
(-/+ B2)	35	4	1	3	3	5	23	97%	66%
total	232		15⋆	33	156	5	23	94%	76%

A = kindergarten, B = schoolchildren, C = outpatient clinic patients

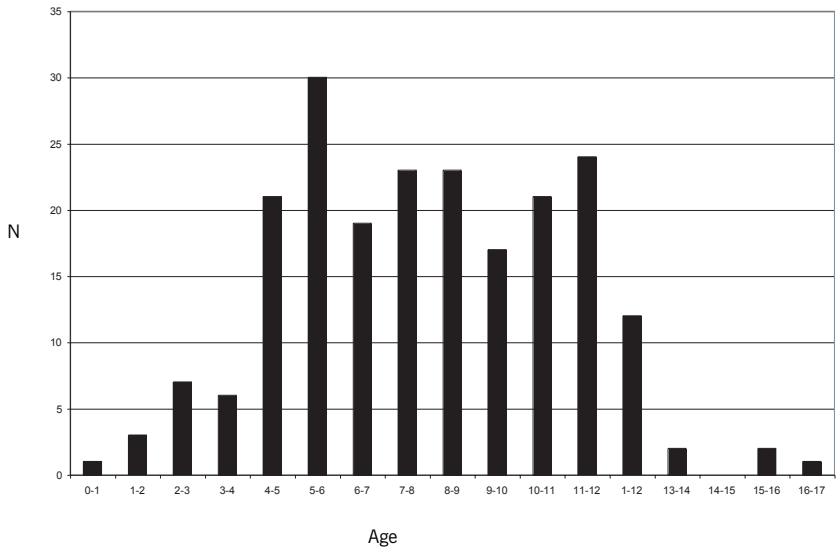


Figure 1. Age distribution of children able to perform Rint measurement

Table 3. Feasibility of Rint measurements in pre school children (n = number).

	n	No successful measurement	One successful measurement	Two sucessful measurements	At least one succesful measurement
0-1 year	1	1	0	0	0
1-2 years	2	2	0	0	0
2-3 years	8	0	5	3	8 (100%)
3-4 years	9	2	3	4	7 (78%)
Total	20	5	8 (35%)	7 (40%)	15 (75%)

B. Validity

Rint measurements of 212 children were evaluated before or without bronchodilation. The mean inter-measurement coefficient of variation (CV) was 7.1(6.1). CV correlated significantly with both age (r = -0.214, p=0.004) and height (r = -0.215, p =0.004). There were no significant differences between girls and boys, or between asthmatic and healthy children.

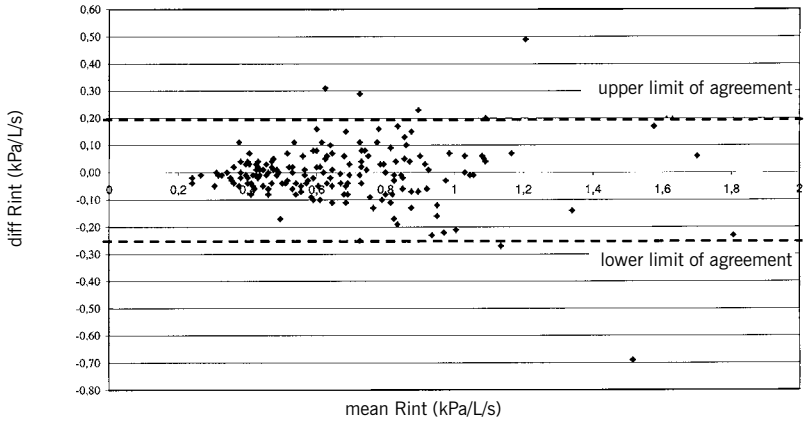


Figure 2. Analysis of agreement between MicroRint values of two consecutive measurements (Bland Altman plot [13]).

The mean difference between 2 consecutive measurements was -0.005 (+0.11) kPa.L^{-1}.s, indicating that 95% of the values of Rint in the second measurement fell between -0.23 and +0.21 kPa.L^{-1}.s (lower and upper limits of agreement, Figure 2). There was a significant inverse correlation between the absolute difference between two measurements and both age ($r = -0.283$, $p<0.001$) and height ($r = -0.256$, $p<0.001$)
The mean intra-measurement CV was 12.2 (5.5)%. There was a significant correlation between CV and both age ($r = -0.277$, $p<0.001$) and height ($r = -0.317$, $p<0.001$). No significant differences were found between girls and boys or between asthmatic and healthy children. Reliability coefficients of 1-10 interruptions are shown in Figure 3. The use of one single interruption (n=1) would result in a Rint value with a reliability coefficient of 0.90. An increase in the number of interruptions would increase the reliability coefficient of the subsequently measured Rint value.

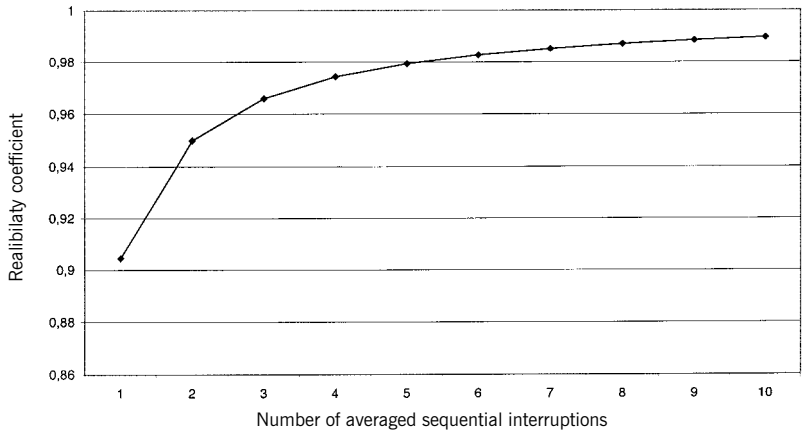


Figure 3. Reliability coefficients of the Rint value calculated as an average of n sequential interruptions.

C. Normal values

The mean Rint of healthy children was 0.64 (0.26) kPa.L^{-1}.s. There was a significant correlation between age and Rint ($r = -0.80$, $p<0.001$) and between height and Rint ($r = -0.81$, $p<0.001$). Figure 4 shows the Rint values for healthy children in relation to their height. This curvilinear relation was best represented by the regression formula:

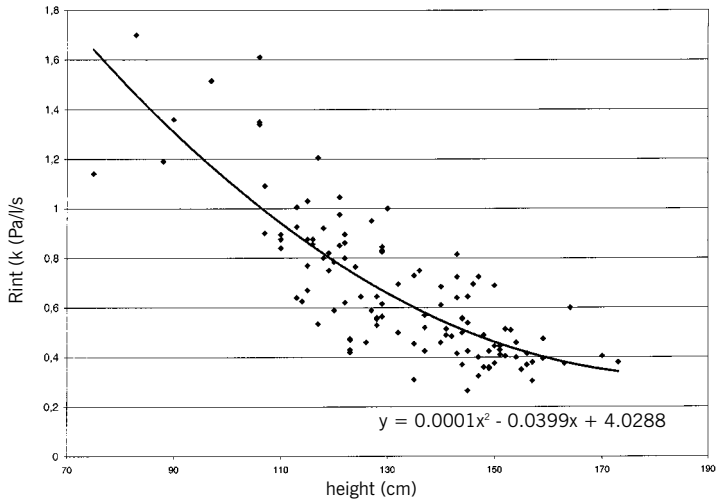
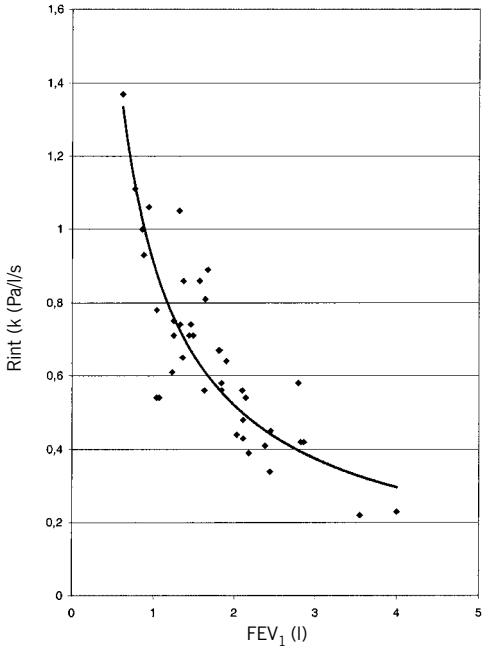


Figure 4. Rint values in healthy children versus height.

Figure 5. Rint values in asthmatic children versus FEV_1.



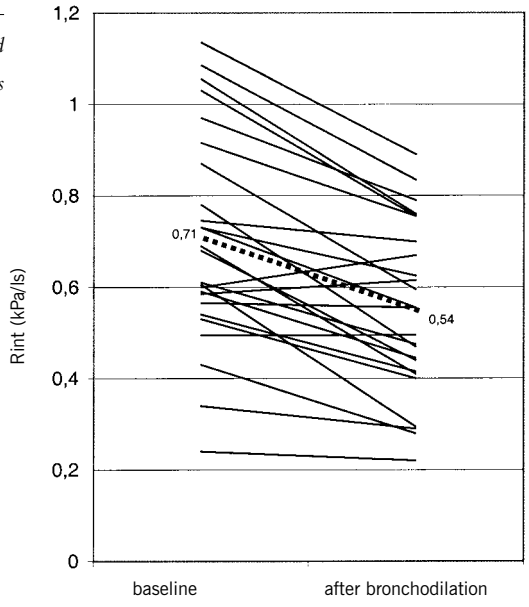
Rint (kPa.L^{-1}.s) = 0.0001x(height)^2 - 0.0399x(height) + 4.0288, with height expressed in cm. (R^2 = 0,65). Addition of age to this model did not improve R2. There were no differences between boys and girls.
For asthmatic children the mean Rint value was 0.70 (+0.27) kPa.L^{-1}.s,

which was not significantly different from normal values and was also significantly correlated with age and height. There was a large overlap between the Rint values of healthy and asthmatic children, irrespective of a doctor's diagnosis or a questionnaire based diagnosis of asthma.

Table 4. Correlation between Rint and MEFV parameters in 42 asthmatic children (r= correlation coefficient)

	r	p
FVC	-0.775	<0.001
FEV_1	-0.797	<0.001
PEF	-0.754	<0.001
MEF50	-0.65	<0.001
MEF75	-0.63	<0.001

Figure 6. Rint values before (baseline) and after bronchodilation in 29 asthma patients (dashed line is mean value).



D. Comparison with MEFV measurements

Rint correlated significantly with FEV_1 in asthmatic children (r = -0.800, p<0.001, Figure 5). Significant inverse correlations were observed between Rint and absolute values of FVC, PEF, MEF25, MEF50 and MEF75 (Table 4), but not between Rint and MEFV parameters presented as percentage of predicted.

E. Reversibility

After bronchodilation a significant increase in mean FEV_1 from 1.59 (+0.60) L to 1.69 (+0.69) L (mean increase +0.10 (+0.13) L, p < 0.001) coincided with a significant decrease in mean Rint from 0.71 (+0.21) $kPa.L^{-1}.s$ to 0.54 (+0.18) $kPa.L^{-1}.s$ (mean decrease -0.15 (+0.11) $kPa.L^{-1}.s$, p < 0.001) (Figure 6). In only 8 children an increase of more than 8% of FEV_1%pred. was observed. 21 pairs were concordant (increase in FEV_1 and decrease in Rint). However, the linear correlation between changes in Rint and FEV_1 was not significant (r=0.12, p=0.59).

Discussion

We evaluated the feasibility and repeatability of the MicroRint© in a group of asthmatic and healthy children. The majority of children of all ages was able to perform Rint measurements and repeatability was good. Rint values showed a significant correlation with absolute MEFV parameters. Although in most asthmatic patients a decrease in Rint was found after bronchodilation, there was no linear correlation between changes in Rint and changes in FEV_1.

A. Feasibility

The setting for measuring Rint was either a simple office setting in schools (and day care centers) or the outpatient department. Measurements were performed by rather inexperienced medical students, formerly unknown

with the method, who received only minimal instructions about use of the device before starting Rint measurements. All children were inexperienced with MicroRint measurements. We tried to distract the children from "conscious breathing" by playing games, parental presence or observer attendance. Parents were encouraged to attend the measurements in order to reassure their children and encourage the correct use of the device; ideally there should be a quiet testing area with sufficient "quiet" distraction. The use of a facemask (without nose clips) might enable measurements in smaller children but may also introduce problems such as leakage, increase of dead space, intranasal obstructions and nasal breathing[7]. Klug and Bisgaard used a facemask with a built-in non compressible mouthpiece in order to prevent nasal breathing and to support the cheeks[7]. In a recent study Child et al found higher values of Rint using a mouth piece compared to face mask. They were equally reproducible, but values were not interchangeable[18].

In our study, children 4 years and older were generally quite able to co-operate in MicroRint measurements, which led to reliable results. In younger children co-operation was less easily achieved. In the present study only 40% of 1-3 year old children were able to perform two measurements; similar data were reported by Bridge and co-workers, who performed successful reversibility testing in 53%, 71% and 91% of 2, 3 and 4 year old children, respectively[6].

B. Validity

Inter-measurement variability of two tests, 30-60 seconds apart, was small. The mean difference between two Rint measurements was comparable with data found by Bridge et al[7]. These differences decreased with increasing age (and height) as could be expected. In our study the variability is low compared to earlier reports[12], especially when we take into account that measurements were performed in inexperienced children and by relatively inexperienced medical students. Intra-measurement variability for individual measurements consisting of 5-10 interruptions was also small, especially in the older children. Both intra- and inter-measurement variability were independent of gender, diagnosis and bronchodilation, which augments the applicability.

The small inter-measurement variability allows for the application of this technique in bronchial challenge testing, using the "variance based" provo-

cation dose (giving a change in Rint to "baseline Rint + 2 SD"). This method proved to be a very good discriminator between healthy and asthmatic[19].
Reliability coefficients for statistical evaluation of the stability of Rint after 1-10 interruptions showed that even after one or two interruptions a reliable Rint value can be found, which indicates that the premise to use a minimum of 5 acceptable interruptions to measure Rint is acceptable. In the present study after 5 interruptions the reliability coefficient rose to 0.98. In an earlier study we evaluated the reliability coefficients of tidal breathing flow pattern analysis in quietly breathing children; reliability coefficients were much lower[20], indicating that MicroRint measurements can be performed in a much shorter time span.

C. Reference values

We found a significant correlation between height (and age) and Rint, reflecting a decrease in airway resistance during growth. The data were not log-transformed to achieve normal distribution prior to the fit. In this study only a general impression of height-Rint correlation was presented. In a recent study we presented reference values for children 3-13 years of age, using log-transformed data[21].
The range was wide and no differences were found between healthy and asthmatic children.
There were no relevant gender differences. Few data on reference Rint values were available until recently. Van Altena et al. evaluated Rint values in adults and reported a mean Rint of 0.38 (+0.17) $kPa.L^{-1}.s$ and a significant relationship between Rint and both age and height[22]. For a more extensive use of the interrupter technique in children reference values are needed for the (whole) pediatric age group. Until now no reference values are available for children over 7 years of age. In young children reference data were presented in two recent studies[23,24]. In 1998 Klug and Bisgaard published reference values of Rint for 2-7 year old children, related to height[8]; they also found a wide range and that a single measurement could not demonstrate airway obstruction. In preschool children Mckenzie et al found significant differences between children with recurrent wheezing and both healthy controls and recurrent coughers[24]. The present study failed to distinguish healthy from asthmatic subjects using only baseline values. This might be due to the fact that these patients were symptom free during examination and were probably only mildly affected (normal FEV_1%pred).

Recently we found in a study on ICS efficacy that baseline FEV_1 in mildly asthmatic children is often in the normal range[25]. Probably also Rint in mild asthmatics can be in the normal range.This may explain the inability of a single Rint measurement to discriminate between healthy and asthmatics.
Recent studies showed comparable results for airway resistance measured by impulse oscillometry, e.g. Hellinckx et al. found no difference in respiratory system resistance at 5 Hz ($R_{rs}5$) between healthy and asthmatic children, nor in changes after bronchodilation[26].

D. Comparison between Rint and MEFV parameters

We found a significant curvilinear relation between maximal expiratory flow volume parameters and Rint. The Rint values correlated well with FEV_1, FVC and PEF, but only when absolute values were concerned. The latter is caused by the fact that during growth there is an absolute gradual decrease of airway resistance and increase of air flows, but of course not of pulmonary function parameters, expressed as percentage of predicted. Comparable results were reported by Mijnsbergen et al. who found a correlation coefficient of -0.74 in asthmatic patients and -0.58 in CF patients[27]. Two other studies compared FEV_1 and interrupter conductance (Gint), the reciprocal of Rint; both reported highly significant correlations between Gint and absolute FEV_1 and PEF values[3,28].

E. Reversibility testing

As with FEV_1 and many other pulmonary function test parameters baseline Rint measurements could not differentiate between asthmatic and healthy children. There was a significant decrease of airway resistance after bronchodilation, coinciding with a small increase in FEV_1 and PEF. In our group of asthma patients with rather mild airway obstruction only small changes in airway resistance and patency could be expected. Mean percentual improvement of Rint values after bronchodilation was higher than that of FEV_1 (22.5% versus 6.3%). In this study reversibility testing was not performed in healthy children. The latter has been performed in a recent study by Beydon et al. In a group of 5.3 (1.4) year old children they found a change (% of predicted values) in expiratory Rint of -12% (95% CI -46% to+22%)[29].

In our very young children, the repeatability was relatively poor, which restricts reversibility testing. If we consider a decrease in Rint greater than two SD of variance (i.e. 0.22 $kPa.L^{-1}.s$) to reflect reversibility, this reversibility was found in only a small percentage of children with proven reversibility, shown by FEV_1 measurements. Bridge and co-workers studied reversibility in wheezy pre-school children and found a significant decrease in most children; however, because no MEFV measurements were performed in these children the correlation with FEV_1 was unknown[6]. McKenzie et al compared Rint reversibility in healthy, coughing and wheezing preschool children and showed that percentual Rint decrease is less in healthy preschool children compared to wheezing children[30].
We found a poor and non-significant correlation between changes of FEV_1 and Rint after bronchodilation. Morrison et al reported comparable results in young CF patients[9]. To our knowledge no studies have evaluated this correlation in adults (MEDLINE search 1965-2001). In our opinion the poor correlation between changes in FEV_1 and Rint is probably due to the fact that measures of lung function obtained from a forced expiratory maneuver may have different physiologic implications than those measured during tidal breathing, as was also mentioned by other investigators[3,12]. This and the fact that these children were probably only mildly asthmatic may explain the lack of correlation between FEV_1 and Rint changes.

We conclude that MicroRint® measurement provides a feasible and repeatable method for measuring airway resistance in children of all ages. Normal values show a highly significant correlations with age and height. The correlation with MEFV measurements is good. A single measurement cannot identify airway obstruction and reversibility testing shows a significant decrease in many asthmatic children, although not significantly correlating with changes in FEV_1.

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Measurements of interrupter resistance. Reference values for children 3-13 years of age

5.2

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Abstract

The interrupter technique is a convenient and sensitive technique to study airway function in subjects who cannot actively participate in (forced) ventilatory function tests. Reference values for pre-school children exist but are lacking for children over the age of 7. We obtained reference values for expiratory interrupter resistance (Rinte) in 208 healthy Dutch Caucasian children 3-13 years of age. A curvilinear relationship between Rint and height was observed, similar to published airways resistance data measured plethysmographically. No significant differences in cross-sectional trend or level of Rint were observed according to gender. Based on the reference equation: 10log (Rinte) = 0.645 - 0.00668 x standing height(cm) kPa/L/s and residual standard deviation (0.093 kPa/L/s), Z-scores can be used to express individual Rint values and to describe intra- and interindividual differences. Rint provides a tool for clinical and epidemiological assessment of airway function in a large age range.

Introduction

The interrupter technique is one of the few lung function tests which can be used for assessment of airway calibre in young children[1-3]. With this technique, measurements of the resistance of the respiratory system (Rint) can be carried out quickly, with minimal co-operation of the child. Rint measurements have been shown to be reproducible[1,4-6], sufficiently sensitive to detect (sub)clinical airway obstruction[6,7], and correlate satisfactorily with measurements of airway resistance[4,8,9]. The technique can not only be used as a tool to screen for airway obstruction, but also to assess the responses to bronchodilating and bronchoconstricting agents[1,3,10]. It is especially suitable for pre-school children because it only requires passive co-operation. However, passive measurements of airway function may also be required for clinical research in older children, or in older children who are unable to perform forced expiratory manoeuvres because of developmental disorders or neuromuscular disease. Till now, reference data are available for young children[6,7,11,12] and adults[13], but not for children over 7 years of age. The aim of the present study was to expand the previous data set in order to better describe relationships between expiratory resistance and body size. We obtained normal Rint values during expiration (Rinte) in 208 healthy Caucasian children aged 3-13 years, from a general population. Measurements were preferably made during expiration rather than during inspiration because Rinte appears to be more sensitive to detect changes in resistance within children due to respiratory infections, and to discriminate better between children with and without respiratory symptoms or disease as compared to Rinti[6].

Methods

Dataset

Rint measurements were carried out using identical equipment and the same measurement protocol in 2 sets of healthy Dutch Caucasian children aged 1-13 years, recruited from 2 day-care centres, 2 kindergartens, and 2

elementary schools. Information on respiratory symptoms, eczema, allergy, parental smoking, doctors diagnosis of asthma, and asthma medication was obtained using modified ISAAC questionnaires[14]. Children were included in the reference population when they had no respiratory symptoms in the month prior to or during the measurements. Exclusion criteria were: history of asthma, recurrent rhinitis, eczema, cardiorespiratory or other chronic disease, known anatomical abnormalities of the upper or lower airways, and vocal cord disorders. We intended to obtain reference values from a normal population rather than from an ideal population[15]. Therefore, mild respiratory symptoms not requiring medical care in the past, and involuntary exposure to parental smoking without a history of respiratory symptoms or disease were no exclusion criteria. The study and its protocol were approved by the medical ethics committees of the medical centres and by the principals and boards of the institutes involved. Informed consent was given by the parents of all participating children. When children refused co-operation, no Rint measurements were attempted.

Equipment

Interrupter resistance was assessed using the MicroRint (Micro Medical Ltd, Rochester, UK), as described previously[6]. Rint was calculated using the back extrapolation technique to t=0 ms after shutter closure during 100 ms[1]. Daily calibrations of pressure and flow (volume) were carried out using a manometer and a 2 litre precision pump. All measurements were carried out with a filter (Micro Medical Ltd, Rochester, UK) in place to prevent contamination and dysfunctioning[16].

Measurement protocol

The protocol has been described previously[6]. After the supervisor of the children explained the purpose of the measurements, a measurement was demonstrated on the supervisor and subsequent measurements were carried out in groups of 2-4 children at a time, in a familiar and quiet room. Children were seated and no physical exercise was allowed during 10 minutes prior to the measurements. During measurements, children were instructed to breathe quietly, sitting upright while the cheeks and chin were

supported from behind by the investigator. The head was positioned in slight extension and a nose clip was used. The position of the MicroRint was adjusted on a support arm to facilitate unobstructed breathing. A minimal number of 5 correct tracings (maximal 10) was obtained at the peak of expiratory tidal flow, because expiratory interruptions seem more sensitive in detecting airways obstruction than those during inspiration[6]. Tracings were rejected in the cases of: tachypnoea, usage of the vocal cords, extreme neck flexion or extension, or leakage of the mouth piece. Tracings not showing the timing of interruption on the flow tracing, or tracings with a horizontal or declining pressure signal suggesting leakage at the mouth, or altered ventilation pattern were discarded as well (illustrated in Figure 2).

