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Radiological and functional changes over 3 years in young children with cystic fibrosis

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Short title: Lung disease progression in CF children

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Abstract

The aim of this study was to evaluate airway disease progression assessed by chest radiology, expiratory interrupter resistance ($Rint_{exp}$), and spirometry in young children with CF over a 3-year interval.

Two chest radiographs combined with two $Rint_{exp}$ measurements, in a 3 year interval, were performed in 21 preschool children (mean (SD) age 3.2 (0.9) years) and 30 school children with CF (mean (SD) age 7.2 (1.9) years). Chest radiographs were scored using five different CF scoring systems and $Rint_{exp}$ measurements were expressed as height adjusted Z-scores. Spirometry was assessed in school children and results were expressed as percent predicted.

Chest radiograph scores worsened significantly over the 3 year period and there was a tendency towards more pronounced changes, especially for the Wisconsin score in preschool children. Most preschool and school children had $Rint_{exp}$ Z-scores within normal range at start and follow-up, and annual change in $Rint_{exp}$ Z-score was not significant. In school children only forced expiratory volume in 1 second as percentage of forced vital capacity (FEV_1%FVC) declined significantly during the study period.

In young children with CF, chest radiograph scores worsen significantly over time even while lung function remains stable.

Keywords: cystic fibrosis, chest radiograph scores, interrupter resistance, preschool children

Introduction

Chronic airway infection and inflammation in cystic fibrosis (CF) lung disease lead to structural lung damage, pulmonary dysfunction and eventually to respiratory insufficiency. CF lung disease starts at a very young age and ideally, treatment should also start at onset or even before onset of lung disease. Therefore sensitive measures of structural and functional lung damage are needed to objectively assess lung disease progression and to evaluate effect of treatment.

Structural lung damage in CF can be assessed by chest radiology and high resolution computed tomography (HRCT) scanning. An annual chest radiograph and the use of chest radiograph scoring systems are recommended by the European CF Consensus Committee [1] and several different CF chest radiograph scoring systems [2-6] have been developed. In older children with CF with moderate to severe disease severity, there is good correlation between pulmonary function tests (PFTs, especially forced expiratory volume in 1 second (FEV_1)) and chest radiograph scores in cross-sectional studies [4,6,7]. Longitudinal evaluation of bronchopulmonary disease in children with CF using chest radiology showed disease progression from about the ages of 5 years, even when spirometry still remained stable [8-10]. However, in preschool children the sensitivity of chest radiographs as a measure of disease progression and the relationship with functional parameters is unclear.

Lung function can be assessed by PFTs (especially spirometry) and although forced expiratory volume in 1 second (FEV_1) is still considered gold standard in daily CF practice, in young CF children peripheral flows such as forced expiratory flow between 25% and 75% of expiratory vital capacity ($FEF_{25-75\%}$) seem more sensitive [11] . In most children spirometry is feasible from the age of 4-6 years, but standards for quality control are lacking for preschool children [12-14]. Therefore alternative PFTs, such as the expiratory interrupter resistance ($Rint_{exp}$) measurement, have been developed for this age group [15-20]. $Rint_{exp}$ measurements

can be performed without sedation, are easily applicable in general practice, are effort-independent, and reference values for children between 3 and 13 years of age are available [18]. $Rint_{exp}$ measurements might be of use in detecting early lung function abnormalities in children with CF. However, data on the value of Rint measurements in CF patients are not conclusive [12,17,18,20] and longitudinal measurements of Rint have never been related to structural damage assessed by chest radiology.

The purpose of our study was to evaluate the sensitivity of structural and functional parameters of lung disease progression in young children with CF. We prospectively studied disease progression in preschool (children aged < 5 years) and school children (children aged >5 years) using simple chest radiograph scores, $Rint_{exp}$ measurements, and spirometry.

Methods

Study population

The CF Centre Utrecht of the University Medical Centre Utrecht (Utrecht, The Netherlands), a tertiary academic hospital, uses annual chest radiographs and PFT measurements (including spirometry and $Rint_{exp}$ measurements) to monitor lung disease in patients with CF.

We studied 21 preschool children and 30 school children who attended the CF Centre for their annual check-up between April 2002 and June 2003, and had a routine chest radiograph and $Rint_{exp}$ measurement on the same day both that year and after 3 years. All school children performed spirometry at visit 1 and 2. Measurements were performed when children were clinically stable. Informed consent was obtained from the parents of all participating children.

Chest radiographs

Chest radiographs (anteroposterior and lateral view) were blinded and scored in random order by two different observers (HA and CvdE) according to the following five cystic fibrosis chest radiograph scoring systems: Chrispin-Norman scoring (best score 0, worst score 38) [2], adjusted Chrispin-Norman scoring (best score 0, worst score 42) [3], Wisconsin scoring (best score 0, worst score 100) [4], Northern scoring (best score 0, worst score 20) [5] and Brasfield (Birmingham) scoring system (best score 25, worst score 4) [6].The systems score different abnormalities such as hyperinflation, linear markings, nodular cystic lesions, and large lesions (segmental or lobar atelectasis or consolidation). Both observers randomly scored 8 chest radiographs for a second time after 3 months to establish intraobserver variability. Previously it has been stated that a cut-off value of 5 for the

Wisconsin score and 21 for the Brasfield score are associated with mild but potentially irreversible lung damage [10].

