Monitoring of Cystic Fibrosis Lung Disease Using Computed Tomography

Monitoren van longziekte bij cystic fibrosis met computed tomografie

The work presented in this thesis was conducted at the Departments of Pediatric Respiratory Medicine and Pediatric Radiology (Erasmus MC-Sophia, Rotterdam, the Netherlands), the Departments of Medicine and Respirology (St Pauls Hospital), the Department of Radiology (Vancouver General Hospital), the iCAPTURE Center for Cardiovascular and Pulmonary Medicine and the University of British Columbia (All: Vancouver, BC, Canada), the Children's Radiological Institute (Columbus Children's Hospital, Columbus, OH, USA) and the Departments of Pediatric Pulmonology and Radiology (Queens Silvia Hospital, Göteborg, Sweden).

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He heals, forgives, loves and saves.
Children and weak receive a special place.
Women and man are equal in his eyes.

To Jesus, my daily inspiration

&

To Rianne, my wife

Contents

Chapter 1

General introduction and aim of study

General introduction

Cystic fibrosis (CF) is an autosomal recessive lethal multi-organ disorder. Over 1000 mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene have been described and there is a wide range of phenotypical expressions even within one CFTR genotype. Morbidity and mortality in CF patients are primarily related to lung disease that is characterized by thick mucus of abnormal composition in the airways. The resultant chronic airway infection and inflammation leads to structural and functional abnormalities early in life and eventually to death from respiratory insufficiency. Very little is known, however, about the mechanisms by which early chronic airway infection and inflammation affect growth of airways and alveoli in CF patients. Lung growth will become a relevant issue in the light of possible early intervention and improved survival. The structural lung abnormalities in CF predominantly occur in the airways and consist of airway wall thickening and bronchiectasis.

For clinical management of CF related lung disease to be effective, onset and progression of the lung disease is commonly closely monitored, either indirectly by monitoring lung function or more directly by monitoring lung structure. Pulmonary function tests (PFTs), such as spirometry and body plethysmography, are considered the most important tools for monitoring lung function from the age of 5-6 years onwards. Chest radiography at least once a year is one of the tools to monitor lung structure. Another tool is computed tomography (CT) scanning. CT scanning provides information of structural lung damage that is not only more detailed but also more closely related to the pathologic changes in CF compared to that obtained from chest radiography. Studies in the early nineties have shown that CT scans are more sensitive than chest radiographs in the early detection of CF related structural lung abnormalities. CT scoring systems were also found to correlate moderately to good with PFTs. Moreover, CT scans revealed structural abnormalities in some CF patients with normal PFTs.

Various scoring systems have been developed to quantify the structural lung abnormalities on CT scans of CF patients. Unfortunately, for several of these the interobserver and intraobserver reproducibility is not tested or not described. As a comparative evaluation is lacking as well, it is hard to determine which scoring system(s) would best serve the purpose.

In addition to scoring, CT scans are also used for quantitative measurements of airway wall and lumen dimensions. Quantitative CT analysis techniques have been validated for other lung diseases, such as chronic obstructive pulmonary disease (COPD), but have not yet been systematically studied in CF. Longitudinal studies in CF comparing changes in CT scores or quantitative CT measures with PFTs are still lacking.

Repetitive CT scanning introduces radiation exposure. It is unknown, however, whether the risk of radiation exposure outweighs the potential benefit of monitoring CF patients using CT scans.

The issues outlined above need to be addressed in order to determine the risk/benefit ratio of monitoring CF related lung disease using CT scans.

Aim of the study

The aims of this thesis are:
1) To evaluate the reproducibility of present CT scoring systems for the detection of structural lung abnormalities in CF
2) To evaluate quantitative airway measurements in CF
3) To assess in longitudinal studies the sensitivity of CT scans and PFTs for the monitoring of onset and progression of lung damage in children and adults with CF
4) To develop a computational model for studying the risks associated with CT scanning in CF and to evaluate if the dose per CT scan can be reduced
5) To evaluate the potential of CT scanning to measure lung dimensions throughout the growth period

The studies addressing these aims are described in this thesis. First, **chapter 2** presents the available knowledge of monitoring lung disease in children and adults with CF at the time of the start of the studies. **Chapter 3** describes the validation of five published CT scoring systems for CF patients. In addition, it describes the use of quantitative CT measurements of airways and arteries in CF patients. In **chapter 4** the studies on the sensitivity of CT and PFTs for monitoring onset and progression of CF lung disease are described. Chapter **4.1** describes longitudinal changes in CT and PFTs in a Dutch cohort of 48 children with CF detected with the use of CT scoring systems. Chapter **4.2** describes those changes in a Swedish cohort of 72 children and 47 adults with CF. Chapter **4.3** describes in a smaller sample of the Dutch cohort the use of quantitative CT measurements of airway wall thickening and bronchiectasis in addition to the CT scoring systems. **Chapter 5** is focused on radiation risks associated with CT scanning in CF. In chapter **5.1** the computation model to study radiation risks related to repetitive CT scanning in CF is described. Chapter **5.2** describes a study to determine whether the number of CT images and therefore the dose per CT scan could be reduced without any significant loss of information in children with CF. In **Chapter 6** two studies are described (chapters **6.1** and **6.2**) in which CT scans of control subjects were used to study the relationship between airways, arteries, airspaces (alveoli) and subject height throughout the growth period. These studies provide normative data that can be used to study lung growth in disease. In chapter **7.1** of **chapter 7** a summary of the studies described in this thesis is given. In chapter **7.2** the implications of our findings are discussed. Chapter **7.3** provides directions for future research.

Chapter 2

Monitoring of cystic fibrosis lung disease

Based in part on:

Pim A de Jong, Nestor L Müller, Peter D Paré, Harvey O Coxson. Computed Tomographic Imaging of the Airways: Relationship to Structure and Function. *Eur Resp J* 2005. **26** (1):140-52.

Chapter 2.1 Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder, with a prevalence of approximately one in 3000-3500 in live-born Caucasians in the United States of America [1]. The genetic defect leads to a dysfunctional or absent chloride channel protein; i.e. the cystic fibrosis transmembrane conductance regulator (CFTR) protein [2]. Over 1000 causative mutations in CF have been described. The relationship between genotype and phenotype is weak [2]. Hence, genotyping is of little help in predicting the course of disease. Even within one CFTR genotype there is a wide variability in clinical expression. The dysfunctional or absent CFTR protein leads to multi-organ dysfunction and to shorter life expectancy [2]. Lung abnormalities are the major cause of the morbidity and mortality [2]. Advances in patient management and improvements in nutritional, antibiotic [3], anti-inflammatory [4] and mucolytic [5, 6] treatment of CF lung disease have improved median survival from less than 1 year in 1940 to over 32 years in 2000 [7-9].

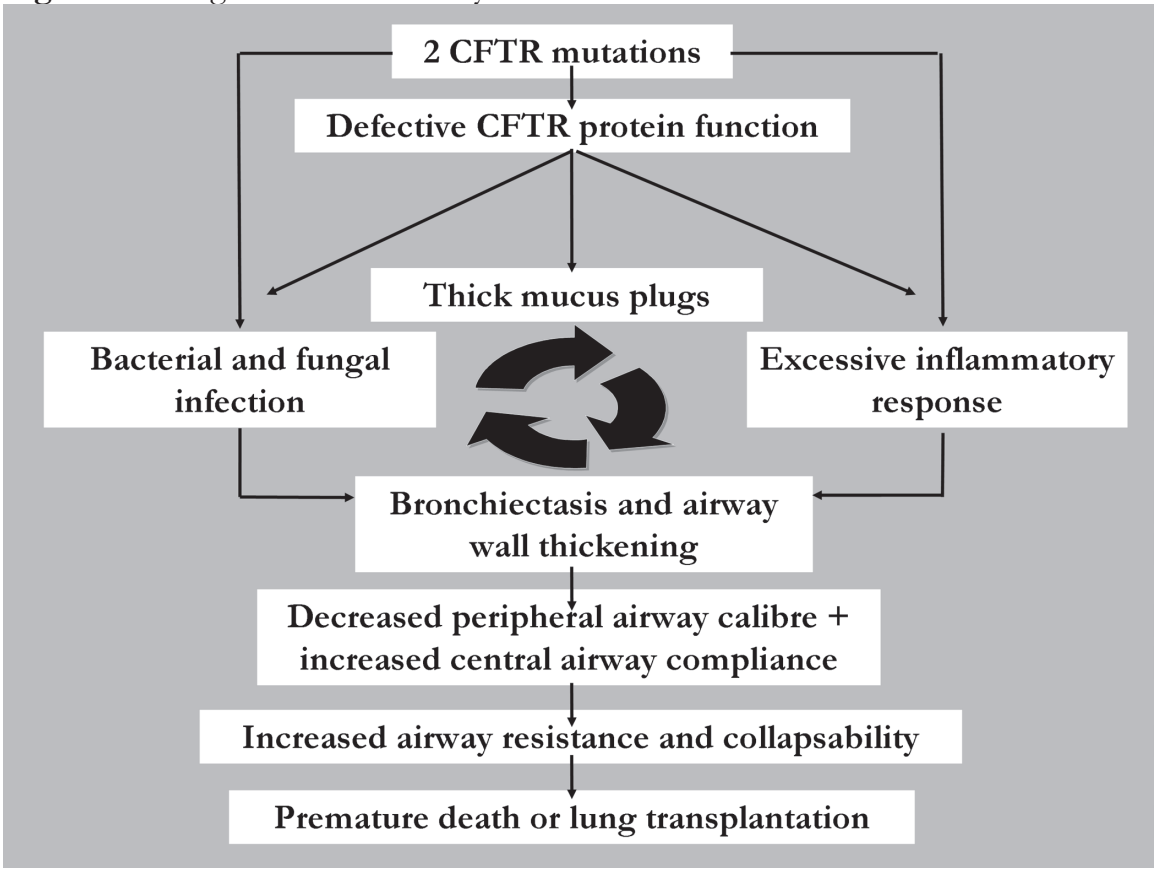
Pathophysiology of CF lung disease

CF lung disease starts and remains predominantly located in the airways. Parenchymal changes are less frequent and tend to occur later in the disease process. The characteristic mucous plugging, infection and inflammation in the airways lead to structural changes such as airway wall thickening and bronchiectasis [2, 10, 11]. The structural changes eventually lead to functional abnormalities of the lungs. This translates into reduced exercise tolerance, cough and dyspnea, decline in quality of life and shorter life expectancy [12, 13] (Figure 1).

Inflammation and infection

In most CF patients the onset of neutrophil mediated inflammation occurs in the first few years of life. In addition, most patients show chronic bacterial infection of the lower airways early in life [14-16]. Common pathogens found early in life include: Staphylococcus *aureus*; Haemophilus *influenzae*; Pseudomonas *aeruginosa*; and less frequently Aspergillus *fumigatus* [2]. It is generally accepted that the inflammatory response is excessive and contributes to the structural lung damage in CF [2, 10]. However, it is still debated whether infection always precedes the inflammatory response [14-16, 19-23], possibly because there is considerable regional heterogeneity of the early infection [17, 18].

Figure 1 Pathogenesis of CF airway disease



In cystic fibrosis (CF), two mutations in the cystic fibrosis transmembrane (CFTR) gene lead to an absent or dysfunctional CFTR protein. This in turn results in abnormally thick mucus of abnormal composition and mucous plugging in the airways, thereby creating a beneficial environment for chronic bronchial bacterial and fungal infections. In addition the airways show abnormal inflammatory responses. All three – mucous plugs, infection and inflammation – lead to structural abnormalities, mainly in the airways, which then interact in a vicious circle. The structural abnormalities, such as bronchiectasis and airway wall thickening, eventually lead to functional abnormalities of the airways. Finally, CF lung disease leads to lung transplantation or premature death.

Changes in airway structure

Only few (quantitative) pathology data are available concerning airway abnormalities in CF. As most pathologic studies were done on end-stage lungs, these data have limited validity for early lung disease. Over the last two decades the management of CF lung disease has substantially improved. It is likely, therefore, that consecutive generations of CF patients show different structural abnormalities. Autopsy studies have shown that at birth CF patients have macroscopically normal airways [2, 24-29]. Then the earliest manifestation of airway disease is mucous plugging of bronchi and bronchioles in the first weeks of life [2, 24, 30, 31]. Autopsy data suggest that airway abnormalities start in the peripheral airways [11, 30, 32, 33]. The mucous plugging and abnormal mucus composition are likely to facilitate bacterial infection and the ensuing bronchiolectasis, bronchiectasis and thickening of the airway walls [11, 24, 31, 34-

[36]. Autopsy specimens revealed that the prevalence of bronchiectasis increases with age from 20% at 0-4 months to 75% at 2-6 years and 100% at older ages [37]. In addition, 67% of children in the 0-4 month old group had mucopurulent plugging of the airway lumen and all children in that age group had inflammation of the bronchial walls [37]. These findings suggest that the onset of abnormalities in the larger airways occurs early in life. The bronchiectasis seen in autopsy specimens was characterized by widely dilated central bronchi with obliterated peripheral airways [38-40]. The airway wall thickening was correlated to the severity of airway inflammation [35, 41]. The severity of airflow obstruction in lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma is proportional to the severity of airway wall thickening [41, 42]. A similar correlation was reported in CF. Airway wall thickness was increased threefold compared to COPD [35]. In addition, the smooth muscle area and epithelial height were markedly increased and the area of cartilage was decreased. Furthermore, like in other studies, a marked destruction of the epithelial layer was described [43, 44]. Airway wall thickening, destruction of the epithelial layer and loss of cartilage are all likely to contribute to the airflow obstruction in CF patients [35].

Changes in lung parenchyma

The lung parenchyma is relatively little affected in CF. Even at later stages of the disease the extent of parenchymal abnormalities remains relatively small. Parenchymal abnormalities consist of emphysema, bullae and consolidations or atelectasis. Although uncommon, emphysema has been observed in two-year-old children and also in 41% of 10 to 24-year-old patients in an autopsy study [37, 40].

Changes in lung vasculature

The bronchial arterial circulation is markedly hypertrophied in CF [45]. In contrast, the major branches of the pulmonary arterial circulation are reduced in size and there are fewer small pulmonary arteries (diameter< 500 μm) [34, 36, 46]. It was hypothesized that the pulmonary arterial system fails to develop completely and that it is hypoxia that makes small arterial branches disappear as the disease progresses [46].

CF lung disease and lung growth

The available pathology data indicate that the structural abnormalities in CF lungs start to develop in the first weeks or months after birth. Noteworthily, the human lungs are not fully developed at birth [47]. Most of the alveoli develop in the first two years of life [48]. In addition, both airways and alveoli increase in size throughout childhood [47]. Early CF lung disease is likely to affect postnatal growth of airways and alveoli, but this has not yet been shown and requires further investigation.

Clinical monitoring of CF lung disease

For clinical management of CF lung disease to be effective, it is believed that the onset and progression of lung abnormalities must be closely monitored. Therefore in routine clinical practice close attention is paid to the following components of CF related lung disease: infection; inflammation; lung structure; and lung function.

Adequate monitoring enables to individualize treatment. Lung infection can be monitored by sputum, throat swabs and bronchoalveolar lavage fluid cytology and cultures and blood serology [49-51]. For monitoring of lung inflammation, blood markers, induced sputum and bronchoalveolar lavage fluid can be used [2, 52, 53]. In the remainder of this chapter we will focus on the evaluation of lung function (chapter 2.2) and lung structure using chest radiographs (chapter 2.3) and computed tomography (CT, chapter 2.4) as tools to monitor lung disease in CF patients.

Chapter 2.2 Monitoring of lung function

Traditionally, parameters derived from pulmonary function tests (PFTs) are considered the gold standard to monitor CF related lung disease. Spirometric or flow volume parameters such as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and mid-expiratory flow (FEF_{25-75}) are used both in clinical management and in clinical studies [2]. Most children aged five-seven years or older will be able to perform a flow volume maneuver. Even a high proportion of three-year-olds were found to be able to do so with training [54]. In children aged six years or older lung volumes can be measured using whole body plethysmography and spirometry. Most clinics will perform a flow volume measurement at each clinical visit and more extensive lung function measurements, including whole body plethysmography, (once yearly) at the annual check up.

Spirometry

The use of PFTs as a monitoring tool has several advantages. The flow-volume maneuver is inexpensive, fast and carries no risk for the patient. Yet there are several limitations as well.

- Firstly, the signal-to-noise ratio for the obtained parameters is relatively low since the measurement depends on the patient's co-operation. For this reason it is a challenge to do a flow volume maneuver in children younger than six years of age. In addition, the results of PFTs are expressed as percent predicted of reference values obtained in a sample of the general population. The use of these reference values introduces variability especially in the years of the pubertal growth spurt [55].
- Secondly, PFTs are insensitive to localized or focal disease.
- Thirdly, most PFTs parameters, such as FEV_1 and FVC, are insensitive to early lung disease which occurs especially in the peripheral airways. The FEF_{25-75} is a relatively more sensitive parameter to early changes [6, 11], but has a higher variability compared to FEV_1 and FVC.
- Fourthly, PFTs do not inform on the nature of the structural abnormalities since PFTs parameters are influenced by many factors, e.g. effort by the

patient; mucous plugging; bronchiectasis; atelectasis; airway dimensions; and airway and parenchyma mechanics. PFTs parameters can be considered a composite score of all these factors.

- Fifthly, many CF children nowadays show normal spirometry at the age of five or six years [56, 57] and functional tests can remain stable over several years, limiting its usefulness in monitoring early disease in children with CF.
- Finally, on the other end of the spectrum PFTs are weak predictors of the two-year mortality in CF [58].

Alternative lung function tests

Apart from spirometry, various other lung function tests have been proposed for the detection and follow-up of lung disease in CF. Body plethysmography is a more demanding technique in comparison with flow volume measurements. It allows to measure lung volumes such as total lung capacity (TLC) and residual volume (RV). The ratio of RV to TLC is thought to be a sensitive test of air trapping and a relatively early sign of small airway disease [2]. A more recent and promising development is the use of gas mixing techniques to detect inhomogeneity of ventilation within the lungs. Abnormalities of ventilation can be found early in the disease by measuring lung clearance indices using multiple breath inert gas washout tests of helium or sulphur hexafluoride (SF_6) [59]. These tests, however, have not yet been widely used to monitor CF patients. A variety of other functional tests have been developed to study CF lung disease in an early phase [19-21, 54, 59-67]. A discussion of these tests is beyond the scope of this thesis, but they have been reviewed by others [61].

Chapter 2.3 Monitoring of lung structure using chest radiography

Chest radiographs are widely used to monitor lung structure, both for the annual check up and for the monitoring of exacerbations. This routine is mostly started from the time when CF is diagnosed.

The advantage of chest radiography over other structural imaging techniques such as CT scanning is the lower radiation exposure to the patient and the low costs. Cross-sectional studies reported a strong correlation between chest radiograph scores and surrogate end-points for CF such as the FEV_1 [68-72].
However, chest radiography has some major limitations.

- Firstly, the terminology used by radiologists to describe, for instance, linear markings or nodular cystic lesions does not closely correlate with the

pathology seen in CF. Correct interpretation of the nature of the structural lung abnormalities on chest radiographs is difficult since a chest radiograph is a two-dimensional superimposed projection of a three–dimensional, complex structure.

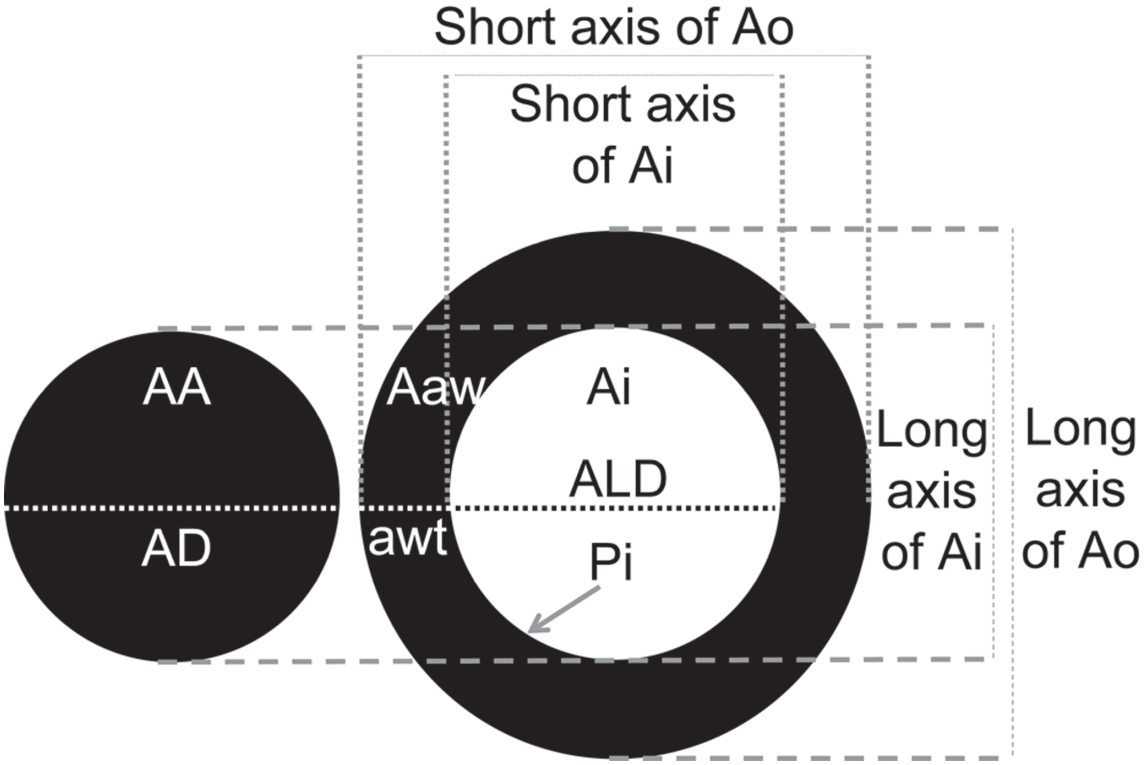
- Secondly, the prognostic value of chest radiograph abnormalities is unknown.
- Thirdly, there are conflicting results concerning the reproducibility of the various chest radiograph scoring systems for CF [57, 68-74]. While some studies reported good inter- and intraobserver agreement [69, 70, 72], others found a poor reproducibility [57, 68, 71, 74]. Comparison between these studies is hampered by differences in statistical methods used to calculate reproducibility. For example, one study reported intraclass correlation coefficients of 0.74, 0.73 and 0.61 for three scoring systems (intraclass correlation <0.8 represents less than good agreement) [71]. In contrast, another study reported a very low interobserver variability of only -1.0 to 6.7% of the mean of the observers for six scoring systems [69].
- Fourthly, longitudinal data have consistently shown that the annual rate of worsening in FEV_1 is greater than the annual rate of worsening in chest radiograph scores [70, 73].
- Fifthly, data on the sensitivity of chest radiograph scores to detect CF lung disease at an early stage are limited and conflicting. While in one study chest radiographs were found to show abnormalities at an earlier stage than FEV_1 [57], in another study this was the other way round [73].
- Finally, quantitative measurements of airway lumen dimensions are limited to the first two generations of the airway tree and measurements of airway wall dimensions are not possible on chest radiographs.