Data analysis

The individual Rinte data were expressed as median values because individual data are not normally distributed[6]. Reference values for Rinte were described based on a model assuming a linear or curvilinear relationship with the standard independent variables standing height, weight, and age. Because of physiological similarities between Rint and plethysmographically obtained R_{aw}, we hypothesised that an exponential model with standing height would make the best fit for the Rinte data, similarly as published reference equations for R_{aw}[17,18]. Trends of residuals with height or age were assessed from linear regression analyses. The threshold for statistical significance was set at p=0.05.

Results

Subjects

The first dataset consisted of 135 healthy Dutch children (60 boys) studied in Rotterdam, the Netherlands, who were selected from a survey in which the parents of 698 children were asked for participation. Permission was given for 341 (49%) children: 36 refused participation, and 12 failed to complete the measurements. Of the remaining 293 children 135 (39%) met the inclusion criteria and completed the measurements. This included 54

healthy children described previously[6]. The second dataset consisted of 79 Dutch children (41 boys) studied in Utrecht, the Netherlands. These were selected from a study in which parents of 445 children were asked for participation. For 212 (48%) of these children such permission was obtained. In 200 children reliable Rint measurements were carried out of whom 79 (40%) met the inclusion criteria listed above. Both studies were carried out in suburban parts of the cities, inhabited with middleclass income Dutch families. Only 2 out of the 24 children who failed to complete the measurements were older than 4 years of age. Anthropometric data of all 214 children are summarised in Table 1. The children from dataset 1 were slightly younger than those from dataset 2 (Table 2). The coefficients of variation from dataset 1 showed a trend to be larger than that from dataset 2 (Table 2). This seemed to be explained by the differences in age between centres: Especially below the age of 6 yrs , there was a negative correlation between coefficient of variation and age ($r=-0.21$, $p=0.004$). Because reliable measurements could only be obtained in 6 children younger than 3 years of age the reference equation was based on the 208 children 3-13 years.

Table 1. Anthropometric data of the reference population.

Age range (n)	Gender M/F	Mean (SD) height	Mean (SD) weight
1-3 yrs (6)	4/2	88.2 (6.8)	12.9 (2.5)
3-4 yrs (8)	3/6	104.9 (6.2)	17.2 (2.0)
4-5 yrs (17)	7/10	109.5 (3.7)	18.6 (2.1)
5-6 yrs (28)	12/16	116.4 (4.3)	21.1 (2.0)
6-7 yrs (29)	12/17	119.8 (4.9)	22.8 (3.0)
7-8 yrs (25)	13/12	129.9 (4.6)	26.5 (3.5)
8-9 yrs (29)	8/21	133.1 (7.5)	29.1 (6.2)
9-10 yrs (21)	15/6	142.3 (5.0)	35.1 (5.2)
10-11 yrs (17)	10/8	149.1 (4.3)	39.1 (6.7)
11-12 yrs (24)	11/13	154.7 (6.7)	41.1 (6.7)
12-13 yrs (8)	6/2	156.7 (10.6)	47.8 (12.9)

Table 2. Differences between 2 data sets. ⋆: p<0.03, unpaired t-tests.

	Dataset 1 (Rotterdam)	Dataset 2 (Utrecht)
Age (yrs, mean(SD))	7.4 (2.6)	8.4 (2.9)⋆
Standing Height (cm, mean(SD))	128 (18)	133 (20)⋆
Weight (kg, mean (SD))	27.2 (9.3)	30.7 (11.5)⋆
Boys/Girls	62/76	41/38
Coefficient of Variance (%, median(range))	11.7 (1.2 - 21.4)	6.9 (0 - 35)

Reference equation for Rint

An inverse, curvilinear relationship was found between Rinte, and the independent variables standing height, age and weight. When standing height was used in an exponential model instead of a linear model with Rinte, the explained variance increased from 59 to 63 % and the residual standard deviation (RSD) decreased from 0.150 to 0.093 kPa/L/s. Residuals of the exponential model were homoscedastically distributed, demonstrating no trend with standing height (Figure 1). When age was added next to

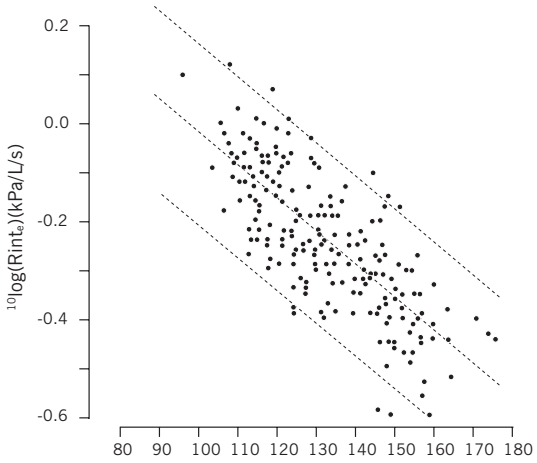

Figure 1. Relationship between^{10}log(Rinte) and standing height for 208 children. The solid and dotted lines illustrate the exponential model (mean and 95% confidence bands).

Figure 2a

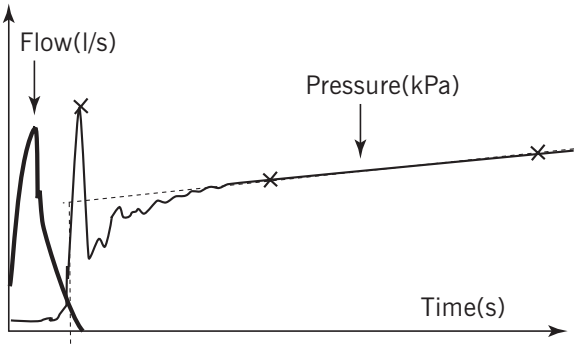

Figure 2b

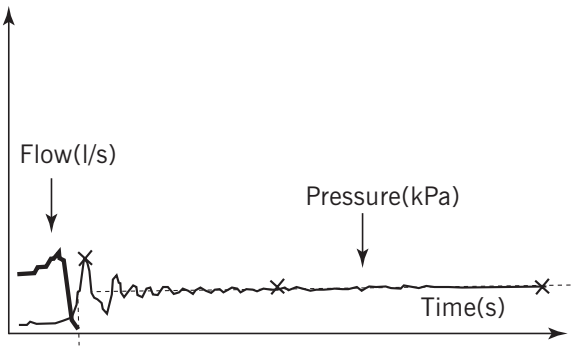

Figure 2c

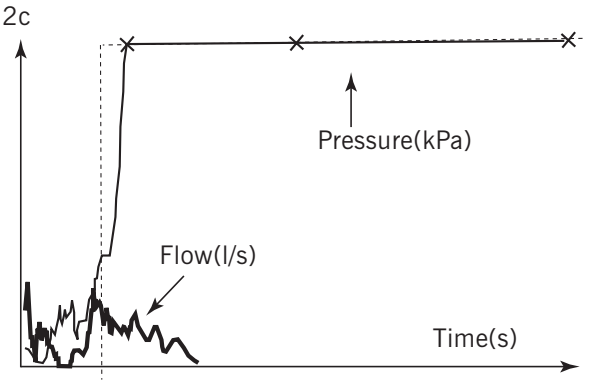

Figure 2a-c. Examples of Rinte recordings. Fig 2a: correct manoeuvre, clearly visible timing of interruption on the flow tracing and approved interpolation and extrapolation of pressure signal. Fig2b: Visible leakage at the mouth, and a horizontal pressure signal following interruption. Fig2c: Flow signal affected by the usage of the vocal cords, and horizontal pressure signal.

standing height in an exponential model, the explained variance increased with less than 3%, and the improvement of RSD was less than 0.0003 kPa/L/s. When age was used as the only independent variable in an exponential model with Rinte, the explained variance was 64% (RSD = 0.091 kPa/L/s), but the distribution of the residuals became heteroscedastic for subjects older than 10 years. In the age range>10 years, the variability of standing height for age was larger than in the younger subjects. Using weight as the only independent variable, explained variance was 49%, (RSD=0.108 kPa/L/s).

Reference equations for Rinte are:

linear model:

Rinte = 1.927 - 0.00992 x standing height (cm) kPa/L/s

r = -0.77, RSD = 0.150 kPa/L/s ($p<0.001$).

exponential model:

10 log (Rinte) = 0.645 - 0.00668 x standing height (cm) kPa/L/s

r = -0.79, RSD = 0.093 kPa/L/s ($p<0.001$).

Based on the exponential model, the mean (SEM) of standardised residuals for 97 boys and 111 girls were -0.079 (0.096) kPa/L/s and 0.071 (0.097) kPa/L/s, respectively, with a mean (95% CI) difference between boys and girls of 0.15 (-0.12, 0.42) kPa/L/s. No trend was observed between standing height and standardised residuals for boys or girls. The separate regression equations from the 2 datasets did not differ significantly in a multiple regression model that included centre ($p=0.33$) and interaction between standing height and centre ($p=0.59$).

Discussion

Few studies have reported reference equations for the interrupter technique in young school children[6,7,11,12], but for older children these are lacking. Because of the possible applications for this technique in a larger age range (epidemiological and clinical research, children unable to participate in active lung function measurements), we obtained normal values for Rinte in 208 healthy Caucasian children between the ages 3 and 13 years. In our

previous study a linear model to describe the relationship between height and Rinte was considered satisfactory[6] but in the present study, due to the larger range for height, an exponential model appeared more appropriate because of a curvilinear relationship. This pattern is consistent with reports of data of R_{aw} in healthy children[19].

This is the largest study of Rinte in healthy pre-school and school children studied so far. Despite the large number of observations, we could not demonstrate a significant sex-related difference in airway patency. This suggests that a possible small difference of airways resistance between sexes is not clinically relevant, or that it can not be detected measuring resistance of the respiratory system with this technique.

We used height and not age as independent variable because of physiological arguments, and not because the relationship between height and Rinte was statistically superior. It is conceivable that body size can function as a proxy for airway calibre, whereas age may indirectly reflect airway size in children below the age of 13 years as well, but not in adolescents or adults. Age may be equally valid and a more convenient independent variable in reference equations for Rinte[7], but this is probably limited to young children only. Indeed, the variability of the residuals in the children over 10 years of age from the present study was considerably increased compared to that in children below that age, which is explained by a larger variation of height for age.

Because the residuals of the exponential model were normally distributed (with RSD=0.093 kPa/L/s), individual measurements can be expressed as Z-scores:

Z=(10 log(measured Rinte) -10 log (predicted Rinte))/RSD, which facilitate comparisons within and between individuals. As long as there is no international standardisation for Rinte measurements[20], reference equations are likely to differ according to the equipment and protocol of shutter timing and back-extrapolation, as well. In the protocol of the present study, interruptions were programmed at peak tidal expiratory flow which appears to standardise inflation level[6,9].The linear model of the present study fits remarkably well with the reference equation (Rint = 1.993-0.0092 x height(cm) - 0.0009 x age(yrs)) kPa/L/s of van Altena et al.[13] who studied Rint in 172 adults and teenagers, although the exact measurement procedure was not described and the population and equipment differed markedly. Our results are not comparable with those of Klug et al.[11] who programmed inspiratory interruptions at 50 ml above FRC. The effect of this procedure might have been that with increasing body size, interrup-

tions occurred at progressively lower inflation levels. This could very well explain the lesser slope with height and lower explained variance of their reference equations.

It is difficult to compare Rint values with those of measurements of R_{aw} or R_L from healthy populations because of differences in technique, and population characteristics, but our reference equation compares favourably with those of Dab et al.[17] (log R_{aw} = 0.712-0.0064 x height(cm)), and those of Helliessen et al.[18] (logR_L = 0.627-0.0068 x height(cm)).

We were able to measure Rinte reliably in only 6 children younger than 3 years of age and do not recommend routine assessment of Rint below 3 years of age because of low feasibility in that age range[6]. The use of face masks in those children may enhance the feasibility of the test, but Rint measurements obtained using face masks can differ from those obtained with mouthpieces[21]. This will depend on compliance and resistance of the mask, and on the degree of airways obstruction. Rint measurements using face masks may require specific reference equations. For young children over 3 years of age, the interrupter technique remains probably one of the most convenient and sensitive tests for airway function available, with the possibility to use the same technique over a wide age range.

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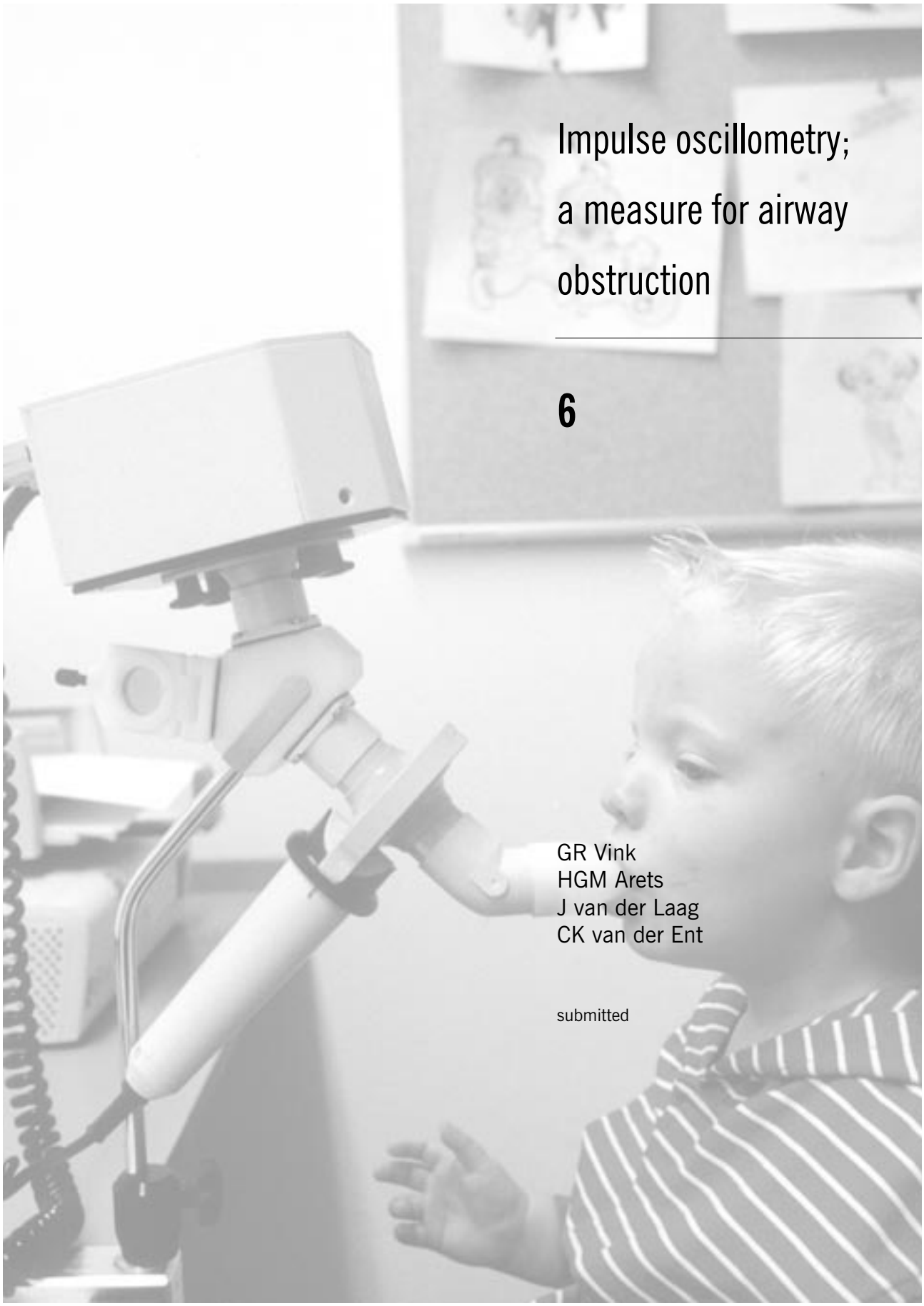

Impulse oscillometry; a measure for airway obstruction

6

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submitted

Abstract

The Impulse Oscillometry System (IOS) was introduced as a new technique to assess airflow obstruction in patients who are not able to perform forced breathing manoeuvres, like subjects with cerebral palsy, severe mental retardation and young children. This study evaluates the sensitivity and specificity of IOS parameters to quantify changes in airflow obstruction in comparison with FEV_1 and PEF measurements.

Measurements of FEV_1, PEF and Resistance (R) and Reactance (X) at frequencies of 5 to 35 Hz were performed in 19 children with asthma before, during and after methacholine challenge and subsequent bronchodilation.

All parameters changed significantly during the tests. Values of R5 and R10 correlated with FEV_1 ($r = -0.71$, and -073, respectively, $p<0.001$), as did values of X5 and X10 ($r = 0.52$, and 0.57, respectively, $p<0.01$). Changes in R preceded changes in PEF and FEV_1 during methacholine challenge. The area under the Receiver Operating Characteristic curve to predict a 15% fall in FEV_1 showed better sensitivity and specificity for R5 (area under the curve 0.85) compared to PEF (0.79) or R10 (0.73).

We conclude that IOS parameters can be easily used as an indirect measure of airflow obstruction. This might be helpful in patients who are not able to perform forced breathing manoeuvres. In individual subjects, R values measured at 5 Hz showed to be superior to PEF measurements in the detection of a 15% fall in FEV_1.

Introduction

Lung function tests can often contribute to proper therapeutic strategies and follow-up of patients with lower respiratory illnesses. The forced expiratory volume in the first second (FEV_1) is regarded as the 'gold standard' for the assessment of airflow obstruction and general consensus exists about criteria for performance and standardization of this measurement[1]. Unfortunately, some categories of patients, such as mentally retarded patients and young children, have a high risk for lower respiratory illnesses, but are not able to perform forced expiratory manoeuvres.

Respiratory disease is the major cause of death in children with cerebral palsy[2,3], with a 140 fold increased mortality risk[4]. Because modern technologies for assessment of pulmonary function and treatment of pulmonary obstruction are not routinely applied in children with intellectual disability and young children, recognition and treatment of respiratory diseases might not be adequate in this group[5]. In young children the incidence of lower respiratory illnesses and wheezing is increasing[6].

Children with severe neuromuscular disorders and children under the age of five rarely can generate forced expiratory manoeuvres that meet the above mentioned acceptability and reproducibility standards[7]. Also a relatively simple forced breathing test as peak expiratory flow (PEF) measurement is difficult to perform for these patients. During infancy several other lung function tests can be performed (e.g. partial flow volume curves, occlusion techniques), but most of these tests are limited to the first two years of life and can only be performed in research laboratories because of high technical requirements[8]. For large numbers of patients with lower respiratory illnesses lung function test facilities are very limited.

Recently, impulse oscillometry was introduced as a new technique for the assessment of airflow obstruction in children[9]. The Impulse Oscillometry System (IOS) does not require active co-operation of the patient and has become commercially available. The purpose of this study was to evaluate the sensitivity and specificity of IOS parameters to quantify changes in airflow obstruction. In order to compare the method with conventional forced breathing tests as the 'gold standard' for airflow obstruction, the study was performed in children who were able to perform FEV_1 and PEF measurements.

Subjects

We studied 19 children (7 boys) with asthma attending the outpatient paediatric pulmonology department of the Wilhelmina Children's Hospital, Utrecht (age range 5 - 17 years). They all had moderate to severe asthma according to the International Consensus Report on Diagnosis and Treatment of Asthma[10] and were treated with inhaled corticosteroids (beclomethasone dipropionate or budesonide 200-800 microgram daily) and rescue medication (salbutamol or terbutaline). All children were free of symptoms in the period of the study. All children had a baseline FEV_1 of more than 70% of predicted. The children were not allowed to use bronchodilators during a period of at least 24 hours prior to the test.
The study was approved by the Hospital Medical Ethics Committee, and informed consent from the parents was obtained prior to inclusion in the study.

Methods

Forced flow volume measurements

Maximal expiratory flow volume (MEFV) measurement was performed in all children, with use of a pneumotachometer system with Lilly head (MasterScreen Pneumo, Erich Jaeger, Germany). The best MEFV curve, according to the ATS criteria, from at least 3 trials was used[1]. Children who were not able to reach the ATS criteria of acceptability and reproducibility were not included into the study. All values were corrected to body temperature, ambient pressure saturated (BTPS) conditions. For reference values data of Zapletal were used[11].

Peakflow measurements

Peak expiratory flow (PEF) was measured using a calibrated Wright spirometer (Clement Clarke International Ltd, London, UK). The children

were in a standing position and were instructed to exhale maximally after inhalation to total lung capacity. The best value of three repeated measurements was recorded.

Impulse Oscillometry (IOS)

The impedance of the total respiratory system was measured using a commercially available oscillometry system which has been described elsewhere[9] (Masterlab-IOS, Erich Jaeger, Germany). During tidal breathing through a mouthpiece on a Y-piece an impulse generator produced brief pressure pulses at intervals of 0.2 sec. The power spectrum of the pulse was constant from 0 to 5 Hz and had a decrease of 20 dB in the range up to 40 Hz. These pressure fluctuations were superimposed on the spontaneous breathing pattern and were measured at the mouth by means of a differential pressure transducer with a total resistance below 50 Pa/l/sec and a pressure range of ± 1 kPa. The digitised pressure and flow signals were sampled at a rate of 200 Hz and were fed into a fast Fourier transformation, which transformed the complex pulse signals into their elementary sinusoidal components. The spectral ratio of the amplitude of the pressure wave signal to the resulting flow signal constituted the Impedance (Z) of the total respiratory system, from which the total resistance (R) and reactance (X) of the respiratory system were calculated[12,13]. In this study mean R and X values were calculated over a measurement period of 60 sec in the frequency range 5 - 35 Hz. During IOS measurement the children were sitting upright, their head resting against the back of the chair. They were instructed to breath quietly through a mouthpiece. To reduce loss of energy in the upper airways their cheeks and chin were supported by the hands of the investigator who was standing behind the patient.

Study protocol

After baseline IOS, FEV_1 and PEF measurement methacholine challenge was performed according to a standardised protocol. Methacholine bromide aerosols were generated by calibrated DeVillbiss 646 nebulizers which were attached to a Rosenthal dosimeter. During quiet breathing from FRC to TLC the dosimeter was triggered. After performing baseline measurements normal saline was inhaled to rule out non-specific reactions and subse-

quently methacholine was administered in doubling doses (3, 6, 12, 24, 50, 98, 196, 392 and 784 microgram methacholine). Three minutes after every dose of methacholine IOS, FEV_1 and PEF measurements were performed, each time in this same sequence. To prevent an unfavourable effect of deep inhalation on IOS parameters, IOS measurements were always performed immediately before FEV_1 and PEF measurements. Performance of all tests took 3 minutes. Provocation was continued until the dose at which FEV_1 had dropped 20% or more from baseline (PD_{20}). After achieving PD_{20} 400 microgram of salbutamol dose-aerosol was administered via a spacer device (Volumatic). Fifteen minutes after administration of salbutamol, all tests were performed in the same sequence as at baseline.

Statistical analysis

Distributions of parameters are summarised by mean (standard deviation), unless indicated otherwise. For comparison of paired data paired Student's t-tests were used. To study the relationship between FEV_1, PEF and IOS parameters Pearson's correlation coefficients were calculated. Both for t-tests and correlation coefficients statistical significance was assumed if p-values were < 0.05. Changes in FEV_1, PEF and R during methacholine challenge are expressed as percentage of baseline value. X values can not be expressed in this way, because these values range from negative to positive and cross the zero value in many children. In order to stratify the results of bronchial challenge for all children, the methacholine doses are expressed as the number of doubling doses prior to the maximal dose for each child. To describe the sensitivity and specificity of changes in PEF and IOS parameters in response to bronchial challenge in comparison to changes in FEV_1 receiver operating characteristic curves (ROC) were used[14]. The area under the ROC curve is a measure for the overall discriminatory performance of a test.