$Rint_{exp}$ and spirometry

In all children airway resistance was measured using the MicroRint® (Micro Medical Limited, Kent, UK), as described in previous studies [15,16,19]. A successful $Rint_{exp}$ measurement consisted of a median $Rint_{exp}$ value of at least 5 out of 10 interruptions and $Rint_{exp}$ was calculated using the back extrapolation technique to t=0 ms after shutter closure during 100 ms [15,21]. $Rint_{exp}$ values in children with CF were expressed as height adjusted Z-scores, using data from a Dutch healthy control population [19].

All school children performed spirometry at visit 1 and visit 2 (Masterlab, Hochberg, Germany). Spirometry results FEV_1, forced vital capacity (FVC), maximal expiratory flow at 50% of vital capacity (MEF_{50}), the forced expiratory flow at 75% of expiratory vital capacity (FEF_{75}),the forced expiratory flow at 75% of expiratory vital capacity (FEF_{75}), the forced expiratory flow at 75% of expiratory vital capacity (FEF_{75}), and the forced expiratory flow between 25% and 75% of expiratory vital capacity (FEF_{25-75}), were expressed as percentage of predicted values using the data from Zapletal [22]. FEV_1 was also expressed as percentage of FVC (FEV1%FVC). Abnormal lung function was defined as a FEV_1 % pred < 85%.

Lung structure and lung function over time

The average of the chest radiograph scores of the two observers were used. Data obtained at the first visit are reported as chest $radiograph_1$, $Rint_{exp}$ $Z\text{-}score_1$ and PFT_1, and at the second visit as chest $radiograph_2$, $Rint_{exp}$ $Z\text{-}score_2$, and PFT_2. Δchest radiograph is the annual change for a chest radiograph scoring system (chest $radiograph_2$-chest $radiograph_1$/time interval), $\Delta Rint_{exp}$ Z-score the annual change for $Rint_{exp}$ Z-score ($Rint_{exp}$ Z-

score$_2$- Rint$_{exp}$ Z-score$_1$/time interval), and ΔPFT the annual change for PFTs (PFT$_2$-PFT$_1$/time interval). To compare the annual changes of the five chest radiograph scoring systems, Δchest radiograph was also expressed as a percentage of the maximal obtainable score for that system. Except for the Brasfield scoring system since the best score for this system is 25 and the worst score is 4. A positive value for Δchest radiograph indicates an increase of structural abnormalities for all chest radiograph scoring systems except for the Brasfield scoring system, where a negative value for Δchest radiograph indicates an increase of structural abnormalities. A positive value for ΔRint$_{exp}$ Z-score indicates an increase in resistance and thus a worsening of lung function. A negative value for ΔPFT indicates a decline in lung function.

Statistical analysis

Intra- and interobserver variability of composite chest radiograph scores were calculated using intraclass correlation coefficients. To determine whether chest radiograph scores and/or Rint$_{exp}$ Z-score and/or PFTs changed significantly over time in preschool and in school children, Student's *t*-tests (paired)were performed for ΔRint$_{exp}$ Z-score, ΔPFT, and Δchest radiograph. Mean differences between the parameters at visit 1 and 2 were expressed as mean annual decline by dividing the mean difference by time interval. The relationships between chest radiographs, Rint$_{exp}$ Z-scores, and PFTs and between Δchest radiograph, ΔRint$_{exp}$ Z-score, and ΔPFT were evaluated using the Spearman correlation coefficients. Finally, changes in chest radiograph scores and Rint$_{exp}$ Z-score over time were compared between preschool and school children using SAS PROC mixed models). Results were considered statistically significant when the p-value was <0.05. Data are presented as mean ± standard deviation (SD). Analysis was performed using the Statistical Package for the Social

Science (SPSS version 12.0, Chicago, IL USA) and SAS statistical package (SAS Institute Inc. Cary, NC, USA).

Results

Study population

Characteristics of the preschool and school children are shown in table 1. Mild but potentially irreversible lung damage (Wisconsin score >5, Brasfield score < 21) was found in 5 of the 21 (24%) preschool children for both the Wisconsin score and 7 of the 21 (33%) for the Brasfield score, and in 12 of the 30 (40%) school children for the Wisconsin score and 15 of the 30 (50%) school children for the Brasfield score at visit 1.

Most preschool children had $Rint_{exp}$ Z-scores that were within normal range (mean ± 2 Z-scores) both at visit 1 (9.5% had a $Rint_{exp}$ Z-score >2 SD) and at visit 2 (19% had a $Rint_{exp}$ Z-score >2 SD). In school children 13% had a $Rint_{exp}$ Z-score >2SD at visit 1 and 23% at visit 2 (figures 1A and 1B). Only 7 of the 30 (23%) school children had abnormal lung function (FEV_1 <85%) at visit 1.

Reproducibility of the scoring systems

Intraclass correlation coefficients (r-values) between both observers for the different scoring systems were moderate (r varying from 0.60 to 0.65). Intraclass correlation coefficients for intraobserver variability were moderate to good (HA varying from r=0.57 for the Northern scoring system to r=0.88 for the adjusted Chrispin-Norman scoring system, and CvdE varying from r=0.78 for the adjusted Chrispin-Norman scoring system to r=0.91 for the Wisconsin scoring system).