Since the early nineties high-resolution CT (HRCT) has frequently been reported to be more sensitive than chest radiographs to detect structural lung abnormalities in CF. In 1989 Hansell and Strickland [75], two radiologist, stated HRCT to be more accurate than chest radiographs in locating the disease process in CF [75]. Others reported normal chest radiographs in 17 of 38 adult CF patients and only 3 of those 38 had a normal HRCT [76]. Bronchiectasis could be demonstrated on HRCT in 23 of the 38 patients, whereas it was observed with chest radiographs in only 3 patients. A similar phenomenon was observed in CF children [77], with 25% of them having a normal chest radiograph co-occurring with an abnormal HRCT scan. Later studies all have confirmed the limited ability of chest radiographs to detect early CF lung disease relative to HRCT [78-82].

Chapter 2.4 Monitoring of lung structure using computed tomography

Technical advances in CT allow direct assessment of airway structure in vivo (Figure 2). The first report of this technique in CF was published in 1986 [83] and followed by several cross-sectional studies [20, 75, 76, 78-81, 84-98]. One cross-sectional study showed that 12 of 34 CF patients had a normal FEV_1 despite evidence of focal areas of airway lesions on their CT scans [79], which would suggest that CT may be more sensitive than the gold standard FEV_1 for the detection of early lung disease in CF patients.

Figure 2 CT estimated dimensions of airway and accompanying pulmonary artery

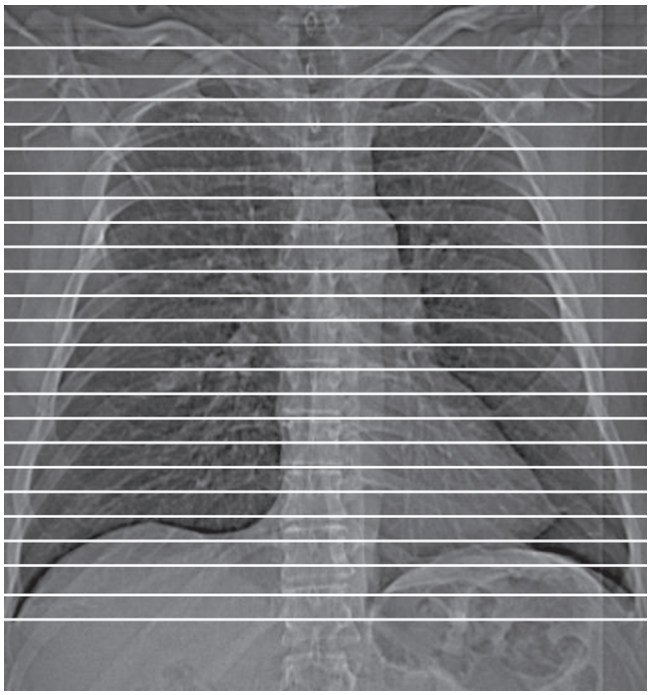


This schematic representation shows the various measurements that can be made on CT images of airways and the accompanying vessels. Linear measurements include the airway perimeter (Pi), the long and short axes of the outer airway area (Ao) and the lumen area (Ai), wall thickness (Awt), airway lumen diameter (ALD), airway outer diameter (AoD = ALD + 2 * Awt) and arterial diameter (AD). Ratios of various linear dimensions include the airway lumen diameter to arterial diameter (ALD/AD), airway wall thickness to arterial diameter (Awt/AD), airway wall thickness to airway lumen diameter (Awt/ALD) as well as long to short axis ratios which are measures of the obliquity of the section. The area dimensions include the airway lumen area (Ai), airway wall area (Aaw), outer airway area (Ao = Aaw + Ai) and arterial area (AA). Ratios of various areas include the airway lumen area to arterial area (Ai/AA), airway wall area to arterial area (Aaw/AA) and percent wall area (WA%= Aaw/Ao*100%). The square root of wall area (SqrtAaw) is often derived since it is relatively linearly related to Pi. Finally, airway dimensions can be referenced to body surface area (eg Aaw/BSA and Awt/BSA).

CT scan acquisition

CT scans designed to assess airway structure involve thin slice images (typically 1-2 mm axial) acquired using a "stop and shoot" protocol and reconstructed using an edge-enhancing algorithm, known as the HRCT protocol (Figure 3). To reduce the radiation burden as well as the scanning time, a gap of 10 millimeters is kept between images. For full-lung helical CT scanning, the images are acquired while the CT scanner table moves continuously. Until the recent introduction of multi-detector row CT scanners, the usefulness of this technique was limited by a relatively long scanning (breath-hold) time and high radiation exposure. These scanners allow much faster scanning at lower radiation dose relative to the old single detector scanners and will be useful in future studies in CF.

Figure 3 'Stop and shoot' high-resolution CT protocol



Common CT protocols for imaging of the airways include thin sections and an edge-enhancing algorithm commonly referred to as high-resolution CT (HRCT). These scans are performed during breath-hold. The patient in supine position on the CT scanner table is asked to take a deep breath and to hold it. During the breath-hold a 1-mm thick CT section is taken, the table is moved 10 mm and a second section is taken. Then the patient is given the opportunity to breathe normally for a short period and the procedure is repeated till the lungs are fully covered (approximately 25 sections). In more recent protocols the patient is then asked to exhale as far as possible and hold breath. During this breath-hold three expiratory images are taken at specified locations.

HRCT scoring systems

The data provided by a CT scan are a series of images. For use in clinical trials and in clinical research these graphic data must be converted to numerical data. In CF, various HRCT scoring systems have been used for this conversion since 1991 [78-81, 91-

[95, 98]. These all make use of a composite score systematically evaluating a number of features on CT scans (Table 1). HRCT scoring studies have been useful in studying CF lung disease. They have confirmed pathologic studies by demonstrating that in many patients the onset of airway disease occurs early in life (Table 2). Several cross-sectional studies demonstrated a strong correlation between lung function parameters and HRCT scoring systems [80, 94, 95, 98]. However, in young children lung function parameters and HRCT scoring systems were found to correlate only weakly or not at all [84, 93] (Table 3). All studies were cross-sectional in design. A variety of semi-quantitative scoring systems was used of which the intra- and interobserver variation was often poorly defined (Table 4). The components of the scoring systems are ill-defined and there is no consensus on which system is to be preferred to follow up CT scans of CF patients.

Table 1 Overview of components of the various CT scoring systems for CF

System:	Bhalla	Nathanson	Maffesanti	Santa-	Helbich	Brody	Robinson
Year:	1991	1991	1996	maria 98	1999	1999	2001
Scoring per:	BPS	12 zones	4 zones	BPS	BPS	Lobes	lobes
Bronchiectasis	*	*	*	*	*	*	*
Airway wall thickening	*		*	*	*	*	*
Mucous plugging	*	*		*	*	*	*
Sacculation or abscess	*				*		
Bullae	*			*	*		
Emphysema	*				*		
Atelectasis or consolidation	*			*	*		*
Air trapping				*			*
Acinar nodules				*			
Septal thickening				*			
Ground glass opacities				*			
Mosaic perfusion					*		
Alveolar consolidation			*			*	
Atelectasis, bullae and cysts			*			*	
Overinflation			*			*	

BPS = broncho-pulmonary segments
* Included in the scoring system

Table 2 Prevalence (%) of airway abnormalities on CT in CF

Study	Year	Mean age ± SD (range)	N	BE	AWT	MP central	MP Peri-pheral	GG	AT
Helbich	1999	2.4 ± 1.5 (0-5)	20	45	40	10	NI	50	NI
Stiglbauer	1992	4.8 (0.3-9.7)	24	65	91	48	NI	4.2	NI
Shah	1997	8.9 (6-12)	8	100	100	88	50	13	NI
Marchant	2001	9.3 (2.8-11.9)	16	100	0	50	NI	NI	NI
Helbich	1999	9.4 ± 3.1 (6-16)	61	80	77	52	NI	59	NI
Demirkazik	2001	6 (0.4-18)	40	65	97.5	30	NI	NI	100
Dakin	2002	12.2 ± 4.3 (6-19.4)	34	91	79	77	58	72	NI
Santamaria	1998	13.2 (6.75-24)	30	90	53	63	17	13	NI
Maffessanti	1996	13 ± 6 (5-28)	36	89	43	26	80	81	NI
Nathanson	1991	14.1 ± 1.7 (0.5-35)	28	96	NI	61	NI	NI	NI
Taccone	1992	19.1 (9-39)	39	87	100	NI	NI	NI	NI
Robinson	2001	17.3 ± 7.2 (9-33)	17	100	100	76	NI	NI	100
Helbich	1999	22.1 ± 4.1 (17-32)	36	100	98	72	NI	69	NI
Bhalla	1991	5-42	14	85.7	92.9	64.3	NI	NI	NI

SD is standard deviation, N is number of patients studied, NI not included in the scoring system, BE is bronchiectasis, AWT is airway wall thickening, MP is mucous plugging, GG is ground glass pattern, AT is air trapping

Patient selection criteria were the following: Helbich prospectively and retrospectively studied all stable patients from their outpatient clinic. Stiglbauer studied CF patients prospectively, inclusion criteria were not reported. Shah prospectively included 8 stable patients and 19 patients during an exacerbation, inclusion criteria were not reported. Marchant included 16 stable CF patients who were diagnosed through neonatal screening, inclusion criteria were not reported. Demirkazik prospectively included 40 CF patients followed at their clinic, inclusion criteria were not reported. Dakin included their routine annual and biennial check up CT scans, other inclusion criteria were not reported. Santamaria included 30 CF patients when they had mild or moderate symptoms, other inclusion criteria were not reported. Maffessanti included 36 stable CF patients, other inclusion criteria were not reported. Nathanson included 25% of the CF patients in their clinic, inclusion criteria were not reported. Taccone did not report any inclusion criteria. Robinson prospectively included patients who had a clinically defined acute excacerbation and who were older than 8 years and had a FEV_1 greater than 30% predicted. Bhalla prospectively included 14 CF patients, inclusion criteria were not reported.

Table 3 Correlation of CT-score with pulmonary function tests in CF

Study	Year	Mean age ± SD (range)	N	FEV_1		MEF		RV/TLC	
				R^2	P	R^2	P	R^2	P
Logan	1990	17 (15-19)	30	0.41	<0.01	NE	NE	NE	NE
Nathanson	1991	18.8 ± 1.6	19	0.77	<0.01	0.74	<0.01	0.69	<0.01
Bhalla	1991	5-42	14	0.18	NS	NE	NE	NE	NE
Stiglbauer	1992	4.8 (0.3-9.7)	24	NG	NS	0.55	0.02	NE	NE
Maffessanti	1996	13 ± 6 (5-28)	36	0.43	<0.01	NE	NE	NE	NE
Shah	1997	8.9 (6-12)	8	0.11	0.04	NE	NE	NE	NE
Santamaria	1998	13.2 (6.75-24)	30	0.25	<0.1	NE	NE	0.16	0.02
Helbich	1999	12.2 ± 3.1 (0-32)	117	0.49	0.01	0.71	0.001	0.23	0.001
Demirkazik	2001	6 (0.4-18)	14	0.44	0.01	0.26	NS	NE	NE
Marchant	2001	9.3 (2.8-11.9)	16	0.42	0.01	NE	NE	NE	NE
Robinson	2001	17.3 ± 7.2 (9-33)	17	0.29	0.03	0.52	0.001	0.38	0.01

NE not evaluated in the study, NG correlation was evaluated but the coefficient was not given, MEF included FEF_{25-75}, MEF_{50} and MEF_{25}, NS not a significant correlation ($p>0.05$)

Patient selection criteria were the following: Logan randomly selected patients from the outpatient clinic. Patients were excluded when they had intravenous antibiotics or hospitalisation in the past six weeks for respiratory complications. Nathanson included 25% of the CF patients in their clinic, inclusion criteria were not reported. Bhalla prospectively included 14 CF patients, inclusion criteria were not reported. Stiglbauer studied CF patients prospectively, inclusion criteria were not reported. Maffessanti included 36 stable CF patients, other inclusion criteria were not reported. Shah prospectively included 8 stable patients and 19 patients during an exacerbation, other inclusion criteria were not reported. Santamaria included 30 CF patients when they had mild or moderate symptoms, other inclusion criteria were not reported. Helbich prospectively and retrospectively studied all stable patients from their outpatient clinic. Demirkazik prospectively included 40 CF patients followed at their clinic, inclusion criteria were not reported. Marchant included 16 stable CF patients who were diagnosed through neonatal screening, other inclusion criteria were not reported. Robinson prospectively included patients during a clinically defined acute exacerbation who were older than 8 years and had a FEV_1 greater than 30% predicted.

Table 4 Inter- and intraobserver variability of CT-score in CF

Study	Year	Interobserver variability	Intraobserver variability
Bhalla	1991	SD = 1.02	NA
Nathanson	1991	R=0.82, 0.85, 0.76	NA
Santamatia	1998	COV = 4.9%	NA
Nasr	2001	COV = 49.1%	NA
Robinson	2001	R=0.94	R=0.78

SD = standard deviation, COV = coefficient of variation = absolute mean differences x 100 / overall mean, R = correlation coefficient, NA = not assessed

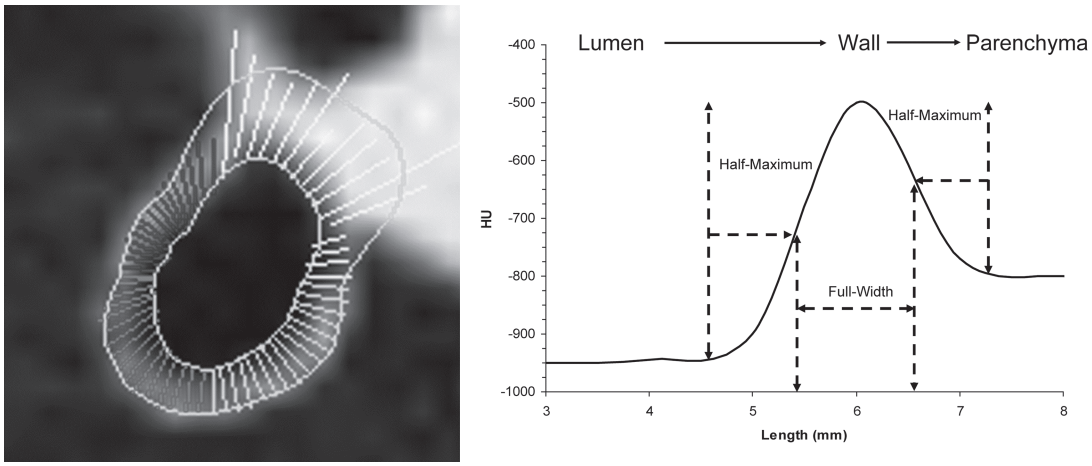
Quantitative airway analysis

The quantitative nature of CT enables measurements of airway, arterial and parenchymal dimensions. Several quantitative CT analysis techniques to measure airway dimensions have been developed and employed in asthma and COPD [99-102]. In the initial studies of airway dimensions by CT, the investigators used manual tracing of the airway images [103-106]. Manual tracing, however, is extremely time-consuming and prone to bias and error. Computer aided and automated techniques are now available to measure airway wall and lumen and arterial dimensions, the most commonly reported of which relies on the "Full-Width-At-Half-Maximum" or "half-max" technique (Figure 4) [100, 107]. Although this method provides a standardized and unbiased measurement it has its limitations. For instance, comparison of CT scan measurements using this method with phantoms of tubes embedded in material resembling lung parenchyma and animal and human lung specimens [107], reveals that the CT scans consistently over-estimate airway wall area and underestimate lumen area. These systematic errors arise from factors including:

- The limited spatial resolution of the CT scanner
- The angle of orientation of the airway within the CT slice
- The inability of the scanner to detect edges (the point spread function)
- The reconstruction algorithm used
- The analysis technique used
- The inability to visualize the folding of the epithelium.

Quantitative studies of airway dimensions in children with CF will be challenging as airway size changes with lung growth, and because mucous plugging or lack of comparable CT sections preclude the identification of airways on subsequent scans. To our knowledge, no CF studies have been reported that used quantitative techniques to measure airway wall and lumen dimensions on CT. The most important potential benefit of quantitative CT analysis would be the reduction of observer variability relative to that of the HRCT scoring systems. In addition the time required to analyze a CT scan can potentially be reduced.

Figure 4 An airway wall measurement using the full-width at half-maximum algorithm.

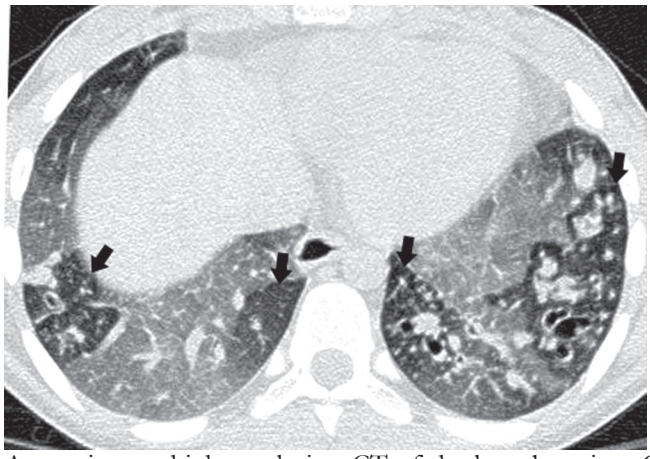


A representative x-ray attenuation (hounsfield units (HU)) curve for a ray that passes from the lumen through the airway wall and into the parenchyma is shown. The thickness of the wall is determined using the half-maximum point of the change in x-ray attenuation as the ray enters and exits the wall. The inset shows a magnified view of an airway. The rays can be seen to start at the lumen boundary of the wall and extend to the outer edge. Note that some rays extend into the pulmonary artery because the artery has similar x-ray attenuation values as the airway wall. Those rays can be manually deleted and the airway outer border is extrapolated from the remaining rays using a mathematical spline function.

Quantitative small airway analysis

CT can indirectly visualize small airways abnormalities. To that purpose expiratory CT scans are performed to assess the extent and degree of gas trapping (Figure 5) [108-114]. The extent of gas trapping can be quantified on expiratory scans with techniques similar to those used to quantify low attenuation areas in emphysema [108, 111, 112, 115, 116]. A limitation of the use of expiratory CT scans is that patients have difficulty holding their breath at low lung volume. The feasibility of this technique may be improved by using spirometric gating [117]. No studies have been reported that quantified gas trapping on CT scans of CF patients.

Figure 5 Gas trapping on an expiratory CT scan in a CF patient



An expiratory high-resolution CT of the lung base in a CF patient demonstrates bilateral areas of air trapping. The image clearly shows black areas in both lower lobes where air is trapped.

Radiation Risk

Radiation exposure is an important issue for any studies that include repetitive CT scanning. Infants and young children are at higher risk of radiation induced cancer than older children, who are more susceptible than adults [92, 118-124]. Therefore, most airway research has been restricted to older adults (over 55 years of age) whose risk is very low [122]. Data comparing radiation exposures from different sources are available. In a Swiss survey the dose of a lateral plus antero-posterior chest radiograph was about 0.17 milli Sievert (mSv) and that of a chest CT scan with contiguous 10-mm thick slices was 9.0 mSv [125]. The dose of the CT scans reported in the Swiss survey is 10 times higher than the dose of a HRCT [122]. The radiation dose for a HRCT would therefore be 0.9 mSv or five times the dose of the chest radiograph. To put these numbers in perspective: 140-350 transatlantic flying hours with a subsonic aircraft or 60-150 transatlantic flying hours with a Concorde result in a radiation exposure of 1 mSv [126]. Natural background radiation in the USA to cosmic radiation, natural radioactivity and domestic radon results in an average exposure of ~3 mSv / year. Model data to estimate the risk of inducing lethal cancers using various CT protocols are needed to determine the risk/benefit ratio. In addition studies are needed to determine the CT protocol that produces the lowest possible dose per CT examination with acceptable image quality and diagnostic yield.

Use of CT in Clinical Care

CT scanning as a tool to monitor lung structure in CF patients has received little attention. Most CF centers monitor their patients using chest radiographs and PFTs. However, both the Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands) and the Queens Silvia Children's Hospital (Göteborg, Sweden) have been using repetitive CT to monitor lung structure since 1996, replacing the antero-posterior and lateral chest radiographs applied until then. This new routine was initiated because the literature had documented that chest radiographs were not

sensitive enough to detect early CF lung disease. Hence, the aim was to monitor not only lung function but also to adequately monitor lung structure. As CF patients had shorter life expectancy it was assumed at that time that the benefits of a more sensitive monitoring would outweigh the disadvantages of the higher radiation exposure from CT compared with chest radiographs. The possible benefits of this strategy were evaluated in cohorts in both hospitals (this thesis).

Use of CT in Research Trials

CT must have been shown to provide a valid outcome surrogate before it can be used as a primary endpoint in clinical trials of CF lung disease. An outcome surrogate is a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint. In CF the only outcome surrogate currently accepted by the Food and Drug Administration (FDA) is FEV_1. Outcome surrogates must meet strict criteria in order to ensure accurate results from clinical trials [127]. For CT scanning to become an outcome surrogate, data are needed on 1) the reproducibility of CT scoring systems and 2) the extent to which CT scoring systems and quantitative airway measurements in relation to PFTs are sensitive to detect onset and progression of CF lung disease. To our knowledge, at the start of our evaluation in 2001 only one small clinical trial included CT in the protocol [97].

References

1. Kosorok MR, Wei W, Farrell PM. The Incidence of Cystic Fibrosis. *Statistics in Medicine* 1996; **15:** 449-462.
2. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **168** (8)**:** 918-51.
3. Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993; **328** (24)**:** 1740-6.
4. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995; **332** (13)**:** 848-54.
5. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994; **331** (10)**:** 637-42.
6. Quan JM, Tiddens H, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. 2001; **139** (6)**:** 813-20.
7. Kulich M, Rosenfeld M, Goss CH, Wilmott R. Improved survival among young patients with cystic fibrosis. *J Pediatr* 2003; **142** (6)**:** 631-6.
8. Fiel SB, FitzSimmons SC, Schidlow DV. Evolving Demographics of Cystic Fibrosis. *Am J Respir Crit Care Med* 1994; **15** (5)**:** 349-355.
9. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993; **122** (1)**:** 1-9.
10. Tiddens H, Silverman M, Bush A. The role of inflammation in airway disease: remodeling. *Am J Respir Crit Care Med* 2000; **162** (2 Pt 2)**:** S7-S10.
11. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34** (3)**:** 228-31.