Results

Mean age of the children was 10.5 (3.5) years, height 146.6 (19.8) cm and weight 42.5 (14.6) kg.

Table 1. Values of FEV_1, PEF, R, and X at baseline after bronchial challenge and after subsequent bronchodilation in 19 children with mild to moderate asthma. All changes were significantly different from the prior level (all p values < 0.001).

	Baseline	post-challenge	Post-bonchodilator
FEV_1 (ml)	2251 (780)	1776 (639)	2351 (779)
PEF (ml)	2740 (873)	2310 (795)	2870 (869)
R5 (kPa/L/s)	.84 (.32)	1.27 (.36)	.70 (.29)
R10 (kPa/L/s)	.71 (.24)	.92 (.21)	.60 (.22)
R15 (kPa/L/s)	.62 (.21)	.75 (.18)	.53 (.17)
R20 (kPa/L/s)	.57 (.19)	.67 (.17)	.50 (.15)
R25 (kPa/L/s)	.54 (.17)	.63 (.16)	.50 (.13)
R35 (kPa/L/s)	.54 (.16)	.63 (.15)	.51 (.13)
X5 (kPa/L/s)	-.13 (.12)	-.35 (.25)	-.08 (.08)
X10 (kPa/L/s)	-.13 (.12)	-.36 (.21)	-.08 (.10)
X15 (kPa/L/s)	-.08 (.11)	-.26 (.14)	-.02 (.09)
X20 (kPa/L/s)	-.02 (.09)	-.15 (.10)	-.05 (.08)
X25 (kPa/L/s)	.04 (.08)	-.06 (.08)	.11 (.07)
X35 (kPa/L/s)	.18 (.06)	.11 (.09)	.23 (.06)

At baseline all children had normal lung function according to FEV_1 (mean 100.4 (17.1) % of predicted). After the maximal dose of methacholine FEV_1 fell significantly with simultaneously significant changes in PEF, R and X values at all frequencies ($p < 0.001$, Table 1). After inhalation of salbutamol all lung function parameters changed significantly compared to the post-challenge level ($p < 0.001$, Table 1). The largest changes in absolute values of R and X for both bronchoprovocation and bronchodilation were observed at the lower values of the frequency spectrum (especially at 5 and 10 Hz). No significant differences between baseline and post-bronchodilator values for any of the lung function parameters were observed (Table 1). Results of Pearson correlation coefficients between the 'gold standard' FEV_1 and PEF and R and X values are shown in Table 2. PEF, R5-35 and X5-25 correlated significantly with FEV_1, but X35 did not. The highest coefficients of correlation between FEV_1 and R and X values were seen at the lower frequencies (5, 10 and 15Hz).

Table 2. Pearson correlation coefficients between 'gold standard' measurements FEV_1 and PEF, R, and X values in 19 children with mild to moderate asthma.

	FEV_1
PEF	.83**
R5	-.71**
R10	-.73**
R15	-.71**
R20	-.70*
R25	-.63*
R35	-.65*
X5	.52*
X10	.57**
X15	.58**
X20	.58**
X25	.51*
X35	.02

** $p < 0.001$, * $p < 0.01$

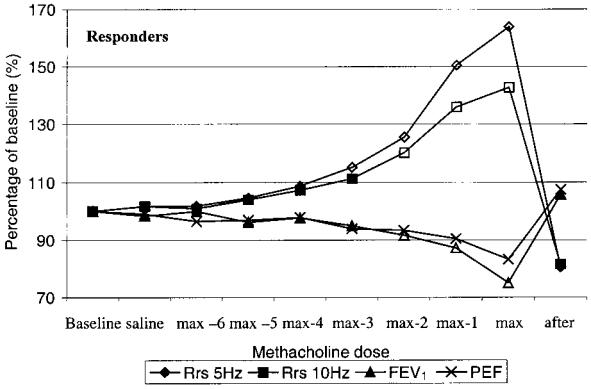

Figure 1. Relative changes in FEV_1, PEF, R5, and R10 (expressed as percentage change from baseline level) during methacholine challenge (expressed as number of doses prior to the maximal dose) and subsequent bronchodilation (after) in 14 children with a fall in FEV_1 of more than 20%. The open symbols represent changes statistically different from baseline value.

In 14 of all 19 children who completed the bronchial challenge test a more than 20% fall in FEV_1 was achieved (responders). The mean PD20 in these children was 98 microgram. In five children no threshold was achieved (non-responders). Figure 1 shows the relative changes during the challenge test of FEV_1, PEF and R5 and R10 (expressed as percentage of the absolute baseline value) of the responders. Figure 1 shows concomitant significant changes in FEV_1, PEF, and R10 from methacholine dose max-2, while R5 was already significantly increased from methacholine dose max-3. The rise in resistance (especially in R5) values preceded the fall in FEV_1 and PEF. In the non-responders also concomitant changes in FEV_1, PEF, R5 and R10 were observed, but these changes were not statistically significant (except for R5 at dose max-1).

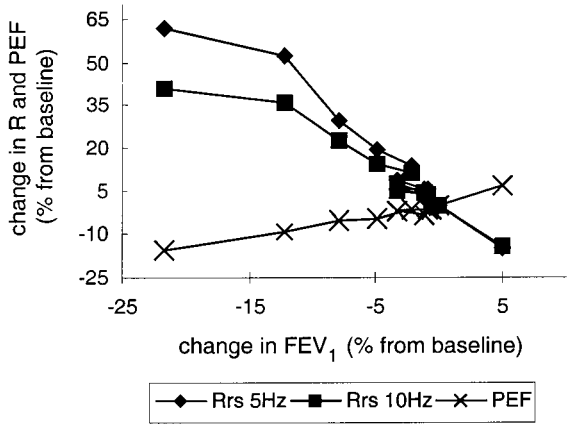

Figure 2. Relative changes in PEF, R5, and R10 (expressed as percentage change from baseline level) compared to the relative changes in FEV_1 during methacholine challenge and subsequent bronchodilation in 19 children with asthma.

Figure 2 shows the relationship between mean changes (expressed as relative changes compared to baseline values) in FEV_1 and in PEF, R5 and R10 during bronchoprovocation (negative changes) and bronchodilation (positive changes). This Figure shows a linear relationship between changes in FEV_1 and PEF, but a curvilinear relationship between changes in FEV_1 and R5 and R10.

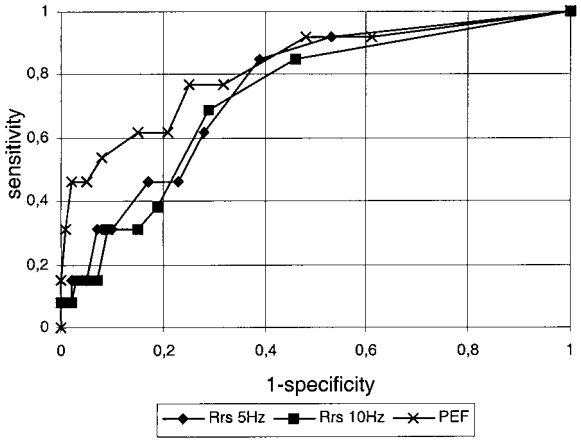

Figure 3. Receiver operating characteristic curve describing the relationship between sensitivity and specificity of changes in PEF, R5, and R10 to detect a 20% fall of FEV_1 during methacholine challenge.

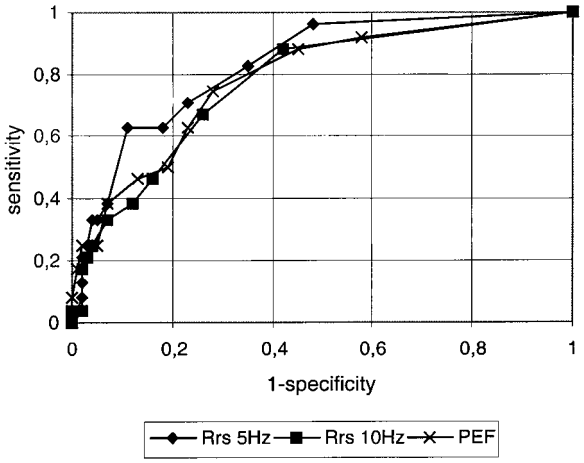

Figure 4. Receiver operating characteristic curve describing the relationship between sensitivity and specificity of changes in PEF, R5, and R10 to detect a 15% fall of FEV_1 during methacholine challenge.

A ROC curve of the sensitivity and specificity of changes in PEF and R5 and R10 as a measure to detect a 20% fall in FEV_1 during bronchial challenge is shown in Figure 3. The area under the ROC curve for PEF > R5 > R10 (0.80, 0.75, and 0.68, respectively). Because this study showed that the rise in resistance values preceded the fall in FEV_1 and PEF (Figure 1) a second ROC curve was constructed, combining sensitivity and specificity of changes in PEF and R5 and R10 to predict a 15% fall in FEV_1 (Figure 4). The area under the ROC curve for R5 > PEF > R10 (0.85, 0.79, and 0.73, respectively). An increase in R5 of 50% to baseline showed an optimal combination of sensitivity and specificity to detect a 15% fall in FEV_1 (0.63 and 0.89 , respectively).

Discussion

The present study showed significant changes in all lung function parameters after methacholine and salbutamol induced changes in airflow obstruction in children with asthma. Resistance (R) and reactance (X) values as measured with IOS were significantly correlated with the 'gold standard' FEV_1, R-values correlated better with FEV_1 than X-values. The sensitivity of R and X to experimentally induced changes in airway obstruction was best at the lowest frequencies, especially at 5 to 15 Hz. This study also showed that during bronchial challenge a rise in resistance values preceded the fall in FEV_1, which shows that both parameters are likely to reflect different pathophysiological aspects of airflow obstruction.

FEV_1 is a widely accepted and well standardised parameter of airflow obstruction[1]. In patients with neuromuscular diseases and in children under the age of five years, the parameter is often not useful, because FEV_1 measurement requires forced expiratory manoeuvres. These groups of patients lack co-ordination and co-operation. Kanengiser and Dozor showed that only 32% of children aged three to five years do meet the ATS criteria of reproducibility[7]. Therefore, in this study we studied children aged 5 to 17 years, to be sure of a reliable 'gold standard' for airflow obstruction. All children met the ATS criteria of acceptability and reproducibility[1].

Home PEF meters are often recommended in monitoring airflow obstruction and bronchial hyperresponsiveness in patients with asthma[15,16]. In this study PEF measurements were performed to compare the sensitivity and specificity of this well-known parameter with the values of the relatively new IOS parameters.

PEF values were strongly correlated with FEV_1 values (Table 2), and fell significantly after bronchial challenge and restored to baseline values after subsequent bronchodilation (Table 1). Changes in FEV_1 linearly correlated with somewhat smaller changes in PEF (Figure 2). These results show that PEF values can be easily used in population-based studies as a surrogate when FEV_1 is not available as a 'gold standard' for airway obstruction. However, in individual subjects the use of PEF values to detect a predefined level of airflow obstruction is hampered by suboptimal sensitivity and specificity of the parameter (Figures 3 and 4). The PEF results of the present study in children confirm the data from literature[17] and are in line with findings in adults[18].

In this study results of a relatively recently described technique, the Impulse Oscillation System (IOS) were compared with results of forced breathing tests. The indices derived from IOS (R and X) are in principle comparable to those obtained by the pseudo random noise method of Landsèr and coworkers[19]. This method has proved to be valuable for measuring lung function and bronchial hyperresponsiveness in young children[20]. High technical requirements to the recording systems, energy loss in the upper airways and lack of sensitivity, especially at the higher frequencies impeded widespread use of oscillation techniques. Recently, the Impulse Oscillation System became commercially available and good sensitivity of R and X measured at 5Hz for methacholine induced lung function changes were described in 2-4 and 4-6-year-old children[21,22]. The method is easy to perform and might be helpful as a routine diagnostic.

In this study significant changes in mean values of both R and X values at all frequencies were observed after bronchoprovocation and subsequent bronchodilation (Table 1). Significant correlation of R and X values with FEV_1 was observed, especially when measured at low frequencies (5 - 10 Hz) (Table 2). Other studies also showed that R and X values, especially R values at 5Hz were most sensitive to changes in airflow obstruction[21-23]. In a recent study R_5 and X_5 values were used to study lung function in groups of young asthmatic children[24]. These data show that IOS R and X values measured at 5 and 10 Hz can be useful in population-based studies, which can be attractive in patients who are not able to perform forced

breathing manoeuvres, like patients with neurological or muscular disorders and young children.

When lung function parameters are used to quantify changes in airflow obstruction, changes have to be expressed relative to baseline values. In children, lung function parameters are most time related to weight or height, and this also true for R5 and X5 values[25]. Both deterioration (e.g. during bronchial challenge) and improvement (e.g. during reversibility testing) of lung function changes in children are to be expressed as a percentage of baseline values[26]. In this study changes in R values but not in X values can be expressed in this way. X values range from negative to positive in many subjects (Table 1). Expression of changes in X-values as a percentage of baseline values would result in unrealistic or impossible numbers. For this reason only R values are helpful to quantify relative changes in individual subjects.

In this study a gradual increase in R values was observed during bronchial challenge both in children who reached a FEV_1 related PD20 level (Figure 1) and those who did not. The increase in R values during the challenge in the non-responder group was not statistically significant (except for R5 at methacholine dose max -1). In the responder group, R values were already rising (R5 significantly at methacholine dose max -3) while FEV_1 values were still unaffected (Figure 1). The relationship between changes in FEV_1 and changes in R5 and R10 were further analysed in Figure 3. This Figure shows a curvilinear relationship between changes in FEV_1 and R values, with large changes in R5 and R10 when FEV_1 changes from 100 to 90% of baseline value and rather small changes of R5 and R10 when FEV_1 further decreases from 90 to 80% of baseline value. The curvilinear relationship between changes in FEV_1 and changes in R5 and R10, in contrast to a linear relationship between changes in FEV_1 and PEF suggest that FEV_1 and R values are likely to reflect different pathophysiological aspects of airflow obstruction. FEV_1 is measured during maximal expiration from the maximal inspiratory lung volume, while R values are measured during tidal breathing. Airway resistance is known to be related to lung volume[27]. Changes in FEV_1 values are largely caused by changes in airflow limitation, while R values are more directly related to airway calibre.

The present study shows that the sensitivity and specificity of R5 and R10 to detect a 20% fall in 'gold standard' FEV_1 do not exceed the performance of PEF values, resulting in a smaller area under the ROC curve (Figure 3). However our results showed that changes in R were more sensitive to detect smaller changes in FEV_1 in subjects with normal baseline lung func-

tion. The best combination of sensitivity and specificity to detect a 15% fall in FEV_1 was observed when an increase of 50% compared to baseline R5 values was chosen as cut-off point. The area under the ROC curve for R5 (0.85) exceeded the area for PEF and R10 (0.79 and 0.73, respectively, Figure 4), but was also superior to the area under the curve for PEF in the detection of a 20% fall in FEV_1 (0.80, Figure 3). These findings suggest that IOS R5 measurements can be used as a parameter in bronchial challenge testing in individual subjects with normal baseline lung function.

In conclusion, R and X values can easily be acquired using the IOS. They showed significant changes during changes in airflow obstruction and have significant correlation with FEV_1. In groups of patients, R5 and X5 can be used as an indirect measure of airflow obstruction. In individual patients R5 showed to be superior to PEF measurements in the detection of a 15% fall in FEV_1. Although the parameters do not exactly reflect the 'gold standard' FEV_1, this technique might be helpful in patients who are not able to perform forced breathing manoeuvres.

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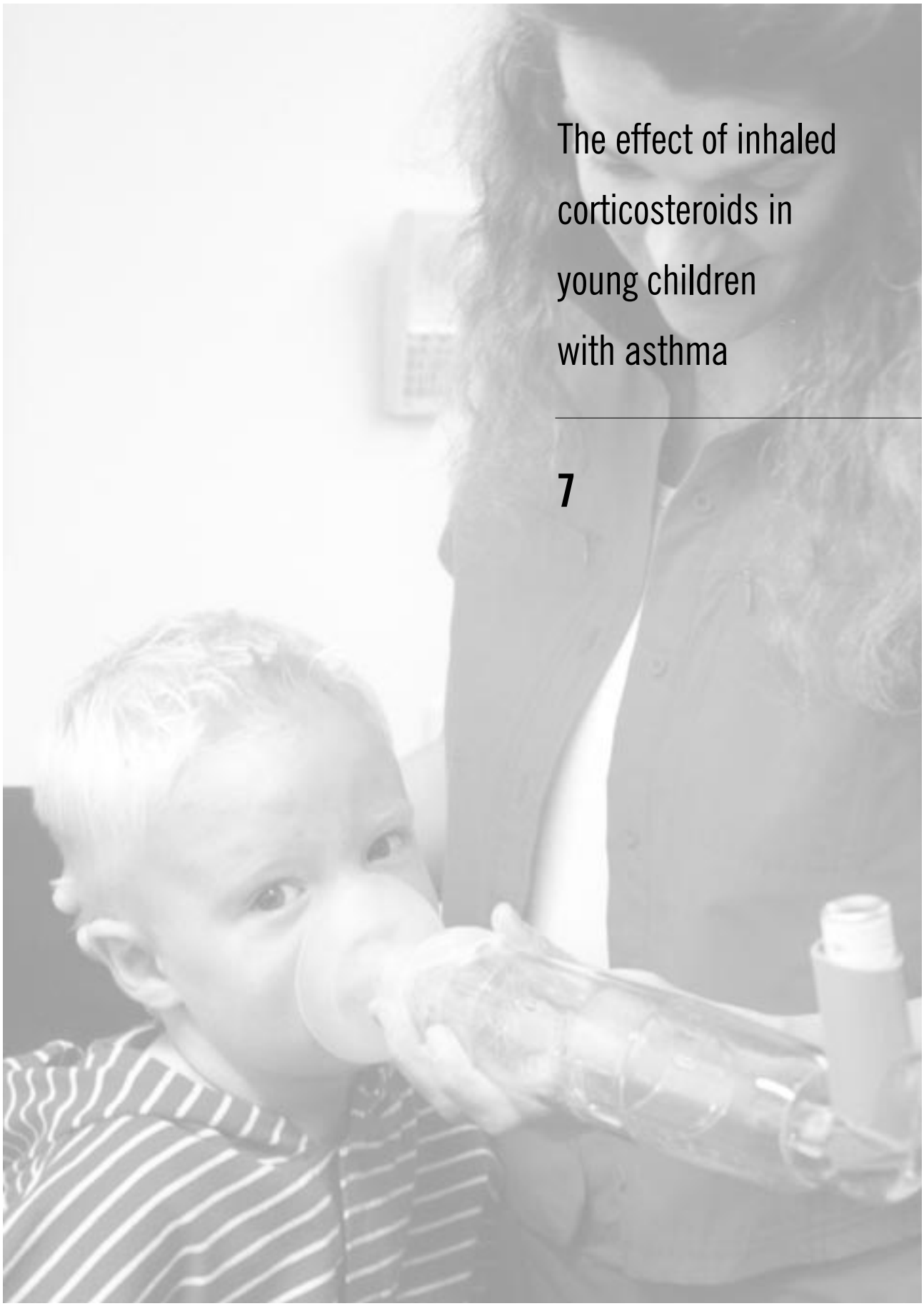

The effect of inhaled corticosteroids in young children with asthma

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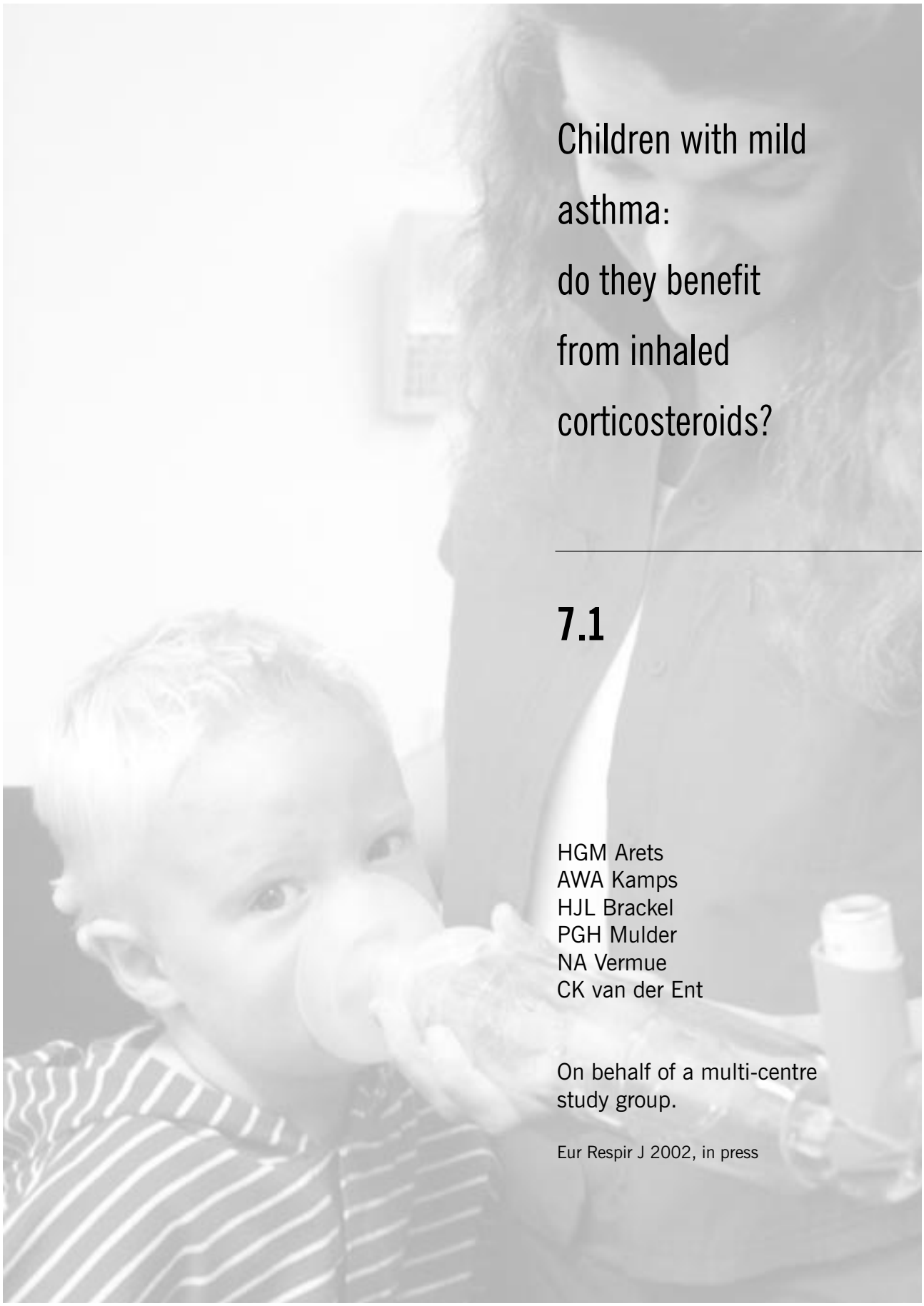

Children with mild asthma: do they benefit from inhaled corticosteroids?

7.1

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On behalf of a multi-centre study group.

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Abstract

In children with mild asthma, who show hardly any abnormalities in pulmonary function, objective measurement of the effect of inhaled corticosteroids (ICS) is difficult.

We evaluated the short term effect of fluticasone propionate (FP) in these children, using both subjective and objective parameters. 68 children (5-10 years old) were randomly assigned to either FP 250 μg or placebo twice daily as pMDI via spacer during 12 weeks. Symptom scores, use of rescue medication, wheezing, parent global evaluation and pulmonary function tests (PFTs) including forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF) and bronchial responsiveness were evaluated.