Lung structure over time

All chest radiograph scores except the Northern score worsened significantly over time in preschool children (Wisconsin $p<0.05$ and all other scores $p<0.001$, see table 2). Figure 2 shows the changes in Chrispin-Norman score with increasing age. There was no statistically significant difference in change in Chrispin-Norman score over time between preschool and school children (as is illustrated in figure 2). The mean changes in radiograph scores expressed as a percentage of the maximal scores were 2.2, 2.6, 0.4, and 1.7% per year for Chrispin-Norman, adjusted Chrispin-Norman, Wisconsin and Northern, respectively. In school children only the Chrispin-Norman and adjusted Chrispin-Norman score worsened significantly over time (table 2). The mean changes in radiograph scores expressed as a percentage of the maximal scores in school children were 1.3, 1.5, 0.0, and 0.5% per year for Chrispin-Norman, adjusted Chrispin-Norman, Wisconsin and Northern, respectively. Preschool children showed a tendency towards more pronounced changes in chest radiograph scores over time but this was only statistically significant for the Wisconsin score ($p=0.04$). Individual progression of lung disease over time, scored by the Chrispin-Norman score is illustrated in figure 3.

Lung function over time

$Rint_{exp}$ Z-scores did not change significantly over time in preschool and school children. We also assessed changes in $Rint_{exp}$ Z-scores in CF patients with no or only mild signs of pulmonary hyperinflation on their chest radiograph. Only 15 children showed no or only mild hyperinflation. Difference in progression of Rint Z-score between children with no or only mild hyperinflation versus moderate to severe hyperinflation was 0.02 ± 0.92 versus 0.37 ± 1.6 ($p=0.51$). When comparing preschool children with school children, $Rint_{exp}$ Z-scores appeared higher in school children but this difference was not statistically significant.

In school children only FEV_1%FVC worsened significantly over time (annual decline 1.94% ($p<0.01$)). We plotted individual changes in FEV_1%FVC versus age over time for all school children and 8 preschool children that were able to perform spirometry at both visits as is shown in figure 4.

Correlation between lung structure and lung function

In preschool children there was no significant correlation between chest radiograph and $Rint_{exp}$ Z-score at visit 1 and visit 2 at cross-sectional data analysis. Longitudinal data analysis also showed no significant correlation between all Δchest radiograph scores and $\Delta Rint_{exp}$ Z-score. In school children we also found no significant correlation between chest radiograph and $Rint_{exp}$ Z-score at visit 1 and visit 2, or between chest radiograph and PFT at visit 1. There was however a significant but moderate correlation between the Chrispin-Norman and adjusted Chrispin-Norman score and FEV_1% pred, MEF_{50}% pred, FEF_{25-75} % pred and FEV_1%FVC at visit 2. The Wisconsin score correlated significantly but weakly with FEV_1% pred, FEV_1%FVC, and FEF_{25-75} % pred and the Brasfield score correlated significantly but weakly with FEV_1% pred, and $MEF_{25-75\%}$ % pred at visit 2.

Discussion

In this study we evaluated the capability of chest radiograph scores, $Rint_{exp}$ measurements, and spirometry to detect and monitor progression of lung damage in young children with CF. Chest radiograph scores worsened significantly over a 3 year period in both preschool and school children. In our study group the annual changes for the Wisconsin score were less than those observed in the large Wisconsin trial cohort described previously [8]. Comparisons are hampered by the fact that the Wisconsin trial group is subdivided in 4 groups: screened, non-screened, and patients with or without *Pseudomonas aeruginosa*. Besides differences in the number of children included and duration of follow-up between the Wisconsin trial and our study, the time of inclusion is different. In the Wisconsin trial, children were included from 1985 till 1998. In past years major changes in detection techniques and treatment regimen for *Pseudomonas aeruginosa* have been implemented in daily CF care, making comparison of our cohort with the Wisconsin trial cohort more difficult. In our cohort 5 preschool children and 6 school children had a positive sputum culture with *Pseudomonas aeruginosa* at visit 1. These children did not show faster progression than the children without *Pseudomonas aeruginosa*. In the Wisconsin trial however children with acquisition of *Pseudomonas aeruginosa* at young age showed marked progression of the Wisconsin chest radiograph scores after the age of 10 years. Follow-up in our cohort is too short to come to the same conclusion.

Preschool children showed a tendency towards a faster decline in chest radiograph scores than did school children, and this difference was statistically significant for the Wisconsin score. The Chrispin-Norman score and adjusted Chrispin-Norman score showed the greatest annual decline in both preschool and school children. On the other hand Wisconsin, Northern and Brasfield scores did not change significantly in school children. At inclusion already 24-33% of preschool children and 40-50% of school children had a chest radiograph score that resembled mild but potentially irreversible lung damage [10]. In this study set up radiograph scores were more sensitive to monitor disease progression than

functional parameters, especially in young children. This suggests that in young children chest radiographs can be helpful in follow up of CF lung disease progression. Chest radiographs can sensitively measure changes from normality to mild lung disease and these changes already appear in preschool children. School children scored in our study had normal lung function both at visit 1 and 2. In school children bronchiectasis become an important morphological change and HRCT of the chest is considered the gold standard for diagnosing bronchiectasis [23]. This might in part explain why chest radiograph scores in school children in this study showed less progression over the three year period than the scores in preschool children.