12. Bradley J, McAlister O, Elborn S. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. *Eur Respir J* 2001; **17** (4)**:** 712-5.
13. Gee L, Abbott J, Conway SP, Etherington C, Webb AK. Quality of life in cystic fibrosis: the impact of gender, general health perceptions and disease severity. *J Cyst Fibros* 2003; **2** (4)**:** 206-13.
14. Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *Bmj* 1995; **310** (6994)**:** 1571-2.
15. Armstrong DS, Grimwood K, Carlin JB, et al. Lower airway inflammation in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med* 1997; **156** (4 Pt 1)**:** 1197-204.
16. Rosenfeld M, Gibson RL, McNamara S, et al. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis. *Pediatr Pulmonol* 2001; **32** (5)**:** 356-66.
17. Meyer KC, Sharma A. Regional variability of lung inflammation in cystic fibrosis. *Am J Respir Crit Care Med* 1997; **156** (5)**:** 1536-40.
18. Gutierrez JP, Grimwood K, Armstrong DS, et al. Interlobar differences in bronchoalveolar lavage fluid from children with cystic fibrosis. *Eur Respir J* 2001; **17** (2)**:** 281-6.
19. Dakin CJ, Numa AH, Wang H, Morton JR, Vertzyas CC, Henry RL. Inflammation, infection, and pulmonary function in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **165** (7)**:** 904-10.
20. Dakin CJ, Pereira JK, Henry RL, Wang H, Morton JR. Relationship between sputum inflammatory markers, lung function, and lung pathology on high-resolution computed tomography in children with cystic fibrosis. *Pediatr Pulmonol* 2002; **33** (6)**:** 475-82.
21. Nixon GM, Armstrong DS, Carzino R, et al. Early airway infection, inflammation, and lung function in cystic fibrosis. *Arch Dis Child* 2002; **87** (4)**:** 306-11.
22. Karp CL, Flick LM, Park KW, et al. Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. *Nat Immunol* 2004; **5** (4)**:** 388-92.
23. Tirouvanziam R, Khazaal I, Peault B. Primary inflammation in human cystic fibrosis small airways. *Am J Physiol Lung Cell Mol Physiol* 2002; **283** (2)**:** L445-51.
24. Zuelzer WZ, Newton WA. The pathogenesis of fibrocystic disease of the pancreas. *Pediatrics* 1949; **4:** 53-69.
25. Reid L, de Haller R. The bronchial mucous glands--their hypertrophy and change in intracellular mucus. *Bibl Paediatr* 1967; **86:** 195-9.
26. Oppenheimer EH. Similarity of the tracheobronchial mucous glands and epithelium in infants with and without cystic fibrosis. *Hum Pathol* 1981; **12** (1)**:** 36-48.
27. Chow CW, Landau LI, Taussig LM. Bronchial mucous glands in the newborn with cystic fibrosis. *Eur J Pediatr* 1982; **139** (4)**:** 240-3.
28. Sturgess J, Imrie J. Quantitative evaluation of the development of tracheal submucosal glands in infants with cystic fibrosis and control infants. *Am J Pathol* 1982; **106** (3)**:** 303-11.
29. Ornoy A, Arnon J, Grebner EE, Jackson LG, Bach G. Early prenatal diagnosis of mucolipidosis IV. *Am J Med Genet* 1987; **27** (4)**:** 983-5.
30. Ruzal-Shapiro C. Cystic Fibrosis An Overview. *Radiol Clin North Am* 1998; **36** (1)**:** 143-161.
31. Wentworth P, Gough J, Wentworth JE. Pulmonary changes and cor pulmonale in mucoviscidosis. *Thorax* 1968; **23** (6)**:** 582-9.
32. Oppenheimer EH, Esterly JR. Medical mucoid lesions of the pulmonary artery in cystic fibrosis, pulmonary hypertension, and other disorders. *Lab Invest* 1974; **30** (4)**:** 411-6.
33. Mellins RB. The site of airway obstruction in cystic fibrosis. *Pediatrics* 1969; **44** (3)**:** 315-8.
34. Tomashefski JF, Jr., Bruce M, Goldberg HI, Dearborn DG. Regional distribution of macroscopic lung disease in cystic fibrosis. *Am Rev Respir Dis* 1986; **133** (4)**:** 535-40.
35. Tiddens HA, Koopman LP, Lambert RK, et al. Cartilaginous airway wall dimensions and airway resistance in cystic fibrosis lungs. *Eur Respir J* 2000; **15** (4)**:** 735-42.
36. Hamutcu R, Rowland JM, Horn MV, et al. Clinical findings and lung pathology in children with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **165** (8)**:** 1172-5.

37. Bedrossian CW, Greenberg SD, Singer DB, Hansen JJ, Rosenberg HS. The lung in cystic fibrosis. A quantitative study including prevalence of pathologic findings among different age groups. *Hum Pathol* 1976; **7** (2)**:** 195-204.
38. Hogg JC, Williams J, Richardson JB, Macklem PT, Thurlbeck WM. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. *N Engl J Med* 1970; **282** (23)**:** 1283-7.
39. Reid LM. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950; **5** (3)**:** 233-47.
40. Sobonya RE, Taussig LM. Quantitative aspects of lung pathology in cystic fibrosis. *Am Rev Respir Dis* 1986; **134** (2)**:** 290-5.
41. Tiddens HA, Paré PD, Hogg JC, Hop WC, Lambert R, de Jongste JC. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med* 1995; **152** (1)**:** 260-6.
42. Cosio M, Ghezzo H, Hogg JC, et al. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med* 1978; **298** (23)**:** 1277-81.
43. Leigh MW, Kylander JE, Yankaskas JR, Boucher RC. Cell proliferation in bronchial epithelium and submucosal glands of cystic fibrosis patients. *Am J Respir Cell Mol Biol* 1995; **12** (6)**:** 605-12.
44. Dovey M, Wisseman CL, Roggli VL, Roomans GM, Shelburne JD, Spock A. Ultrastructural morphology of the lung in cystic fibrosis. *J Submicrosc Cytol Pathol* 1989; **21** (3)**:** 521-34.
45. Henig NR, Glenny RW, Aitken ML. A hypertrophied bronchial circulatory system may participate in gas exchange. *Lancet* 1998; **351** (9096)**:** 113.
46. Ryland D, Reid L. The pulmonary circulation in cystic fibrosis. *Thorax* 1975; **30** (3)**:** 285-92.
47. Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. *Pediatr Pulmonol* 1996; **21** (6)**:** 383-97.
48. Thurlbeck WM. Postnatal human lung growth. *Thorax* 1982; **37** (8)**:** 564-71.
49. Doring G, Hoiby N, Wagener JS, Headley AA, Littlewood JM. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. *J Cyst Fibros* 2004; **3** (2)**:** 67-91.
50. Wagener JS, Headley AA, Littlewood JM. Cystic fibrosis: current trends in respiratory care. *Respir Care* 2003; **48** (3)**:** 234-45; discussion 246-7.
51. Littlewood JM. Good care for people with cystic fibrosis. *Paediatr Respir Rev* 2000; **1** (2)**:** 179-89.
52. Sagel SD. Noninvasive biomarkers of airway inflammation in cystic fibrosis. *Curr Opin Pulm Med* 2003; **9** (6)**:** 516-21.
53. De Rose V, Rosenfeld M, Gibson RL, et al. Mechanisms and markers of airway inflammation in cystic fibrosis. *Eur Respir J* 2002; **19** (2)**:** 333-40.
54. Marostica PJ, Weist AD, Eigen H, et al. Spirometry in 3- to 6-year-old children with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **166** (1)**:** 67-71.
55. Merkus PJ, Tiddens HA, de Jongste JC. Annual lung function changes in young patients with chronic lung disease. *Eur Respir J* 2002; **19** (5)**:** 886-91.
56. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr* 1997; **131** (6)**:** 809-14.
57. Farrell PM, Li Z, Kosorok MR, et al. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. *Pediatr Pulmonol* 2003; **36** (3)**:** 230-40.
58. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002; **166** (12 Pt 1)**:** 1550-5.
59. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J* 2003; **22** (6)**:** 972-9.
60. Tepper RS, Montgomery GL, Ackerman V, Eigen H. Longitudinal evaluation of pulmonary function in infants and very young children with cystic fibrosis. *Pediatr Pulmonol* 1993; **16** (2)**:** 96-100.
61. Gappa M, Ranganathan SC, Stocks J. Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. *Pediatr Pulmonol* 2001; **32** (3)**:** 228-45.

62. Ranganathan SC, Dezateux C, Bush A, et al. Airway function in infants newly diagnosed with cystic fibrosis. *Lancet* 2001; **358** (9297)**:** 1964-5.
63. Ranganathan SC, Bush A, Dezateux C, et al. Relative ability of full and partial forced expiratory maneuvers to identify diminished airway function in infants with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **166** (10)**:** 1350-7.
64. Castile RG, Iram D, McCoy KS. Gas trapping in normal infants and in infants with cystic fibrosis. *Pediatr Pulmonol* 2004; **37** (5)**:** 461-9.
65. Ranganathan SC, Goetz I, Hoo AF, Lum S, Castle R, Stocks J. Assessment of tidal breathing parameters in infants with cystic fibrosis. *Eur Respir J* 2003; **22** (5)**:** 761-6.
66. 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** (11)**:** 1209-16.
67. Gustafsson PM, Kallman S, Ljungberg H, Lindblad A. Method for assessment of volume of trapped gas in infants during multiple-breath inert gas washout. *Pediatr Pulmonol* 2003; **35** (1)**:** 42-9.
68. Weatherly MR, Palmer CG, Peters ME, et al. Wisconsin cystic fibrosis chest radiograph scoring system. *Pediatrics* 1993; **91** (2)**:** 488-95.
69. Terheggen-Lagro S, 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** (6)**:** 441-5.
70. Slattery DM, Zurakowski D, Colin AA, Cleveland RH. CF: an X-ray database to assess effect of aerosolized tobramycin. *Pediatr Pulmonol* 2004; **38** (1)**:** 23-30.
71. Sawyer SM, Carlin JB, DeCampo M, Bowes G. Critical evaluation of three chest radiograph scores in cystic fibrosis. *Thorax* 1994; **49** (9)**:** 863-6.
72. Conway SP, Pond MN, Bowler I, et al. The chest radiograph in cystic fibrosis: a new scoring system compared with the Chrispin-Norman and Brasfield scores. *Thorax* 1994; **49** (9)**:** 860-2.
73. Rosenberg SM, Howatt WF, Grum CM. Spirometry and chest roentgenographic appearance in adults with cystic fibrosis. *Chest* 1992; **101** (4)**:** 961-4.
74. Farrell PM, Li Z, Kosorok MR, et al. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003; **168** (9)**:** 1100-8.
75. Hansell DM, Strickland B. High-resolution computed tomography in pulmonary cystic fibrosis. *Br J Radiol* 1989; **62** (733)**:** 1-5.
76. Santis G, Hodson ME, Strickland B. High resolution computed tomography in adult cystic fibrosis patients with mild lung disease. *Clin Radiol* 1991; **44** (1)**:** 20-2.
77. Lynch DA, Brasch RC, Hardy KA, Webb WR. Pediatric pulmonary disease: assessment with high-resolution ultrafast CT. *Radiology* 1990; **176** (1)**:** 243-8.
78. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179** (3)**:** 783-8.
79. Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. *J Thorac Imaging* 1996; **11** (1)**:** 27-38.
80. Nathanson I, Conboy K, Murphy S, Afshani E, Kuhn JP. Ultrafast computerized tomography of the chest in cystic fibrosis: a new scoring system. *Pediatr Pulmonol* 1991; **11** (1)**:** 81-6.
81. Santamaria F, Grillo G, Guidi G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest Be obtained? *Pediatrics* 1998; **101** (5)**:** 908-13.
82. Shale DJ. Chest radiology in cystic fibrosis: is scoring useful? *Thorax* 1994; **49** (9)**:** 847.
83. Jacobsen LE, Houston CS, Habbick BF, Genereux GP, Howie JL. Cystic fibrosis: a comparison of computed tomography and plain chest radiographs. *Can Assoc Radiol J* 1986; **37** (1)**:** 17-21.
84. Stiglbauer R, Schurawitzki H, Eichler I, Vergesslich KA, Gotz M. High resolution CT in children with cystic fibrosis. *Acta Radiol* 1992; **33** (6)**:** 548-53.
85. Taccone A, Romano L, Marzoli A, Girosi D, Dell'Acqua A, Romano C. High-resolution computed tomography in cystic fibrosis. *Eur J Radiol* 1992; **15** (2)**:** 125-9.

86. Logan PM, O'Laoide RM, Mulherin D, O'Mahony S, FitzGerald MX, Masterson JB. High resolution computed tomography in cystic fibrosis: correlation with pulmonary function and assessment of prognostic value. *Ir J Med Sci* 1996; **165** (1)**:** 27-31.
87. Lugo-Olivieri CH, Soyer PA, Fishman EK. Cystic fibrosis: spectrum of thoracic and abdominal CT findings in the adult patient. *Clin Imaging* 1998; **22** (5)**:** 346-54.
88. Donnelly LF, Gelfand MJ, Brody AS, Wilmott RW. Comparison between morphologic changes seen on high-resolution CT and regional pulmonary perfusion seen on SPECT in patients with cystic fibrosis. *Pediatr Radiol* 1997; **27** (12)**:** 920-5.
89. Shah RM, Sexauer W, Ostrum BJ, Fiel SB, Friedman AC. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation. *AJR Am J Roentgenol* 1997; **169** (2)**:** 375-80.
90. Brody AS. Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? *Pediatrics* 1998; **101** (6)**:** 1071.
91. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29** (10)**:** 731-5.
92. Brody AS. Thoracic CT technique in children. *J Thorac Imaging* 2001; **16** (4)**:** 259-68.
93. Demirkazik FB, Ariyurek OM, Ozcelik U, Gocmen 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** (1)**:** 54-9.
94. Helbich TH, Heinz-Peer G, Eichler I, et al. Cystic fibrosis: CT assessment of lung involvement in children and adults. *Radiology* 1999; **213** (2)**:** 537-44.
95. Helbich TH, Heinz-Peer G, Fleischmann D, et al. Evolution of CT findings in patients with cystic fibrosis. *AJR Am J Roentgenol* 1999; **173** (1)**:** 81-8.
96. Marchant JM, Masel JP, Dickinson FL, Masters IB, Chang AB. Application of chest high-resolution computer tomography in young children with cystic fibrosis. *Pediatr Pulmonol* 2001; **31** (1)**:** 24-9.
97. 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** (5)**:** 377-82.
98. Robinson TE, Leung AN, Northway WH, et al. Spirometer-triggered high-resolution computed tomography and pulmonary function measurements during an acute exacerbation in patients with cystic fibrosis. *J Pediatr* 2001; **138** (4)**:** 553-9.
99. King GG, Muller NL, Whittall KP, Xiang QS, Paré PD. An analysis algorithm for measuring airway lumen and wall areas from high-resolution computed tomographic data. *Am J Respir Crit Care Med* 2000; **161** (2 Pt 1)**:** 574-80.
100. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000; **162** (3 Pt 1)**:** 1102-8.
101. Hoffman EA, Clough AV, Christensen GE, et al. The comprehensive imaging-based analysis of the lung: a forum for team science. *Acad Radiol* 2004; **11** (12)**:** 1370-80.
102. Hoffman EA, Reinhardt JM, Sonka M, et al. Characterization of the interstitial lung diseases via density-based and texture-based analysis of computed tomography images of lung structure and function. *Acad Radiol* 2003; **10** (10)**:** 1104-18.
103. Webb WR, Gamsu G, Wall SD, Cann CE, Proctor E. CT of a bronchial phantom: factors affecting appearance and size measurements. *Invest Radiol* 1984; **19:** 394-8.
104. Seneterre E, Paganin F, Bruel JM, Michel FB, Bousquet J. Measurement of the internal size of bronchi using high resolution computed tomography (HRCT). *Eur Resp J* 1994; **7:** 596-600.
105. Okazawa M, Muller N, McNamara AE, Child S, Verburgt L, Paré PD. Human airway narrowing measured using high resolution computed tomography. *Am J Respir Crit Care Med* 1996; **154** (5)**:** 1557-62.

106. McNamara AE, Muller NL, Okazawa M, Arntorp J, Wiggs BR, Paré PD. Airway narrowing in excised canine lung measured by high-resolution computed tomography. *Journal of Applied Physiology* 1992; **73:** 307-316.
107. Nakano Y, Whittall KP, Kalloger SE, Coxson HO, Paré PD, English JC. Development and Validation of Human Airway Analysis Algorithm Using Multidetector Row CT. *Proceedings of SPIE* 2002; **4683:** 460-469.
108. Newman KB, Lynch DA, Newman LS, Ellegood D, Newell JD, Jr. Quantitative computed tomography detects air trapping due to asthma. *Chest* 1994; **106** (1)**:** 105-9.
109. Mitsunobu F, Ashida K, Hosaki Y, et al. Complexity of terminal airspace geometry assessed by computed tomography in asthma. *Am J Respir Crit Care Med* 2003; **167** (3)**:** 411-7.
110. Mishima M, Hirai T, Itoh H, et al. Complexity of terminal airspace geometry assessed by lung computed tomography in normal subjects and patients with chronic obstructive pulmonary disease. *Proc. Natl. Acad. Science USA* 1999; **96:** 8829-8834.
111. Gevenois PA, Scillia P, de Maertelaer V, Michils A, De Vuyst P, Yernault JC. The effects of age, sex, lung size, and hyperinflation on CT lung densitometry. *AJR Am J Roentgenol* 1996; **167** (5)**:** 1169-73.
112. Gevenois PA, De Vuyst P, Sy M, et al. Pulmonary emphysema: quantitative CT during expiration. *Radiology* 1996; **199:** 825-829.
113. Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. *Eur Respir J* 2003; **22** (6)**:** 965-71.
114. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123** (5)**:** 1655-63.
115. Coxson HO, Mayo JR, Behzad H, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol* 1995; **79** (5)**:** 1525-30.
116. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; **159** (3)**:** 851-6.
117. Robinson TE, Leung AN, Moss RB, Blankenberg FG, al-Dabbagh H, Northway WH. Standardized high-resolution CT of the lung using a spirometer-triggered electron beam CT scanner. *AJR Am J Roentgenol* 1999; **172** (6)**:** 1636-8.
118. Pierce DA, Preston DL. Risks from low doses of radiation. *Science* 1996; **272** (5262)**:** 632-3.
119. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. *Radiat Res* 1996; **146** (1)**:** 1-27.
120. Preston DL, Kato H, Kopecky K, Fujita S. Studies of the mortality of A-bomb survivors. 8. Cancer mortality, 1950-1982. *Radiat Res* 1987; **111** (1)**:** 151-78.
121. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 2003; **160** (4)**:** 381-407.
122. Mayo JR, Aldrich J, Muller NL. Radiation exposure at chest CT: a statement of the Fleischner Society. *Radiology* 2003; **228** (1)**:** 15-21.
123. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001; **176** (2)**:** 289-96.
124. Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. *Pediatr Radiol* 2002; **32** (4)**:** 228-3; discussion 242-4.
125. Aroua A, Bize R, Buchillier-Decka I, Vader JP, Valley JP, Schnyder P. X-ray imaging of the chest in Switzerland in 1998: a natiowide survey. *Eur Radiol* 2003; **13:** 1250-1259.
126. Bottollier-Depois JF, Chau Q, Bouisset P, Kerlau G, Plawinski L, Lebaron-Jacobs L. Assessing Exposure to Cosmic Radiation on Board Aircraft. *Adv Space Res* 2003; **32** (1)**:** 59-66.
127. Temple RJ. A regulator authority's opinion about surrogate endpoints. Clinical measurements on drug evaluation. New York: Wiley, 1995.

Chapter 3

Computed tomography scoring systems and quantitative measurements

Chapter 3.1 Computed tomography in children with cystic fibrosis: comparison of scoring systems and measurements of bronchi and arteries

The purpose of this study was to retrospectively compare thin-section computed tomographic (CT) scores obtained with five scoring systems for assessment of pulmonary disease in children with cystic fibrosis and to determine additional value of bronchial and arterial dimension measurements. Scores obtained with five thin-section CT scoring systems were compared. A score of 0 indicated the absence of abnormalities; a higher score meant that more structural abnormalities were seen. Three observers assigned scores and then reassigned scores after intervals varying from 1–2 weeks to 1–2 months at review of thin-section CT scans obtained in 25 children with cystic fibrosis. Interobserver and intraobserver reliability was calculated with intraclass correlation coefficients. Quantitative measurements of bronchial and arterial dimensions were obtained. Thin-section CT scores were correlated (Spearman correlation) with bronchial and arterial dimensions and with results of pulmonary function tests (PFTs), such as forced expiratory volume in 1 second (FEV_1). Scores with all five scoring systems were reproducible, with intraclass correlation coefficients of 0.74 and higher ($P < .05$), and showed significant correlations with FEV_1 ($R = -0.73$ to -0.69, $P < .01$). Ratio of bronchial diameter to accompanying pulmonary arterial diameter was correlated with thin-section CT scores but not with FEV_1. Ratio of bronchial wall thickness to accompanying pulmonary arterial diameter was not correlated with thin-section CT scores or PFT results. We concluded that thin-section CT scores were reproducible and were correlated with PFT results and that measurements of bronchial dimensions were not significantly related to scores or PFT results.

Based on:

Pim A. de Jong, Mark D. Ottink, Simon G.F. Robben, Maarten H. Lequin, Wim C.J. Hop, Johan J.E. Hendriks, Peter D. Paré and Harm A.W.M. Tiddens. Pulmonary Disease Assessment in Cystic Fibrosis: Comparison of CT Scoring Systems and Value of Bronchial and Arterial Dimension Measurements. *Radiology* 2004; **231**: 434–439.

Introduction

Cystic fibrosis is the most frequently inherited autosomal recessive disease in whites, with an incidence of one in 3,600 in the Dutch population. Cystic fibrosis is a lethal disease; when it was described by Fanconi [1] and Andersen [2] more than 60 years ago, the median survival was less than 1 year. Presently, median survival is 32.3 years and is increasing [3]. Despite increased longevity, pulmonary dysfunction causes major morbidity in cystic fibrosis, and more than 90% of the mortality is caused by pulmonary complications [4]. It is therefore critically important to monitor progression of lung disease for clinical treatment and to evaluate new treatments. The standard for assessment of lung disease in cystic fibrosis is pulmonary function tests (PFTs); however, conventional PFTs are not very sensitive in the detection of early lung damage [5]. In addition, the conventional PFTs are reliable only in children older than 5 years. There is evidence that pulmonary disease starts early in life in the majority of patients [6, 7], and this suggests that therapy should be started before routine PFTs can be performed. These facts illustrate the need for a relatively noninvasive and sensitive test for lung disease that can be applied in infancy.