FP treated versus placebo treated children showed significant changes in % symptom free days (OR FP versus placebo =1.9, p=0.03), use of β2-mimetics (OR=3.08, p<0.01), morning (+16L/min, p<0.01) and evening PEF (+19 L/min, p<0.01), FEV_1%pred (+4.6%, p=0.04) and wheezing (OR=0.38, p=0.04). No significant improvements were found for parent global evaluation, absolute values of FEV_1, nor for PD20.

These findings show that ICS are effective in children with mild asthma. This effect can be assessed by both objective and subjective parameters. Even when pulmonary function is normal early start of ICS should be considered.

Introduction

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory drugs in the treatment of asthma in both children and adults. They reduce symptoms and number of hospitalisations, improve pulmonary function and bronchial hyperresponsiveness (BHR)[1-3] and are more effective than β2-agonist alone[4]. International guidelines consider ICS to be indicated in moderate to severe asthma, but more recent studies promote their use as well in less symptomatic and also in younger patients, because this approach might prevent permanent impairment of pulmonary function and irreversible structural airway remodelling[5-7]. However, until now international consensus reports do not recommend the use of ICS in subjects who have only mild and infrequent symptoms and who have normal airway calibre most of the time[8].

In patients with severe and moderate asthma PFT parameters abnormal and can be used as effect parameters to evaluate ICS treatment. However, these parameters are often in the normal range in patients with mild asthma. In children these normal ranges are wide and PFT parameters could be decreased in a relative sense and show improvement after proper treatment. Especially in young children there is a lack of proper effect parameters. Symptom scores and the use of short-acting β2-agonists are the most frequently used parameters, but these are sensitive to placebo effects (4). There are only few studies on the short[9,10] or long term effect[11] of ICS in children with mild asthma. Especially placebo controlled studies are rare[12-14].The aim of this study was to evaluate the effect of short term treatment with ICS on both subjective and objective disease parameters in 5-10 year old children with mild asthma.

Patients and Methods

Patients

5-10 years old children with a doctor's diagnosis of asthma[15] were recruited. Patients were excluded if prior to the study they had used systemic cor-

ticosteroids in the last 2 months, ICS >100 μg budesonide (BUD) or beclomethasone dipropionate (BDP) daily in the last 4 weeks, salbutamol >1600 μg daily during more than 30% of days of the last year prior, if they had been hospitalised for asthma in the last 2 weeks or if they had other respiratory disorders, systemic disease or anatomical abnormalities. Written informed consent was obtained from parents of all participating patients.
Power analysis was performed with percentage of days without asthma symptoms as calculated from the diary cards as the primary outcome variable. For the power calculation the change from baseline of this variable was used. The standard deviation of this change was set at 30 percent points. The clinically relevant difference of change from baseline between the placebo group and the FP group was set at 20 percent points. To detect this difference with 80% power, 35 patients per treatment group were needed, given a test size of 5% (two sided).

Study Design and methods

This was a multi-centre, double blind, placebo controlled, randomised, parallel group study. Patients were recruited from one paediatric pulmonology outpatient clinic of a university hospital, one asthma centre and seven general hospitals. The study was approved by all local ethic committees.
Subjects were randomly assigned to use either two puffs of FP 125 μg or two puffs of placebo bd from a pMDI via a plastic spacer device (Volumatic, Glaxo Wellcome, Zeist, The Netherlands) during 12 weeks.
During the whole study salbutamol 200 μg via spacer was allowed as rescue medication. Exacerbation of asthma, defined as an increase in asthma symptoms not controlled with salbutamol up to 8 times 2 puffs daily, was treated at the discretion of the investigator with prednisolone 1-2 mg/kg daily during 3 days.
At visit 1, at the beginning of a 2 week run in period, the study was explained, medical history, concurrent medication and demography were recorded, together with the presence or absence of wheezing and PFTs were performed. Parents and children were instructed to use the PEF meter at home, to fill out the daily record card (DRC) and to use rescue medication if necessary. After comprehensive instructions they were able to inhale medication properly via a spacer device and perform PEF measurements. Only patients using BDP or BUD < 100 μg daily, prior to the study, were instructed to continue this medication throughout the study in addition to

the study medication.
At visit 2 after 14±3 days only patients with symptoms on at least 50% of days during the run in period were randomised, excluding patients who used rescue medication > 8 puffs/day on >4 days during the run in period. Further visits were scheduled 3, 11 and 12 weeks later (visit 3, 4 and 5 respectively). At all visits baseline PFTs were performed. At visit 2 and 4 bronchoprovocation tests were performed after baseline PFT. At every visit adverse events, concurrent medication, asthma exacerbations and compliance with the study were checked.

Assessments

Throughout the study the parents filled out a DRC for presence of asthmatic symptoms, use of rescue medication, both morning and evening PEF, adverse events and concurrent medication.
PEF measurements were performed using the Personal Best PEF meter (Healthscan, Cedar Grove, NJ, USA). The highest value of a minimum of three acceptable measurements was recorded.
Maximal expiratory flow volume (MEFV) measurements were performed conform the ECCS recommendations[16] using a pneumotachometer system (Masterscreen Pneumo, Erich Jaeger, Würzburg, Germany). The best of three technically good measurements was recorded. The following parameters were recorded: FEV_1 and FEV_1 as percentage of predicted (FEV_1%pred)[17]. No bronchodilator had been used less than 8 hours before PFT.
Bronchial responsiveness was measured using methacholine bromide provocation according to a standardised protocol[18].
At all visits wheezing, defined as the presence of a prolonged audible expiratory phase during auscultation and/or use of accessory respiratory muscles, was judged on physical examination by the same paediatrician. During the last visit the parents were asked to rate the effect of study medication on symptoms on a scale from 1 (strongly improved) to 4 (worsened).

Data analysis

The symptoms and use of rescue medication were summarised daily as symptom-free (yes/no) and rescue medication-free (yes/no). Within each

patient these daily scores constituted a series of repeated 0/1 data that were analysed using a generalised linear model for repeated measurements with model fitting based on Generalised Estimating Equations (GEE)[19]. Because of the binary (0/1) outcome scores, the binomial distribution was assumed with the dependency of the probability parameter on the explanatory variables modelled through a logistic function. The day to day correlation structure of the outcome scores was assumed to be first order auto-regressive ("AR(1)"). In the logistic model the treatment effect was represented by an odds ratio (OR) (95% confidence interval (CI)) of active relative to placebo treatment. Adjustment was made for the percentage of (%) symptom free (or rescue medication free) days during the baseline period as continuous cavort and for time under treatment defined by four consecutive periods of three weeks as a within patient factor. The point of dividing the treatment period in four equal periods of 3 weeks was to find a general categorical treatment by time interaction without having to assume a priori a linear trend in this treatment by time interaction. The interaction between treatment and time was tested. If this interaction turned out to be significant with $p < 0.10$, then the treatment effect was presented per period. Else, one overall treatment effect (assumed to be constant in time) was presented.

Morning and evening PEF values, measured at home were used to calculate 3-week averages per patient for each of the four 3-week periods, for morning and evening separately. These averages constituted the four repeated measurements of the outcome variable, which were analysed using mixed model ANOVA. The independent variables in this analysis were treatment group (a 2-level between patient factor) and period (a 4-level within patients factor); the average PEF per patient over the baseline period was included in the model as a continuous cavort. An AR(1) correlation structure between the repeated measures was assumed. The treatment by period interaction was tested and dealt with as described for DRC data.

Repeated PFTs were performed at baseline and three times during the 12 weeks treatment period. In a mixed model analysis of variance (ANOVA) the values of each PFT parameter during treatment were compared between the two treatment groups, adjusted for period (3 levels) and baseline measurement of the outcome variable at hand. Also the treatment by period interaction was tested and dealt with as described for DRC data. No structure was assumed for the (co)variance matrix of the residuals.

The dose of methacholine causing a 20% decrease of FEV_1 (PD20) was analysed as doubling doses after ln_2-transformation using non-parametric

tests, because values higher than 8 were coded as 8. The PD20 at visit 3 was compared between the two treatment groups, using the Mann-Whitney test. Within group changes from baseline were tested using the paired Wilcoxon test. PD20 was also analysed after dichotomization in hyperresponsive yes (ln_2 PD20 < 8) versus no. The measurement at visit 3 was compared between the two treatment groups using logistic regression analysis, with the baseline score as covariant. The treatment effect could then be expressed as an OR, adjusted for baseline.
There were four repeated physical examinations during the 12 weeks treatment period: visit 2 to 5. The absence or presence of wheezing was analysed using the same generalised linear model as described for DRC parameters. The between visit correlation structure of the responses was left unstructured. The treatment effect was represented by an OR (95% CI) of active versus placebo.
The parent global evaluation for both treatment arms was compared using the χ^2 trend test.

Results

88 patients entered the run in period. 20 patients were withdrawn before randomisation, due to insufficient asthmatic symptoms (n=14), too frequent use of rescue medication (n=1), poor compliance (n=2), an asthma exacerbation (n=1), adverse effect of salbutamol (n=1) and withdrawal of parental informed consent on second thoughts (n=1) during the run in period. 68 patients were randomised and completed the study.
Patient baseline characteristics are shown in Table 1. There were no significant differences between withdrawn patients and included patients nor between patients in both treatment arms. During the run in period mean symptom scores and clinical scoring indices were low and mean pulmonary function parameters were within normal ranges.
Prior to the study 6 patients received maintenance treatment with budesonide (4) or beclomethasone < 100 μg daily (2). These ICS were continued by 1 (3%) and 5(15%) of FP and placebo treated patients respectively. There were no significant differences between both treatment arms in number of asthma exacerbations, adverse events, concurrent medication, and compliance with the study.

Table 1. Patient demographics and baseline characteristics

	fluticasone	Placebo	drop outs
n	35	33	20
sex F/M	16/19	10/23	5/15
age(yrs)	6.86 (1.5)	6.97 (1.48)	6.55 (1.7)
height(cms)	127 (10.2)	126 (10.4)	124.1 (9.8)
weight(kg)	24.6(4.4)	27.4 (6.7)	25.2 (5.2)
% symptom free days (%)	16.2 (20.7)	10.6 (15.9)	
% rescue med free days (%)	49.4 (36.3)	45.8 (38.3)	
FEV_1 (L)	1.54 (0.37)	1.53 (0.39)	
FEV_1 (%pred)	104.1 (10.8)	99.8 (17.0)	
bronchodil. response (FEV_1%pred)	6.9 (6.2)	10.9 (6.2)	
FVC (%pred)	99.0 (10.8)	94.1 (18.7)	
tPTEF/tE (%)	27.4 (7.7)	26.4 (7.6)	
PEF morning at home(L/min)	213.4 (63.9)	210.6 (58.6)	
PEF evening at home(L/min)	219.1 (62.3)	219.8 (58.0)	
PEF at laboratory (L/min)	231.7 (68.6)	228.6 (70.5)	
ln_2 PD20	6.8 (1.9)	5.8 (2.1)	

Values are presented as mean (SD) unless stated otherwise. Percentage of symptom free and percentage of rescue free days were calculated from the 14 ±3 days during the run in period. ln_2 PD20 was measured at visit 2. All other baseline characteristics were determined at the beginning of the run in period.

Symptom score, use of rescue medication and home PEF assessments.

The mean % symptom free days increased from 14% during the run in period to 25-49% in the placebo versus 42-66% in the FP treated group over the four consecutive periods (Figure 1). The estimated OR for FP versus placebo was 1.93 (95% CI 1.05-3.54; p=0.04). There was no suspicion that the OR changed in time (p=0.89).

The mean % rescue medication free days increased from 48% to 57-67% in the placebo versus 83-86% in the FP treated group over the four periods (Figure 2). The estimated OR of FP versus placebo was 3.08 (95% CI:1.49-6.36; p<0.01) without suspicion of changes of OR in time (p=0.76).

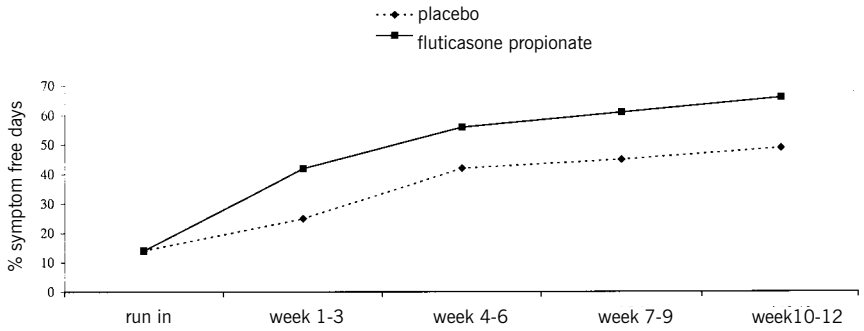

Figure 1. Changes in % symptom free days adjusted for baseline during 12 weeks of treatment with study medication.

The mean difference in PEF between the FP and placebo treated group varied significantly over the periods ($p<0.10$) both for morning ($p=0.01$) and evening ($p=0.09$) values. Mean PEF was higher in the FP treated than in the placebo treated group (Figure 3). For morning PEF the mean differences between both groups was 16 L/min ($p<0.01$), varying from 11 to 24 L/min, for evening PEF this was 19 L/min ($p<0.01$), varying from 14 to 26 L/min. For all periods these effects were significant.

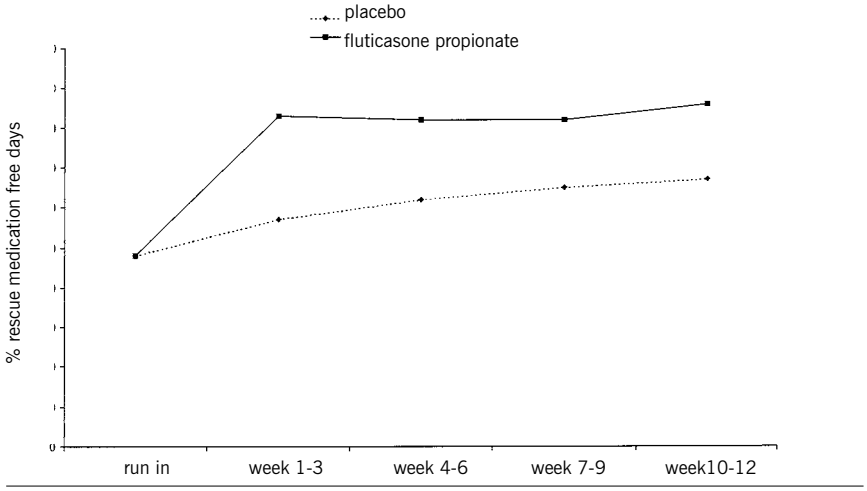

Figure 2. Changes in % rescue medication free days adjusted for baseline during 12 weeks of treatment with study medication.

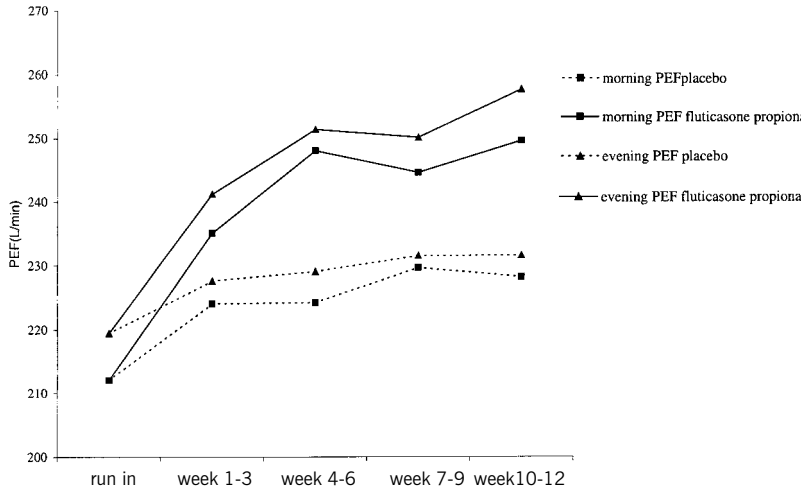

Figure 3. Changes in morning and evening PEF values adjusted for baseline during 12 weeks of treatment with study medication.

Pulmonary function tests

Compared to placebo treated children absolute values of FEV_1 (FEV_1abs) showed no significant change (+0.06 L, p=0.08), but there was a small but significant increase in FEV_1%pred in the FP treated children (+4.6%, p=0.04) (Figure 4).

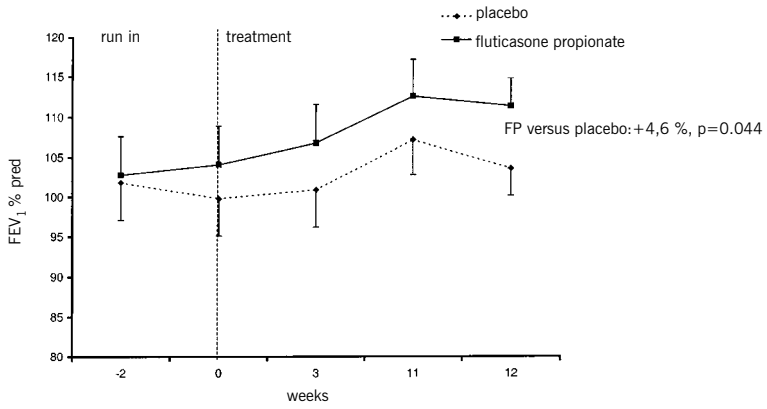

Figure 4. Changes in FEV_1%pred (+ SE) during 12 weeks of treatment with study medication.

After 11 weeks of treatment ln_2 PD20 was significantly higher in the FP treated group compared to placebo (7.14 versus 5.96, p=0.04) but there was no significant difference between the two groups in change of ln_2 PD20 from baseline to week 11 (p=0.11).

Wheezing score.

At the end of treatment 32 of 35 FP treated (91%) and 26 of 33 (79%) placebo treated patients showed normal wheezing scores. This difference was not statistically significant (p=0.11), but significant improvement in wheezing score were seen in the FP versus placebo group at visit 4 (p=0.008 respectively), not at other visits. The OR for FP versus placebo for wheezing was 0.38 (95%CI 0.15-0.96, p=0.04) for the whole study period.

Parent global evaluation

71% of parents of FP treated versus 52% of placebo treated children reported an improvement of symptoms. Increasing symptoms were experienced by 15% of parents of placebo versus 0% of FP treated children. This difference was not significant (p=0.062).

Discussion

In this study the effects of ICS in 5-10 year old children with mild asthma was compared to placebo, using both subjective and objective parameters. Treatment with FP significantly improved % symptom free days, % rescue medication free days, both morning and evening PEF values, FEV_1%pred and wheezing score. No significant improvements were found for parent global evaluation, absolute values of FEV_1 and PD20.
In mildly symptomatic adult patients there is evidence of airway inflammation, improving after treatment with ICS[20]. In adults improvement of night time symptoms, rescue medication use and morning PEF were recorded as well[21].

Until now only few studies evaluated the effect of ICS in children with mild asthma[9-13]. Most of these studies were performed in older children and using different effect parameters. Partially contradictory results were found. Effects were found on symptom scores. Some found improvement of PEF values[9,10], others did not or found only improvements in evening, not in morning PEF[12,13]. Hoekx et al. found a significant improvement of PEF values in older children after 8 weeks of treatment with both FP 400 μg and budesonide 400 μg, despite the fact that at the beginning of the study the lung function was near normal. However, the latter study was not placebo controlled and patients were not steroid naive[10]. An improvement of bronchial responsiveness in children with mild asthma was described in two papers[12,13]. In contrast to the present study, no significant effect on FEV_1 was found in most studies[9-13].

The present study provides further evidence for a positive effect of ICS in children with only mild asthma. The conjecture that asthma in the patients studied was mild is supported by the fact that at an age > 5 years most of the patients were not treated with anti-inflammatory agents, on average had mild symptoms, pulmonary function and bronchial responsiveness were rather normal and salbutamol use was low. Still improvements in both subjective and objective effect parameters were found. Most prominent were changes in symptom scores and use of rescue medication, but significant changes were found in PFT results as well. No significant changes in BHR were recorded.

The use of symptom scores and use of rescue medication is easy and can be used even in young children who cannot perform lung function tests. The participating patients were selected on basis of symptoms and the use of B2 agonists, so that bias because of regression to the mean may have caused part of the improvements in both the treatment and placebo groups.

Although baseline FEV_1%pred values were high (>100% pred) and reversibility was poor in contrast to other studies[12,13] a small, though significant improvement in FEV_1%pred was recorded after only 12 weeks of treatment. The only comparable study was performed by Jonasson et al[12]. In a later study, they also found a significant dose response effect on FEV_1 in a 24 months follow up study with ICS in 122 mildly asthmatic children[14]. Recently, in a large, placebo controlled, long term study, the Childhood Asthma Management Program Research Group found significant improvements of pre bronchodilator FEV_1%pred and FEV_1/FVC (%) in mildly to moderately symptomatic 5-12 year old children after 4-6 years treatment with BUD. However, the improvement of FEV_1%pred was

attributed to a smaller stature in the BUD treated group. Also airway responsiveness and symptom control improved[11].

The present study shows that in children with mild asthma pulmonary function can improve after only short term treatment. Improvements are only small but significant, especially when normal baseline parameters are considered. Normal lung function in children with symptoms of asthma does not rule out airway obstruction, improving after proper treatment.

As in earlier reports this study demonstrated that after the start of ICS treatment the improvement of PEF and symptoms often precede the improvement of other lung function parameters[4]. In the present relatively short study it could be expected that these parameters would change most prominently. The improvement of PFT parameters gradually increased during the study (Fig 3 and 4). Earlier studies in children with normal lung function may have been too short or the ICS dose too low to observe these effects.

In the present study no changes in BHR were found in both treatment arms. The finding of BHR in this study population indicates that airway inflammation is present even in mild asthma. Although this finding supports treatment with ICS, no significant benefit of treatment on BHR could be established in the present study. As mentioned before this may be due to the relatively short treatment period and is in agreement with the existing concept that improvement of BHR is a relatively late response after institution of ICS and that improvement can continue over years. Van Essen Zandvliet et al showed that reduction in BHR increases gradually and only stabilises after 20 months of treatment with ICS[4]. The value of long term treatment and the possible preventive effects on remodelling still need to be established.

Normally lower doses of ICS are used for treatment of children with moderate (or mild) asthma. However larger doses are sometimes used by paediatricians and paediatric pulmonologists especially in a step down therapy. With the present dose we did not expect serious adverse reactions in this relatively short study, while optimal treatment effects could be expected, compared to placebo.

In conclusion, in 5-10 year old children with mild asthma treatment with FP results in improvement of symptoms, salbutamol use, PEF and FEV_1%pred. These findings suggest that normal lung function does not rule out airway obstruction and even in young patients with mild asthma early start of ICS maintenance might be considered. In view of these results and the emerging knowledge of long term airway remodelling in patients with chronic asthma treatment of mildly asthmatic patients with ICS is recommended.