One of the drawbacks of using CF chest radiograph scores is that interpretation of the abnormalities seen on a chest radiographs is not always straight forward. Increased densities for example can be interpreted in various ways and this can cause a greater interobserver variability of scores. Interobserver and intraobserver variability of the chest radiograph scores used in this study was moderate to good.. For several years now, use of HRCT of the chest is advocated since HRCT seems to be more sensitive than chest radiographs in detecting structural abnormalities in children with mild CF [24-26]. Even in young children and infants with CF, HRCT can detect structural abnormalities [27,28]. Several cross-sectional studies showed good correlation between HRCT scores and chest radiograph scores [24,25,29]. Although HRCT is sensitive in detecting structural abnormalities [27], especially in young patients, implementation of sequential CT-scanning into daily CF-care is hampered by several factors. HRCT of the chest causes higher radiation dosage and a subsequent higher risk for cancer compared to chest radiographs [30], is more expensive, and although scan time of modern scanners have become so short that images can be obtained while the child is spontaneously breathing, HRCT in very young children still requires sedation. Studies comparing changes in HRCT scores with changes in chest radiograph scores in children over a longer period of time are lacking. In our study we show that chest radiograph scores worsen

in both preschool and school children while lung function was stable. Considering these results and current limitations of implementation of CT-scanning in daily CF care, there still seems to be a valuable role for chest radiograph scores in monitoring structural lung damage in daily clinical practice and possibly in long-term clinical trials. Especially since the radiation burden is reduced even further by excluding the lateral film [31]. Radiation burden and the increased risk of cancer that is related to repeated HRCT scans compared to chest radiographs should remain a topic of discussion since survival in CF has increased significantly over time.

Despite significant abnormalities of chest radiograph scores most preschool and school children had a $Rint_{exp}$ Z-score within normal range both at visit 1 and visit 2, and annual change in $Rint_{exp}$ Z-score was not significant. These findings suggest that $Rint_{exp}$ measurements do not sensitively discriminate between children with CF and healthy children and that longitudinal evaluation of $Rint_{exp}$ measurements are not sensitive enough to detect early progression of lung disease in CF. The between-occasion repeatability of Rint is poor and the variation in bronchial tone is high, limiting the usefulness of repeated $Rint_{exp}$ measurements in monitoring disease progression in CF [32]. Furthermore, most patients in this study had signs of hyperinflation as was established on their chest radiograph. CF patients with pulmonary hyperinflation can compensate by elevating their resting end-expiratory level, a pathophysiologic feature, that is not recognized by Rint measurements. In accordance with our results, no consistent abnormal levels or increases in Rint were found in a 4- year prospective study of inspiratory respiratory resistance measured by interrupter technique in young children with CF [20].

We found no correlation between structural damage assessed by chest radiograph scores and lung function at visit 1. This is not at all surprising since one only expects to find correlations between functional features and structural alterations of a common origin. It

would be interesting to compare for example pulmonary hyperinflation with functional residual capacity or nodular cystic lesions with gas exchange. These comparisons are complicated by the fact that most of the children included in this study were too young to perform other PFTs than interrupter resistance measurements and spirometry. We compared progression of $Rint_{exp}$ Z-score between children with no to mild signs of hyperinflation on their chest radiograph and children with moderate to severe hyperinflation but found no statistically significant difference. In school children we also found no correlation between chest radiograph scores and spirometry at visit 1 but we did find a moderate but significant correlation between most chest radiograph scores and spirometry at visit 2. A possible explanation for the moderate but significant correlation between chest radiograph scores and spirometry at visit 2 is that at visit 2 a larger part of the children had a FEV_1% pred <85%, suggesting more advanced lung disease, and consequently a better correlation with structural abnormalities, as has been shown previously [7]. Other possibilities are, higher inflation level when chest radiograph is taken and better technical abilities due to learning at higher age.

Longitudinal analysis of PFT decline in school children showed no statistically significant worsening except for FEV_1%FVC. A significant change in FEV_1/FVC ratio (expressed as Z-score) has been described previously by de Jong and colleagues in a larger group of older children with CF [33]. In a different study by the same investigator no significant annual decline in percent predicted values of FEV_1/FVC ratio was described [27]. Significant but slow deterioration of percentage predicted FEV_1/FVC ratio was however described in a longitudinal study assessing effect of mucoid *Pseudomonas aeruginosa* infection on lung disease progression [9]. Whether or not the FEV_1/FVC ratio is a sensitive measure in detecting early and mild lung disease in CF remains to be answered, since neither percentage predicted nor FEV_1/FVC ratio Z-score is usually considered a primary endpoint in CF trials. Depending on the stage of lung disease, different spirometric parameters have

different sensitivities in detecting changes [34]. FEV_1%FVC might thus be a more sensitive spirometric parameter in early CF lung disease than FEV_1 and should be included as an endpoint in clinical trials in early CF lung disease.

In conclusion, this study shows that there is a significant annual deterioration of routine chest radiograph scores in young children, especially in preschool children. A proportion of preschool children already have abnormal chest radiographs while $Rint_{exp}$ Z-scores are within normal range in most children with CF. $Rint_{exp}$ is not a good measure to monitor pulmonary disease progression in groups of children with CF. Spirometry (except FEV_1%FVC) in school children remained stable in our studied group and correlated only moderately with chest radiographs. Radiograph scores therefore represent a more sensitive measure than PFTs to evaluate lung disease progression in young children with mild CF lung disease.

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References

1. Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2005;4:7-26.

2. Chrispin AR, Norman AP. The systematic evaluation of a chest radiograph in CF. *Pediatr Radiol* 1974; 2:101-106.

3. Put van der JM, Meradji M, Danoesastro D, Kerrebijn KF. Chest radiographs in cystic fibrosis. A follow-up study with application of a quantitative scoring system. *Pediatr Radiol* 1982; 12:57-61.

4. Weatherly MR, Palmer CGS, Peter ME, Green CG, Fryback D, Langhough R, Farrell PM. Wisconsin cystic fibrosis chest radiograph scoring system. *Pediatrics* 1993;91:488-495.