In the last decade, the use of thin-section computed tomography (CT) in cystic fibrosis has increased. In 1991, Bhalla et al [8] published a scoring system designed to quantify structural lung abnormalities in patients with cystic fibrosis by using thin-section CT. Since then, a number of additional scoring systems and modifications of scoring systems have been proposed, and they are frequently used for both clinical treatment and research purposes [9]. Thin-section CT scoring systems are a potentially useful outcome measure surrogate in patients with cystic fibrosis [10]. To date to our knowledge, there is limited experience with the use of these scoring systems for assessment of pulmonary disease in children with cystic fibrosis, and there have been no systematic comparisons of the scoring systems. In addition, the quantitative nature of thin-section CT allows precise measurements of bronchial and arterial dimensions, and these may have added value in the assessment of lung abnormalities in patients with cystic fibrosis.

Thus, the purpose of our study was to retrospectively compare thin-section CT scoring systems of Bhalla et al [8], Helbich et al [11], Santamaria et al [12], Brody et al [10], and Castile et al [13] for assessment of pulmonary disease in children with cystic fibrosis and to determine the additional value of measurements of bronchial and arterial dimensions.

Methods

Study Population

Twenty-five children and adolescents with cystic fibrosis (17 male patients, eight female patients) were randomly selected for this study. The mean age was 10.7 years (range, 5.5–17.3 years). All patients were followed up at Sophia Children's Hospital, Erasmus Medical Center Rotterdam, the Netherlands, where biennial thin-section CT scans and PFTs are part of our routine clinical protocol. Cystic fibrosis was diagnosed with a positive sweat test, the presence of a genotype for known cystic fibrosis mutations, or an abnormal potential difference measured across the nasal mucosa (to determine the function of the cystic fibrosis transmembrane conductance protein), or all of these. The ethics review board of the hospital approved the retrospective study and did not require informed consent.

Thin-Section CT and Evaluation

Thin-section CT scans were obtained (Prospeed SX; GE Medical Systems, Milwaukee, Wis) with the patients in the supine position after they were instructed to take a deep breath and hold their breath for at least 5 seconds. During each breath hold, approximately two lung sections were obtained. A complete thin-section CT series included on average 25 (range, 16–34 sections) 1.0-mm-thick sections that were acquired with 10-mm intervals from the lung apex to the lung base. Scanning parameters were as follows: 120 kV, 160 mA (120 mA in children younger than 9 years), 1-second scanning time, and a field of view of 350 mm (250 mm in children younger than 9 years). Scans were reconstructed with a reconstruction algorithm (Detail; GE Medical Systems) and printed with window settings appropriate for the imaging of pulmonary parenchyma (window width, –600 HU; window level, 1,500 HU).

We selected five thin-section CT scoring systems [8, 10–13] for evaluation. These systems can be categorized into two groups: lobar scoring systems [10, 13], in which a score is assigned to each lung lobe separately, and segmental scoring systems [8, 11, 12], in which a score is assigned to each bronchopulmonary segment separately. With all systems, a score is assigned in a semiquantitive way to a subset of the following abnormalities: bronchiectasis; peribronchial thickening; mucous plugging; sacculations or abcesses; bullae; emphysema, air trapping, or hyperinflation; collapse or consolidation; mosaic perfusion or ground-glass opacities; acinar nodules or alveolar consolidation; and thickening of intralobular and interlobular septa. These abnormalities were considered to be the variables and were assigned scores that ranged from 0 to 3. The total scores were derived as composites of the variables that were assigned these scores. The scores assigned to the variables were used in the calculation of the Kappa (κ) statistic. The total scores ranged from 0 (indicating absence of abnormalities) to 92, 100, 27, 29, and 25 (indicating maximal abnormalities) for scoring systems of Castile et al [13], Brody et al [10], Helbich et al [11], Santamaria et al [12], and Bhalla et al [8], respectively.

Hereafter, these scores will be referred to as the Castile, Brody, Helbich, Santamaria, and Bhalla scores.

Thin-section CT scans were assigned scores by three observers. Observers 1 and 2 were 5th-year medical students who underwent intensive training in how to score the thin-section CT scans. Observer 3 was a senior radiologist. After the training period, a consensus meeting was held to further standardize the scoring between the three observers. For the scoring methods used in this study, no reference images were available. All 25 scans were assigned scores in random order, and observers assigned scores independently and were blinded to patient characteristics. To evaluate intraobserver variability, random subsets of 10 scans were assigned scores a second time after 1–2 weeks (observer 1), 2–4 weeks (observer 2), and 1–2 months (observers 1 and 3).

Measurements of bronchial dimensions on the CT scans were performed by using a workstation (GE Medical Systems, Milwaukee, Wis) with software (version AW 3.1; GE Medical Systems) that supported the CT scanner used in this study. All visible bronchus-artery pairs that appeared to be round were magnified five times, and two perpendicular lines were traced through the center of each bronchus and the accompanying pulmonary artery. One line was vertical and the other was horizontal to the plane of gravity. The software program constructed a profile of the Hounsfield units along the lines, and the observer calculated the cutoff level for the inner and the outer wall according to the full-width-at-half-maximum principle [14].

Since bronchial diameter and bronchial wall thickness change as a function of airway generation, we calculated ratios of bronchial and arterial dimensions rather than absolute values. One of the ratios was calculated by dividing the mean outer bronchial diameter by the mean diameter of the accompanying pulmonary artery, and this was the bronchus-artery ratio. This ratio has previously been reported as an indicator of bronchial dilatation or bronchiectasis [8]. In the case of bronchiectasis, the simple measurement of bronchial wall thickness divided by bronchial luminal diameter could cause spurious underestimation of intrinsic bronchial wall thickening. Thus, to obtain an estimate of bronchial wall thickness, we used the ratio of the mean bronchial wall thickness divided by the mean diameter of the accompanying pulmonary artery, and this was the thickness-artery ratio. This calculation was determined with the assumption that there is no change in arterial diameter as pulmonary disease progresses in cystic fibrosis. On average, an observer assigned scores on each scan in 10 minutes for the lobular systems [10, 13] and in 15 minutes for the bronchopulmonary systems [8, 11, 12].

PFT Results

The PFT results used for this study were obtained with PFTs performed most closely in time to the time that the thin-section CT scans were obtained. Twenty children were evaluated with PFTs and thin-section CT on the same day. For three children,

thin-section CT was performed on a different day from that on which the PFTs were performed for logistic reasons (intervals between CT and PFTs were 5, 12, and 23 days).

PFT results were obtained by using a diagnostic system (MasterLab; Jäger, Wurzburg, Germany). The results were expressed as the percentage of predicted values for forced expiratory volume in 1 second (FEV_1) [15], forced vital capacity (FVC) [15], and forced expiratory flow between 25% and 75% of expiratory vital capacity ($FEF_{25–75}$) [16]. The ratio of FEV_1 to FVC was calculated and expressed as a percentage. Additional measurements included airway resistance (Raw), residual volume (RV), and total lung capacity (TLC). Values for these measurements were obtained by using a body plethysmograph. The RV/TLC ratio was calculated and expressed as a percentage.

Statistical Analysis

Interobserver and intraobserver reliability of the scoring systems was tested with the intraclass correlation coefficient (R_i) and Bland-Altman plots. Values of R_i greater than 0.80 are generally considered to represent good agreement between observers. Interobserver and intraobserver reliability of the various scoring system variables of each of the five scoring systems was evaluated with the κ-statistic. The κ-values of <0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00 are generally considered to represent poor, fair, moderate, good, and very good agreement, respectively. The mean and individual scores of three observers were used to calculate the Spearman correlation, or *R*, between the scoring systems and that between the scoring systems and PFT results. Furthermore, the Spearman correlation was calculated for the quantitative thin-section CT measurements (thickness-artery and bronchus-artery ratios) with mean thin-section CT scores and with PFT results. Normal distribution of all ratios (thickness-artery, bronchus-artery, FEV_1/FVC, and RV/TLC) was tested by using the Shapiro-Wilk test. A software package (SPSS, version 10.0; SPSS, Chicago, Ill) was used for statistical analysis. Data were expressed as the mean ± SD and range. A difference with a *P* value less than .05 was considered significant.

Results

Study Population

Table 1 shows age and PFT data. Table 2 shows the prevalence of abnormalities observed at thin-section CT in this study population. Technically satisfactory thin-section CT scans were obtained in children who could hold their breath for at least 5 seconds. Although motion artifact was present on some scans, no scans were excluded because of motion artifact. Two patients were too young to perform reliable PFTs. Thus, all comparisons between CT scores and PFT results were limited to 23 patients.

Table 1 Patient characteristics and PFT results

Characteristic and PFT*	mean	SD	Range
age (years)	10.7	3.6	5.5 - 17.3
male/female	17/8		
FEV_1	76	23	36 – 118
FVC	86	17	48 – 118
FEV_1/FVC	76	13	45 - 95
FEF_{25-75}	63	38	8 - 140
R_{aw}	141	75	56 – 310
RV	143	48	88 – 256
TLC	100	9	78 – 114
RV/TLC ratio (%)	34	10	20 – 60

* Unless specified otherwise, data are expressed as percentage predicted

Table 2 Prevalence of abnormalities at thin-section CT

Abnormality	Prevalence (%)*
Bronchiectasis	76
Peribronchial thickening	85
Mucous plugging	79
Sacculations or abcesses	11
Bullae	8
Emphysema, air trapping, or hyperinflation	1
Collapse or consolidation	51
Mosaic perfusion or ground-glass opacities	12
Acinar nodules or alveolar consolidation	42
Thickening of interlobular and intralobular septa	4

* Data were calculated as follows: 100 times the number of subjects with the abnormality divided by the total number of subjects

Thin-Section CT Scoring Systems

Interobserver variability of scoring systems: Interobserver variability was generally good (Table 3). The Bland-Altman plots illustrated that the most important differences between the observers were at the lower scores. The κ-coefficients were less than 0.61 for most scoring system variables. For mosaic perfusion, acinar nodules, and airspace disease, κ-coefficients were less than 0.40 for all comparisons.

Intraobserver variability of scoring system: Intraobserver variability was good (R_i > 0.80) when the interval was shorter than 1 month. Even when the interval was longer than 1 month, correlations were generally good (R_i > 0.74). Intraobserver variability for the variables of the scoring systems was good; all κ-coefficients were greater than 0.61.

Table 3 Interobserver and intraobserver variability

Scoring system	Interobserver variability			Intraobserver variability*			
	Observer 1 vs 2	Observer 1 vs 3	Observer 2 vs 3	Observer 1 at 1-2 weeks	Observer 2 at 2-4 weeks	Observer 1 at 1-2 months	Observer 3 at 1-2 months
Castile	0.76	0.74	0.93	0.95	0.92	0.74	0.80
Brody	0.80	0.80	0.98	0.96	0.87	0.91	0.93
Helbich	0.80	0.86	0.95	0.97	0.96	0.92	0.86
Santamaria	0.80	0.86	0.94	0.94	0.95	0.90	0.81
Bhalla	0.78	0.85	0.95	0.97	0.94	0.92	0.87

Note.—Data are intraclass correlation coefficients
* Data are scores reassigned after intervals noted

Thin-section CT scoring and PFT results: All five scoring systems showed a strong and highly significant correlation with values for FEV_1, FVC, $FEF_{25–75}$, and FEV_1/FVC ratio (Table 4). The relationship between Bhalla score and FEV_1 is shown in Figure 1. The correlation coefficients were highest for the relationships between thin-section CT scores and the $FEF_{25–75}$ value and lowest for the relationships with the FVC value; *R* values for the relationships between scores and values for FEV_1 and FEV_1/FVC ratio were intermediate. Raw and TLC values were correlated significantly with scores achieved with all scoring systems. Values for RV and RV/TLC ratio did not show significant relationships (Table 4). The correlation coefficients did not differ substantially when individual scores from the three observers were used rather than mean scores. The correlation between the scoring systems was strong; *R* values ranged from 0.94 to 0.99. There was no significant correlation between mean scores and bronchial wall thickness, expressed as the thickness-artery ratio. The marker for the estimate of the severity of bronchiectasis (bronchus-artery ratio) was correlated significantly with scores achieved with all five scoring systems. The *R* values were as follows: Castile score, 0.59; Brody score, 0.60; Helbich score, 0.50; Santamaria score, 0.51; and Bhalla score, 0.50. Neither the thickness-artery ratio nor the bronchus-artery ratio showed a significant correlation with PFT results, although the relationship between the bronchus-artery ratio and values for FEV_1 and FEV_1/FVC ratio approached significance ($P = .07$). All ratios, except the thickness-artery ratio, could be described with normal distributions. We used the Spearman correlation coefficient, which is adequate for nonnormal distributions.

Table 4 Thin-section CT scoring systems and PFTs

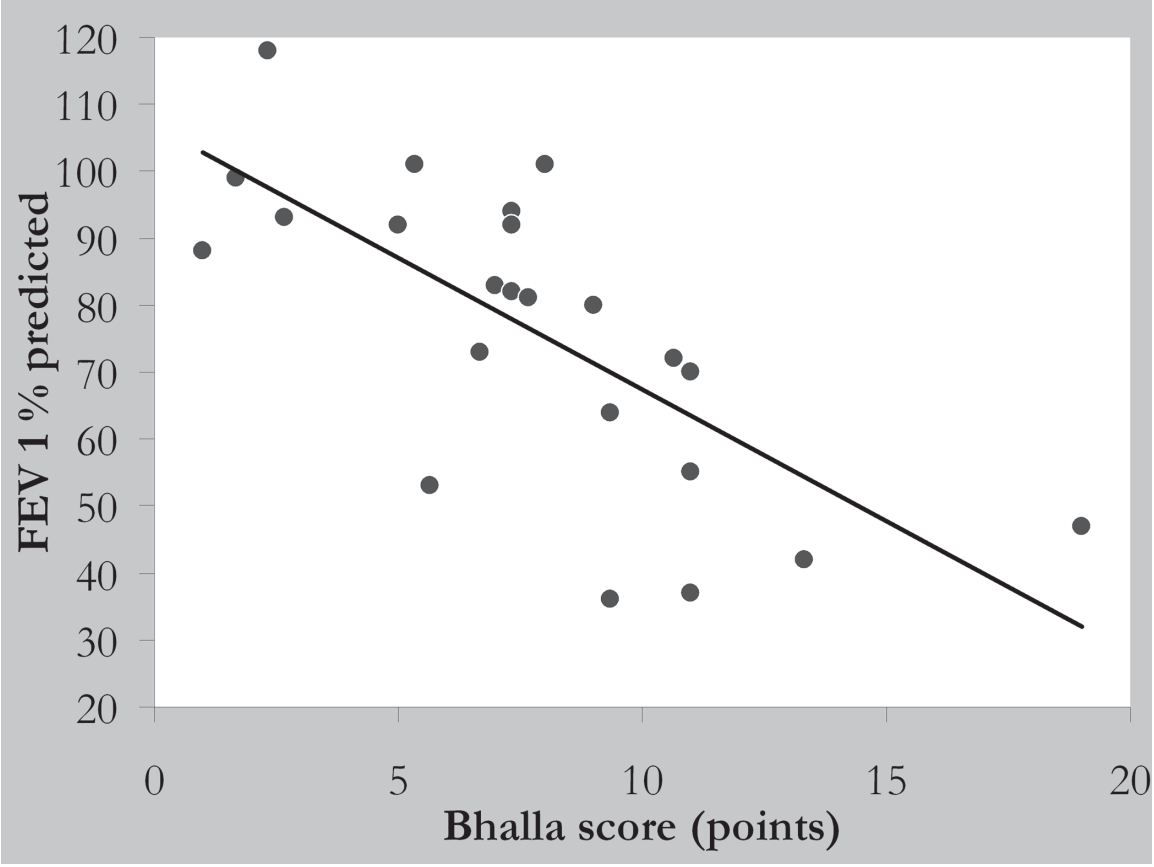
PFT*	Castile score	Brody score	Helbich score	Santamaria score	Bhalla score
FEV_1	-0.69†	-0.69†	-0.72†	-0.70†	-0.73†
FVC	-0.54†	-0.52‡	-0.58†	-0.54†	-0.57†
FEF_{25-75}	-0.76†	-0.79†	-0.83†	-0.82†	-0.82†
FEV_1/ FVC	-0.72†	-0.73†	-0.75†	-0.74†	-0.78†
R_{aw}	0.67†	0.59‡	0.56‡	0.58‡	0.65‡
RV	0.13	0.07	0.06	0.16	0.11
TLC	-0.63‡	-0.71†	-0.65†	-0.57‡	-0.66†
RV/TLC-ratio (%)	0.37	0.27	0.33	0.28	0.33

Note.—Data are Spearman correlation coefficients

* Unless specified otherwise, data are expressed as percentage predicted

† $P < .01$, ‡ $P < .05$

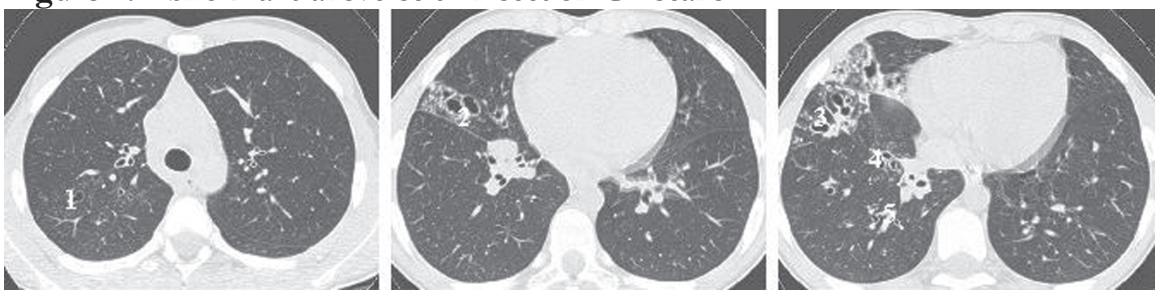
Figure 1 Graph shows relationship between Bhalla score and FEV_1 value ($R = –0.73$, $P < .01$).



Discussion

The results of this study show that the semiquantitative scoring systems that are frequently used to detect pulmonary abnormalities with thin-section CT in patients with cystic fibrosis are comparable and robust. There was good interobserver and intraobserver variability, and this observation indicated that these measurements are reliable and reproducible. Furthermore, there was good correlation between scores achieved with these thin-section CT scoring systems and PFT results, especially the FEV_1, $FEF_{25–75}$, FEV_1/FVC ratio, Raw, and TLC values. Correlation of the scoring systems with each other was very good. The agreement between the total score of the radiologist and that of the students illustrates that it is possible for nonqualified observers to be trained in the use of thin-section CT scoring systems. These data do not allow the selection of a best scoring system. Such selection will depend not only on the reproducibility but also on the sensitivity of the system to early changes, its ability to track the progression of pulmonary abnormalities over time, and the time required for an observer to assign an adequate score to a scan. In the present study, 10–15 minutes was needed for each observer to assign a score to a scan; because of the time required, it seems unlikely that routine use of scoring systems, at least as implemented by a radiologist, will be adopted. Despite the excellent correlations between PFT results and the scores derived with the thin-section CT scoring systems, abnormalities may be observed on CT scans in patients with normal PFT measurements (Figure 2) [17]. These observations suggest that at least in some instances thin-section CT may be more sensitive to early lung damage in patients with cystic fibrosis.

Figure 2. Abnormal transverse thin-section CT scans



Obtained in a 13-year-old boy with normal PFT results as follows: FEV_1, 99 percentage predicted; FVC, 92 percentage predicted; FEV_1/FVC ratio, 90%; and FEF_{25-75}, 95 percentage predicted. Thin-section CT scores were as follows: Castile score, 22 (range, 0-92); Brody score, 17 (range, 0-100); Helbich score, 12 (range, 0-27); Santamaria score, 13 (range, 0-29); Bhalla score, 12 (range, 0-25). Left: Scan shows bronchiectasis with a diameter of the artery that was two to three times that of the artery at an intermediate location *(1)*. Center: Scan shows cysts in the periphery of the lung *(2)*, bronchiectasis with a diameter of the artery that was one to two times that of the artery at a central location *(3)*, and mucus-plugged bronchus *(4)*. Right: Scan shows cysts in the periphery of the lung *(5)*.

Although the scoring systems were reliable and the scores were correlated well with PFT results, we were concerned about three observations in our study.

First, our data showed a lower reproducibility with longer intervals (1–2 months) between repeat measurements. In part, this finding may be related to the fact that there were gaps between the scoring sessions during which the observers were not routinely scoring CT scans. These gaps might have caused some loss of recall of the scoring systems, as well as of the findings of the consensus meeting. This result suggests that a new training period for observers may be needed after a 1–2-month interval. In addition, it might be useful to develop standardized definitions and reference images to reduce intraobserver and interobserver variability even further.

Second, our results showed a lower interobserver reproducibility for most scoring system variables than for the total score. Many variables had a low κ-coefficient, even after the consensus meeting. An example of one such variable is mosaic perfusion. When we examined the thin-section CT scans closely, almost all scans had some signs of mosaic perfusion, and there was no description of how other authors defined this abnormality. Although all scoring systems except that of Castile et al [13] were designed for inspiratory thin-section CT scans, some investigators designated a low-attenuation area as "hyperinflation" and others identified such an area as "gas trapping." The prevalence of air trapping reported in this study is lower than that previously reported [10–12, 17]. In the routine follow-up of our patients, we restricted ourselves to the use of inspiratory thin-section CT scans, which are less sensitive in the depiction of air trapping relative to expiratory thin-section CT scans. Currently, we measure air trapping in children who are 6 years old and older by using the combination of helium spirometry and body plethysmography. It is unclear whether it is worthwhile to add more radiation to our standard clinical CT protocol to obtain expiratory CT scans on which air trapping could be scored more reliably. Because of the large variability in nomenclature, we believe that a uniform nomenclature and clear definitions of abnormalities must be developed for use in thin-section CT scoring systems to obtain objective and reproducible thin-section CT data for follow-up of patients and for clinical trials.

The third concern is the increased variability between observers that was evident when the scores were low. If these systems are to be useful in the early detection and longitudinal assessment of lung abnormalities in cystic fibrosis, they should have sufficient resolution of the lower end of the scoring system scale.

An additional way to quantify structural lung damage is with the measurement of bronchial dimensions on thin-section CT scans. We measured the size of the bronchi relative to the accompanying artery (bronchus-artery ratio) and the thickness of the bronchial wall relative to the accompanying artery (thickness-artery ratio). The bronchus-artery ratio, which is a well-recognized measure of bronchiectasis [8], was correlated significantly with thin-section CT scores, presumably because a subjective assessment of bronchial dilatation is an important component of all the scoring systems. However, bronchial wall thickness was not correlated significantly with thin-section CT scores. None of these measurements was correlated significantly with PFT

results, although the relationship between the bronchus-artery ratio and values for FEV_1 and FEV_1/FVC ratio approached significance. These data suggest that, with the technology and algorithms we employed, quantitative bronchial measurements did not add value to the scoring systems. Further research is necessary to determine the role of bronchial measurements and their correlation with disease severity, as well as their interobserver and intraobserver variability.