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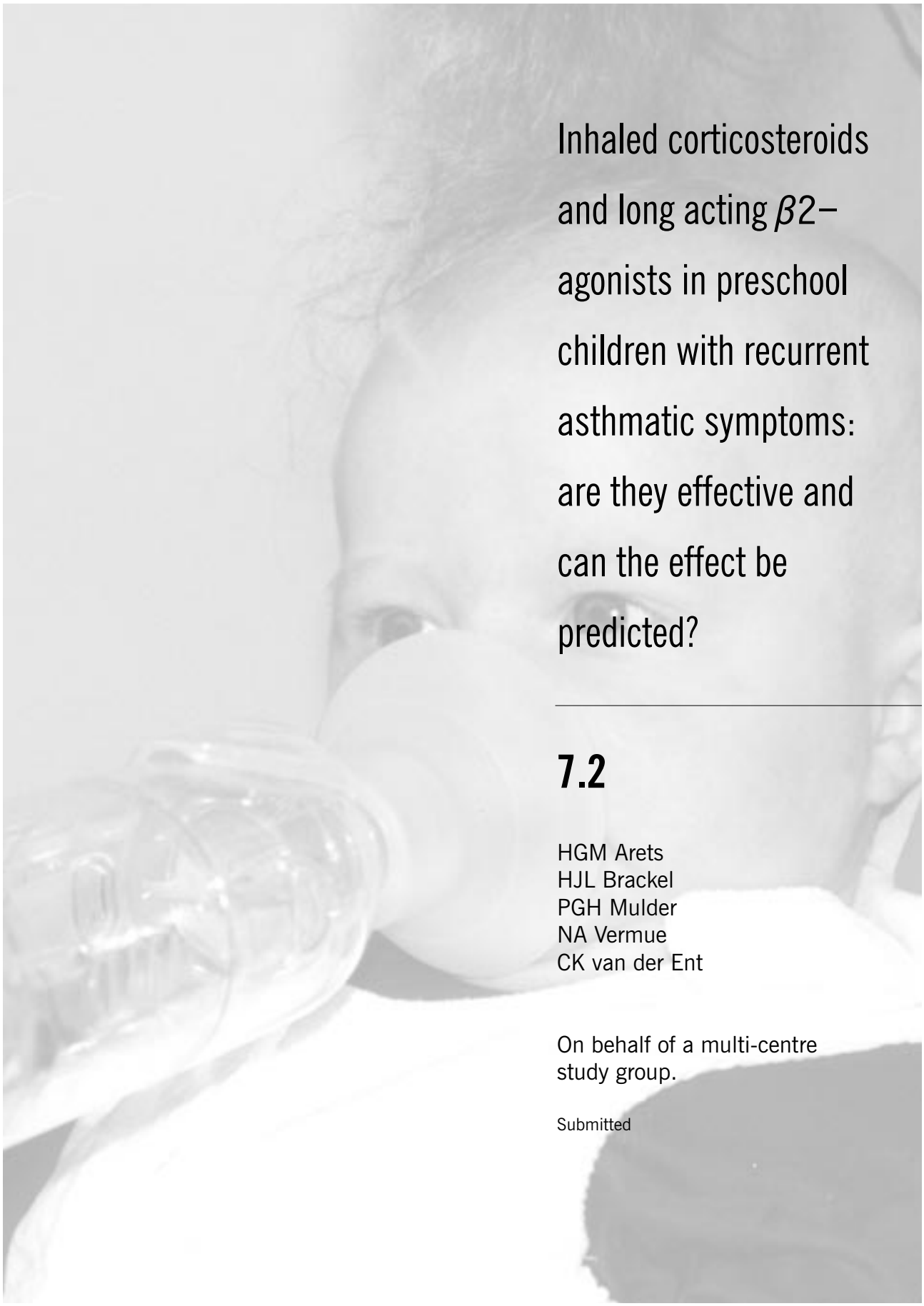

Inhaled corticosteroids and long acting $\beta 2$–agonists in preschool children with recurrent asthmatic symptoms: are they effective and can the effect be predicted?

7.2

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On behalf of a multi-centre study group.

Submitted

Abstract

We evaluated the short term effects of inhaled corticosteroids in pre-school children with recurrent or chronic asthma-like symptoms, using both subjective and objective parameters. The predictive power of several baseline characteristics for this effect was studied too.

99 children (1-4 years old) were randomly assigned to receive either fluticasone propionate (FP) 250 µg or placebo twice daily during 6 weeks. Changes in symptom scores, use of rescue medication and pulmonary function test (PFT) parameters were assessed. Interrupter resistance (Rint), oscillation resistance and reactance (R5 and X5) and time and volume to peak tidal expiratory flow divided by total expiratory time (or volume) (*t*PTEF/*t*E and VPTEF/VE respectively) were measured.

FP treated children showed significant improvements of Rint ($p = 0.024$), *t*PTEF/*t*E ($p = 0.009$) and VPTEF/VE ($p = 0.003$), compared to placebo. Almost significant changes were found for R5 ($p = 0.13$) and X5 ($p = 0.07$). No significant changes in % symptom free days or % rescue medication free days were found. PFT improvement could not be predicted from baseline characteristics, but children with decreased baseline pulmonary function showed the best improvement of subjective markers.

We conclude that the effect of 6 weeks treatment with ICS in pre-school children with asthma-like symptoms is best demonstrated by PFT markers, not by subjective markers. Decreased pulmonary function appears to predispose to a beneficial effect.

Introduction

During early childhood as many as 40% of children experience recurrent asthmatic symptoms such as wheezing, cough or breathlessness[1]. In more than half of these children symptoms disappear around the age of 6 years. These symptoms are thought to reflect congenitally narrow airways, which predispose to wheezing during viral infections[2]. In other children symptoms persist and the latter group is eventually labelled as asthma. Pulmonary function testing (PFT) in asthmatic children shows bronchial hyperresponsiveness and bronchodilator responsiveness. Many of these patients have a positive family history for atopy and personal skin prick test positivity and increased levels of total and specific IgE.

The treatment of asthma with inhaled corticosteroids (ICS) has shown to be effective and safe in adults and older children[3,4]. There is a tendency to treat young children with recurrent asthmatic symptoms in a similar way. However, in most of these patients the diagnosis of asthma is uncertain and the effect of ICS is less well established.

Few studies concentrate on the effect of ICS in pre-school children. Some small clinical trials showed variable effects of continuous, prophylactic treatment with ICS in pre-school children[5-10]. Recently some bigger studies showed improvement in "subjective" effect parameters during treatment with ICS[11,12].

One of the major problems in evaluating the effect of ICS in pre school children is the lack of proper objective effect parameters. In most studies only subjective parameters as symptom scores, use of rescue medication and number of exacerbations were used. Objective effect parameters of ICS have been used scarcely in pre-school children[13].

Although there are certain "predictors" of asthma in pre school children, there is no readily available instrument to identify pre-school children with recurrent asthmatic symptoms who will benefit from ICS treatment.

The purpose of this study was to evaluate both the subjective and objective effects of ICS treatment in symptomatic 1-4 year old children with recurrent or chronic respiratory symptoms and to determine specific patient characteristics and risk factors that might predict these effects.

Methods

The primary efficacy endpoint of this study was the effect of treatment on percentage (%) of symptom free days and the secondary endpoints the effect on % rescue free days and change in lung function parameters.
This was a prospective double blind, placebo controlled, randomised, parallel group study, conducted at the outpatient departments of 8 centres in the Netherlands (one paediatric pulmonology department of a university hospital and seven general hospitals) conform the Declaration of Helsinki and Good Clinical Practice[14]. The study was approved by all local ethic committees and written informed consent was obtained from parents of all participating patients.
For the power calculation the change from baseline of % symptom free days was used. The standard deviation of this change was set at 29 percent points (calculated from the study by Bisgaard et al.[11]. The clinically relevant difference of change from baseline between the placebo group and the FP group was set at 15 percent points. To detect this difference with 75% power, 50 patients per treatment group were needed, given a test size of 5% (two-sided). Study drugs were randomly assigned numbers in blocks and arbitrarily distributed among sites and each patient was assigned a medication number on entry. Treatment assignments were not known to patient nor investigator during or after the trial.

Study population.

Children aged 12-48 months with a documented history of recurrent (≥ 5 periods of ≥ 10 days during the last year) or persistent (≥ 1 month) asthmatic symptoms (coughing, wheezing and/or breathlessness) were recruited for this study. Patients were excluded if they had used systemic corticosteroids or inhaled corticosteroids in the 2 months and 1 month before the run in period, respectively. Patients were excluded if they had used salbutamol ≥ 800 µg daily during more than 30% of days of the year prior to the study, had been hospitalised for their asthma in the 2 weeks prior to the study or had other respiratory disorders, systemic disease or anatomical abnormalities.

Study design.

At visit 0, at the beginning of a 2 week run in period, the study was explained and medical history, concurrent medication and demography were recorded. Parents were instructed to fill out a daily record card. Children proved to be able to inhale study medication and rescue medication using a plastic spacer (Babyhaler (BH), Glaxo Wellcome, Zeist, The Netherlands) with support of their parents. During the run in period all patients used placebo 2 puffs twice daily to minimise placebo effects due to changes of therapy routine. Throughout the study patients used inhaled salbutamol 200 μg, 1 puff delivered via the pMDI and spacer, each time as needed for relief of asthmatic symptoms. Parents were instructed to wash the spacer once monthly, or more often if necessary and let it dry on air.
At visit 1, after 14±3 days, all patients who had shown any respiratory symptoms (coughing, wheezing and/or dyspnoea) on at least 50% of days during the run in period were definitively included. Patients who experienced an exacerbation of symptoms that had to be treated with extra inhaled or systemic steroids during the run in period or patients who needed >4 puffs of salbutamol 200 μg during >7 days during the run in period were excluded.
During the following week patients received salmeterol xinaphoate 25 μg per puff twice daily. After 7 days the effect of salmeterol was checked via a telephone call and the parents were instructed to restart placebo 2 puffs twice daily during the following week (wash out period).
At visit 2, 14 (±3) days after visit 1, pulmonary function tests were performed and blood samples taken for allergy markers.
For the next 6 weeks subjects were randomly assigned to use either two puffs of fluticasone propionate (FP) 125 μg or placebo twice daily.
Three weeks after visit 2 a telephone call was made for control and reassurance of treatment.
At visit 3, 6 weeks (± 3 days) after visit 2, pulmonary function tests were performed, study medication was stopped and parents were instructed to use rescue medication on demand (wash out period).
At the final visit 4, 4 weeks(±3 days) later study medication was stopped and further treatment was started at the discretion of the investigator. The study was completed with follow-up telephone contact after 2 weeks.

Assessments

Patient history, daily record card check, parent global evaluation, subjective effect of rescue medication and physical examination were performed at all visits. Pulmonary function tests were performed before (visit 2) and after (visit 3) treatment.

Daily record cards

Throughout the study the parents filled out a daily record card, rating their child's asthmatic symptoms (coughing, wheezing and/or shortness of breath) on a scale from 0 to 4 for both daytime (0 = no symptoms, 1 = once short symptoms, 2 = more than once symptoms, 3 = frequent symptoms and 4 = almost continuous symptoms) and night-time (with 0 = no symptoms, 1 = once symptoms, without waking up, 2 = waking up through symptoms once, 3 = waking up through symptoms more frequently and 4 = hardly or not sleeping at all). Also the number of salbutamol puffs (rescue medication), adverse events and concurrent medication were recorded.

Clinical scoring index and physical examination

The clinical scoring index provided a description of the general impression of the paediatrician about the patient's asthma related physical condition. Both pulmonary auscultation and inspection were rated, ranging from 0 (=normal breathing, no wheezing), 1 (= expiratory wheezing without use of accessory respiratory muscles), 2 (=in and expiratory wheezing without use of accessory respiratory muscles), 3 (=in and expiratory wheezing with mild use of accessory respiratory muscles) to 4 (=wheezing audible without stethoscope and marked use of accessory respiratory muscles).

Pulmonary function tests

In 7 centres tidal breathing analysis (TBA) was performed, in 3 centres interrupter resistance (Rint) measurement and in the academic centre also impedance measurements with the impulse oscillation system (IOS) were performed. When applicable the order of performance was TBA, followed by IOS and finally Rint.

TBA was performed by a fully computerised TBA system (Master Screen Paediatric, Erich Jaeger, Würzburg, Germany) with use of a mouthpiece[15,16]. We used *t*PTEF/*t*E (time to peak tidal expiratory flow divided by total expiratory time) and VPTEF/VE (expiratory volume to peak tidal

expiratory flow divided by total expiratory volume) as measures of airway obstruction.

Airway resistance was measured by the interrupter technique (Rint), using a commercial device (MicroRint, MicroMedical Ltd, Rochester, UK) as described previously[17]. Rint was calculated using the back extrapolation technique to t = 0 ms after shutter closure during 100ms[18].

Subjects were, if necessary, supported by parent or guardian. After explanation of the technique at least one practice attempts was made before really starting the procedure. They were instructed to breath quietly, sitting upright with slightly extended neck and the chin and cheeks supported by the investigator. A nose clip was used. After a period of quiet breathing in response to a trigger during expiration at the peak tidal expiratory flow a single shutter closed automatically within 10 ms and stayed closed for 100 ms. After 10 interruptions a minimal number of 5 correct tracings was obtained. From these the median value was recorded. The logarithm of this median value was used in the statistical analyses. Tracings were rejected in case of tachypnoea, usage of vocal cords, irregular or forced breathing or leakage.

The impedance of the total respiratory system was measured using a commercially available oscillometry system (Masterlab-IOS, Erich Jaeger, Germany), which has been described elsewhere[19]. In this study mean R and X values were calculated over a measurement period of 60 sec in the frequency range 5 - 35 Hz. We used only values measured at 5 Hz (R5 and X5). During IOS measurement the children were sitting upright, their head resting against the back of the chair. They were instructed to breath quietly through the face mask. To reduce loss of energy in the upper airways their cheeks and chin were supported by the hands of the investigator who was standing behind the patient.

All lung function tests of a patient were performed on the same time of the day and, if possible in these young children, all PFTs were repeated 15 minutes after administration of salbutamol 800 μg through pMDI and spacer.

Efficacy of salbutamol rescue medication

After the run-in period the parents were asked to judge the efficacy of the salbutamol medication to treat the symptoms of their child, by using the following questionnaire: "After the inhalation of the salbutamol rescue medication the symptoms of my child have: 1 = strongly improved, 2 = improved, 3 = unchanged, 4 = increased, 5 = strongly increased. Salbutamol efficacy was also measured as bronchodilator response (BDR)

using all three PFTs: BDR = $Rint_{pre}/Rint_{post}$, $tPTEF/tE_{pre}$ - $tPTEF/tE_{post}$ and $R5_{pre}$ - $R5_{post.}$

Efficacy of salmeterol

During the run-in period and the salmeterol test period the parents recorded the symptoms and salbutamol use in the daily record card. The data were averaged over the week before and the week during the salmeterol test. The differences of the scores were investigated for their modifying strength on the efficacy of fluticasone versus placebo. The efficacy of salmeterol was also checked by parent global evaluation, asking the parents to judge the clinical course at the end of the salmeterol test week, using the same questionnaire as stated under Parent Global Evaluation.

Predictors of effect

Data for the following determinants were analysed for possible modification of ICS effect:

1. Medical history: age category (1 to 2, 2 to 3, 3 to 4 yrs), sex (male/female), height (cms), number of atopic subjects in first degree relatives (0, 1, > 2), smoking history of the parents (0, 1 or 2 parents), number of exacerbations in the past 12 months, living conditions (pets, floor covers, humidity) (yes/no), reported other allergic manifestations (yes/no), eczema (yes/no) frequent rhinitis (yes/no) and frequency of symptoms (frequent = ≥ 75% of days, infrequent = < 75% of days during run in).
2. Wheezing at physical examination at one or more visits (yes/no)
3. Laboratory tests: total IgE and RAST (positive versus negative).
4. Pulmonary function parameters ($tPTEF/tE$ above median versus under median, Rint above versus under median) and BDR at visit 2. We did use neither R5 nor X5 under versus above median because of the small numbers of children performing IOS.
5. Subjective evaluation of the effect of salbutamol rescue medication at visit 1.
6. Parent global evaluation: perceived efficacy of rescue medication and of 1 week treatment with salmeterol 50 μg bd via pMDI with Babyhaler.
7. Change of symptoms (described in the daily record card) during treatment with salmeterol, compared to the run in period.

Data analysis

The symptoms and use of rescue medication were summarised daily as symptom-free (yes/no) and rescue medication-free (yes/no). Within each patient these daily scores constituted a series of repeated 0/1 data that were analysed using a generalised linear model for repeated measurements with model fitting based on Generalised Estimating Equations (GEE)[20]. Because of the binary (0/1) outcome scores, the binomial distribution was assumed with the dependency of the probability parameter on the explanatory variables modelled through a logistic function. The day to day correlation structure of the outcome scores was assumed to be first order auto-regressive ("AR(1)"). In the logistic model the treatment effect was represented by an odds ratio (OR) (95% confidence interval (CI)) of active relative to placebo treatment.
The percentage of symptom-free and rescue free days were calculated in each child, during the last week before randomisation and during the 6-weeks treatment period. Adjustment was made for the % symptom free (or rescue medication free) days during the baseline period as continuous covariate and for time under treatment defined by three consecutive periods of two weeks as a within patient factor; also the interaction between treatment and time was tested. If this interaction turned out to be significant with $p < 0.10$, then the treatment effect was presented per period. Else, one overall treatment effect (assumed to be constant in time) was presented.

The change in the percentages of symptom free and rescue free days and nights during the salmeterol test week were tested using the paired Wilcoxon test.
PFTs were performed before (visit 2) and after the 6 weeks treatment period (visit 3). In an analysis of co-variance (ANCOVA) the values of each PFT parameter after treatment was compared between the two treatment groups, adjusted for baseline measurement of the outcome variable at hand.
Partial correlation analysis, adjusted for treatment group, was used to correlate changes in symptoms and salbutamol use with changes in PFT parameters.
Initial patient characteristics were investigated for their possible modifying role of therapy effect on the % symptom-free and rescue free days and on the PFT variables. This was done by including and testing the interaction

between the initial patient characteristics and treatment in the above-mentioned logistic regression and ANCOVA models. As there were many of these patient characteristics available and the study was not specifically powered to detect their interactions with treatment, these analyses were of a more exploratory nature. In order not to rule out a priori the detection of a potential effect modifying role, a p-value < 0.10 was considered significant.

Results

131 subjects started the run in period, 32 subjects were excluded after this run in period because of too little symptoms (n=29), parental unwillingness to proceed the study (2) and salbutamol use >4 puffs per day during 10 of 14 days during run in (1). Patient characteristics are presented in Table 1. There is a preponderance of males, but this inequality is equally distributed in both treatment arms.

The effect of ICS

Improvements of subjective effect parameters were seen in both treatment arms. In the total group of treated patients there were no significant differences between placebo and FP treated children for percentage of symptom free days or nights and percentage of rescue free days or night (Figure 1). Also changes in symptom scores did not show significant differences between FP and placebo (Figure 2).

TBA measurements were performed in all 99 children and were possible in 43 of placebo and 42 of FP treated patients at visit 2. At visit 3 these figures were 43 and 38 respectively. In 86 children Rint measurements were performed. These were possible in 25 of placebo, 20 of FP at visit 2 and 24 and 25 respectively at visit 3. IOS was performed in 40 children and possible in 12 and 8, and 11 and 7 children respectively.

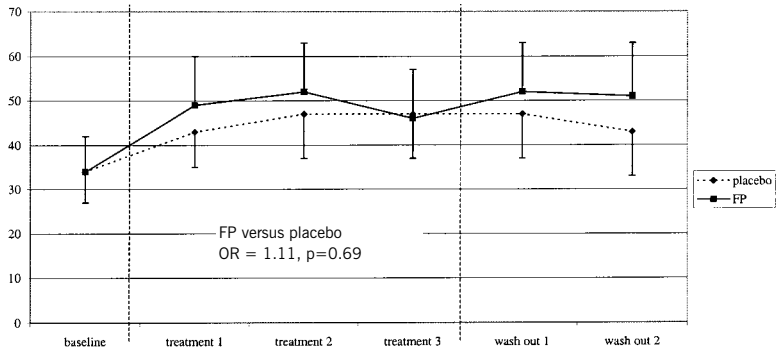
TBA parameters improved significantly in the FP treated children, compared to placebo treated children (*t*PTEF/*t*E +4.61% versus -1.0%, p = 0.009 and VPTEF/VE +3.61% versus -0.17%, p = 0.003) (Figure 3). Significant improvement was also seen for Rint (-0.18 kPa/L/s versus

Table 1. Patient characteristics

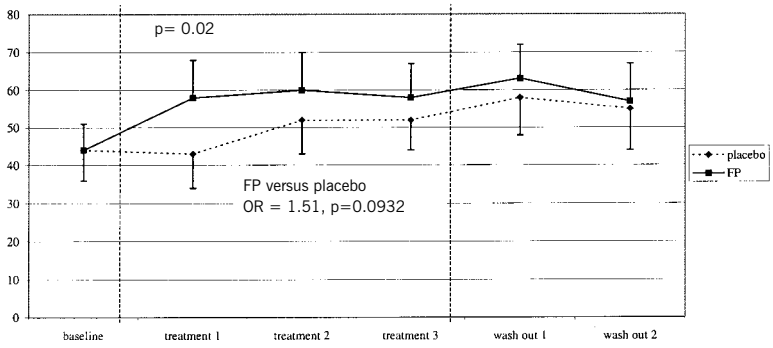
		fluticasone propionate	placebo	total
no		48	51	131
sex	M/F	36/12	38/13	98/33
height	cm	91.4 (8.9)	90,6 (10.2)	90.7 (9.1)
weight	kg	14.1 (2.2)	13,6 (2.9)	13.8 (2.6)
age	yrs	1.9 (0.9)	1.8 (0.9)	1.9 (0.9)
birthweight	kg	3.3 (0.7)	3.3 (0.8)	3.3 (0.7)
no of exacerbations during last year		7.8 (4.1)	6.6 (4.7)	6.6 (4.4)
ATOPY				
no of atopic 1st line relatives	0	13	12	42
	1	16	13	35
	>2	19	26	54
IgE	U/ml	71.8 (140.0)	72.5 (109.8)	70.6 (124.1)
positive RAST not measured	Y/N	17/30	17/33	
history of allergic disease	Y/N	5/43	11/40	18/113
allergic rhinitis	Y/N	15/33	19/32	48/83
eczema	Y/N	11/37	10/41	26/105
ENVIRONMENTAL EXPOSURE				
smoking mother	Y/N	8/40	8/43	24/106
smoking father	Y/N	18/30	14/37	42/88
smoking pregnancy	Y/N	5/43	7/44	18/112
floor covers living room	Y/N	3/44	8/43	25/106
floor covers sleeping room	Y/N	14/34	15/36	37/94
humidity high living room	Y/N	9/39	7/44	19/112
humidity high sleeping room	Y/N	9/39	8/43	20/111
PETS				
birds	Y/N	4/44	1/50	8/123
dogs	Y/N	10/38	10/41	25/106
cat	Y/N	12/36	12/39	29/102
other	Y/N	7/41	5/46	15/116
no pets	Y/N	24/24	31/20	75/56
PHYSICAL EXAMINATION				
wheezing at physical examination	Y/N	8/40	10/41	

Values are presented as means (SD) unless stated otherwise.

% symptom free days



% symptom free nights



+0.16 kPa/L/s, p = 0.024) (Figure 4). Although there was improvement of R5 and X5 this did not reach significance in this small group (p = 0.13 and 0.07 respectively).