5. Conway SP, Pond MN, Bowler I, Smith DL, Simmonds EJ, Joanes DN, Hambleton G, Hiller EJ, Stableforth DE, Weller P. The chest radiograph in CF: a new scoring system compared with the Chrispin-Norman and Brasfield scores. *Thorax* 1994;49:860-862.

6. Brasfield D, Hicks G, Soong S, Tiller RE. The chest roentgenogram in CF: a new scoring system. *Pediatrics* 1979;63:24-29.

7. Terheggen-Lagro SWJ, Truijens N, van Poppel N, Gulmans V, van der Laag J, van der Ent C. Correlation of six different cystic fibrosis chest radiograph scoring systems with clinical parameters. *Pediatr Pulmonol* 2003;35: 441-445.

8. Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, Lai HC, Rock MJ, Splaingard ML.Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003;168: 1100-1108.

9. Li Z, Kosorok MR, Farrell PM, Laxova A, West SHE, Green CG, Collins J, Rock MJ, Splaingard ML. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. *JAMA* 2005;293:581-588.

10. Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, Lai H-C, Makholm LM, Rock MJ, Splaingard ML. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. *Pediatr Pulmonol* 2003;36:230-240.

11. Quan JM, Tiddens HA, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, Wohl ME, Konstan MW, Pulmozyme Early Intervention Trial Study Group. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;139:813-820.

12. Beydon N, Amsallem F, Bellet M, Boule M, Chaussain M, Denjean A, Matran R, Pin I, Alberti C, Gaultier C. Pulmonary function tests in preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2002;166:1099-1104.

13. Aurora P, Stocks J, Oliver C, Saunders C, Castle R, Chaziparasidis G, Bush A; London Cystic Fibrosis Collaboration. Quality control for spirometry in preschool children with and without lung disease. *Am J Respir Crit Care Med* 2004;169:1152-1159.

14. Arets HG, Brackel HJ, van der Ent CK. Forced expiratory manouvres in children: do they meet the ATS and ERS criteria for spirometry? *Eur Respir J* 2001;18:655-660.

15. Merkus PJFM, Mijnsbergen JY, Hop WCJ, de Jongste JC. Interrupter resistance in preschool children: Measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001;163:1350-1355.

16. Arets HGM, Brackel HJL, van der Ent CK. Applicability of interrupter resistance measurements using the MicroRint in daily practice. *Resp Med* 2003;97:366-374.

17. Oswald-Mammosser M, Charloux A, Donato L, Albrech C, Speich JP, Lampert E, Lonsdorfer J. Interrupter technique versus plethysmography for measurement of respiratory resistance in children with asthma or cystic fibrosis. *Pediatr Pulmonol* 2000;29:213-220.

18. Carter ER, Stecenko AA, Pollock BH, Jaeger MJ. Evaluation of the interrupter technique for the use of assessing airway obstruction in children. *Pediatr Pulmonol* 1994;17:211-217.

19. Merkus PJFM, Arets HGM, Joosten T, Siero A, Brouha M, Mijnsbergen JY, de Jongste JC, van der Ent CK. Measurements of interrupter resistance. Reference values for children 3-13 years old. *Eur Respir J* 2002;20:907-911.

20. Nielsen KG, Pressler T, Klug B, Koch C, Bisgaard H. Serial lung function and responsiveness in cystic fibrosis during early childhood. *Am J Respir Crit Care Med* 2004;169:1209-1216.

21. Phagoo SB, Wilson NM, Silverman M. Evaluation of a new interrupter device for measuring bronchial hyperresponsiveness to bronchodilator in 3 year old children. *Eur Respir J* 1996;9:1374-1380.

22. Zapletal A, Samanek M, Paul T. Lung function in children and adolescents. Methods, reference values. In: Zapletal A, ed. Progress in Respiration Research.Basel, Switzerland: Karger 1987:114-218.

23. Munro NC, Cooke JC, Currie DC, Strickland B, Cole PJ. Comparison of thin section tomography with bronchography for indentifying bronchiectatic segments in patients with chronic sputum production. *Thorax* 1990;45:135-139.

24. Santamaria F, Grillo G, Guidi G, Rotondo A, Raia V, de Ritis G, Sarnelli P, Caterino M, Greco L. Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? *Pediatrics* 1998;101:908-913.

25. Demirkazik FB, Ariyürek OM, Özçelik U, Göçmen A, Hassanabad HK, Kiper N. High resolution CT in children with cystic fibrosis: correlation with pulmonary functions and radiographic scores. *Eur J Radiol* 2001;37:54-59.

26. Nasr SZ, Kuhns LR, Brown RW, Hurwitz ME, Sanders GM, Strouse PJ. Use of computerized tomography and chest X-rays in evaluating efficacy of aerosolized recombinant human DNase in cystic fibrosis patients younger than age 5 years: a preliminary study. *Pediatr Pulmonol* 2001;31:377-382.

27. de Jong PA, Nakano Y, Lequin MH, Mayo JR, Woods R, Pare PD, Tiddens HA. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004;23: 93-97.

28. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004;144:154-161.

29. Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. *J Thorac Imaging* 1996;11:27-38.

30. Berrington de Gonzalez A, Samet JM. What Are the Cancer Risks from Using Chest Computed Tomography to Manage Cystic Fibrosis? *Am J Respir Crit Care Med* 2006; 173: 139-140.

31. Benden C, Wallis C, Owens CM, Ridout DA, Dinwiddie R. The Chrispin-Norman score in cystic fibrosis: doing away with the lateral view. *Eur Respir J* 2005;26:894-897.

32. Child F. The measurement of airways resistance using the interrupter technique (Rint). *Paediatr Respir Rev* 2005 Dec;6:273-277.