It has been shown that thin-section CT scans are superior to chest radiographs to monitor structural aspects of pulmonary disease in cystic fibrosis [18]. Radiation dose is of concern, however, since life expectancy is increasing in patients with cystic fibrosis [19]. The radiation dose of the thin-section CT protocol we used is approximately 12 times that of a chest radiograph [20]. Although this dose is not as high as has been suggested by some authors [21], one needs to exercise caution. Because of concern regarding the balance between radiation and benefits from the additional information about lung structure, clinical centers for cystic fibrosis are performing biennial rather than annual thin-section CT examinations. New ways to further reduce the dose of radiation at thin-section CT must be found, and optimal scanning parameters for the pediatric age group have to be determined [19]. Researchers in several studies have already shown that low-dose thin-section CT, with a 40%–50% reduction of radiation dose, is possible without affecting image quality [22–25].

To conclude, the results of this study show that adequate thin-section CT scans can be obtained in young children who have cystic fibrosis. Structural abnormalities observed on thin-section CT scans can be assigned scores in a reproducible fashion with currently available scoring systems. These findings support the use of thin-section CT to monitor progression of structural lung abnormalities in cystic fibrosis. Such use can be important for both patient treatment and therapeutic studies.

References

1. Fanconi G. Das coeliakie syndrom bei angeborener zystischer pancreas fibromatose und bronchiektasen. *Wien Med Wochenschr* 1936; **86**: 753-756.
2. Andersen D. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *Am J Dis Child* 1938; **56**: 344-399.
3. Nasr SZ. Cystic fibrosis in adolescents and young adults. *Adolesc Med* 2000; **11**: 589-603.
4. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med* 1996; **154**: 1229-1256.
5. Becklake MR, Permutt S. Evaluation of tests of lung function for "screening" for early detection of chronic obstructive lung disease In: The lung in the transition between health and disease. New York, NY: Marcel Dekker, 1979.
6. Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DW. Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med* 1995; **151**: 1075-1082.
7. Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. *Pediatr Pulmonol* 1997; **24**: 137-142; discussion 159–161.

8. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**: 783-788.
9. 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.
10. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**: 731-735.
11. Helbich TH, Heinz-Peer G, Eichler I, et al. Cystic fibrosis: CT assessment of lung involvement in children and adults. *Radiology* 1999; **213**: 537-544.
12. Santamaria F, Grillo G, Guidi G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? *Pediatrics* 1998; **101**: 908-913.
13. Castile RG, Long FR, Flucke RL, Hayes JR, McCoy KS. Correlation of structural and functional abnormalities in the lungs of infants with cystic fibrosis (abstr). *Pediatr Pulmonol* 2000; **20**: A427.
14. Amirav I, Kramer SS, Grunstein MM, Hoffman EA. Assessment of methacholine-induced airway constriction by ultrafast high-resolution computed tomography. *J Appl Physiol* 1993; **75**: 2239-2250.
15. Quanjer PH, Borsboom GJ, Brunekreff B, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995; **19**: 135-142.
16. Wang X, Dockery DW, Wypij D, Fay ME, Ferris B, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**: 75-88.
17. 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.
18. Taccone A, Romano L, Marzoli A, Girosi D, Dell'Acqua A, Romano C. High-resolution computed tomography in cystic fibrosis. *Eur J Radiol* 1992; **15**: 125-129.
19. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001; **176**: 289-296.
20. van der Bruggen-Bogaarts BA, Broerse JJ, Lammers JW, van Waes PF, Geleijns J. Radiation exposure in standard and high-resolution chest CT scans. *Chest* 1995; **107**: 113-115.
21. DiMarco AF, Briones B. Is chest CT performed too often? *Chest* 1993; **103**: 985-986.
22. Lucaya J, Piqueras J, Garcia-Pena P, Enriquez G, Garcia-Macias M, Sotil J. Low-dose high-resolution CT of the chest in children and young adults: dose, cooperation, artifact incidence, and image quality. *AJR Am J Roentgenol* 2000; **175**: 985-992.
23. Ambrosino MM, Genieser NB, Roche KJ, Kaul A, Lawrence RM. Feasibility of high-resolution, low-dose chest CT in evaluating the pediatric chest. *Pediatr Radiol* 1994; **24**: 6-10.
24. Mayo JR, Hartman TE, Lee KS, Primack SL, Vedal S, Muller NL. CT of the chest: minimal tube current required for good image quality with the least radiation dose. *AJR Am J Roentgenol* 1995; **164**: 603-607.
25. Zwirewich CV, Mayo JR, Muller NL. Low-dose high-resolution CT of lung parenchyma. *Radiology* 1991; **180**:413-417.

Chapter 4

Sensitivity of computed tomography and lung function

Chapter 4.1 Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis

For effective clinical management of cystic fibrosis (CF) lung disease it is important to closely monitor the start and progression of lung damage. The aim of this study was to investigate the ability of high-resolution computed tomography (HRCT) scoring systems and pulmonary function tests (PFT) to detect changes in lung disease. CF children (n=48) had two HRCT scans in combination with two PFT 2 yrs apart. Their scans were scored using five scoring systems (Castile, Brody, Helbich, Santamaria and Bhalla). "Sensitivity" was defined as the ability to detect disease progression. In this group of children, HRCT scores worsened and PFT remained unchanged or improved. Of the HRCT parameters, mucous plugging and the severity, extent and peripheral extension of bronchiectasis worsened significantly. Relationships between changes in HRCT scores and PFT were weak. Substantial structural lung damage was evident in some children who had normal lung function. These data show that high-resolution computed tomography is more sensitive than pulmonary function tests in the detection of early and progressive lung disease, and suggest that high-resolution computed tomography may be useful in the follow up of cystic fibrosis children and as an outcome measure in studies that aim to reduce lung damage.

Based on:

Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. P.A. de Jong, Y. Nakano, M.H. Lequin, J.R Mayo, R. Woods, P.D. Paré´, H.A.W.M. Tiddens. *Eur Respir J* 2004; **23**: 93±97

Introduction

In cystic fibrosis (CF), chronic bacterial infection leads to progressive structural lung damage and to pulmonary dysfunction. It is generally accepted that early and aggressive therapy could delay the progression of lung disease. To evaluate the efficacy of such treatment it is important to monitor the progression of lung damage closely. Pulmonary function tests (PFT) are considered the gold standard for the monitoring of lung disease in children of aged >6 yrs. However, since lung function is only indirectly related to lung structure, it is likely that high-resolution computed tomography (HRCT) is more sensitive than PFT in the detection of structural changes [1]. Some CF centres have adapted periodic HRCT on a routine basis to evaluate the progression of CF lung disease in combination with PFT. However, it is unclear what method should be used to analyse the HRCT and whether HRCT is more sensitive in detecting pulmonary disease progression in CF. It could be that PFT and HRCT provide complementary information and should be performed in parallel to assess progression.

The aim of this study was to investigate the sensitivity of five different HRCT-scoring systems and PFT to detect changes in CF structural lung disease over time.

Methods

Study population
Since 1996, Sophia Children's Hospital (Rotterdam, The Netherlands), a tertiary academic hospital, has monitored CF patients using annual PFT and biennial HRCT scans. All children with CF who had two HRCT scans (HRCT1 and HRCT2) in combination with two routine PFT (PFT1 and PFT2) were selected for this follow-up study (n=48). CF was diagnosed by a positive sweat test and/or genotyping for known CF mutations and/or an abnormal potential difference measured across the nasal mucosa. The ethical review board of the hospital approved the study.

Lung structure
All HRCT scans were acquired using a GE Prospeed SX scanner (General Electric Medical Systems, Milwaukee, WI, USA). During the scanning procedure, children were not sedated, they were scanned in the supine position, and instructed to take a deep breath and hold it for ≥5 s. A complete HRCT series contained ~ 25 1-mm thick slices at 10-mm intervals from lung apex to lung base. Scanning parameters were 120 kV, 160 mA (≤9 yrs of age 120 mA), 1-s scanning time and a field of view of 350 mm (≤9 yrs of age 250 mm). Scans were reconstructed with a detail reconstruction algorithm (General Electric Medical Systems) and printed using window width 1,500 Hounsfield units (HU) and window level -600 HU. All HRCT scans were scored in random order by an experienced single observer blinded as to the date of

the scan, patient identification and the PFT. Five different HRCT-scoring systems were used: Castile *et al* [2], Brody *et al* [3], Helbich *et al* [4], Santamaria *et al* [5], and Bhalla *et al* [6]. In a previous study, in which the observer of this study participated, these five scoring systems were shown to be reliable between and within observers [7]. All slices were used to score the lung lobes and the lingula [2, 3] or the bronchopulmonary segments of the lung [4-6]. The systems score bronchiectasis, bronchial wall thickening, mucous plugging, atelectasis, bulla, cysts, consolidation, acinar nodules, septal thickening and/or air trapping in a semiquantitative fashion. A score of zero means "no abnormalities" in each system. Maximal scores are 92, 100, 27, 29 and 25 for Castile, Brody, Helbich, Santamaria and Bhalla scores, respectively.

Lung function

All PFT were done within 1 month of the HRCT scanning using a Jaeger diagnostic system (MasterLab, Jaeger, Germany). Most scans were performed on the same day (71 of 96 scans) as the PFT. All HRCT scans were done as part of a routine check-up and thus patients were scanned in a relatively stable condition and not during an exacerbation. PFT results were expressed as percentage of predicted values: forced expiratory volume in one second (FEV_1) [8], forced vital capacity (FVC) [8], forced expiratory flow between 25% and 75% of expiratory vital capacity (FEF_{25-75}) [9], airway resistance (Raw) [10], residual volume (RV) [10], total lung capacity (TLC) and RV/TLC [10]. The ratio FEV_1/FVC and the ratio RV/TLC were expressed as a percentage (FEV_1/FVC % and RV/TLC %). Twelve patients were younger than patients studied by Wang *et al* [9] in the development of the prediction equation for FEF_{25-75}. Body plethysmography (TLC, RV and Raw) was performed in 33 of the 48 children. Normal lung function was defined as a FEV_1 of >85% predicted.

Lung structure and lung function over time

Data obtained at the first evaluation are reported as HRCT1 and PFT1, and data obtained at the second evaluation are reported as HRCT2 and PFT2. ΔHRCT is the annual change for a scoring system ((HRCT2-HRCT1)/time interval). To compare the annual changes of the five HRCT-scoring systems, ΔHRCT was also expressed as a percentage of the maximal obtainable HRCT score for that system. ΔPFT is the annual change expressed as % pred for a lung function parameter ((PFT2-PFT1)/time interval). A positive value for ΔHRCT indicates an increase of structural abnormalities and for ΔPFT an improvement in lung function. ΔHRCT and ΔPFT were evaluated for the whole group and separately for children younger than and older than 10 yrs of age. ΔHRCT and ΔPFT were also evaluated as a function of age and baseline disease severity (HRCT1 and first FEV_1 % pred).

Statistical analysis

For the purpose of this article, the term sensitivity is not used in the statistical sense but rather as a measure of the techniques' ability to track pulmonary disease progression in CF. It was assumed that, on average, CF lung disease would be progressive over 2 yrs and that the method that detected the largest change was most

"sensitive". The relationships between HRCT1 and PFT1, HRCT2 and PFT2, between ΔHRCT and ΔPFT and between ΔHRCT, ΔPFT, HRCT1, PFT1 and age were evaluated using the Spearman correlation coefficient. T-tests (unpaired) were performed for ΔHRCT and ΔPFT to determine whether HRCT and/or PFT changed significantly in the whole group and for children below and above 10 yrs of age. Wilcoxon-signed ranks tests were used to determine which of the HRCT abnormalities changed significantly. Statistical significance was set at a p-value of > 05. Data are presented as mean±SD and range.

Results

Study population

Characteristics of the 48 children (28 male) are shown in Table 1. At HRCT1, 15 children had normal lung function (31%). HRCT scores were 13.7±8.7, 8.1±6.8, 6.1±2.9, 6.4±3.2 and 6.1±2.9 for Castile, Brody, Helbich, Santamaria and Bhalla, respectively.

Table 1 Patient characteristics

	Mean ± SD HRCT1	Mean ± SD HRCT2	Mean annual change
Age yrs	11.05 ± 3.3	13.04 ± 3.3	Interval: 1.99
Body height m	1.37 ± 0.21	1.47 ± 0.20	0.047 *
Body weight kg	32.5 ± 12.1	38.6 ± 13.9	3.46 *
FEV_1 % pred	74.3 ± 18.2	76.0 ± 21.0	1.24
FVC % pred	85.5 ± 15.7	85.1 ± 16.2	- 0.11
FEF_{25-75} % pred	58.8 ± 31.2	59.9 ± 32.0	-1.30
FEV_1/FVC %	75.4 ± 10.6	77.6 ± 9.8	0.39
R_{aw} % pred	136.1 ± 61.8	143.4 ± 76.0	0.10
RV % pred	136.6 ± 42.1	129.9 ± 40.2	- 8.49 *
TLC % pred	98.0 ± 13.2	96.8 ± 11.2	- 1.06
RV/TLC %	33.2 ± 9.4	31.6 ± 9.7	- 2.11 *
Castile score	17.7 ± 9.7	22.4 ± 11.4	2.39 *
Brody score	12.1 ± 8.7	16.3 ± 10.2	2.21 *
Helbich score	8.4 ± 3.7	10.1 ± 3.8	0.88 *
Santamaria score	8.9 ± 4.0	10.7 ± 4.1	0.91 *
Bhalla score	8.2 ± 3.4	10.0 ± 3.6	0.87 *

Data are presented as mean±SD. HRCT: high-resolution computed tomography; FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; FEF_{25-75}: forced mid-expiratory flow; Raw: airway resistance; RV: residual volume; TLC: total lung capacity *: $p<05$ in 1 yr with the one-sample t- test (unpaired)

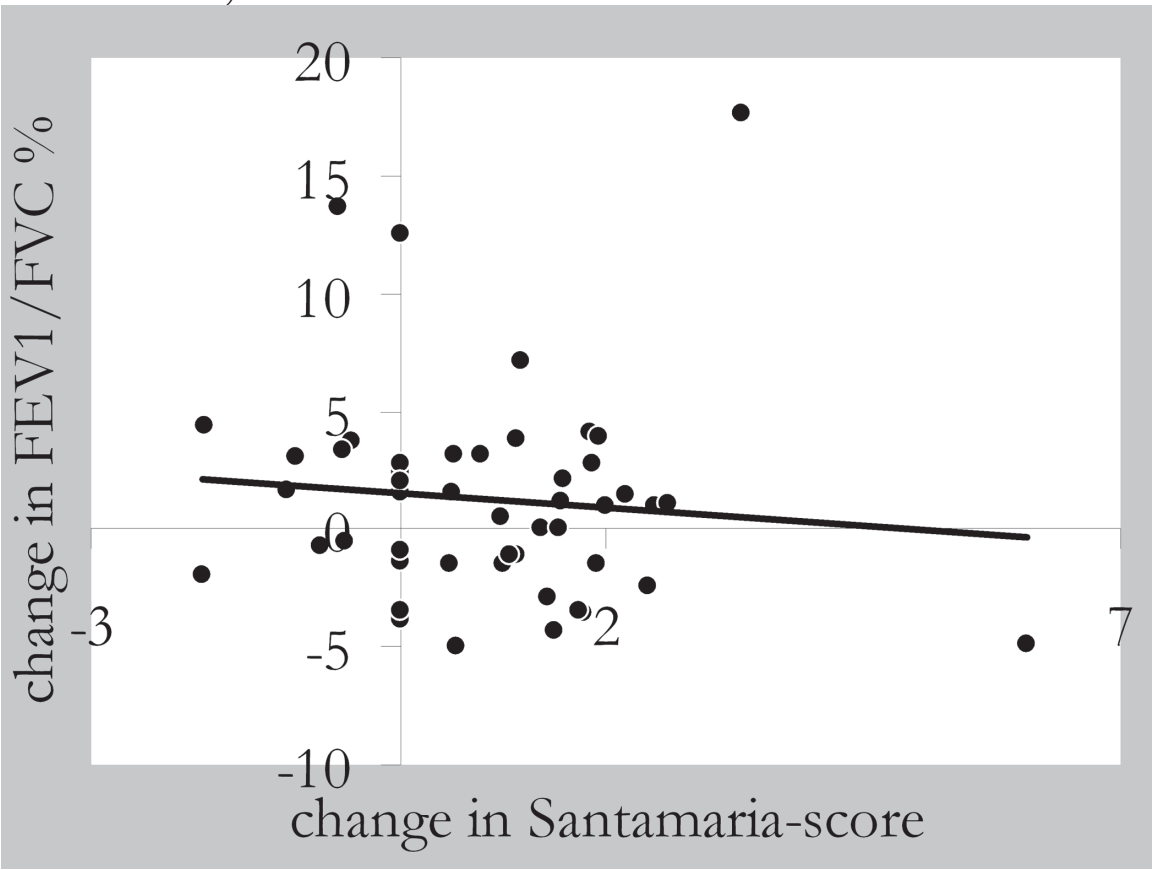
Lung structure and lung function over time

All HRCT scores worsened significantly. The mean changes for the whole group expressed as a percentage of the maximal scores were 2.6, 2.2, 3.3, 3.1 and 3.5% per year for Castile, Brody, Helbich, Santamaria, and Bhalla, respectively. Spirometric parameters (ΔFEV_1, ΔFVC, ΔFEF_{25-75} and $\Delta FEV_1/FVC$) did not change significantly. RV % pred, RV/TLC % and RV/TLC % pred decreased by 8.9% ($p=0.004$), 2.4% ($p=0.0005$) and 0.66% ($p<0.0001$) per year, respectively. Raw and TLC did not change significantly. The subgroup analysis of children below and above 10 yrs of age showed the same results, with the exception that RV % pred remained unchanged in the children >10 yrs of age. ΔHRCT and ΔPFT did not differ as a function of baseline disease severity or age, with the exception of significant relationships between age and ΔRV % pred ($R=0.53$, $p=0.001$) and between age and ΔRV/TLC % ($R=0.46$, $p=0.008$). Of the HRCT scan parameters only mucous plugging ($p=0.001$) and the severity ($p=0.005$), extent ($p<0.0001$) and peripheral extension ($p=0.02$) of bronchiectasis worsened significantly. Of the 48 patients, the severity of bronchiectasis increased in 15, the score for the extent of bronchiectasis increased in 19 and the score for the peripheral extension of bronchiectasis increased in eight. In only three patients there was a reduction of the severity of bronchiectasis (in all three cases, the airway lumen diameter changed from ~ 2 times vessel diameter to ~ 1-2 times vessel diameter). One patient showed a reduction in the peripheral extension score.

Correlation between lung structure and lung function

Cross-sectional data showed a significant correlation between HRCT1 and first FEV_1 ($R<-0.49$, $p<0.0001$), and between HRCT2 and second FEV_1 ($R<-0.58$, $p<0.0001$). Longitudinal data showed significant but weak correlation between ΔPFT and ΔHRCT: $\Delta FEV_1/FVC$ *versus* ΔSantamaria ($R=-0.31$, $p=0.04$), ΔRaw *versus* ΔHelbich ($R=0.37$, $p=0.04$), ΔRaw *versus* ΔSantamaria ($R=0.38$, $p=0.03$), ΔRV *versus* ΔBrody ($R=0.35$, $p=0.04$), ΔRV/TLC *versus* ΔBrody ($R=0.38$, $p=0.03$), and ΔRV/TLC *versus* ΔHelbich ($R=0.41$, $p=0.02$). The relationship between $\Delta FEV_1/FVC$ and ΔSantamaria is shown in Figure 1.

Figure 1 The weak correlation (R=-0 31, p=0 04) between changes in lung function (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC)) over a 1-yr period and structural changes on high-resolution computed tomography (HRCT; Santamaria score) is shown.



Patients with improved lung function have a change in FEV_1/FVC above 0, and patients with progressive structural lung damage have a Santamaria score above 0.

Discussion

In this study, the ability of five different HRCT-scoring systems and pulmonary function tests were compared to detect and monitor progression of lung damage in 48 children with CF.

The most striking finding of this study is that structural abnormalities as scored on HRCT scans increased significantly, independently of the scoring system used, while lung function parameters remained unchanged or even improved. This shows that HRCT was more sensitive than PFT in monitoring CF lung disease under the assumption that CF lung disease is progressive. In addition, the authors showed that it was predominantly the severity, extent and peripheral extension of bronchiectasis that worsened significantly. The bronchiectasis most likely represents irreversible

structural damage. The irreversibility of bronchiectasis is supported by the fact that none of the patients who had bronchiectasis on HRCT1 were without bronchiectasis on HRCT2. There are a number of possibilities why the structural abnormalities on HRCT were not reflected by the PFT. Firstly, the signal-to-noise ratio for PFT is likely to be less than that of HRCT since PFT depend more on patient co-operation than HRCT, especially for the younger children, and since PFT are more difficult to perform than a breath-hold on the HRCT table. Indeed, the HRCT can be scored even when there is minor motion artefact or some variation in inflation level. Furthermore, the results of PFT are expressed as % pred with reference to a large population sample and this can introduce variability related to the pubertal growth spurt [11]. In addition, HRCT can detect local abnormalities such as small areas of atelectasis and bronchiectasis that may be functionally insignificant. PFT provide a global estimate of the lung integrity [1].

In this study RV % pred improved for the whole group, but remained unchanged for the children >10 yrs of age. The improvement in RV may, therefore, be a reflection of patient effort. For the young children it is more difficult to reach RV during expiration. However, the RV/ TLC % and RV/TLC % pred improved slightly in the children >10 yrs of age. This suggests that the improvement in RV/TLC % pred is only partially caused by an effect of age.

The second important finding of this study is that the structural damage was irreversible in most patients irrespective of their change in PFT. In many patients the change in HRCT was dissociated from changes in PFT. Approximately one-half of the patients who had improved lung function had progressive structural lung disease.

The third important finding is that substantial structural lung damage was present on HRCT scans even in children who had lung function within the normal range. This supports the conclusions of earlier studies that conventional PFT are relatively insensitive to detect the onset and early progression of lung disease in CF [1, 7, 12]. These results indicate that the current monitoring strategy using PFT may fail to detect disease progression and suggest that studies using PFT to monitor treatment response may underestimate treatment effects. Therefore, it is possible that because of flawed outcome measures, the optimal treatment regime to minimise the progression of structural lung damage in CF patients is as yet unknown.