Efficacy of salmeterol

During one week salmeterol treatment there were improvements in % symptom free days (p = 0.004), % symptom free night (p = 0.06), rescue

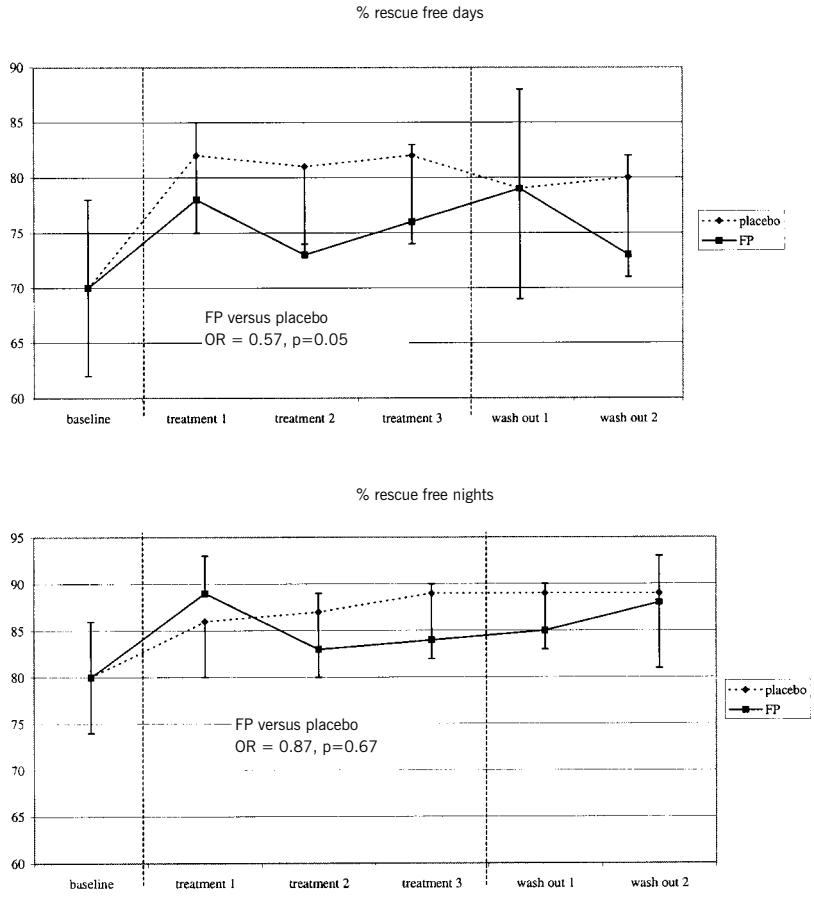


Figure 1. Changes in % of symptom free days, % of symptom free nights, % of rescue free days and % of rescue free nights, before, during and after treatment with study medication (SD).

free days (p <0.001) and rescue free nights (p =0.03), compared to the week preceding salmeterol treatment.

Predictors of effect of ICS

The numbers of subjects with a positive family history, positive history of allergy, eczema, allergic rhinitis, IgE levels, RAST positivity, and wheezing

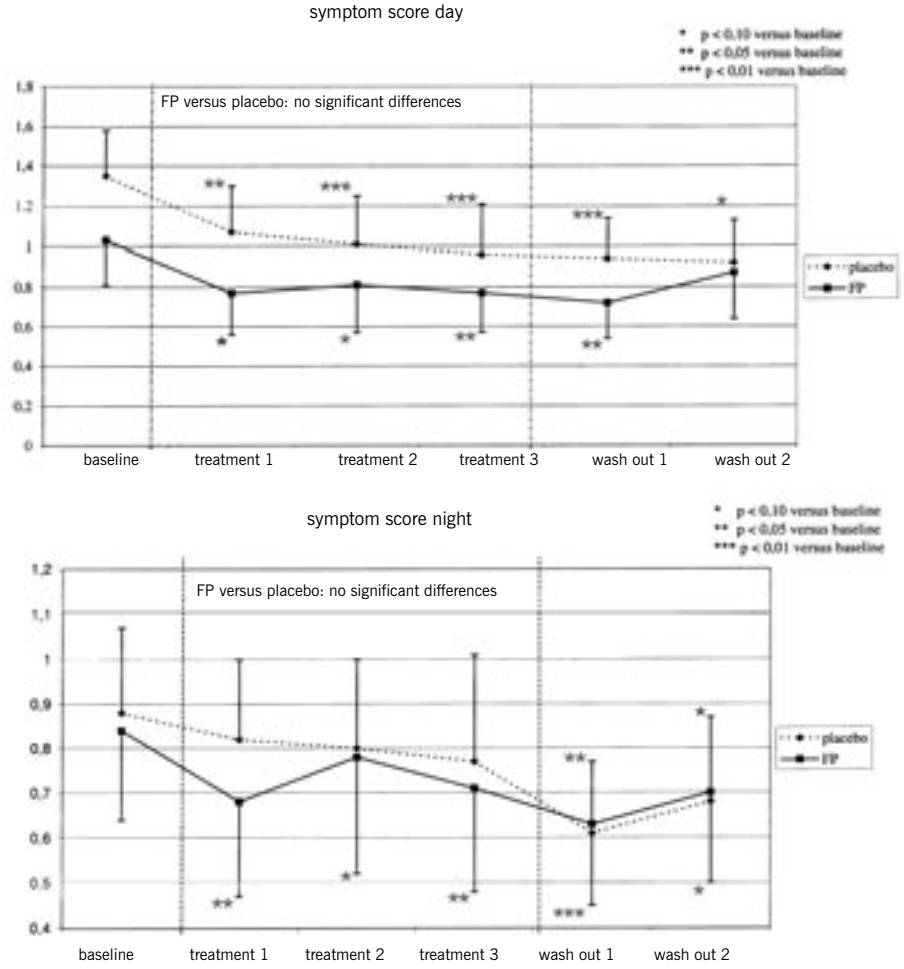


Figure 2. Changes in mean symptom scores, before, during and after treatment with study medication (SD).

at physical examination are presented in Table 1. Neither these markers nor bronchodilator response were significantly related to ICS effect. Also frequency of symptoms during run in period and number of exacerbations during the preceding 12 months were not related to ICS effect.

Improvements in % symptom free days during salmeterol therapy were unrelated to improvements of both subjective and objective effect parameters during ICS treatment.

Baseline pulmonary function was not significantly related to pulmonary function improvement, but significant improvements of some subjective

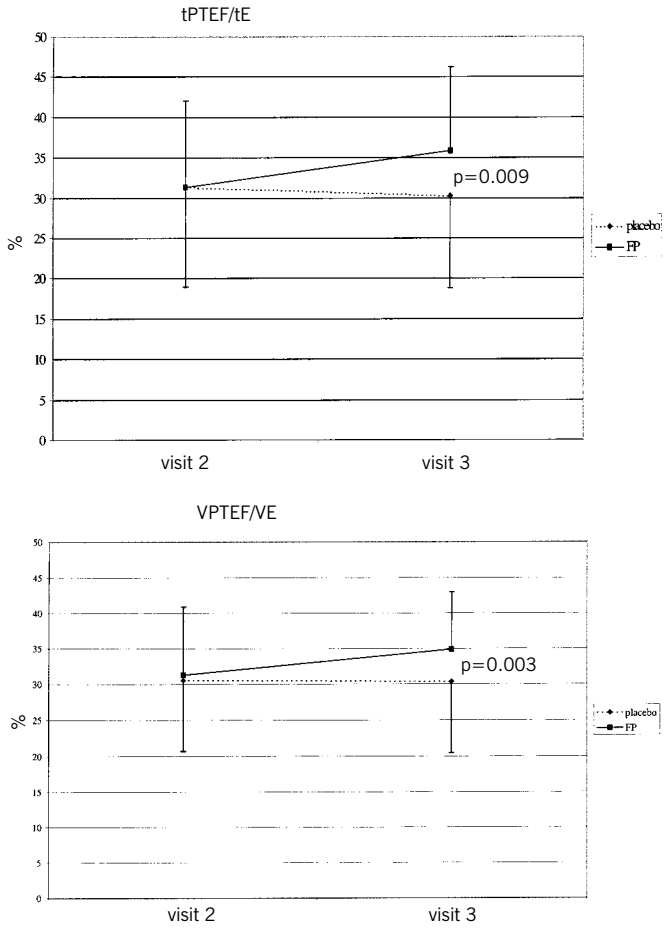


Figure 3. Changes in tPTEF/tE and VPTEF/VE during treatment with study medication (SD).

disease markers were seen in children with decreased airway patency (high Rint and low *t*PTEF/*t*E), with OR varying from 2.12 to 4.01 for Rint and 1.17 to 7.39 for *t*PTEF/*t*E (Table 2).

There were significant correlations between some markers of indoor environment and ICS effect on some subjective markers. Especially patients living in houses with carpets and biparental smoking showed significant improvements in symptoms and use of rescue medication during ICS treatment (Table 3). However, the presence of pets was correlated with less improvement in % symptom free days and nights

Table 2

	% symptom free days		%symptom free nights		%rescue free days		%rescue free nights	
	OR	p	OR	p	OR	p	OR	p
FP vs placebo effect								
Rint >mean[a] (n=20)	1.36	0.61	**3.01**	**0.04**	0.92	0.89	2.11	0.26
Rint <mean[b] (n=21)	0.64	0.39	1.11	0.84	**0.31**	**0.002**	0.52	0.31
difference	2.12	0.36	2.72	0.18	**2.97**	**0.09**	4.01	0.13
FP vs placebo effect								
tPTEF/tE <mean[a] (n=43)	1.09	0.83	**1.92**	**0.05**	0.89	0.79	1.74	0.21
tPTEF/tE >mean[b] (n= 42)	0.98	0.94	1.12	0.77	0.27	**0.0006**	**0.24**	**0.02**
difference	1.17	0.84	1.65	0.31	3.2	**0.04**	**7.39**	**0.008**

Fluticasone versus placebo effect (measured by daily record card parameters) for groups with better[a] versus worse[b] pulmonary function. The FP versus placebo effect is expressed as Odds ratio (OR) for both groups. Then the OR is given for the "worse" versus "better" group. Significant OR is presented in bold.

Table 3

	% symptom free days		%symptom free nights		%rescue free days		%rescue free nights	
	OR	p	OR	p	OR	p	OR	p
carpets living room (n=11)	1.3	0.87	**7.97**	**0.0008**	0.39	0.5	2.87	0.33
hard floors living room (n=87)	1.19	0.52	1.3	0.3	**0.59**	**0.08**	0.9	0.75
difference	1.09	0.96	**6.13**	**0.007**	0.66	0.77	3.18	0.31
carpets sleeping room (n=29)	2.2	0.14	3.75	**0.004**	1.29	0.65	1.6	0.5
hard floor living room (n=69)	0.85	0.55	1.05	0.85	**0.4**	**0.0045**	0.68	0.3
difference	2.59	0.12	3.57	**0.018**	**3.22**	**0.07**	2.35	0.28
current smoking 2 parents (n=11)	1.69	0.13	**1.92**	**0.04**	0.97	0.94	1.74	0.24
current smoking 1 parent (n=26)	0.94	0.89	1.98	0.15	**0.36**	**0.08**	0.52	0.23
current smoking no (n=62)	**0.15**	**0.0001**	**0.4**	**0.09**	**0.18**	**0.0017**	0.73	0.61
difference between 2 vs no smoking parents	**11.3**	**0.0001**	**4.8**	**0.04**	**5.39**	**0.03**	2.38	0.21
pets yes (n=44)	0.68	0.31	0.82	0.61	0.5	**0.07**	0.64	0.38
pets no (n=55)	1.71	0.11	**2.6**	**0.002**	0.72	0.37	1.14	0.76
difference	**0.40**	**0.07**	**0.32**	**0.02**	0.69	0.48	0.56	0.4

Fluticasone versus placebo effect (measured by daily record card parameters) for groups with several indoor environment characteristics (as reported by parents). The FP versus placebo effect is expressed as Odds ratio (OR) for specific groups. Then the OR is given for first versus last mentioned group. Significant OR are presented in bold.

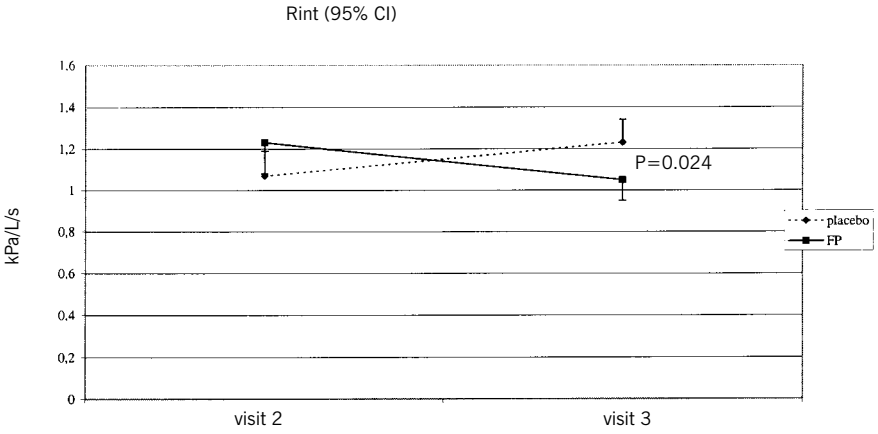


Figure 4. Changes in Rint during and after treatment with study medication (SD).

Discussion

In the present study, evaluating the effects of ICS in pre-school children with recurrent or chronic asthmatic symptoms we found beneficial effects on pulmonary function parameters, not on subjective parameters. There were no single predictors for pulmonary function improvement but subjective improvement was seen in patients with signs of airway obstruction on pulmonary function measurement. Especially generally recognised indicators of asthma such as bronchodilator response, atopy, positive family history and wheezing were found to be unrelated to ICS effectiveness in this study.

Both symptom scores and use of rescue medication are sensitive to placebo effect. In younger children this effect is expected to exist too, also when symptoms are interpreted and presented by parents or caregivers. Therefore, a placebo controlled study design is necessary. We treated all patients during the run in period with placebo via Babyhaler to minimise placebo effects during the study period and to be sure that good inhalation technique was practised.

Among others, the Dutch consensus on treatment of young children with asthmatic symptoms[21-23] suggest to test patients on their response to a short

acting bronchodilator as an indicator for asthma before starting ICS therapy. However subjective evaluation of the effect of a short acting bronchodilator is difficult, both for parents and doctors. That's why we evaluated also the response to a long acting bronchodilator as a test for bronchodilator response. However no correlation with ICS efficacy was found.

The dose of ICS used in the present study was higher than the recommended dose in daily practice to reach an all or not effect. The short period of intervention decreased the chance for important side effects. However, this relatively short period might also be a reason for not fully established effects on individual effect parameters.

Bisgaard et al have shown that in pre-school children with asthmatic symptoms treatment with fluticasone propionate 100 and 200 μg daily via Babyhaler is effective and safe. They found significant effects on symptoms, use of rescue medication and exacerbation frequency. There was no dose dependent effect[11]. In a retrospective analysis they pointed to the cost-effectiveness of FP treatment in these children[24]. In children with recurrent viral wheeze some authors found a beneficial effect of inhaled corticosteroids but in 1995 Wilson could not proof any prophylactic effect of ICS in this patient group[10].

The present study is a support to the use of objective effect parameters and especially pulmonary function measurements to evaluate the effect of ICS and other interventions. There are no earlier studies on the effect of ICS on TBA parameters in younger children nor on the usability of TBA parameters or Rint to predict the ICS effect. The only study that also used objective disease markers to evaluate the ICS effect in pre-school children was performed by Nielsen and Bisgaard[13]. They found a significant improvement of Rint, R5 and X5 after 8 weeks of 800 μg budesonide daily in 2-5 year old moderately asthmatic children, most of whom had been on ICS treatment before the run in period[13]. Although in this study the symptom severity was probably greater compared to the present study, results were rather comparable and they also found effects on pulmonary function tests to be more significant than effects on subjective parameters.

It seems reasonable that many pre-school children with recurrent asthmatic symptoms are incorrectly treated when given inhaled steroids, because the diagnosis can not adequately be made. Especially children who present with recurrent or persistent cough, but without a history of wheeze are rarely asthmatic[25]. This was recently confirmed in a study by McKenzie et al. who showed that recurrent coughers without wheeze are rarely atopic although they may show bronchodilator response[26].

Roorda et al. found that especially children with chronic persistent symptoms and a positive family history for asthma are the ones responding best to treatment with fluticasone propionate[12]. Their findings were not confirmed in the present study. Few primary patient factors could predict a positive ICS effect. The present study is the first that uses pulmonary function parameters to predict ICS efficacy. Only a subgroup with high Rint or low *t*PTEF/*t*E showed significant correlation with a positive FP versus placebo effect on subjective disease markers. Although this finding has to be confirmed in future studies, it shows that pulmonary function tests using recently developed pulmonary function techniques might offer a possibility to determine a subgroup of pre school children with asthmatic symptoms with optimal benefits from ICS treatment.

A remarkable finding was the beneficial effect in a subgroup of children growing up in an unfavourable indoor environment (smoking, carpets). This finding is difficult to interpret but might indicate that children living under non-optimal environmental conditions have more pronounced inflammation and therefore may be expected to show more beneficial effects from ICS treatment. On the contrary, it could also mean that after optimisation of the home situation an additive effect of ICS can not be expected.

In general, this study shows that the effect of ICS in pre-school children with asthmatic symptoms can not be derived from experiences in asthmatic school children and adults. The international consensus to treat pre-school children in a similar way as adults, i.e. based on the presence of atopy, wheezing and a positive family history and effect of bronchodilators is not supported by this study. Different "asthma phenotypes" with probably different inflammatory patterns[27-29] might show different reactions to ICS therapy. Predictors of asthma appear to be different from predictors of ICS effect (e.g. worse pulmonary function, indoor environment) in young children. It remains unclear if the improvement in pulmonary function in young children is related to the presence of "real" asthma in this group. It could also be that different asthma "phenotypes" show similar responses to ICS treatment.

On the other hand, the present study indicates that objective parameters such as pulmonary function results are more sensitive to ICS effects and might be more useful parameters to use in population studies. Recently performed studies in adults show that pulmonary function tests and especially bronchial hyperresponsiveness can be an additional guide of long term asthma treatment[30]. These PFT results might also support the concept

to treat mild and uncertain asthma, as suggested in recent studies, indicating that early start of ICS treatment for asthma can prevent the development of irreversible, structural airway remodelling[31,32].
Further studies should evaluate efficacy in different subgroups that only differ in asthma "phenotype".
In conclusion, 6 weeks treatment with ICS in pre-school children with recurrent asthmatic symptoms was effective in improvement in objective effect parameters, but not of subjective markers. ICS effect on pulmonary function could not be predicted from baseline pulmonary function testing, but baseline pulmonary function predicted a beneficial subjective effect of ICS. This study suggests that pulmonary function testing can and probably should be implemented in efficacy studies in this age group.

The multi-centre study group consisted of the following physicians: Dr JAAM van Diemen-Steenvoorde and Dr FB Plötz (St Antonius Hospital Nieuwegein), EHG van Leer and FGA Versteegh (Groene Hart Hospital Gouda), Dr PLP Brand and A Kamps (Isala Klinieken Zwolle), Dr GPJM Gerrits (Canisius Wilhelmina Hospital Nijmegen), NJ van de Berg and KL Tjia (Fleveo Hospital Almere), WA Verwijs (Hofpoort Hospital Woerden) and Dr AAPH Vaessen-Verberne (De Baronie Hospital Breda), JH van der Laag and Dr EEM van Essen-Zandvliet (University Medical Centre Utrecht).

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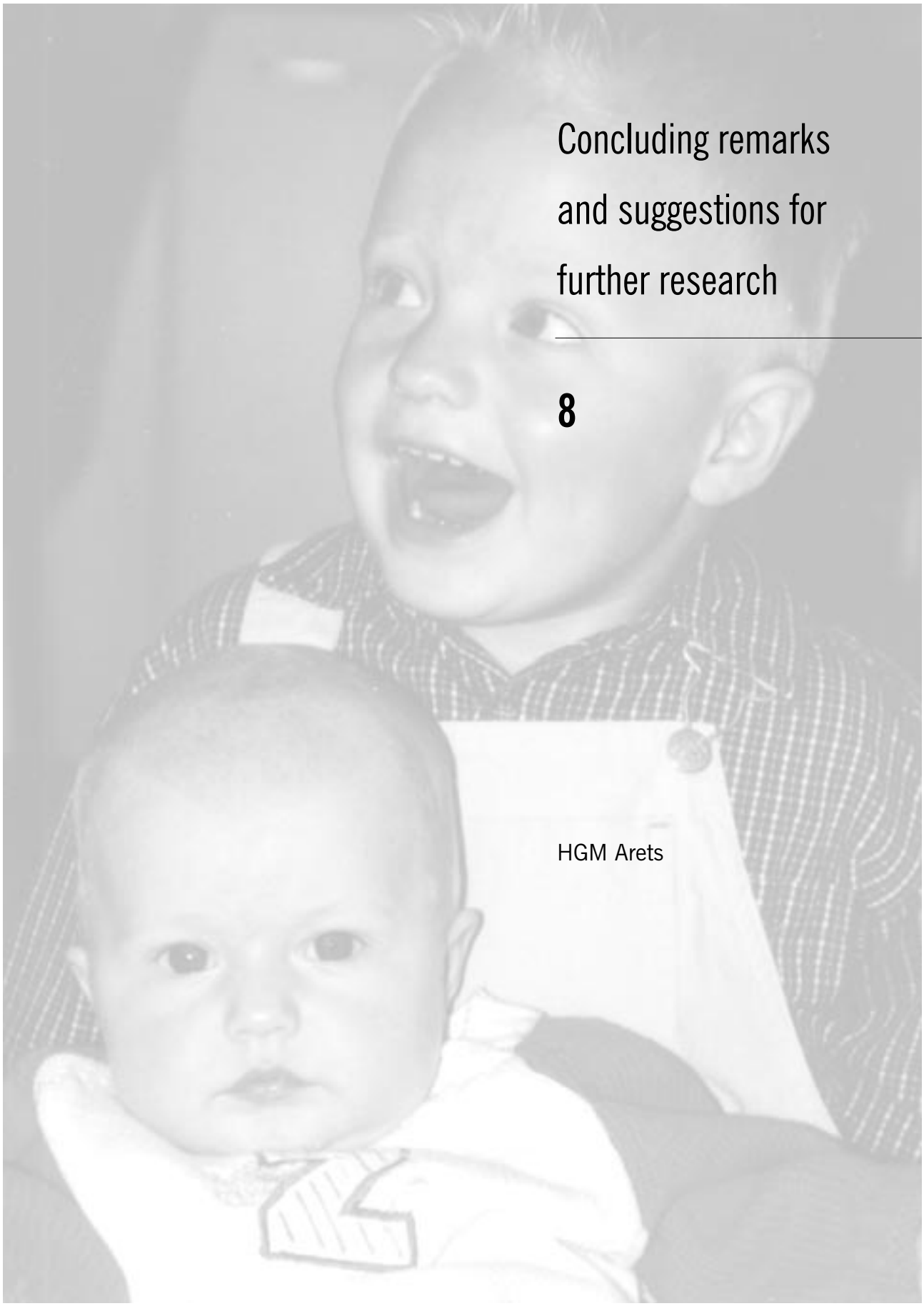


Concluding remarks and suggestions for further research

8

HGM Arets

Introduction

The increasing incidence of respiratory disease in young children is a challenge to the clinician. Apart from medical history and physical examination pulmonary function testing can be a valuable tool for diagnostic and therapeutic evaluation. However, it is important to realise the specific anatomic and physiologic features of (the respiratory system in) the growing child. These features have important implications for feasibility, applicability and clinical importance of PFT results.
Only PFTs that have been standardised internationally should be used; therefore working groups should be installed to provide guidelines for the above mentioned aspects. Moreover, the widespread application of PFTs in (young) children is restricted to techniques that show as many as possible specific characteristics as presented in Chapter 1, Table 2. Also reference values from studies in healthy subjects should be available and they should differentiate between healthy and diseased children.
The studies described in this thesis focus on several aspects of pulmonary function testing in (young) children. Several questions on PFT and clinical applicability have been evaluated in this thesis. However further research should provide insight in unanswered or newly raised questions. Some of the possible suggestions for future research will be discussed below.