33. de Jong PA, Lindblad A, Rubin L, Hop WCJ, de Jongste JC, Brink M, Tiddens HAWM. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. *Thorax* 2006;61:80-85.

34. Tiddens HA. Detecting early structural lung damage in cystic fibrosis.Pediatr Pulmonol 2002;34:228-231.

Table 1. Patient characteristics (mean ± SD) of the preschool and school children with CF at visit 1 and visit 2.

	Preschool children (n=21)		School children (n=30)	
	Visit 1	Visit 2	Visit 1	Visit 2
Age (years)	3.2 ± 0.9	6.0 ± 1.1	7.2 ± 1.9	10.1 ± 1.9
Gender (m/f)	9/13	9/13	16/14	16/14
Body height (m)	0.95 ± 0.09	1.14 ± 0.09	1.24 ± 0.12	1.40 ± 0.12
Body height SDS	-0.92 ± 1.13	-0.93 ± 1.0	-0.40 ± 0.80	-0.56 ± 0.87
Body weight (kg)	14.0 ± 2.2	19.1 ± 3.3	24.3 ± 5.9	32.3 ± 7.6
Genotype				
ΔF508 homozygous	13		20	
ΔF508 compound heterozygous	9		8	
Other/other	0		2	
*Presenting symptoms**				
Meconium ileus	2		1	
Malabsorption	17		25	
Respiratory symptoms	13		18	
PFTs				
$Rint_{exp}$ Z-score	0.14 ± 1.1	0.16 ± 1.4	0.64 ± 1.4	0.75 ± 1.4
FEV_1 % pred		103.4 ± 22.9	95.1 ± 16.3	90.1 ± 15.4
FVC % pred		99.4 ± 17.3	92.4 ± 14.8	92.9 ± 9.3
FEV_1%FVC		89.2 ± 8.4	88.2 ± 7.7	82.0 ± 9.3
MEF_{50} % pred		79.8 ± 30.4	72.9 ± 27.1	71.3 ± 26.3
FEF_{75} % pred		69.1 ± 40.6	59.5 ± 30.8	51.1 ± 29.7

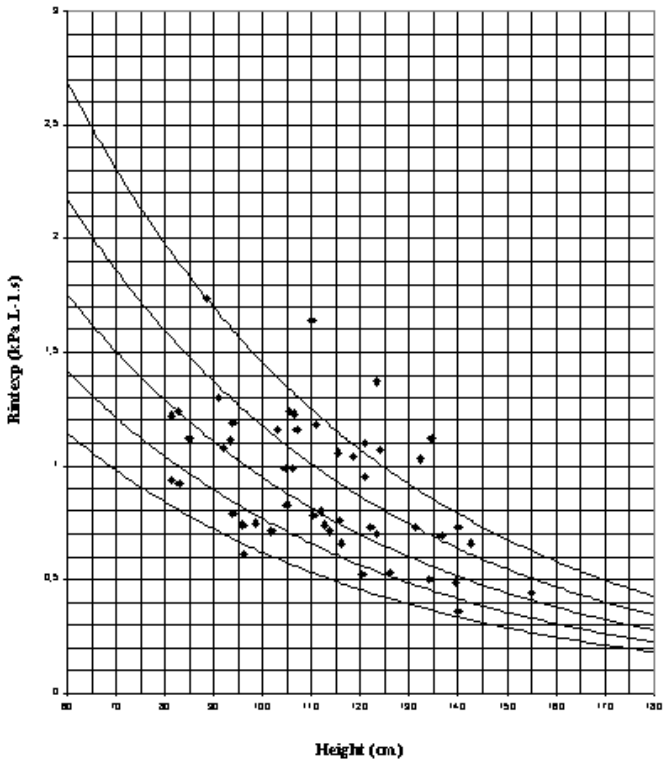
FEF_{25-75} % pred		79.2 ± 32.7	72.1 ± 29.3	66.5 ± 27.4
Radiograph scores				
ChrispinNorman	8.7 ± 4.4	11.0 ± 2.5	10.1 ± 3.2	11.4 ± 3.5
Adjusted Chrispin-Norman	9.8 ± 4.9	12.8 ± 2.6	11.5 ± 3.3	13.2 ± 3.6
Wisconsin	3.6 ± 1.9	4.5 ± 1.6	4.4 ± 1.7	4.5 ± 1.7
Northern	5.1 ± 2.1	6.1 ± 2.0	6.0 ± 1.7	6.4 ± 1.9
Brasfield	20.4 ± 1.7	18.7 ± 1.5	19.6 ± 1.6	19.1 ± 2.0

$Rint_{exp}$; expiratory interrupter resistance, FEV_1% pred; percent predicted forced expiratory volume in 1 second, FVC % pred; percent predicted forced vital capacity, FEV_1%FVC; FEV_1 expressed as percentage of FVC, MEF_{50} % pred; percent predicted maximal expiratory flow at 50% of vital capacity, FEF_{75} % pred; percent predicted forced expiratory flow at 75% of expiratory vital capacity, FEF_{25-75} % pred; forced expiratory flow between 25% and 75% of expiratory vital capacity

* Some children presented with more than one presenting symptom.