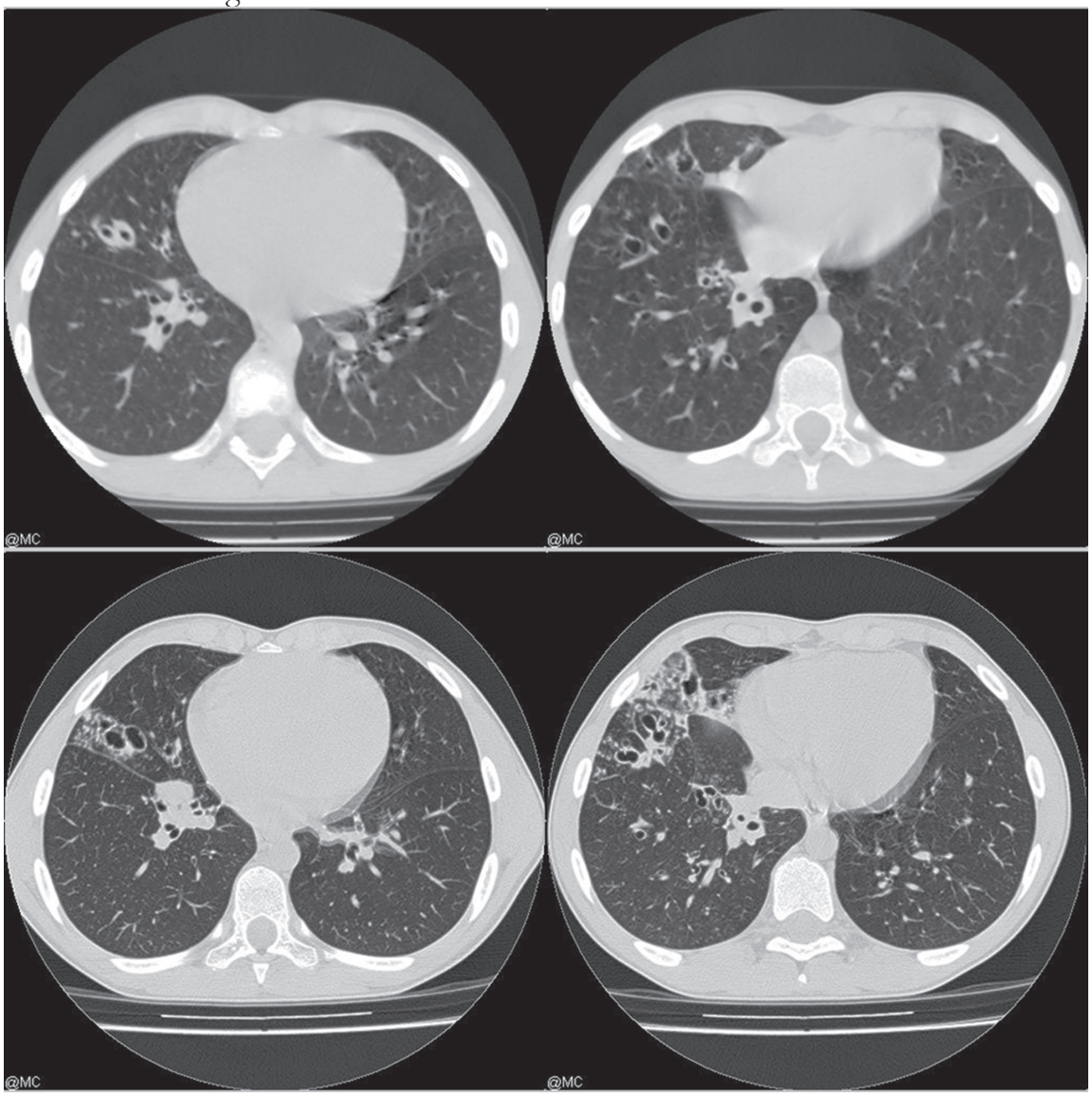
In this study, the HRCT features that changed most over the 2-yr observation period were the severity score for bronchiectasis and mucous plugging. Selective scoring of these parameters, instead of the full range of parameters included in the currently used complex scoring systems, may be more efficient and reproducible. A simplified scoring system may prove to be adequate for patient management and therapeutic trials. Clearly, such a system should be tested in further studies against the complex scoring systems to test this hypothesis.

Monitoring CF patients using HRCT carries potential risk due to the associated radiation exposure. Since the probability of cancer induction from ionising radiation is highest in the paediatric age group [13] and increases with each successive scan, the proposal to employ serial HRCT scans must be balanced against the potential radiation risk. Further research to determine the optimal scan parameters and frequency of HRCT scans for CF monitoring is required.

This study has some limitations. First, only one observer did the scoring. However, in a previous study, in which this observer participated, it was shown that the within- and between-observer variability for the five scoring systems was good [7]. Secondly, clinical outcomes were not measured in these patients and thus it cannot be assessed whether the worsening on HRCT scans affected the clinical management of the patients. However, a case scenario (Figure 2) illustrates how CT scoring could be used in a clinical setting. In this patient more aggressive therapy may have affected disease progression if it had been detected earlier. Larger prospective clinical studies in which CT scans are used in clinical decision making are required to test the importance of this conjecture.

To the best of the author*s'* knowledge, this is the first study that shows that HRCT can reveal progressive, irreversible structural damage in the lungs of cystic fibrosis patients over a 2-yr period; changes that are not associated with deterioration in lung function. Since the evolution of lung function over time may be dissociated from changes in the lung structure it may be advantageous to include high-resolution computed tomography in the standard follow-up of cystic fibrosis patients. Furthermore, these data support the use of high-resolution computed tomography as a measurement tool in therapeutic trials for cystic fibrosis patients, where the outcome measure is a slowing of progression of lung disease. Conversely, high-resolution computed tomography involves significant radiation exposure and in this era of prolonged patient survival in cystic fibrosis, the risk-benefit ratio for routine high-resolution computed tomography assessment needs to be more fully explored.

Figure 2. Patient with cystic fibrosis with improvement of lung function but detoriation of lung structure.



The top panels (a and b) show high-resolution computed tomography (HRCT) scan 1 in a patient of 10 yrs of age. Lung function (% predicted) is as follows: forced expiratory volume in one second (FEV_1) of 86, forced vital capacity (FVC) of 93, forced mid-expiratory flow (FEF_{25-75}) of 80, and FEV_1/FVC of 80. HRCT scores are: Castile 17, Brody 16, Helbich 9, Santamaria 10, and Bhalla 9. The lower panels (c and d) show HRCT2 at 13 yrs of age. Lung function (% pred) is: FEV_1 96, FVC 91, FEF_{25-75} 105, and FEV_1/FVC 90. HRCT scores are: Castile 22, Brody 17, Helbich 12, Santamaria 13, and Bhalla 12.

References

1. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34**: 228-231
2. Castile RG, Hayes JR, Flucke RL, Long FR, McCoy KS. Correlation of structural and functional abnormalities in the lungs of infants with cystic fibrosis. *Pediatr Pulmonol* 2000; **20**: A427
3. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**: 731-735
4. Helbich TH, Heinz-Peer G, Eichler I, et al Cystic fibrosis: CT assessment of lung involvement in children and adults. *Radiology* 1999; **213**: 537-544
5. Santamaria F, Grillo G, Guidi G, et al Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? *Pediatrics* 1998; **101**: 908-913
6. Bhalla M, Turcios N, Aponte V, et al Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**: 783-788
7. Jong de PA, Ottink MD, Robben SG, et al Computed tomography assessment of pulmonary disease in children with cystic fibrosis: various scoring system comparisons and bronchial and arterial measurements. *Radiology* 2004 (in press)
8. Quanjer PH, Borsboom GJ, Brunekreff B, et al Spirometric reference values for white European children and adolescents: Polgar revisited Pediatr Pulmonol 1995; **19**: 135-142
9. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**: 75-88
10. Zapletal A, Samanek M, Paul T. Lung Function in Children and Adolescents Methods, Reference Values. Basel, Karger, 1987
11. Merkus PJ, Tiddens HA, de Jongste JC. Annual lung function changes in young patients with cronic lung disease. *Eur Respir J* 2002; **19**: 886-891
12. 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
13. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimated risks of radiation induced fatal cancer from pediatic CT. *AJR Am J Roentgenol* 2001; **176**: 289-296

4.2 Computed tomography is more sensitive than pulmonary function tests for monitoring lung disease progression in children and adults with cystic fibrosis

Structural lung abnormalities in children with cystic fibrosis (CF) from a single CF centre could be more sensitively monitored with computed tomography (CT) compared to pulmonary function tests (PFTs). The aims of the study were to investigate whether CT scores would also be more sensitive than PFTs to monitor structural disease progression in adults with CF and to investigate whether previous results in children with CF could be reproduced. CT scans and PFTs were retrospectively studied in a cohort of CF-patients aged 5 to 52 years for whom 2 or 3 CT scans in combination with PFTs (FEV_1, FVC, FEV_1/FVC, MEF_{25}, MEF_{50}, RV, TLC and RV/TLC) with a 3-year interval between CT scans were available. All CT scans were scored by two observers. PFTs were expressed as percentage predicted and Z-score. The ethical review board of the hospital where the subjects were followed approved this retrospective study. Of 119 patients included, 92 patients had two and 24 had three CT scans. CT (composite and components scores) and PFTs both worsened significantly ($p<0.02$). However, peripheral bronchiectasis worsened most by 1.7% per year in children ($p<0.0001$) and by 1.5% per year in adults ($p=0.0003$). CT score and its components and PFTs showed similar worsening rates for adults and children ($p>0.09$). Peripheral bronchiectasis score was more sensitive than PFTs or composite CT score and other component scores for monitoring lung disease progression in this cohort of children and adults with CF.

Based on:

Pim A de Jong, Anders Lindblad, Lorenzo Rubin, Wim CJ Hop, Johan C de Jongste, Mela Brink, Harm AWM Tiddens. Computed Tomography Is More Sensitive than Pulmonary Function Tests for Monitoring Lung Disease Progression in Children and Adults with Cystic Fibrosis

Resubmitted to *Thorax*

Introduction

Patients with cystic fibrosis (CF) show progressive worsening in lung structure and function due to chronic infection and inflammation [1-3]. Pulmonary function tests (PFTs) are considered the gold standard for monitoring structural and functional changes [2]. It was found, however, that functional changes can be preceded by structural changes detected on computed tomography (CT) scans [4-8]. CT scoring systems can quantify structural abnormalities in CF in a reproducible fashion [5, 9-13]. A recent study in children from a single CF centre demonstrated that structural lung abnormalities were monitored more sensitively with composite CT scores compared to PFTs, with component CT scores for only bronchiectasis and mucous plugging being progressive and irreversible [6].

The first aim of the present study was to investigate whether CT scores would also be more sensitive than PFTs to monitor structural disease progression in adults with CF. The second aim was to investigate whether the results in children with CF could be reproduced. We hypothesized firstly that CT scores and PFTs would show worsening in adults with equal sensitivity, and secondly that in concordance with previous findings in children CT scores would show worsening whereas PFTs would remain stable.

Methods

Study population

Since 1997, the Swedish CF centre has added CT scans to PFTs in the annual check up for patients aged 5 years and older. The first CT scan was done when the patient obtained reliable PFT results, and CT scans were repeated every third year after. The annual check up was postponed if CF patients had an exacerbation, as evidenced by change in antibiotics regimen necessitated by acute worsening of CF lung disease. Therefore, CT scans and PFTs were performed only when patients were clinically stable. We included all routine CT scans up to April 2004. Patients were diagnosed as having CF when they had a positive sweat test and/or 2 known CF mutations. The cohort was divided in subjects ≤18 years at first scan (children) and >18 years (adults). Pancreatic status and prevalence of chronic Pseudomonas *aeruginosa* infection were assessed at first CT. Chronic Pseudomonas infection was defined as sputum or nasopharyngeal cultures positive for Pseudomonas at 2 or more occasions in 6 months. In all subjects cultures had been obtained monthly. The ethical review board of the hospital where the subjects were followed approved this retrospective study.

Lung structure

Lung structure was evaluated using CT scans. For children a single detector CT scanner (Philips LX, Philips Medical Systems, Best, Netherlands) was used from 1997

to 1999, and a multi-detector row (4 or 8 rows of detectors) CT scanner after 1999 (General Electric light speed ultra, GE Medical Systems, Milwaukee, WI). Scans were obtained using a beam current of 120 mA, an exposure time of 0.5 sec and a beam potential of 120 kV from lung apex to base at 15 mm intervals using 1.25 mm thick slices. For adults a PQ 6000 scanner (Picker International Inc., Highland Heights, OH) was used throughout the study period. Scans were obtained using a beam current of 160 mA, a 1 sec exposure time (160 mAs) and a beam potential of 120 kV from lung apex to lung base at 10 mm intervals using 1.5 mm thick slices.

All scans were reconstructed with a high-spatial frequency algorithm (bone), printed (window width 1400 Hounsfield Unit, window level –400 Hounsfield Unit), blinded to date and patient identification and scored in random order by two independent experienced observers using an adapted scoring system recently developed by Brody et al [13]. This scoring system evaluates the 5 lung lobes and the lingula as a sixth lobe for severity and extent of central and peripheral bronchiectasis, extent of central and peripheral mucous plugging, severity and extent of central and peripheral airway wall thickening, extent of opacities (atelectasis or consolidation) and extent of cysts and bullae. Hyperinflation (gas trapping) was excluded from scoring since not all scans had expiratory images and mosaic perfusion was scored instead. Ground glass pattern was not scored in this study. The maximum composite CT score without air trapping and ground glass pattern and with mosaic perfusion was 180 [13]. In addition, component CT scores were calculated by adding the component scores from the 6 lobes. Maximal component scores for central bronchiectasis, peripheral bronchiectasis, central mucus, peripheral mucus, central airway wall thickening, peripheral airway wall thickening, opacities, mosaic perfusion and cysts or bullae were 18. For statistical analysis the average composite CT score and component CT scores of both observers were expressed on a 0-100 scale (percentage of maximum possible score).

Lung function

Conventional PFTs were done using a dry rolling seal spirometer (MasterLab, Jaeger, Würzburg, Germany). Forced vital capacity (FVC), forced expiratory volume in the first sec (FEV_1), mid expiratory flow at 25% and 50% of VC (MEF_{25} and MEF_{50}), residual volume (RV) and total lung capacity (TLC) were expressed as percentage of predicted values and as Z-scores. The ratio between FEV_1 and FVC and between RV and TLC was calculated and expressed as a percentage, as percent predicted and as a Z-score. For children, prediction equations developed by Quanjer and colleagues [14] were used for FEV_1 and FVC and prediction equations developed by Zapletal and colleagues [15] were used for MEF_{25}, MEF_{50}, RV and TLC. For adults prediction equations from the European Respiratory Society [16] were used for all parameters. Spirometry (FEV_1, FVC, MEF_{25} and MEF_{50}) was done in all patients at each annual check-up. Plethysmography (RV and TLC) was done in 106 out of 119 (89%), 81 out of 92 (88%) and 21 out of 24 (88%) of the patients at the first, second and third check-up, respectively.

Statistical analysis

Interobserver agreement of composite and component CT scores was calculated using intraclass correlation coefficients. An intraclass correlation coefficient >0.8 represents good agreement. Systematic errors in component scores were detected using Bland and Altman plots that express the difference between two observers as a function of their mean [17]. Descriptive statistics for children and adults were calculated for the time of the baseline CT scan. For the purpose of this paper the term sensitivity was not used in the statistical sense but rather as a measure of the techniques' ability to track pulmonary disease progression in CF. We assumed that, on average, CF lung disease is progressive and that the method that detects the largest worsening can be considered the most "sensitive". Annual changes in CT composite score, CT component scores and PFTs over time were evaluated separately for children and adults using repeated measurements analysis of variance (RMANOVA). This analysis includes all measurements in the patients with one, two or three evaluations. Because distributions of MEF_{25} (Z-score) and MEF_{50} (Z-score) were not normal, we used percent predicted values transformed to a ^{10}logaritmic scale for analysis of MEF_{25} and MEF_{50}. For all other PFTs we found it more adequate to use Z-scores as these account for variability of test scores. A positive slope (annual change value) for CT score, RV, TLC and RV/TLC and a negative value for other PFTs indicates worsening of disease. Data are expressed as mean ± SD, and $p<0.05$ was considered significant.

Results

Study population

We included scans of 119 CF-patients, 72 children and 47 adults at the time of first scan. Two scans were available for 92 patients (53 children) and 24 patients had a third CT scan. Baseline characteristics are given in Table 1.

Reproducibility of the scoring system

Intraclass correlation coefficients (r-value) between both observers for CT score were: composite 0.92; bronchiectasis 0.88; opacities 0.80; mucous plugging 0.72; airway wall thickening 0.67; bulla and cysts 0.53 and mosaic perfusion 0.27. Bland and Altman plots evidenced no systematic errors in scoring between both observers for bronchiectasis and bulla or cysts. While for mosaic perfusion and mucous plugging observer 1 (PdJ) scored systematically higher than did observer 2 (LR), for airway wall thickening observer 2 scored higher than did observer 1.

Table 1 Patient characteristics at baseline for children and adults

	Children	Adults
Age (years)	11 ± 4	28 ± 8
Sex (male / female)	37/35	24/23
Pancreatic status (sufficient / insufficient)	11/61	14/33
Chronic Pseudomonas infection (yes / no)	14/58	18/29
FVC (% predicted)	97 ± 18	94 ± 19
FEV_1 (% predicted)	97 ± 21	78 ± 24
RV (% predicted)	98 ± 42	126 ± 47
TLC (% predicted)	95 ± 18	102 ± 12
MEF_{50} (% predicted)	96 ± 34	51 ± 30
MEF_{25} (% predicted)	84 ± 46	41 ± 33
FEV_1/FVC (%)	88 ± 9	70 ± 13
FEV_1/FVC (% predicted)	98 ± 10	84 ± 16
RV/TLC (%)	26 ± 11	33 ± 13
RV/TLC (% predicted)	104 ± 43	120 ± 42
Composite CT-score (points, %)	9 ± 11	17 ± 13

Data given are mean ± SD (standard deviation)

Sensitivity of CT and PFTs for children versus adults

Table 2 shows the slopes of the RMANOVA regression equations of CT and PFTs with age, representing annual changes in CT and PFTs. Interestingly, FEV_1 worsened by 0.07 Z-score in the children ($p=0.03$) and FEV_1/FVC worsened by almost 0.1 Z-score per year in both children ($p=0.002$) and adults ($p=0.02$). Also MEF_{25} and MEF_{50} worsened in children ($p=0.005$ and 0.006, respectively) and adults ($p=0.007$ and 0.005, respectively) and RV worsened in adults ($p=0.01$). All other PFTs remained unchanged ($p>0.07$). Composite CT scores and all CT components scores, except mosaic perfusion score in children and adults and peripheral mucous plugging score in adults, worsened significantly over time in children ($p<0.004$) and adults ($p<0.03$). The strongest worsening rate was observed for peripheral bronchiectasis score in children (1.7% per year, $p<0.0001$) and in adults (1.5% per year, $p=0.0003$). Slopes for none of the parameters did significantly differ between children and adults ($p>0.09$), but composite CT score and RV tended to worsen faster in adults relative to children.

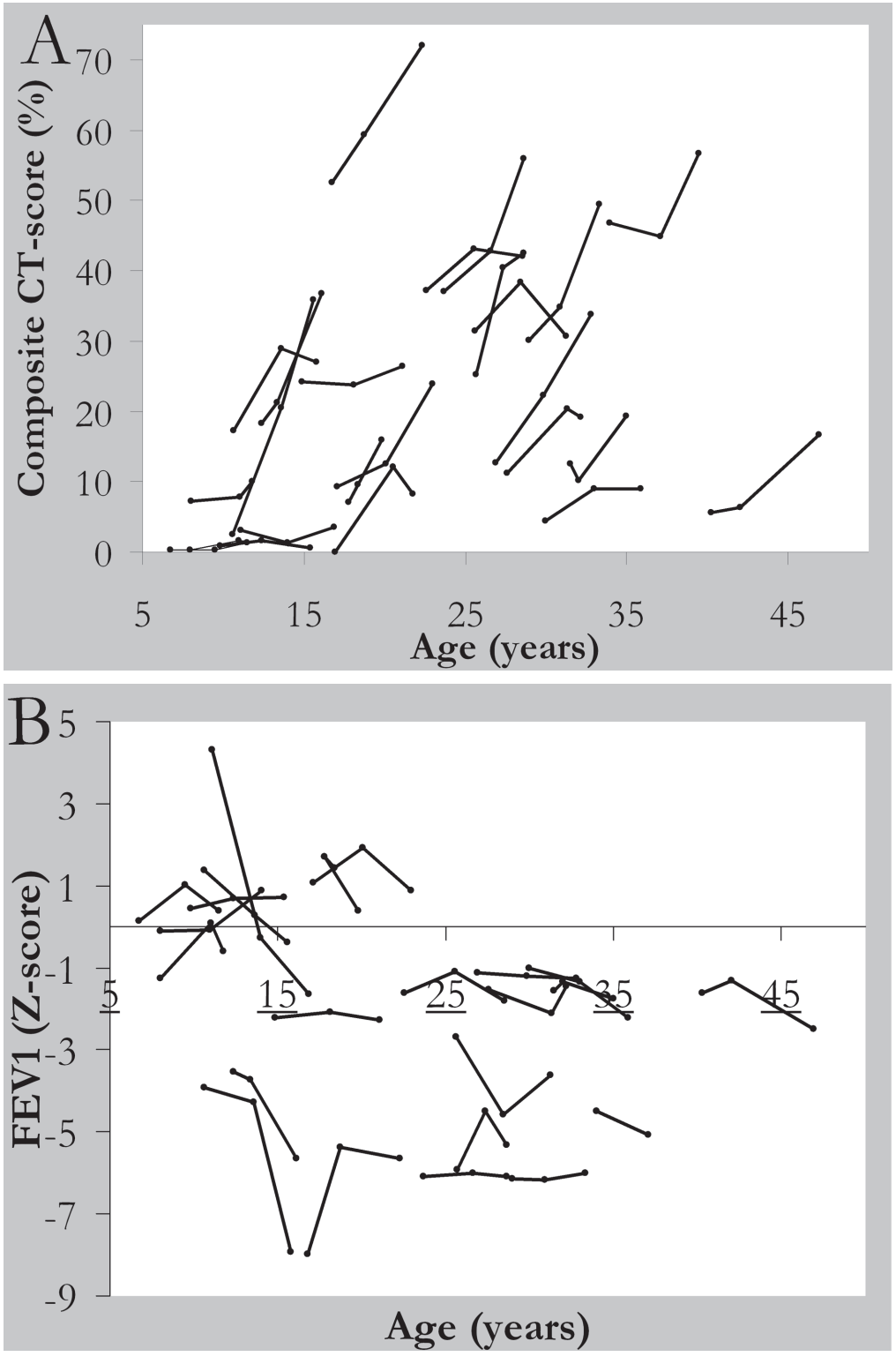
Table 2 Annual changes in pulmonary function test results and composite and component CT-scores in children and adults