Flow volume measurements in young children

Spirometry or flow volume measurements are considered the gold standard of PFT especially when evaluating subjects with obstructive airway disease. However, this method is supposed to be possible only in subjects that show good co-ordination and co-operation in the performance of specific respiratory techniques. Therefore in most children under the age of 6 years reliable FV measurements can not be assumed.
Standardisation of this technique has been performed and criteria for acceptability and reproducibility of curves in individual subjects are available. However these standards are considered in adults and older children and appear to be not applicable in younger age groups. Even many adoles-

cents who perform "technician accepted manoeuvres" fail to fulfil all criteria. The increasing application of this technique (with or without using computerised incentives) in children requires a reconsideration of these standardisation guidelines in this age group. Specific attention should be paid to equipment, environment, technician's skills and procedures when this technique is applied in children, as shown in Chapter 4.1. Many general PFT laboratories and technicians might lack the specific requirements, including dedication, for the performance of FEV_1 in these children.
International reconsideration of standardisation of FV measurements, specifically in young children should be performed. Young children show shorter forced expiration times and it has been suggested that FEV0.5 might be a better indicator of airway obstruction in this age group. Separate criteria for different age groups should be set to enable widespread and well founded application of this useful technique. A proposal for these adaptations is presented in Chapter 4.2. Also specific education to and selection of motivated pulmonary function technicians is necessary.
Last but not least the changing pattern of growth, weight and body composition of Western children, maybe even more specific Dutch children strongly necessitates the development of new reference values (including values for pre-school children) in the Netherlands and other western countries.

Interrupter technique

The recently (re)introduced interrupter technique for measurement of resistance of the respiratory system (Rint) shows many characteristics as mentioned in the introductory chapter. It is cheap, easily applicable and well tolerated. Normal values are presented in Chapter 5.2. However there are several disadvantages. Rint mirrors the resistance that is determined by not only lower airways but also upper airways. This "contamination" increases with age.
Although active co-operation and co-ordination are not required, the applicability in pre-school children is restricted. Reproducibility is worse than other techniques and there is a wide range of normal values. This decreases the clinical relevance of single values in individual subjects to discriminate between healthy and diseased. Also the sensitivity of changing

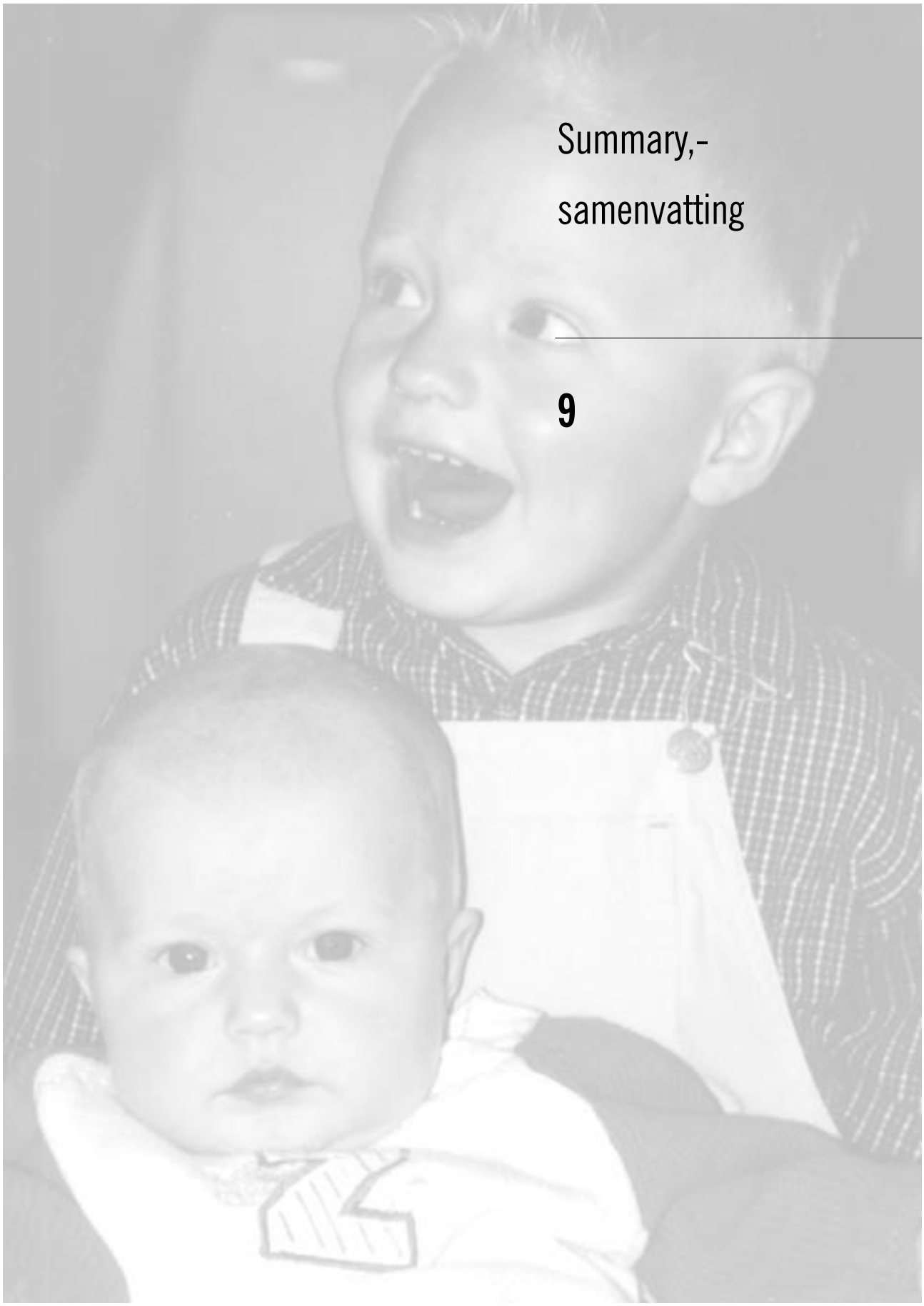
airway obstruction appears to be less than with other techniques. Still it was more sensitive to intervention with ICS than subjective disease markers. Other authors confirmed these findings and also showed its power to distinguish groups of wheezers from both controls and coughers.
Several features of technical nature (e.g. the method of calculating post occlusion pressure) should be standardised before studies can be compared. After standardisation of this technique it seems to be promising for usage e.g. in population studies. The applicability in the individual patient e.g. for measurement of bronchodilator response might also be an important application. Future studies should focus on these aspects to provide further insights.

ICS effects in asthmatic children

The effect of ICS in children and adults with moderate to severe asthma is undisputed and ICS are considered the treatment of choice in these patients. During the last years treatment regimes have shifted to milder and younger patients.
However the efficacy in mild to moderate asthma and in pre-school children is less evidence based and hard to prove, because objective disease markers are either within normal ranges (mild asthma) or not available (pre-school children). The SJOKOLA studies show that both groups show an objective improvement of pulmonary function parameters during treatment with ICS. This effect is even more significant than the effect measured with subjective parameters.
Although these findings support the concept to treat children with mild and uncertain asthma, they do not support the recent national and international consensus on treatment of pre-school asthmatic children with ICS. A treatment based on subjective disease markers, subjective and objective bronchodilator response, presence of atopy, wheezing and a positive family history is not supported by the findings in SJOKOLA 2. Predictors of asthma (e.g. bronchodilator response, atopy) appear to be different from predictors of ICS effect (e.g. worse pulmonary function, indoor environment) in young children. In this relatively small study especially wheezing, bronchodilator response and atopy appeared to be not useful for predicting ICS effect.

It remains unclear if the improvement in pulmonary function in young children is related to the presence of "real" asthma in this group. It could also be that different asthma "phenotypes" show similar responses to ICS treatment.

Further studies should evaluate efficacy in different subgroups that only differ in asthma "phenotype". The findings of SJOKOLA 2 show that also indoor environment, pre-treatment pulmonary function and maybe other factors influence the ICS effect. Therefore these factors can be important confounders and impair the performance of such studies. Probably only studies with large numbers of patients can correct for these confounders and allow to draw some relevant conclusions. Although the SJOKOLA study failed to show effect modification by specific disease or patient characteristics further studies on possible predictors of ICS effectiveness (e.g. inflammation markers, NO, specific symptoms (wheeze versus cough?)) are needed. Therefore international (multi-centre) trials on this subject are required. Only these studies might provide further insights in this important issue.



Summary,- samenvatting

9

Summary

Many (pre-)school children with acute or chronic respiratory problems are seen every day by physicians, both in primary care and in hospitals. In these children, apart from upper and lower airway infections especially recurrent wheezing and asthma are important differential diagnoses. The incidence of asthma and asthma-like diseases is increasing, especially in young children. Although in many children these respiratory symptoms are self-limiting, it is important to recognise early in the course of the disease those children that are at risk to suffer from persistent respiratory diseases and to develop pulmonary function abnormalities and chronic airway remodelling. Only in this way adequate treatment (e.g. inhaled corticosteroids and antibiotics) and prophylaxis (e.g. smoking prevention and adaptation of indoor environment) might prevent long term morbidity and possibly mortality.

In most children diagnosis and treatment of respiratory disease are mainly based on medical history and physical examination. However, the evaluation of objective disease markers, e.g. pulmonary function could be helpful for the assessment of functional abnormalities. Although lung function studies are increasingly used for the diagnosis and assessment of severity and follow up, objective pulmonary function testing is often only possible for older children. Especially in pre-school children respiratory function parameters are rarely available.

Pulmonary function tests can be used to detect and quantify different kinds of pulmonary functional abnormalities, to measure the effect of intervention, to follow the time course of disease and to enable prognosis of disease and disability.

The most often used parameter in subjects with obstructive lung disease is the forced expiratory volume in 1 second (FEV_1), obtained from a maximal expiratory flow volume curve (MEFV). The technique, necessary to perform this manoeuvre requires optimal co-ordination and co-operation and these premises impair the applicability, especially in infants and pre school children, but also in many geriatric patients, older children and even adults. That's why other lung function methods are needed. Although recently several alternative methods have been developed, most have and can not be implemented for use in daily clinical practice and are currently only available in specialised centres. Many of these tests require difficult technical procedures, anaesthetic care or are even invasive.

Clinical application of new or alternative pulmonary function tests in young children is only possible for techniques that are easily performed in children of all ages, do not require much time or sedation and show results quickly. They should be reproducible, cheap, able to distinguish healthy from diseased children, not invasive, applicable during spontaneous breathing, responsive to intervention and useful for follow up. Promising techniques that might fulfil (most of these) requirements are tidal breathing analysis, interrupter resistance measurement and impulse oscillometry.
Adaptation of traditional techniques (MEFV) or standardisation of these newer techniques and availability of reference values might enable more widespread use of these techniques in daily practice. The studies described in this thesis addressed several aspects of pulmonary function testing in preschool and school children.

In **Chapter 2** an overview of literature on general principles of pulmonary and especially airway anatomy, followed by an overview of currently available methods to measure airway mechanics in non-sedated, spontaneously breathing children is presented. Although the functional evaluation of patients with lower airway obstruction is probably best performed using FEV_1, resistance measurement, using the interrupter technique or impulse oscillation, can be applied when MEFV measurements are impossible.
Although several drawbacks of resistance measurements in young children can be mentioned, there are several aspects that make resistance measurements preferable.
Interrupter and oscillation technique, applied during spontaneous tidal breathing, are not very burdensome, are simple, do not require sedation, are non-invasive and require only passive co-operation of the patient. Therefore these techniques are suitable in both daily practice and in a laboratory setting or for research purposes. Another theoretical advantages of these techniques is that they might be more representative of normal breathing, i.e. daily life situations, in contrast to parameters obtained from forced manoeuvres. Also, during childhood the most important pulmonary diseases have an obstructive character and especially peripheral airway resistance is better mirrored by resistance measurements in children than in adults. Last but not least, changes after intervention or in disease are at least similarly reflected by these techniques compared to "gold standards".
The availability of these techniques has come with devices, that are currently tested and presented by commercial manufacturers. Although this does encourage more widespread use of these techniques, it does not imply

that standardisation of these techniques has been performed and e.g. normal values and a good relation to pathophysiology are available.

In **Chapter 3** a short overview is presented of the tidal breathing analysis, one of the pulmonary function techniques that has been subject of several studies in the University Medical Centre Utrecht. The shape of flow pattern during tidal expiration is influenced by peripheral airway obstruction. The time from the start of expiration to peak expiratory flow (*t*PTEF) divided by the total expiratory time (*t*E) is significantly decreased in children with asthma. Experimental studies in the cat have shown that the expiratory flow pattern is the result of mechanical properties of the respiratory system (resistance and compliance) and of post-inspiratory activity of inspiratory muscles.

Chapter 4 is dedicated to the maximal expiratory flow volume (MEFV) curve, considered the "gold standard" of pulmonary function testing at all ages.

Even pre-school children are sometimes able to perform the maximal effort breathing techniques, required for this pulmonary function test. However, children are not small adults and a lot of child-specific items in the performance and interpretation of flow-volume curves can be overlooked, resulting in errors in diagnosis and treatment.
In **Chapter 4.1** we report on the most important conditions for reliable measurement of flow-volume curves at all ages. Especially testing atmosphere and equipment, pulmonary function technician requirements, testing procedure, reliability criteria, report making and interpretation are discussed. For many children the first visit to a pulmonary function laboratory can be considered as the beginning of a long (if not ever) lasting PFT career and "well begun is half done".

Prior to attempting to interpret any MEFV curve (or whatever other pulmonary function test), 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. The performance of a maximal effort expiratory manoeuvre is not easy, as was discussed before. International criteria (ATS and ERS) for the acceptability and reproducibility of spirometry are available for adults but are lacking for children. In a retrospective study flow volume curves, performed by

children of all ages were evaluated for their capability to meet these criteria. Results of this study are described in **Chapter 4.2**. Maximal expiratory flow volume (MEFV) measurements of 446 school-age-children, experienced in performing MEFV manoeuvres and considered acceptable by well trained pulmonary function technicians were evaluated. These curves showed a rapid rise to peak flow at the start and a subsequent gradual decrease of flow during the rest of the maximally prolonged expiratory manoeuvre. Even the curves of these experienced children appeared to be unable to meet all international criteria, although most of their MEFV curves were useful for interpretation. Based on the performance of these children, we made a proposal for adaptation of international criteria for MEFV measurements in children.

Recently an old technique, the interrupter technique, for assessment of airway resistance showed a revival after introduction of a small handheld device, the MicroRint®. This technique is described in **Chapter 5**. The basis of the interrupter technique is that, during transient interruption of the tidal airflow, alveolar pressure and mouth pressure equilibrate within a few milliseconds. The alveolar pressure can therefore be derived from the measurement at the mouth immediately after interruption. If the flow is measured immediately prior to interruption, the ratio of pressure to flow gives the interrupter resistance (Rint).

Together with two students a study was performed to evaluate the applicability of this simple device for measuring airway resistance, to derive normal values and to compare values with maximal expiratory flow volume (MEFV) parameters in asthmatic and healthy children. As described in **Chapter 5.1** the majority of children from the age of 3 years was able to perform Rint measurements and repeatability was good. Applicability is comparable in asthmatic and healthy children and appears to be age dependent. Good correlation with age and height was found. Baseline values could not discriminate healthy from asthmatic children. A significant inverse correlation was found between Rint and MEFV values. After bronchodilation in asthmatic patients there was a significant increase in FEV_1 and decrease in Rint, but changes between the two parameters did not correlate.

Reference values for pre-school children exist but are lacking for children over the age of 7. The results of two comparable studies performed in 208

3-13 year old healthy children in Utrecht and Rotterdam were combined to find reference values for expiratory interrupter resistance (Rinte). A curvilinear relationship between Rinte and height was observed, similar to published airways resistance data measured plethysmographically. No significant differences in cross-sectional trend or level of Rint were observed according to gender. Based on the reference equation: 10log (Rinte) = 0.645 - 0.00668 x (standing height(cm)) kPa/L/s and residual standard deviation (0.093 kPa/L/s), Z-scores can be used to express individual Rint values and to describe intra- and inter-individual differences (**Chapter 5.2**).

Another method to measure resistance (and reactance) of the respiratory system which is applicable in young children is the impulse oscillation technique (IOS).
A sinusoidal oscillatory pressure wave, composed of different frequencies is superimposed on the tidal breathing flow pattern. Pressure waves result in flow oscillations, the magnitude and phase of which are determined by the resistive, elastic and inertial properties of the respiratory system. The pressure and flow signals are recorded at the mouth. For each of these frequencies, the ratio of pressure to flow can be considered (i.e. the impedance Z), which is a complex number of the magnitude of pressure to flow and about the phase shift between these signals. Most often this complex number is represented by its real part, the respiratory resistance (R_{rs}) and its imaginary part, the respiratory reactance (X_{rs}).
This technique provides an alternative method to assess airflow obstruction in patients who are not able to perform forced breathing manoeuvres. The sensitivity and specificity of IOS parameters to quantify changes in airflow obstruction in comparison with FEV_1 and PEF measurements were evaluated in a study in school children (**Chapter 6**). Measurements of FEV_1, PEF and Resistance (R) and Reactance (X) at frequencies of 5 to 35 Hz were performed in 19 children with asthma before, during and after methacholine challenge and subsequent bronchodilation.
All parameters changed significantly during the tests. Values of resistance and reactance correlated with FEV_1 and changes in resistance preceded changes in PEF and FEV_1 during methacholine challenge. Although PEF is a frequently used surrogate measure for airway hyperresponsiveness, the area under the ROC curve to predict a 15% fall in FEV_1 showed better sensitivity and specificity for resistance than for PEF.
We conclude that IOS parameters can be easily used as an indirect measure of airflow obstruction. Although the parameters do not exactly reflect the

'gold standard' FEV_1, this technique might be helpful in patients who are not able to perform forced breathing manoeuvres.

In **Chapter 7** the effect of inhaled corticosteroids in young children with asthmatic symptoms is evaluated using several of the previously described pulmonary function techniques.
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, but also less affected children with less frequent and (mild to) moderate symptoms and pre-school children with asthma-like symptoms. In these children who show hardly any abnormalities in pulmonary function or in whom objective parameters are hardly available, objective measurement of the effect of inhaled corticosteroids (ICS) is difficult.

The effect of treatment with ICS was studied in two groups:
1. 5-10 year old children with mild asthma (SJOKOLA 1)
2. 1-4 year old children with asthma-like symptoms (SJOKOLA 2)

SJOKOLA is short for "*S*teroiden bij *JO*nge *K*inderen als *O*nderhoudsbehande*L*ing van *A*stma" (Steroids in young children as maintenance treatment of asthma).

In the first study 68 children were randomly assigned to either fluticasone propionate (FP) 250 µg or placebo twice daily as pMDI via spacer during 12 weeks. FP treated versus placebo treated children showed significant changes, not only in % symptom free days, morning and evening PEF and wheezing, but also in FEV_1%pred. The latter improvement was only small but significant, especially when we consider that baseline FEV_1%pred values were high (>100% pred). This study therefore shows that normal lung function in children with symptoms of asthma does not rule out airway obstruction, improving after proper treatment. Although no significant improvements were found for tidal breathing parameters these findings show that ICS are effective in children with mild asthma. This beneficial effect can be assessed by both objective and subjective parameters.

During early childhood as many as 40% of children experience recurrent asthmatic symptoms such as wheezing, cough or breathlessness In more than half of these children symptoms disappear around the age of 6 years. These symptoms are thought to reflect congenitally narrow airways, which

predispose to wheezing during viral infections. In other children symptoms persist and the latter group is eventually labelled as asthma. Many of these patients have a positive family history for atopy and personal skin prick test positivity and increased levels of total and specific IgE.

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 the above mentioned uncertainty about the diagnosis and thus uncertainty about the best ways of treatment. There are few studies on the effect of ICS in pre school children and no studies using tidal breathing parameters, impulse oscillometry and interrupter resistance as effect parameters. In a prospective study the effect of ICS in 1-4 year old children with asthmatic symptoms was evaluated using both subjective and objective parameters (**Chapter 7.2**). Although there are certain "predictors" of asthma in pre school children, there is no readily available instrument to identify preschool children with recurrent asthmatic symptoms who will benefit from ICS treatment. Therefore we also searched for the possibilities of several subjective and objective parameters to predict a possible beneficial effect of ICS.

99 children were randomly assigned to receive either fluticasone propionate (FP) 250 µg or placebo twice daily during 6 weeks. We found beneficial effects on pulmonary function parameters, not on subjective parameters. There were no single predictors for pulmonary function improvement but subjective improvement was seen in patients with signs of airway obstruction on pulmonary function measurement. Especially generally recognised indicators of asthma such as bronchodilator response, atopy, positive family history and wheezing were found to be unrelated to ICS effectiveness in this study.

We conclude that the effect of 6 weeks treatment with ICS in pre-school children with asthma-like symptoms is best demonstrated by PFT markers, not by subjective markers. Decreased pulmonary function appears to predispose to a beneficial effect.

This study also shows that the effect of ICS in pre-school children with asthmatic symptoms can not be derived from experiences in asthmatic school children and adults. The international consensus to treat pre-school children in a similar way as older children and adults, i.e. based on the presence of atopy, wheezing and a positive family history and effect of bronchodilators is not supported by this study. Predictors of asthma appear to be different from predictors of ICS effect (e.g. worse pulmonary function, indoor environment) in young children.

In **Chapter 8** conclusions from these studies and suggestions for further research are presented.

Samenvatting

Op het spreekuur van huisartsen en kinderartsen worden dagelijks veel kinderen met acute of chronische luchtwegklachten gezien. Naast luchtweginfecties van de bovenste (keel, neus, oor) en onderste (bronchiën en longen) luchtwegen betreft het vooral ook kinderen met recidiverend hoesten, piepen en/of zagen, b.v. ten gevolge van astma. Het aantal kinderen met astmatische klachten neemt de laatste jaren toe, vooral bij peuters en kleuters. Hoewel luchtwegklachten vaak vanzelf weer over gaan is het belangrijk die kinderen eruit te pikken die risico lopen op chronische luchtwegproblemen, en wellicht blijvende luchtweg- of longafwijkingen, die het dagelijks leven negatief kunnen beïnvloeden. Door deze kinderen (tijdig) te onderkennen en te behandelen kan op korte termijn verbetering worden bereikt en kunnen wellicht problemen in de toekomst worden voorkomen of verminderd.

Bij de meeste kinderen is de diagnose en behandeling geheel gebaseerd op anamnese en lichamelijk onderzoek. Met name de anamnese blijft natuurlijk erg subjectief en er is dan ook behoefte aan objectieve ziekteparameters zoals longfunctieonderzoek. Hoewel longfunctieonderzoek in toenemende mate wordt gebruikt bij schoolkinderen, ontbreekt het aan mogelijkheden bij jongere kinderen.

Longfunctieonderzoek kan bij kinderen met (en zonder) luchtwegklachten o.a. worden gebruikt om verschillende soorten longfunctieafwijkingen te ontdekken en te kwantificeren, om het effect van interventie te meten, om het beloop in de tijd te vervolgen en zo prognoses voor de toekomst te geven.

De meest gebruikte longfunctieparameter is de FEV_1. Dit is het volume lucht dat iemand na maximale inademing tijdens een zo krachtig en lang mogelijke uitademing kan uitblazen in de eerste seconde (forced expiratory volume in 1 second). De techniek om deze manoeuvre goed uit te voeren vraagt om optimale coördinatie en medewerking van de patiënt en derhalve is dit onderzoek vrijwel onmogelijk bij (de meeste) peuters en kleuters. Overigens blijkt dat ook oudere kinderen, vele volwassenen en geriatrische patiënten vaak moeite hebben met deze techniek.