Figure 1. Absolute $Rint_{exp}$ values in preschool and school children with CF compared to the regression line (10 log $Rint_{exp}$ = 0.645-0.00668 x standing height (cm) kPa/L/s ± 1 Z-score and ± 2 Z-score lines) of the Dutch healthy control group a) at visit 1 and b) at visit 2.

a)



b)

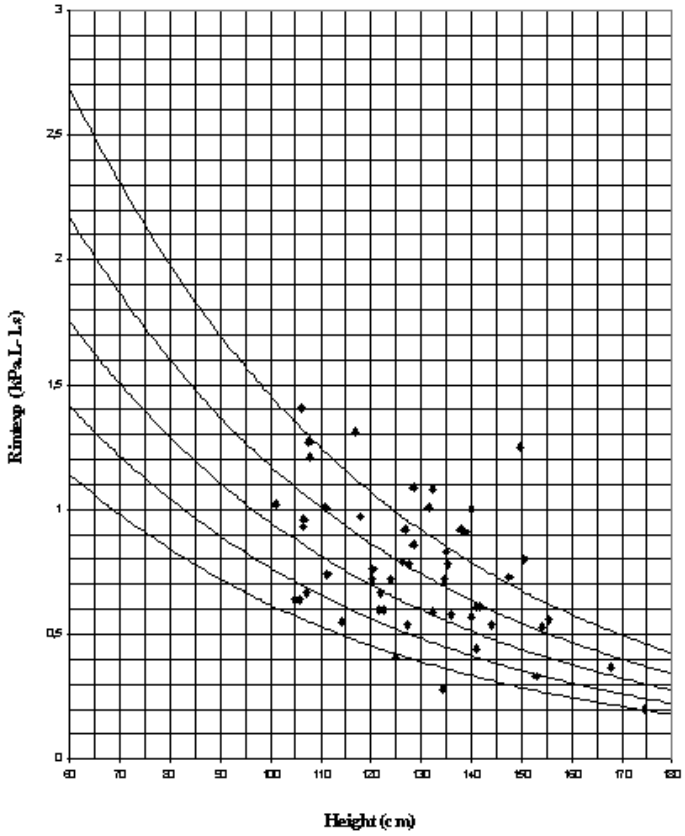

Rinteop (kPa.L-1.s)
Height (cm)
3
2.5
2
1.5
1
0.5
0
60
70
80
90
100
110
120
130
140
150
160
170
180

Table 2. Mean annual change and p-value for different parameters in preschool and school children.

	Preschool children (n=21)		School children (n=30)	
	mean annual change	p-value	mean annual change	p-value
Age (years)	Interval 2.76		Interval 2.89	
Body height (m)	0.070	0.000	0.055	0.000
Body weight (kg)	2.84	0.000	2.71	0.000
PFTs				
$Rint_{exp}$ Z-score	0.05	0.78	0.15	0.182
FEV_1 % pred			-1.62	0.125
FVC % pred			0.05	0.956
FEV_1%FVC			-1.94	0.001
MEF_{50} % pred			-1.20	0.518
FEF_{75} % pred			-2.72	0.14
FEF_{25-75} % pred			-2.56	0.147
Radiograph score				
Chrispin Norman	0.85	0.006	0.50	0.01
Adjusted Chrispin Norman	1.07	0.004	0.64	0.003
Wisconsin	0.35	0.031	0.03	0.977
Northern	0.33	0.110	0.11	0.34
Brasfield	-0.60	0.001	-0.21	0.081

$Rint_{exp}$; expiratory interrupter resistance, FEV_1% pred; percent predicted forced expiratory volume in 1 second, FVC % pred; percent predicted forced vital capacity, FEV_1%FVC; FEV_1 expressed as percentage of FVC, MEF_{50} % pred; percent predicted maximal expiratory flow at

50% of vital capacity, FEF_{75} % pred; percent predicted forced expiratory flow at 75% of expiratory vital capacity, $FEF_{25-75\%}$ % pred; forced expiratory flow between 25% and 75% of expiratory vital capacity

Figure 2. Chrispin-Norman score plotted against age for the whole group at visit 1. Slopes are shown for the group as a whole and for both preschool and school children (regression equation for the group as a whole; y = 0.445 * x + 7.02).