	Children		Adults		Statistical difference between adults and children
	Change	**p-value**	**Change**	**p-value**	**p-value**
FVC (Z-score)	-0.0006	0.98	0.0051	0.88	0.89
FEV_1 (Z-score)	-0.0734	0.03	-0.0397	0.23	0.47
RV (Z-score)	0.0105	0.77	0.1025	0.01	0.09
TLC (Z-score)	-0.0028	0.89	0.0294	0.18	0.28
MEF_{50} (^{10}log%pred)	-0.0119	0.005	-0.0159	0.006	0.53
MEF_{25} (^{10}log%pred)	-0.0133	0.007	-0.0155	0.005	0.75
FEV_1/FVC (Z-score)	-0.0944	0.002	-0.0748	0.02	0.63
RV/TLC (Z-score)	0.0231	0.62	0.0763	0.07	0.39
Composite CT-score (%)	1.007	<0.0001	1.547	<0.0001	0.09
Central bronchiectasis (%)	1.253	0.0002	0.978	0.03	0.60
Peripheral bronchiectasis (%)	1.721	<0.0001	1.521	0.0003	0.66
Peripheral mucous plugging (%)	0.652	0.004	0.391	0.08	0.38
Central AWT (%)	1.389	0.0003	1.076	0.008	0.54
Peripheral AWT (%)	0.931	0.002	0.807	0.02	0.76
Opacities (%)	0.733	0.002	0.737	0.006	0.99
Mosaic glass pattern (%)	-0.354	0.58	0.264	0.38	0.38

Data were obtained using repeated measurement analysis of variance (RMANOVA). Lung structure or function = slope times age plus intercept. MEF_{50} and MEF_{25} (% predicted) were ^{10}log transformed. Being rare, central mucous plugging and bulla or cysts were excluded from analysis. Composite-score adapted from Brody et al [13]. AWT is airway wall thickening

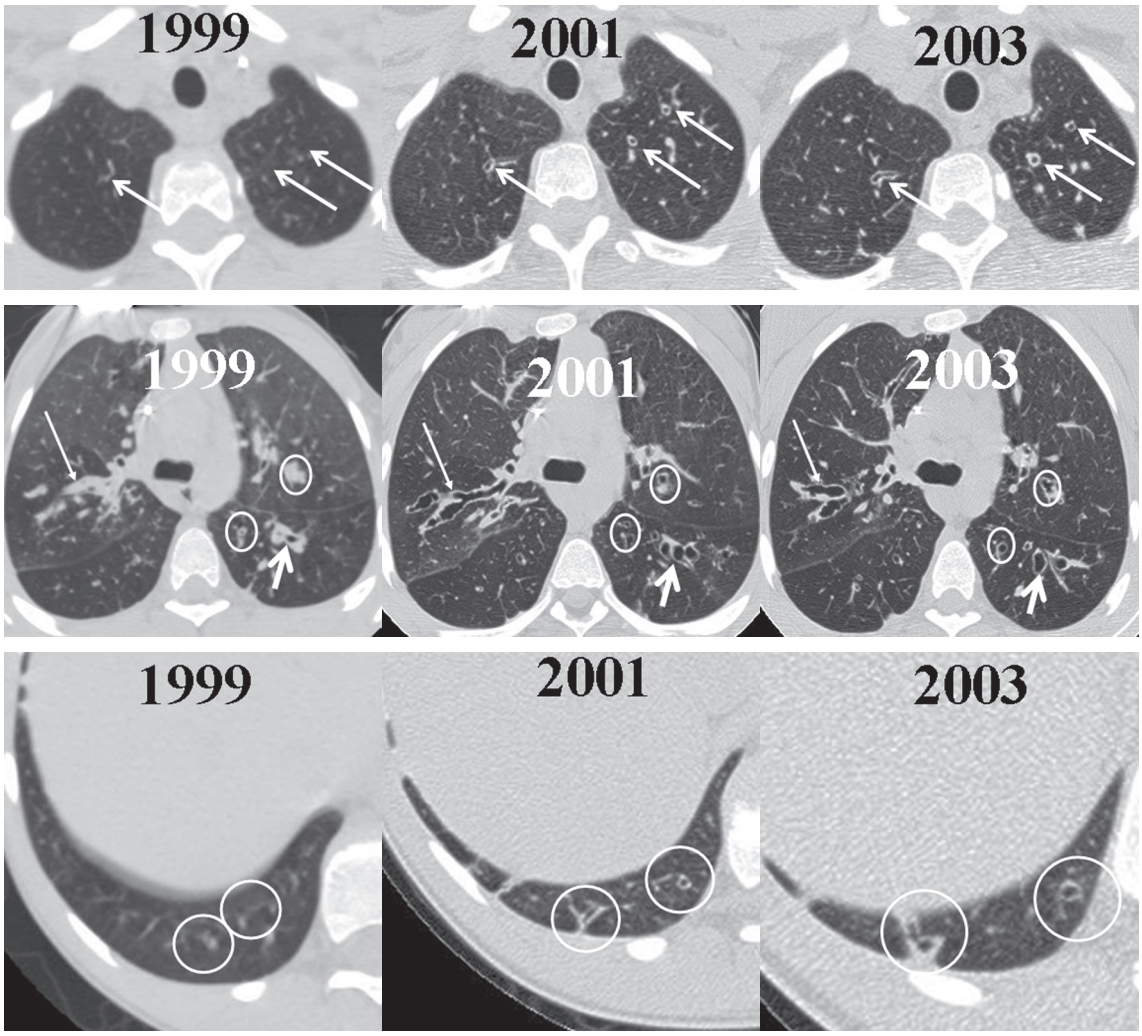
Figure 1 presents the changes over the three evaluations for composite CT score and FEV_1 in the 24 patients who had 3 scans. It is evident that for many patients composite CT score worsened while FEV_1 remained stable. Figure 2 gives an example of progression of structural abnormalities over 4 years despite stable lung function. Forty-six of the 92 patients in this study who had two CT scans (50%) demonstrated stable or improving FEV_1 over three years. Twenty-one of these (46%) showed simultaneously worsening in composite CT score up to 9 percent over three years. On the other hand, 42 (46%) of the patients showed stable composite CT scores over 3 years, 15 of whom (36%) showed worsening in FEV_1 up to 22% predicted over 3 years.

Figure 1 Changes in FEV_1 (a) and composite CT score (b) over 6 years in 24 patients who had three evaluations



Of the 24 patients most demonstrated a stable FEV_1 over six years while the composite CT score [13] demonstrated the expected disease progression.

Figure 2 Worsening of irreversible structural abnormalities and improvement in lung function parameters over 4 years in a patient with cystic fibrosis



Female CF patient, age at CT_1=9.5 years (1999 [I]), at CT_2 12.0 years (2001 [II]) and at CT_3 13.9 years (2003 [III]). Composite CT scores [13] worsened from 21 to 37 to 40. FEV_1 improved from 51 to 61 to 70 % predicted. FVC improved from 67 to 78 to 85 % predicted. FEV_1/FVC improved from 75 to 78 to 82 %. FEF_{25-75} improved from 11 to 14 to 20 % predicted. Arrows in the upper three images ($2a^{I-III}$) represent increase in severity of bronchiectasis and airway wall thickening in both upper lobes. Arrows in the middle three images ($2b^{I-III}$) show decrease in central mucous plugging and increase in size of central bronchiectasis. Encircled areas show decrease in central mucous plugging and an increase in the bronchiectatic size of the airway in the lower lobe. The encircled areas in the lower three images ($2c^{I-III}$) show increased number and size of peripheral bronchiectasis, although there was some motion artefact on the CT scan of 1999.

Discussion

In this retrospective clinical study we firstly hypothesized that in adults CT score and PFTs would be equally sensitive for monitoring structural disease progression. However, in disagreement with our hypothesis we found that peripheral bronchiectasis CT score (1.5% per year) and composite CT score (1.5% per year) showed more worsening than PFTs, and thus CT scoring is more sensitive than PFTs to monitor disease progression in adults.

Our second hypothesis was that in concordance with previous findings in children CT would show worsening while PFTs would remain stable [6]. In contrast to previous findings, however, we found that FEV_1 worsening (0.07 Z-score is approximately 1% predicted) equalled that of the component CT score. The peripheral bronchiectasis CT score nevertheless decreased 70% faster than did both the FEV_1 and the composite CT score. We feel, therefore, that CT in this cohort of children CT was more sensitive than PFTs to detect disease progression, even if this was not reflected in the composite CT score.

There are two possible explanations why the peripheral bronchiectasis CT scores worsened faster than the composite CT scores in the children but not in the adults. First, potentially reversible abnormalities, such as mucous plugging [18, 19], airway wall thickening and mosaic perfusion, might have been more reversible in the children. This would lead to less change over time in the partly reversible composite CT score in relation to the irreversible bronchiectasis CT score. Second, changes in airway wall thickening and mosaic perfusion were more subtle in the children and therefore more difficult to score. Less reproducible scoring of these abnormalities could have introduced more noise and subsequently have reduced the ability to detect disease progression in the children's composite CT scores.
The most likely explanation for discrepancies in PFT findings between this cohort and the previously published cohort is duration of follow-up. The latter was followed for 2 years only, the former for up to 6 years. Furthermore there might be differences between CF centres and between patient populations.

We can only speculate why composite CT scores in the children in this study worsened similarly to PFTs. As the children in the previous study had on average more advanced disease (lower PFTs at baseline), the CT abnormalities might have been less reversible and could therefore have been scored more reproducibly as discussed previously. On the other hand, while in the present study CT images were acquired at 15 mm intervals, the previous study obtained them at 10 mm intervals. As CF airway disease starts heterogeneous, the greater interval between images is likely to have resulted in less sensitive composite CT scores in this study.

Overall, the major finding of this study is that both in children and adults CT was more sensitive than PFTs in monitoring CF lung disease progression, with the peripheral bronchiectasis CT score as the most sensitive parameter. For several reasons the latter is an attractive outcome parameter, both clinically and in trials. First, bronchiectasis can be evaluated relatively easily on CT, witness the good interobserver agreement in this and other studies [5, 13]. Second, while bronchiectasis is argued to be reversible in other diseases [20, 21], it is an irreversible feature in CF [6]. Third, we believe that airway wall thickening (related to airway inflammation), mucous plugging and consolidations all are risk factors for the development of bronchiectasis and bronchiectasis is therefore a highly relevant 'end stage' feature of CF lung disease.

There are several reasons why PFTs worsened less than bronchiectasis on CT. First, PFTs have a high noise to signal ratio and Z scores or percent-predicted values are calculated using reference equations based on a large population. Second, CT can clearly demonstrate focal areas of bronchiectasis that can be scored reproducibly, whereas PFTs values can fluctuate for reasons other than structural airway damage, such as viral infections and patient effort. That PFTs and CT measure different aspects of CF lung disease is also reflected by our observation that composite CT scores worsened in 46% of the patients with stable or improving PFTs. In addition, PFTs worsened in 36% of the patients with stable composite CT score. This discrepancy between lung function and CT findings supports the view that both are needed to adequately determine the state of CF related lung disease. The bronchiectasis CT score appeared to be more sensitive than lung function to monitor disease progression, both in children and adults.

The PFTs findings in this study warrant further consideration. First, we found a significant worsening in MEF_{25} and MEF_{50}, which may be consistent with early lung disease [7]. Unfortunately, MEF_{25} and MEF_{50} have a relative large standard deviation, and changes in Z-scores, that we could not use in this study, may not have been significant. Second, the FEV_1/FVC-ratio changed significantly. Although this parameter is usually not included in the analysis of large clinical trials in CF [22-25], our findings suggest that it may be a relatively sensitive PFT measurement in CF.

Expectedly, the adults in this study were a selected group of long term survivors. Accordingly, the proportion of pancreatic sufficient patients in adults was higher than that in children.

Our study is limited by the fact that we did not evaluate air or gas trapping, while this is an early marker of CF lung disease [13, 26-28]. The sensitivity of this CT abnormality to track disease progression in CF is at present unknown which requires further study.

In conclusion, this study shows in adults and children with CF that routine CT scans worsened while PFTs remained unchanged or worsened less. The CT worsening was

best reflected in peripheral bronchiectasis CT score, which can be scored reproducibly and is irreversible in CF. Our findings indicate that a composite CT score may be less useful than a peripheral bronchiectasis CT score since a composite CT score consists of reversible and irreversible components, and not all components were scored reproducibly in this study. Therefore peripheral bronchiectasis CT score is important to monitor CF patients clinically and it may gain an important role as an outcome parameter in clinical studies in CF.

References

1. Tiddens HA, Koopman LP, Lambert RK, Elliott WM, Hop WC, van der Mark TW, et al. Cartilaginous airway wall dimensions and airway resistance in cystic fibrosis lungs. *Eur Respir J* 2000; **15**(4): 735-42.
2. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **168**(8): 918-51.
3. Tiddens H, Silverman M, Bush A. The role of inflammation in airway disease: remodeling. *Am J Respir Crit Care Med* 2000; **162**(2 Pt 2): S7-S10.
4. Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. *J Thorac Imaging* 1996; **11**(1): 27-38.
5. de Jong PA, Ottink MD, Robben SG, Lequin MH, Hop WC, Hendriks JJ, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2): 434-9.
6. de Jong PA, Nakano Y, Lequin MH, Mayo JR, Woods R, Paré PD, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1): 93-7.
7. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34**(3): 228-31.
8. De Jong PA, Nakano Y, Hop WC, Long FR, Coxson HO, Paré PD, et al. Changes In Airway Dimensions on Computed Tomography Scans of Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 2005.
9. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**(3): 783-8.
10. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**(10): 731-5.
11. Helbich TH, Heinz-Peer G, Fleischmann D, Wojnarowski C, Wunderbaldinger P, Huber S, et al. Evolution of CT findings in patients with cystic fibrosis. *AJR Am J Roentgenol* 1999; **173**(1): 81-8.
12. Santamaria F, Grillo G, Guidi G, Rotondo A, Raia V, de Ritis G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest Be obtained? *Pediatrics* 1998; **101**(5): 908-13.
13. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: Distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr* 2004; **145**(1): 32-38.
14. Quanjer PH, Borsboom GJ, Brunekreff B, Zach M, Forche G, Cotes JE, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995; **19**(2): 135-42.
15. Zapletal A, Samanek M, Paul T. Lung Function in Children and Adolescents. Methods, Reference Values. Basel: Karger; 1987.

16. European Respiratory Society. Standardized lung function testing. *Eur Respir J* 1993; **6**(suppl. 16): 5-40.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**(8476): 307-10.
18. Robinson TE, Leung AN, Northway WH, Blankenberg FG, Bloch DA, Oehlert JW, et al. Spirometer-triggered high-resolution computed tomography and pulmonary function measurements during an acute exacerbation in patients with cystic fibrosis. *J Pediatr* 2001; **138**(4): 553-9.
19. Shah RM, Sexauer W, Ostrum BJ, Fiel SB, Friedman AC. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation. *AJR Am J Roentgenol* 1997; **169**(2): 375-80.
20. Gaillard EA, Carty H, Heaf D, Smyth RL. Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. *Eur J Radiol* 2003; **47**(3): 215-20.
21. Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosibronchiectasis in childhood. *Thorax* 2004; **59**(4): 324-7.
22. Quan JM, Tiddens HA, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, et al. 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**(6): 813-20.
23. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994; **331**(10): 637-42.
24. Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993; **328**(24): 1740-6.
25. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995; **332**(13): 848-54.
26. Dorlochter L, Nes H, Fluge G, Rosendahl K. High resolution CT in cystic fibrosis-the contribution of expiratory scans. *Eur J Radiol* 2003; **47**(3): 193-8.
27. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123**(5): 1655-63.
28. Robinson TE, Leung AN, Northway WH, Blankenberg FG, Chan FP, Bloch DA, et al. Composite spirometric-computed tomography outcome measure in early cystic fibrosis lung disease. *Am J Respir Crit Care Med* 2003; **168**(5): 588-93.

4.3 Changes in airway dimensions on computed tomography scans of children with cystic fibrosis

In cystic fibrosis (CF), chronic bacterial infection and inflammation lead to progressive airway wall thickening and lumen dilatation. We aimed to quantify airway wall thickening and lumen dilatation in children with CF over a 2-year interval. Children with CF (n = 23) who had two computed tomography (CT) scans (CT_{cf1} and CT_{cf2}) combined with pulmonary function tests (PFTs), with a 2-year interval between measurements, were compared with control subjects (n = 21) who had one CT ($CT_{controls}$). On cross-sectional cut airway–artery pairs, airway wall area (WA), airway lumen area (LA) and perimeter, and arterial area (AA) were quantified. LA/AA (= marker of bronchiectasis), airway wall thickness (AWT), and WA/AA (= markers of wall thickness) were calculated. CT scans were scored using four different scoring systems. PFTs were expressed as percent predicted. Airway WA-to-AA ratio was 1.45 ($p < 0.001$) and airway LA-to-AA ratio was 1.92 times higher ($p < 0.001$) in children with CF compared with agematched control subjects. LA/AA and WA/AA remained unchanged from CT_{cf1} to CT_{cf2} and did not increase with age. AWT as a function of airway size increased from CT_{cf1} to CT_{cf2} by 2% (0.03 mm; $p = 0.02$). The change in AWT was inversely related to the change in forced expiratory flow between 25 and 75% of expiratory VC ($p = 0.002$). In conclusion, in CF, quantitative measurements of airways on CT scans show an increased ratio between airway LA and AA and progressive airway wall thickening. Scoring systems show progression of bronchiectasis but unchanged AWT. PFTs remained stable.

Based on:

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Introduction

Chronic bacterial infection and an excessive neutrophil-mediated inflammatory response are important characteristics of pulmonary disease in cystic fibrosis (CF) [1]. These processes lead to structural damage of the airways, including wall thickening and lumen dilatation [2, 3]. At birth, airway dimensions are believed to be normal [3], but structural abnormalities develop early in life and are progressive [4, 5]. Quantitative measurement of airway dimensions could be a sensitive and relevant endpoint for clinical management and for therapeutic interventions in CF related lung disease. Airway abnormalities can be assessed in a reproducible fashion using computed tomography (CT) scoring systems [6–9]. Previous studies using these scoring systems have shown that bronchiectasis together with mucus plugging are the most sensitive components of CF lung disease [4, 10]. Hence, CT scoring systems have been shown to be more sensitive for the detection of airway abnormalities in patients with CF between 5 and 28 years old when compared with conventional pulmonary function tests (PFTs) [4, 10–13]. Similarly, plain chest radiographs were found to be more sensitive than PFTs for patients aged between 0.5 months and 43 years [6, 14–18]. Furthermore, airway wall thickening and mucus plugging, as can be observed on CT scans, was found to be reversible with antibiotic therapy in two studies of patients with CF with ages ranging from 19 to 43 and 9 to 33 years [19, 20]. In diseases like asthma and chronic obstructive pulmonary disease, airway wall thickness (AWT) is related to airway inflammation [21].

A disadvantage of present scoring systems is that the total scores are a composite of various structural abnormalities, including the following: bronchiectasis, airway wall thickening, mucus plugging, mosiac perfusion, atelectasis, consolidation, bulla and cysts, acinar nodules, alveolar consolidation, emphysema, air trapping, overinflation, septal thickening, ground glass opacities, and sacculations or abcesses. The composite CT score makes it difficult to discern the most important structural change in individual patients. In addition, the sensitivity of scoring systems to detect small changes in luminal dilatation and AWT is unknown. Quantitative measurements of airway dimensions have been developed and applied in chronic obstructive lung disease [22, 23]. Therefore, a quantitative measurement of AWT and lumen dilatation could be an important addition to the time-consuming and subjective scoring systems. Although semiautomated airway measurements are still relatively time consuming, software is in development that will allow airways to be measured substantially faster in the near future.

We hypothesized that children with CF have thicker airway walls and more dilated lumens than control subjects and that airway wall thickening and bronchial dilatation would be progressive over 2 years in CF. To test this hypothesis, airway wall and lumen dimensions and dimensions of the accompanying pulmonary artery were

measured on CT using an image analysis system that can measure airways with lumen diameter of 1 mm and above [22, 23]. Some of the results of these studies have been previously reported in the form of an abstract [24].

Methods (The full Methods is a supplement at the end of this chapter)

Study population

CF. Children with CF who had two biennial routine CT scans (CT_{cf1} and CT_{cf2}), during a clinically stable period, in combination with two PFTs (PFT_{cf1} and PFT_{cf2}) were included in this study.

Control. Control subjects were patients without a diagnosis of heart or chronic lung disease who had a thin-slice thoracic CT scan ($CT_{controls}$) performed for a variety of clinical indications (Table 1). The lungs of the control subjects were normal as assessed by the radiologists. Additional details of the study population are provided in an online supplement. The ethical review boards of Erasmus MC/Sophia (Rotterdam, the Netherlands) and Columbus Children's Hospital (Columbus, OH) approved this study.

Table 1 Diagnosis of control subjects

Clinical diagnosis	Reason for CT scan	Findings	Number Of Subjects
Osteochondrosarcoma (1), rhabdomyosarcoma (1), hepatoblastoma (1)	Lung metastasis?	No metastasis	3
Recovered spontaneous pneumothorax	Subpleural blebs?	No blebs	3
Solitary nodule	Follow-up scan	No nodule	3
Chest pain (later diagnosed as reflux)	Lung abnormalities?	Normal lungs	2
Chest wall mass: undefined (1) and osteochondritis (1)	Exact localization and extension	Extra pulmonary mass	2
Recurrent sinusitis	Lung involvement?	Normal lungs	2
Mitochondrial disease	Lung abnormalities?	Normal lungs	1
Aspiration	Foreign body?	No foreign body	1
	Vascular ring?	No vascular ring	1
Lupus like syndrome	Lung involvement?	Normal lungs	1
Pneumonia's in history	Bronchiectasis?	Normal lungs	1
Small pulmonary hemorrhage	Follow-up scan	No hemorrhage	1

CT Scans

CF. CT scans were acquired using 1-mm-thick images and 10-mm intervals from lung apex to base during full-suspended inspiration. CT images were archived and printed on film blinded for patient name, age, and date of the scan.

Control. Volumetric CT scans were obtained from lung apex to base during suspended full inspiration and reconstructed at 1.25-mm thick slices.

CT Scoring

CF. All printed scans were scored using scoring systems published by Bhalla and coworkers [6], Brody and coworkers [7], Helbich and coworkers [8], and Santamaria and coworkers [9] in random order by a single experienced observer.