Daarom bestaat er behoefte aan alternatieve methoden. Hoewel recent enkele nieuwe methoden zijn ontwikkeld zijn deze meestal niet geschikt voor de dagelijkse praktijk, omdat b.v. verdoving gewenst is, apparatuur erg

moeilijk te bedienen of erg duur is of omdat ze invasief zijn. Deze technieken worden daarom vaak alleen bij onderzoek en in gespecialiseerde centra gebruikt.
Klinische toepassing van nieuwe technieken is alleen mogelijk bij jonge kinderen als de uitvoering makkelijk is, niet te lang duurt, reproduceerbaar, niet invasief en niet te duur is. Ook moeten ze zonder verdoving toe te passen zijn, tijdens spontane rustige ademhaling en onderscheid kunnen maken tussen gezond en ziek. Het effect van interventie moet meetbaar zijn en liefst moet dezelfde techniek op alle leeftijden mogelijk zijn zodat follow-up kan plaatsvinden. Technieken die veelbelovend lijken zijn de rustademhalingsanalyse, de interruptie methode en de impulsoscillometrie.
Door aanpassing van bestaande technieken (FEV_1) of door standaardisatie en verdere ontwikkeling van deze nieuwe technieken kunnen we in de toekomst wellicht in de dagelijkse praktijk op een objectieve wijze kinderen met luchtwegklachten in beeld brengen.
De studies beschreven in dit proefschrift hebben betrekking op verschillende aspecten van longfunctieonderzoek bij jonge kinderen.

In **Hoofdstuk 2** wordt een overzicht gegeven van de literatuur over (de ontwikkeling van) anatomie en fysiologie van de luchtwegen en longen. Vervolgens worden de verschillende beschikbare technieken voor longfunctieonderzoek bij spontaan ademende jonge kinderen besproken. Hoewel longfunctieonderzoek waarschijnlijk vooralsnog het best kan plaatsvinden met de FEV_1 kunnen de boven genoemde nieuwe technieken om weerstand te meten zoals de interrupter techniek en impulsoscillatie worden toegepast als de FEV_1 meting niet mogelijk is.
Verschillende technieken om weerstand te meten hebben betrekking op verschillende aspecten van weerstand. Alleen met lichaamsplethysmografie wordt zuiver de luchtwegweerstand gemeten. Deze techniek is echter alleen toepasbaar bij oudere kinderen, volwassenen en (onder sedatie) bij zuigelingen. De middels de interruptie techniek gemeten weerstand is slechts een benadering van de weerstand van het gehele ademhalingsstelsel (behalve luchtwegen ook longweefsel en borstkast). De methode is niet gestandaardiseerd en mede ten gevolge daarvan bestaat er voorlopig nog geen algemene acceptatie van deze techniek. Daar staat tegenover dat de interrupter techniek en impulsoscillatie makkelijk uitvoerbaar zijn bij spontaan ademende kinderen en slechts passieve medewerking vragen van de patiënt. Daardoor lijken deze technieken geschikt voor gebruik in de dagelijkse praktijk, maar ook voor onderzoek bij jonge kinderen. Bovendien

komen steeds meer makkelijk bruikbare en kleinere apparaten ter beschikking, die door de verschillende industrieën worden aangeboden. Hoewel dit een uitgebreidere toepassing van deze technieken zal bevorderen dient verder onderzoek en standaardisatie plaats te vinden, inclusief het bepalen van normaalwaarden, alvorens deze technieken geschikt zijn voor dagelijks gebruik door de verschillende hulpverleners.
Daar staat tegenover dat deze technieken toepasbaar zijn bij spontaan ademende patiënten, dus zonder moeilijke ademhalingsmanoeuvres en dus wellicht meer correlatie hebben met het functioneren tijdens dagelijkse bezigheden. Bovendien zijn de meeste longfunctieafwijkingen op jonge leeftijd het gevolg van afwijkingen in de doorgankelijkheid van perifere luchtwegen en betreft de middels deze technieken bepaalde weerstand met name bij jonge kinderen (meer dan bij volwassenen) de perifere luchtwegweerstand. Tenslotte blijken de technieken effecten van interventie minimaal even goed weer te geven als de "gouden standaard" FEV_1.

Binnen ons ziekenhuis heeft in de jaren 90 veel onderzoek plaatsgevonden met de rustademhalingsanalyse. In **Hoofdstuk 3** wordt een overzicht gegeven van deze techniek. Uit de grafiek die de luchtstroomsnelheid (flow) tijdens ademhaling beschrijft blijkt dat dit patroon bij patiënten met perifere luchtwegobstructie anders is. Dit wordt weergegeven als de ratio van *t*PTEF en *t*E. *t*PTEF is de tijd vanaf het begin van de uitademing tot aan de maximale flow en *t*E de totale uitademingtijd. Deze ratio is duidelijk verminderd bij kinderen met astma. Studies bij katten hebben aangetoond dat dit flowpatroon vooral wordt bepaald door de mechanische eigenschappen van het ademhalingsstelsel (weerstand en compliantie) en de activiteit van inademingspieren tijdens het begin van de uitademing.

Hoofdstuk 4 is gewijd aan de maximale expiratoire flow volume (MEFV) curve, die algemeen beschouwd wordt als de gouden standaard van longfunctieonderzoek op alle leeftijden. Veel kinderen, zelfs peuters en kleuters zijn soms in staat tot de speciale manoeuvres nodig voor het blazen van MEFV curven. Kinderen zijn echter geen kleine volwassenen en vele kindspecifieke aspecten van uitvoering en interpretatie van dit onderzoek bij (jonge) kinderen verdienen aandacht.

In **Hoofdstuk 4.1** bespreken we de belangrijkste voorwaarden voor betrouwbaar gebruik van MEFV onderzoek bij kinderen. Vooral de inrichting van de longfunctieruimte, apparatuur, personeel, instructie van adem-

halingstechniek, betrouwbaarheidscriteria, afdruktechnieken en inter- pretatie worden besproken. Voor veel kinderen kan het eerste bezoek aan een longfunctielaboratorium worden gezien als het begin van en langdurige "longfunctiecarrière" en een goed begin is ook hier het halve werk!

Voorafgaande aan de interpretatie van de MEFV curve (of om het even elke andere longfunctiemeting) dient de kwaliteit van het onderzoek worden beoordeeld. De mate waarin de patiënt zich inspant, meewerkt, de geforceerde techniek goed uitvoert en de reproduceerbaarheid van deze techniek dient optimaal te zijn alvorens het resultaat te beoordelen. Zoals hierboven besproken is de uitvoering van dit onderzoek niet makkelijk. Internationale criteria voor de goedkeuring en reproduceerbaarheid van MEFV curven zijn opgesteld door internationale organisaties, de American Thoracic Society (ATS) en de European Respiratory Society (ERS). Deze criteria hebben betrekking op volwassenen en specifieke criteria voor kinderen ontbreken. Middels een retrospectieve studie hebben we de MEFV curven van kinderen van verschillende leeftijden beoordeeld op de mate waarin ze voldoen aan de criteria voor volwassenen. De resultaten worden beschreven in **Hoofdstuk 4.2**. Hiervoor werden de meest recente MEFV curven gebruikt van 446 kinderen, die ervaring hadden met de uitvoering van dit onderzoek en die volgens onze ervaren kinderlongfunctie-assistenten de techniek prima beheersten. Deze curven toonden een onmiddellijke scherpe piekflow bij start van een maximaal volgehouden uitademingsmanoeuvre. Toch bleken zelfs de curven van deze ervaren kinderen, die er dus technisch prima uitzagen en goed konden worden geïnterpreteerd, niet te voldoen aan alle criteria zoals die bestaan voor volwassenen. Gebaseerd op de prestaties van deze kinderen werd een voorstel gedaan voor aanpassing van de internationale criteria voor kinderen.

Recent werd een reeds langer bestaande longfunctietechniek, namelijk de interruptie techniek, voor het meten van weerstand nieuw leven ingeblazen, mede door het ter beschikking komen van een klein handzaam apparaatje, de MicroRint®. Deze techniek wordt beschreven in **Hoofdstuk 5**. De basis van deze techniek is gelegen in het feit dat gedurende kortdurende afsluiting van de luchtstroom er een snelle equilibratie van de druk in de diepste longdelen (het "alveolaire" compartiment) en de monddruk plaatsvindt. Zo kan de alveolaire druk worden gemeten aan de mond. Als de flow kort voor afsluiting bekend is kan uit de veranderingen van flow en druk de interruptieweerstand (Rint) worden gemeten (weerstand = druk: flow).

Samen met twee medische studenten werd een onderzoek verricht naar de toepasbaarheid van dit apparaatje. Bij gezonde kinderen (op scholen en kinderdagverblijven) en bij astmatische kinderen (op de polikliniek) werden de toepasbaarheid en reproduceerbaarheid vergeleken. Ook werden normaalwaarden verzameld en werd bij astmapatiënten de correlatie met FEV_1 bekeken. Zoals beschreven in **Hoofdstuk 5.1** kon bij het overgrote deel van kinderen vanaf 3 jaar een meting plaatsvinden en de reproduceerbaarheid was goed. Toepasbaarheid was vergelijkbaar bij gezonde en astmatische kinderen en blijkt leeftijdsafhankelijk. Er bestond een goede correlatie met leeftijd en lengte. Rintwaarden bij gezonde en astmatische kinderen waren niet significant verschillend. Bij astmapatiënten werd een significante correlatie met MEFV waarden gevonden. Na inhalatie van een luchtwegverwijder was er een significante stijging van FEV_1 en afname van Rint, maar veranderingen van beide parameters correleerden niet.

Normaalwaarden van Rint zijn er wel voor jonge kinderen maar ontbreken voor kinderen vanaf de leeftijd van 7 jaar. De resultaten van twee vergelijkbare onderzoeken, het hiervoor genoemde en een onderzoek in het Sophia Kinderziekenhuis te Rotterdam, werden gecombineerd. Bij 208 3-13 jaar oude gezonde kinderen werd Rint gemeten. Daarmee konden referentievergelijkingen worden opgesteld die de correlatie van Rint met lengte beschrijven. Er bleek een curvilineair verband tussen de expiratoire Rint en de lengte te bestaan, vergelijkbaar met de referentiewaarden zoals die bestaan voor de luchtwegweerstand gemeten middel lichaamsplethysmografie. Er bestonden geen significante verschillen tussen jongens en meisjes. Gebaseerd op de referentievergelijking 10log (Rinte) = 0.645 - 0.00668 x (lengte (cm)) kPa/L/s en een residuale standaard deviatie (0.093 kPa/L/s), kunnen Z-scores worden gebruikt om de individuele Rint waarde uit te drukken en om intra- en interindividuele verschillen te beschrijven (**Hoofdstuk 5.2**).

Een ander methode om weerstand (en reactantie) van het ademhalingsstelsel te meten en die eveneens te gebruiken is bij jonge kinderen is de impulsoscillatie techniek (IOS). Een sinusoidale drukgolf, samengesteld uit verschillende frequenties wordt aangeboden boven op het spontane rustige ademhalingspatroon. Deze drukgolven resulteren in flowschommelingen, waarvan de grootte en fase (t.o.v. de drukgolf) worden bepaald door de weerstand, elastische eigenschappen en traagheid van het ademhalingsstelsel. De veranderingen van druk en flow kunnen worden gemeten bij de mond

en hieruit kan voor elke frequentie de relatie van druk en flow, de zgn. impedantie (Z) worden berekend. Dit is een complexe weergave van de druk versus flow ratio en van de fase shift van deze signalen. Meestal wordt dit complexe getal dan ook uitgesplitst in weerstandswaarde R en reactantiewaarde X.
Deze techniek biedt een alternatieve methode om luchtwegobstructie te kwantificeren bij patiënten die niet in staat zijn tot geforceerde ademmanoeuvres. De sensitiviteit van deze techniek om veranderingen in luchtwegobstructie in vergelijking met FEV_1 en piekflow (PEF) te meten werd onderzocht (**Hoofdstuk 6**). FEV_1, PEF, R en X (bij verschillende frequenties) werden bepaald bij 19 astmatische schoolkinderen voor, gedurende en na methacholine provocatie en vervolgens na luchtwegverwijding met salbutamol. Alle parameters veranderden significant gedurende deze procedures. Beginwaarden van R en X correleerden met FEV_1 en veranderingen van R gingen vooraf aan veranderingen van PEF en FEV_1 gedurende provocatie. Hoewel de PEF vaak wordt gebruikt als een surrogaatmarker voor luchtweggevoeligheid bleken veranderingen in weerstand R beter te correleren met de gouden standaard FEV_1 dan de veranderingen van PEF. We concluderen dan ook dat IOS parameters kunnen worden gebruikt als een indirecte maat voor luchtwegobstructie. Hoewel ze niet hetzelfde mechanisme als de "gouden standaard" FEV_1 beschrijven, kunnen ze bij patiënten die niet in staat zijn tot geforceerde ademhalingsmanoeuvres worden gebruikt.

In **Hoofdstuk 7** wordt het effect van inhalatiecorticosteroïden bij jonge kinderen met astmatische klachten beschreven. Hierbij wordt naast subjectieve effectparameters ook gebruik gemaakt van enkele hierboven besproken longfunctieparameters.
De onderhoudsbehandeling van astmatische kinderen met inhalatiecorticosteroïden (ICS, ontstekingsremmende medicijnen, ingenomen via speciale apparaatjes tijdens de inademing) heeft de laatste decennia een sterke ontwikkeling doorgemaakt. Er bestaat een tendens om niet alleen patiënten met ernstig astma, maar ook kinderen met minder frequente en minder ernstige klachten te behandelen met ICS. Echter kinderen met mild astma hebben vanzelfsprekend ook mindere afwijkingen van verschillende ziekteparameters (o.a. longfunctie). Dit maakt het ook moeilijker om een verbetering te meten.
Het effect van ICS behandeling werd onderzocht bij twee groepen kinderen:

1. 5-10 jaar oude kinderen met mild astma (SJOKOLA 1)
2. 1-4 jaar oude kinderen met "astmatische klachten" (SJOKOLA 2)

SJOKOLA is een afkorting van "*S*teroiden bij *JO*nge *K*inderen als *O*nderhoudsbehande*L*ing van *A*stma"

In de eerste studie werden 68 kinderen behandeld met fluticason propionaat (FP, Flixotide®) 2x/dag 250 μg of placebo (nepmedicijn) via een voorzetkamer gedurende 12 weken. Uit het onderzoek bleek dat behandeling met FP in vergelijking met placebo een significante vermindering gaf van het % dagen met klachten, verbetering van ochtend- en avondpiekflow en van piepende ademhaling. Ook de FEV_1 als % van voorspeld verbeterde significant (**Hoofdstuk 7.1**). De laatste verbetering was weliswaar klein maar des te opvallender daar de uitgangswaarde binnen normale grenzen viel. Desondanks werd de longfunctie dus "nog beter". Deze studie toont dus dat een "normale "longfunctie" bij kinderen met astmatische klachten niet uitsluit dat er luchtwegvernauwing bestaat, die verbetert middels adequate therapie. Hoewel geen significante verbetering werd gevonden van rustademhalingsparameters toont deze studie dan ook niet alleen aan dat kinderen met mild astma verbeteren onder invloed van ICS maar ook dat dit effect zowel subjectief als objectief meetbaar is.

Een groot aantal jonge kinderen (tot 40%) heeft gedurende de peuter-kleuter jaren astmatisch te duiden klachten als piepen, hoesten en benauwdheid. Bij meer dan de helft van deze kinderen verdwijnen de klachten enkele jaren later. Waarschijnlijk hebben de klachten dan meer te maken met aangeboren nauwere luchtwegen, die extra klachten geven bij b.v. luchtweginfecties. Bij een substantieel deel van de kinderen persisteren klachten echter ook op latere leeftijd. Met name bij deze kinderen wordt dan de diagnose astma gesteld. Vaak is er dan sprake van een familiair voorkomen van allergie, bestaan er positieve huidtesten op allergenen en verhoogde bloedwaarden van totaal en specifiek IgE (maat voor allergie).
Er bestaat een tendens om peuters en kleuters te behandelen als astma (hoewel dus het grootste deel uiteindelijk geen astma zal blijken te hebben!). Of deze therapie effectief is, is nog onduidelijk en slechts weinig onderzoekers hebben dit onderzocht. Hierbij is geen gebruik gemaakt van de longfunctietechnieken zoals boven beschreven.
In de tweede SJOKOLA studie werd het effect van ICS onderzocht bij 1-4 jaar oude kinderen met chronische of frequente astmatische symptomen. Daarbij werd zowel van subjectieve als objectieve effectparameters gebruik

gemaakt (**Hoofdstuk 7.2**).
Hoewel er zoals boven beschreven bepaalde voorspellers van astma bestaan, is onduidelijk welke jonge kinderen wel en welke niet baat hebben bij behandeling met ICS. Daarom zochten we in deze studie ook naar eventuele voorspellers van ICS effectiviteit.
In deze studie werden 99 kinderen behandeld met FP 2x/dag 250 μg of placebo via een voorzetkamer gedurende 6 weken. We vonden bij FP behandelde patiënten in vergelijking met placebo een verbetering van verschillende longfunctieparameters, maar niet van symptomen of klachten. Er waren geen duidelijke voorspellers van de verbetering van longfunctie maar in een groep met slechtere longfunctie werd wel een significante verbetering van symptomen en klachten gevonden. Met name echter de bekende voorspellers van astma (verbetering o.i.v. luchtwegverwijders, allergie, positieve familieanamnese en piepen bij lichamelijk onderzoek) waren geen voorspeller van ICS effectiviteit. Concluderend is het effect van ICS bij 1-4 jaar oude kinderen wel met longfunctie, niet met subjectieve parameters te meten. Wellicht hebben vooral kinderen met een slechte longfunctie baat bij behandeling met ICS.
Deze studie toont ook aan dat het effect van ICS bij jonge kinderen met astmatische klachten niet kan worden vergeleken met ervaringen bij oudere kinderen met astma. De (inter)nationale consensus om deze kinderen te behandelen met ICS indien er sprake is van b.v. allergie, piepen, positieve familieanamnese of effect van luchtwegverwijders wordt door deze studie niet ondersteund. Voorspellers van astma zijn anders dan voorspellers van ICS effect.

In **Hoofdstuk 8** tenslotte worden enkele conclusies uit deze studies getrokken en worden enkele adviezen voor toekomstige studies gegeven.

List of abbreviations

A	age in years
$_{alv}$	alveolar
ANCOVA	analysis of co-variance
ANOVA	analysis of variance
ao	airway opening
AR	auto regressive
ATS	American Thoracic Society
$_{aw}$	airway
$_{awc}$	central airway
$_{awp}$	peripheral airway
BDP	beclomethasone dipropionate
BDR	bronchodilator response
BHR	bronchial hyperresponsiveness
box	body plethysmograph
BTPS	body temperature, ambient pressure, saturated with water vapor
BTS	British Thoracic
BUD	budesonide
C	compliance
CF	cystic fibrosis
CI	confidence interval
CV	coefficient of variation
$_{cw}$	chestwall
$dFEV_1abs$	absolute difference between two highest FEV_1s
$dFEV_1\%$	percentual difference between two highest FEV_1s
dFVCabs	absolute difference between two highest FVCs
dFVC%	percentual difference between two highest FVCs
DRC	daily record card
E	elastance
ECSC	European Community for Steel and Coal
$_{el}$	elastic
EPP	equal pressure point
ERS	European Respiratory Society
$_{ext}$	extrathoracic
η	viscosity of the gas
F	female
FET	forced expiratory time
FEV_1	forced expiratory volume in 1 second
$FEV_1\%FVC$	FEV_1 as a percentage of FVC

FEV_1%pred	FEV_1 as a percentage of predicted
FEV0.5	forced expiratory volume in 0.5 second
FOT	forced oscillation technique
FP	fluticasone propionate
FRC	functional residual capacity
F-V	flow volume
FVC	forced vital capacity
GEE	generalised estimating equations
H	standing height in cm
H*	standing height in meters
Hz	Herz
ICS	inhaled corticosteroids
IgE	immunoglobuline E
in	inside
int	interrupter
IOS	impulse oscillation technique
ISAAC	International Study of Asthma and Allergies in Childhood
ith	intrathoracic
kPa	kilopascal
l	length
L	liter
L	lung
M	male
MEF75/50/25	maximal expiratory flow at 75/50/25 % of FVC
MEFV	maximal expiratory flow volume
mo	mouth
msec	milliseconds
occ	occlusion
oes	oesophagus
OR	odds ratio
out	outside
p	p value
P	pressure
PEF	peak expiratory flow
PFT	pulmonary function testing
pl	pleural
pMDI	pressurised metered dose inhaler
PtcO2	transcutaneous oxygen tension

R	resistance
r	radius
r	correlation coefficient
RAST	radio allergo sorbent test
RC	reliability coefficient
REM	rapid eye movement
Rint	interrupter resistance
Rinte	expiratory interrupter resistance
Rinti	inspiratory interrupter resistance
$_{rs}$	respiratory system
RSD	residual standard deviation
Rx	resistance at x Hz
s	second
S	sitting height in cm
SD	standard deviation
SE	standard error
sG_{aw}	specific airway conductance
SI	sensitivity index
SJOKOLA	Steroiden bij Jonge Kinderen als Onderhoudsbehandeling van Astma (Steroids in young children as maintainance treatment of asthma)
sR_{aw}	specific airway resistance
τ	time constant
TBA	tidal breathing analysis
TLC	total lung capacity
PD_{20}	provocative dose leading to a 20% fall in FEV_1
ROC	receiver operating characteristics
$_{tm}$	transmural
$_{tot}$	total respiratory system
tPEF	time to peak expiratory flow (during MEFV measurement
*t*PTEF	time to peak tidal expiratory flow (during TBA)
*t*E	total expiratory time
V	volume
V'	flow
Vbe	backward extrapolated volume
Vbe%FVC	backward extrapolated volume as a percentage of FVC
VE	total expiratory volume
VPTEF	volume to peak tidal expiratory flow

$V'_{max}FRC$	maximal expiratory flow at FRC level
X	reactance
Xx	reactance at x Hz
yrs	years
Z	impedance

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"Lieve Kors en Amber, papa is weer hier
we gaan nu samen spelen en hebben veel plezier
Lieve Kors en Amber, lieve Kors en Amber,
Lieve Kors en Amber, papa is weer hier"

Curriculum vitae
and
List of publications

Curriculum vitae

Bert Arets werd geboren op 4 mei 1965 te Beek (L). In 1983 werd het VWO diploma behaald aan de "Serviam Scholengemeenschap" te Sittard. Hetzelfde jaar startte hij de studie geneeskunde aan de Universiteit van Maastricht, waar hij in 1990 het artsexamen behaalde. Na een kort verblijf op de kinderafdeling van het "Mangochi District Hospital" te Malawi vervulde hij zijn militaire dienstplicht in het Militair Hospitaal Dr. A. Matthijsen te Utrecht als assistent interne geneeskunde (Hoofd afdeling kolonel-arts Dr M van Zoeren). Vanaf mei 1991 was hij werkzaam in het De Wever Ziekenhuis (tegenwoordig Atrium Medisch Centrum) te Heerlen op de afdeling kindergeneeskunde, eerst als AGNIO en vanaf 1 mei 1992 als AGIO (opleider Dr PMVM Theunissen). De opleiding werd in 1993 voortgezet in het Academisch Ziekenhuis Maastricht (opleiders Prof Dr RH Kuijten en Prof Dr CE Blanco). In februari 1997 werd hij geregistreerd als kinderarts. Gedurende 6 maanden was hij als kinderarts algemene kindergeneeskunde werkzaam op de kinderafdeling met specifieke aandacht voor kinderlongziekten (i.s.m. JJE Hendriks). Vervolgens was hij vanaf 1 september 1997 werkzaam in het Wilhelmina Kinderziekenhuis te Utrecht. Als voorbereiding op de opleiding tot kinderarts-pulmonoloog was hij de eerste 3 maanden werkzaam als kinderarts-fellow op de afdeling intensive care (hoofd Prof. Dr. AJ van Vught). In december 1997 startte hij met de opleiding tot kinderarts-pulmonoloog (hoofd HJL Brackel, later Dr. CK van der Ent). In deze periode werd ook gestart met het onderzoek, dat de basis vormde voor dit proefschrift. Sinds december 2000 is hij staflid op de afdeling kinderlongziekten van het UMC Utrecht.
Bert is getrouwd met Ingrid van Geel. Samen hebben zij twee kinderen: Kors (2000) en Amber (2002).

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