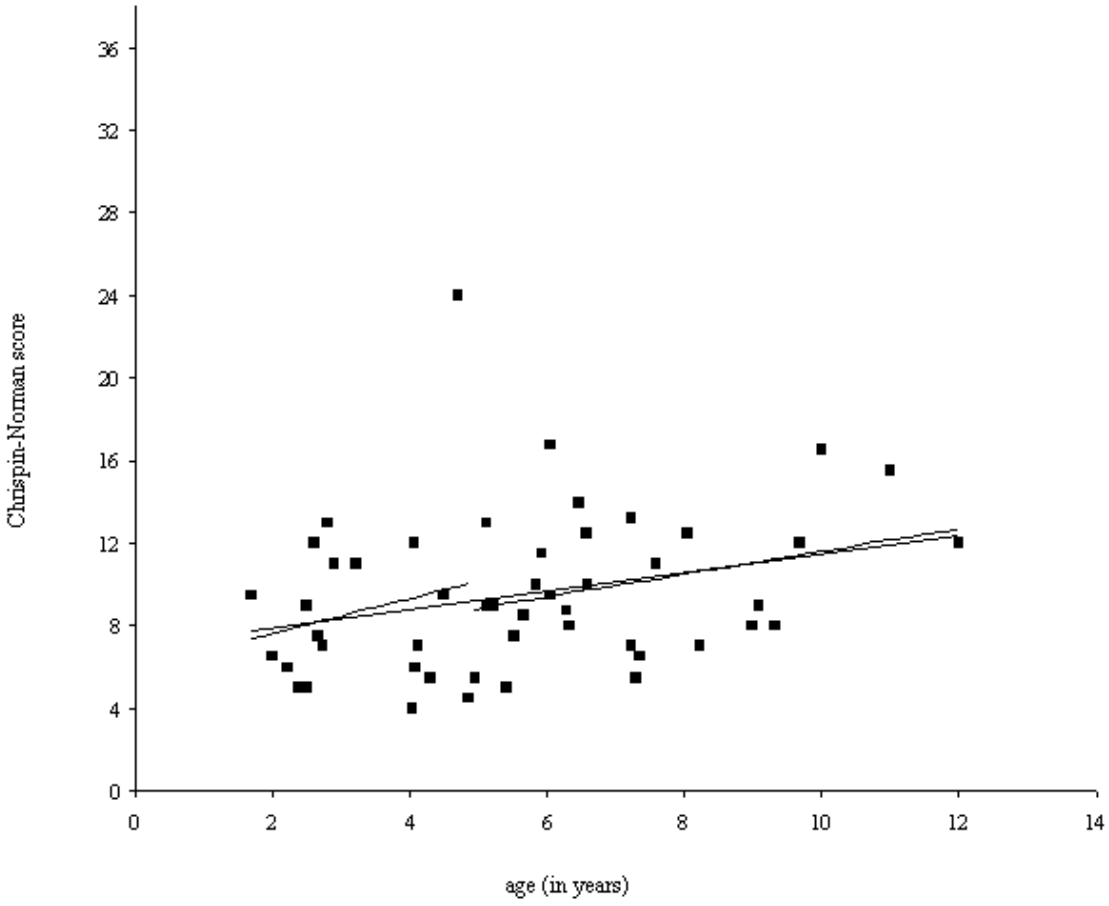


Figure 3. Individual change in Chrispin-Norman score versus age at both visits (regression equation Chrispin-Norman score visit 2= 0.51* Chrispin-Norman score visit1 + 6.36).

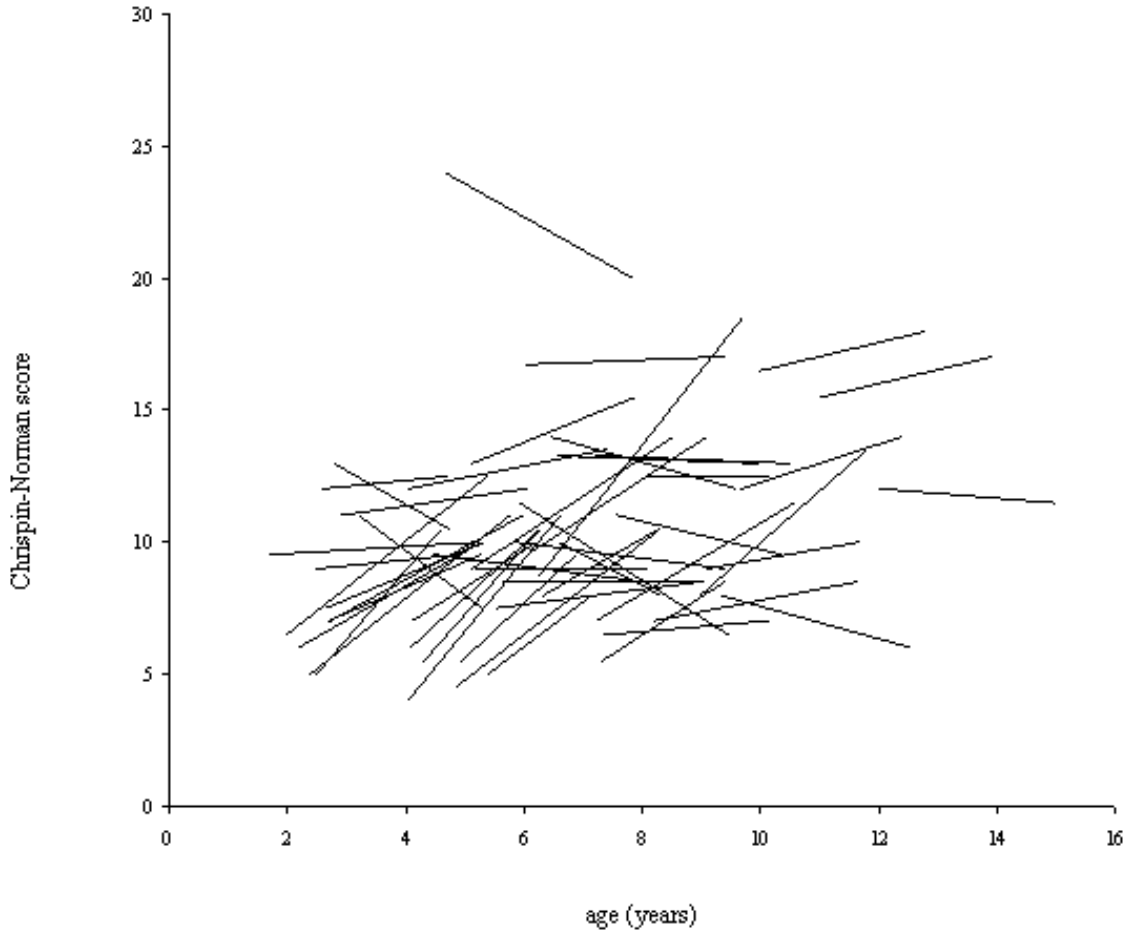


Figure 4. Individual changes in FEV_1%FVC over time for 30 school children and 8 preschool children (regression equation for the group FEV_1%FVC visit2= 0.553* FEV_1%FVC visit1 + 33.38).