Concluding remarks and suggestions for further research
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 FEV$_{0.5}$ 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 (preschool 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.