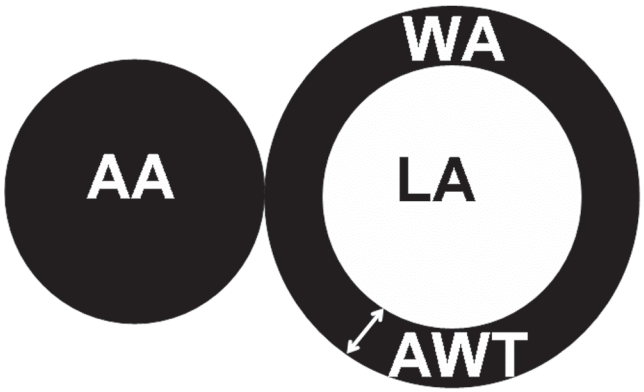
Inspiration during CT Scanning

Lung volume during CT scanning was estimated using a previously described method [25, 26] and expressed as a percentage of predicted total lung capacity (TLC) [27].

Quantitative Analysis of Airways and Arteries

Airway–artery pairs were measured using a previously described method [22, 23]. The following dimensions were measured: airway wall area (WA), airway lumen area (LA), airway lumen perimeter (Pi), and arterial area (AA; *see* Figure 1). AWT and WA/AA were used as markers of airway wall thickening and LA/AA as a marker of bronchial dilatation. Two observers measured 86 randomly selected airway–artery pairs, and one observer remeasured the same airway–artery pairs after 3 months to determine inter- and intraobserver variability. Two observers matched cross-sectioned airway–artery pairs on CT_{cf1} and CT_{cf2}. The matched airway–artery pairs in subjects with CF and all visible cross-sectioned airway–artery pairs in control subjects were measured by one observer.

Figure 1 Airway-artery dimensions



AA = arterial area
LA = airway lumen area
WA = airway wall are
AWT = airway wall thickness (AWT = 2 * square root ((LA + WA) / pi) - 2 * square root (LA / pi))

PFTs

CF. The following lung function parameters were measured and expressed as percent predicted: FEV_1 [28], FVC [28], forced expiratory flow between 25 and 75% of expiratory VC ($FEF_{25–75}$) [29], airway resistance (R_{aw}) [27], residual volume (RV) [27], and TLC [27]. Two ratios were calculated and expressed as a percentage: RV/TLC% and FEV_1/FVC%. Two patients were too young to perform spirometry at the time of the first scan.

$FEF_{25–75}$ was measured in 16 and R_{aw}, RV, and TLC were measured in 18 of 23 children.

Statistical Analysis
A p value of less than 0.05 was considered significant, and data are presented as mean ± SD (range).

Comparison with Published Data
We employed the methods described in this manuscript on infant data which has been previously published by Long *et al.* to enable comparison between children and infants [5].

Results

Study Population
The age of the 23 children with CF (12 male) at CT_{cf1} was 11.1 ± 3.7 (4.0–15.9) years, and at CT_{cf2}, 12.9 ± 3.7 (6.2–17.9) years. The age of the 21 (11 male) control subjects was 11.6 ± 4.7 (3.6–17.2) years. The height of the 23 children with CF at CT_{cf1} was 147 ± 16 (122–174) cm, and at CT_{cf2}, 155 ± 16 (130–180) cm. The height of the 21 control subjects was 144 ± 25 (99–181) cm. PFTs and CT scores at CT_{cf1} of children with CF are shown in Table 2.

Inspiration during CT
There was no significant difference between the lung volume measured on CT_{cf1} (61.7 ± 11.1% predicted TLC) and CT_{cf2} (63.6 ± 8.7% predicted TLC, $p = 0.6$) and CT_{cf1} and $CT_{controls}$ (56.2 ± 21.4% predicted TLC, $p = 0.2$), but it did show a trend toward a higher lung volume in CT_{cf2} compared with $CT_{controls}$ ($p = 0.08$). CT estimated gas volume was 2,429 ± 1,211 (506–5,533), 2,327 ± 787 (1,037–3,606), and 2,823 ± 1,038 (1,111–4,785) ml for $CT_{controls}$, CT_{cf1}, and CT_{cf2}, respectively.

Quantitative Analysis of Airways and Arteries
In children with CF, 619 airway–artery pairs were matched. Mucus plugs were observed in 49 airways on CT_{cf1} and in 127 airways on CT_{cf2}. Therefore, more airways were excluded for analysis on CT_{cf2} (20.5%) versus CT_{cf1} (7.9%), and 443 airway–artery pairs were measured on CT_{cf1} as well as on CT_{cf2}. In the control subjects, 397 airway–artery pairs were measured, and no mucus plugs were observed.

Table 2 Lung function test results and thin section CT scores at time of CT_{cf1} and changes over the study period in children with CF

	PFT_{cf1} and CT_{cf1} Mean ± SD (range)	**Difference (CT_{cf2} to CT_{cf1}) Or (PFT_{cf2} to PFT_{cf1})** Mean ± SD (range)	**P-value**
FEV_1 (%pred)	71 ± 16 (37 to 110)	+ 5 ± 15 (-15 to 40)	0.25
FVC (%pred)	83 ± 16 (48 to 110)	+ 3 ± 14 (-19 to 32)	0.48
FEF_{25-75} (%pred)	54 ± 29 (22 to 132)	- 7 ± 16 (-26 to 80)	0.26
FEV_1/FVC (%)	74 ± 8 (57 to 90)	+ 3 ± 6 (-6 to 20)	0.06
R_{aw} (%pred)	137 ± 72 (57 to 355)	+ 6 ± 57 (-87 to 170)	0.98
RV (%pred)	129 ± 38 (47 to 189)	- 12 ± 29 (-67 to 40)	0.12
TLC (%pred)	97 ± 13 (75 to 118)	+ 1 ± 11 (-19 to 24)	0.91
RV/TLC (%)	32 ± 10 (14 to 60)	- 12 ± 22 (-13 to 6)	0.03
Brody (points)	12 ± 8 (1 to 31)	+ 4 ± 5 (-5 to 18)	0.002
Helbich (points)	8 ± 3 (3 to 15)	+1 ± 2 (-2 to 4)	0.01
Santmaria (points)	9 ± 3 (3 to 16)	+1 ± 2 (-3 to 4)	0.02
Bhalla (points)	8 ± 3 (3 to 15)	+ 1 ± 2 (-1 to 4)	0.005
Bronchiectasis* (points)	1.1 ± 1.1 (0 to 3)	+0.4 ± 0.6 (0 to 2)	0.007
Airway wall thickening* (points)	1.0 ± 0.2 (0 to 1)	+0.04 ± 0.2 (0 to 1)	0.32
Mucous plugging* (points)	1.8 ± 0.9 (0 to 3)	+ 0.3 ± 1.0 (-2 to 2)	0.15

SD is Standard Deviation. P-values are obtained with Wilcoxon Signed Rank test. * Bronchiectasis, airway wall thickening and mucous plugging scores given are obtained using the scoring system of Brody et al [7]

Reproducibility of airway measurements. No systematic intra- or interobserver differences in measurements were observed. Intraclass correlation coefficients for intra- and interobserver variability for WA and LA were greater than 0.99 and greater than 0.97 and greater than 0.99 and greater than 0.98, respectively. The mean interobserver difference was 0.78 ± 3.6% (-10 to 15%) for LA and 0.87 ± 3.2% (-10 to 11%) for WA. The mean intraobserver difference was -0.17 ± 2.2% (-5 to 6%) for LA and 1.02 ± 3.9% (-8 to 12%) for WA. Differences expressed as a percentage decreased with increasing airway size.

Airway lumen dilatation. Figure 2 shows the relation between airway lumen–artery dimensions and age for the children of the present study and the infants of Long and coworkers [5]. The regression equations for these relations are given in Table 3. LogLA/AA showed no significant relationship with age for children with CF (CT_{cf1}, CT_{cf2}) and control subjects ($p > 0.31$). Intercepts for logLA/AA versus age were significantly ($p < 0.0001$) higher for children with CF (CT_{cf1}, CT_{cf2}) relative to control subjects. LA/AA was 1.92 times higher in children with CF compared with control subjects. There was no difference in intercept between CT_{cf1} and CT_{cf2}. The data of Long and coworkers [5] in infants showed that the mean airway lumen/artery ratio between infants with CF and control subjects increased from 0.92 at age 1 month to 1.60 at age 5 years ($p = 0.02$).

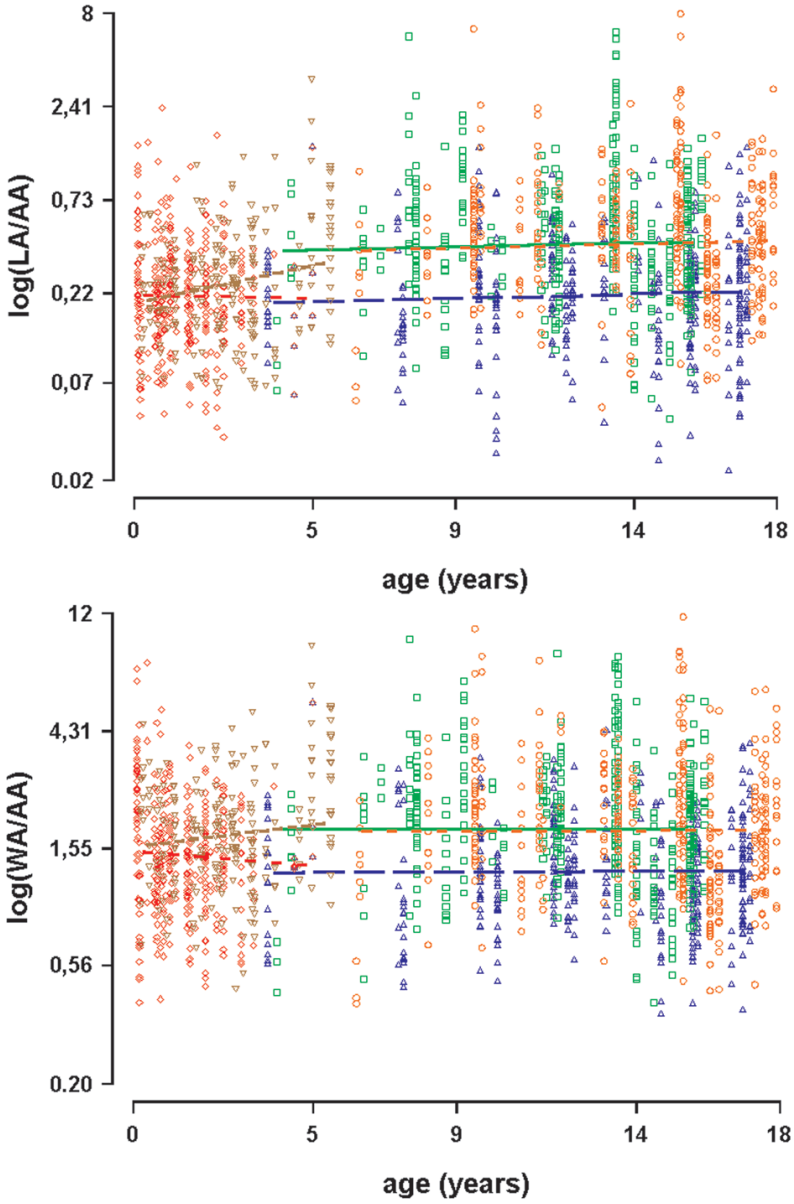
AWT. Figure 2 shows the relation between airway wall–artery dimensions and age for the children of the present study and the infants of Long and others [5]. The regression equations for these relations are given in Table 3. LogWA/AA showed no significant relationship with age for the children with CF (CT_{cf1}, CT_{cf2}) and control subjects ($p > 0.31$). Intercepts for logWA/AA versus age ($p < 0.0001$) were significantly higher for children with CF (CT_{cf1}, CT_{cf2}) relative to control subjects. WA/AA was 1.45 times higher in children with CF compared with control subjects. There was no difference in intercept between CT_{cf1} and CT_{cf2}. The data of Long and coworkers [5] in infants showed that the mean airway wall/artery ratio between infants with CF and control subjects increased from 1.05 at age 1 month to 1.46 at age 5 years ($p = 0.02$). Figure 3 shows the relation between logAWT and logPi (perimeter). The regression equations of these correlations are given in Table 3. LogAWT (Figure 3) showed a significant correlation with logPi ($p = 0.001$). The slope was not significantly different for CT_{cf1} versus CT_{cf2} ($p = 0.16$). The intercept was significantly higher ($p = 0.02$) for CT_{cf2} relative to CT_{cf1}. The difference in intercept was 2%, which corresponds to 0.03 mm.

Table 3 Regression equations of the relationships between airway-artery dimensions and age and airway size for children (present study) and infants (Long et al [5])

	Control subjects		CT_1		CT_2	
	A	**b**	**A**	**b**	**A**	**b**
Children						
Log LA/AA vs age	0.004793	-0.7275	0.004793	-0.4428	0.004793	-0.4490
Log WA/AA vs age	0.000475	0.0981	0.000475	0.2623	0.000475	0.2513
Log AWT vs Pi			0.2772	-0.877	0.2851	-0.8676
Infants						
Log LA/AA vs age	-0.00335	-0.6673	0.04206	-0.7111		
Log WA/AA vs age	-0.01114	0.1809	0.01647	0.1987		

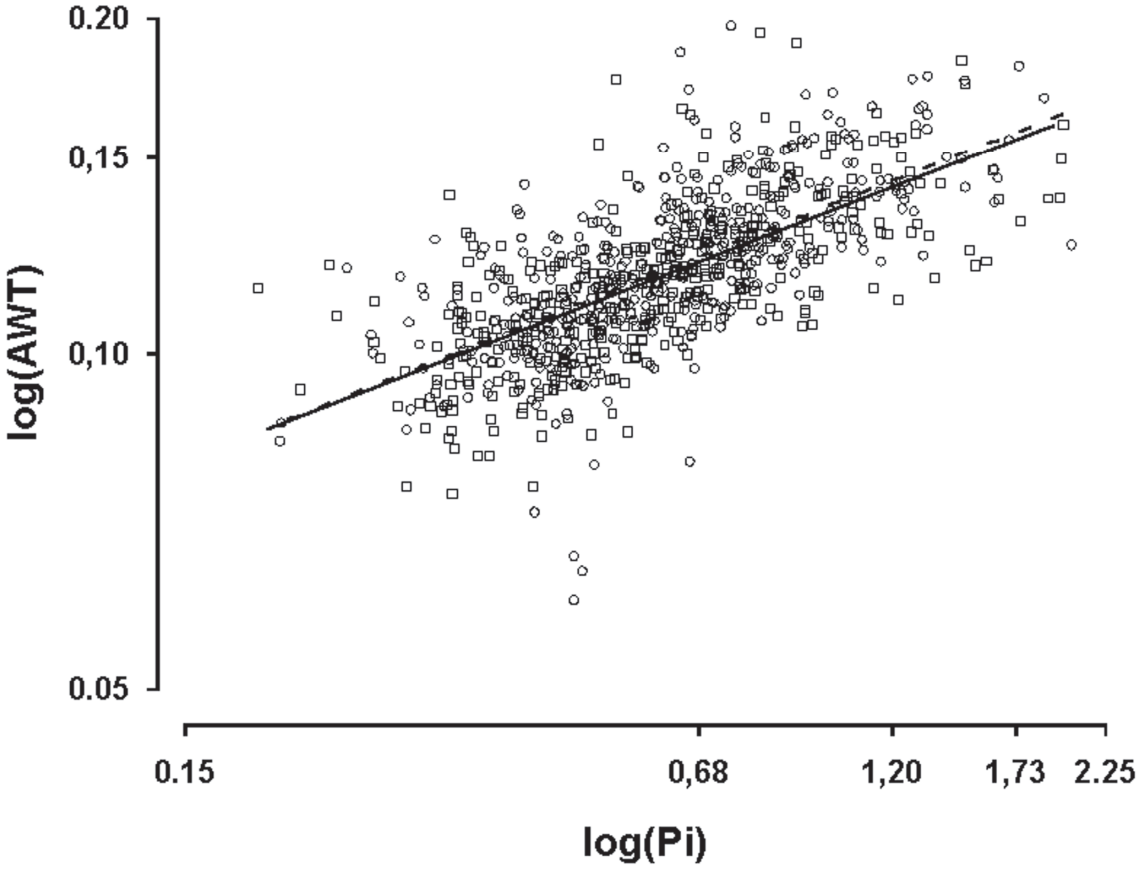
Regression lines ($logX = A * age + b$ and $logX = A * logPi + b$) are calculated with repeated measurement analysis of variance (RMANOVA). A represents the slope and b the intercept of the regression. Infant data are re-analyzed airway-artery pairs in 34 infants with CF and 20 control infants published by Long et al [5].

Figure 2 Relationship of airway-artery ratio and age for children with CF and control subjects in the present study and for infants studied by Long et al [5]



Δ $CT_{controls}$ children, □ CT_{cf1}, ○ are CT_{cf2}, ∇ infants with CF, ◊ control infants. Regression lines are -- -- -- for control children, -- -- -- for CT_{cf1} and - - - - for CT_{cf2}. Regression lines are - - - - for infants with CF and -- -- -- for control infants. Regression lines are calculated with repeated measurement ANOVA method (see Table 3). Regression lines for LA/AA for CT_{cf1} and CT_{cf2} overlap. The regression line for LA/AA for children is 1.9 times higher for CF compared to control subjects. Regression lines for WA/AA for CT_{cf1} and CT_{cf2} overlap. The regression line for WA/AA for children is 1.4 times higher for CF compared to control subjects.

Figure 3 Relationships of airway wall thickness of children with CF against airway lumen perimeter



Open circles (○) are CT_{cf1} and open squares (□) are CT_{cf2}. Regression lines are for CT_{cf1} and - - - - for CT_{cf2}. Regression lines for CT_{cf1} and CT_{cf2} almost overlap. Airway wall thickness (AWT) and airway lumen perimeter (Pi) are given in centimeters and displayed on a logarithmic scale. Regression lines are calculated with repeated measurement ANOVA method (see Table 3). Airway walls at CT_{cf2} are 2% or 0.03 mm thicker than at CT_{cf1} (p=0.02). The increase in AWT correlated with the decrease in FEF_{25-75} % predicted (p=0.002).

Airway–artery dimensions, CT scores, lung function. LA/AA correlated ($p < 0.01$) and WA/AA did not correlate ($p > 0.25$) with CT scores (Bhalla, Helbich, Santamaria, Brody). LA/AA and WA/AA did not correlate significantly ($p > 0.12$) with PFTs (FEV_1, FVC, $FEF_{25–75}$, FEV_1/FVC, R_{aw}, RV, TLC, RV/TLC). For all comparisons, there were no differences between CT_{cf1} and CT_{cf2}.

Changes in airway–artery dimensions, CT scores, CT component scores, and lung function. The change in AWT (ΔAWT) showed a significant negative correlation with the change in $FEF_{25–75}$ ($p = 0.002$) in the 15 children who were able to perform spirometry and for whom we could calculate percent-predicted values for the $FEF_{25–75}$. For each 0.01 mm increase in AWT, the $FEF_{25–75}$ decreased by 0.45% predicted. Changes in the other airway parameters (ΔLA/AA and ΔWA/AA) did not correlate significantly with changes in lung function tests (ΔFEV_1, ΔFVC, $\Delta FEF_{25–75}$,

$\Delta FEV_1/FVC$, ΔR_{aw}, ΔRV, ΔTLC, ΔRV/TLC) or changes in CT scores (ΔBhalla, ΔHelbich, ΔSantamaria, ΔBrody). Changes in bronchiectasis (Δbronchiectasis score) and airway wall thickening scores (ΔAWT score) did not correlate significantly with changes in FEV_1 (ΔFEV_1, $p = 0.47$) or changes in $FEF_{25–75}$ ($\Delta FEF_{25–75}$, $p = 0.11$).

All CT scores worsened significantly over time ($p < 0.02$). Mean changes expressed as percentage of the maximal possible scores were 4, 4, 3, and 4% for Brody, Helbich, Santamaria, and Bhalla, respectively. Of the CT component scores, only the bronchiectasis score worsened significantly ($p = 0.007$), whereas all other component scores remained unchanged ($p > 0.15$; *see* also Table 2). Most PFTs (FEV_1, FVC, $FEF_{25–75}$, FEV_1/FVC, R_{aw}, RV, TLC) remained unchanged with time ($p > 0.06$). Only RV/TLC% improved significantly ($p = 0.03$) by -12% over the 2-year interval (*see* Table 2).

Discussion

This longitudinal study aimed to compare airway wall and lumen dimensions on CT scans of children with CF with those of control subjects and to examine changes in these measures over a 2-year interval in CF. We hypothesized that children with CF would have thicker airway walls and more dilated lumens than control subjects and that airway wall thickening and airway dilatation would be progressive over 2 years in children with CF. To test the hypothesis, dimensions of airway wall and lumen and accompanying pulmonary artery were measured.

The most striking finding of our study was that the mean airway lumen-to-artery ratio was almost double in children with CF compared with control subjects. This increased ratio can be caused by dilatation of the airway and/or by a reduction in size of the accompanying artery. The ratio did not show an increase with age in control subjects or children with CF and remained unchanged over 2 years in CF. This result contrasts with a recent publication that showed a significant increase with age in the airway lumen-to-artery ratio of infants with CF [5]. Therefore, we remeasured that cohort using our method. The reanalysis showed that the airway lumen–artery ratio in infants increased from 0.92 at age 1 month to 1.6 at age 5 years. This suggests progressive bronchial and/or arterial disease in the infants. Beyond age 5, there was a flattening of the curve in children for which several explanations are possible. First, bias could have been introduced by the exclusion of more mucus-plugged airways in the older children. Similarly, more mucus-plugged airways were excluded from the analysis on CT_{cf2} than on CT_{cf1}. This, together with different methods of airway sampling because of differences in scanning protocols between the groups, could have influenced our results. Second, inflation techniques differed between the infants and the children, which may have influenced the results. A third explanation could be that the differences are caused by a center effect because it is known that important

differences exist between centers and patient populations [30]. Finally, it could be that there was a stabilization of the disease process leading to stable airway lumen dimensions after age 5. It might be that treatment is more effective in children of 6 years and older. Most drugs in CF are only used in children 6 years and older because they are able to perform lung function. For example, in our center, most children 6 years and older are treated with rhDNase, whereas few children younger than 6 years are treated with rhDNase.

Our finding, however, appears at contrast with our observation that the scoring systems show a steady significant increase in bronchiectasis in the children with CF. There are a number of possible explanations for the discrepancy between changes in bronchiectasis score and quantitative LA/AA ratio. First, it is known that peripheral airways are important in CF lung pathology [2, 13]. The scoring systems include assessment of peripheral bronchiectasis even when a visible artery does not accompany the airways. Because our quantitative method does not include airways not accompanied by arteries, it is possible that it is insensitive to peripheral airway pathology/peripheral bronchiectasis. Second, sample size could play a role because more airways could be evaluated in the qualitative CT assessment of bronchiectasis than in the quantitative analysis.

It is important to realize that, for the radiologic diagnosis of bronchiectasis in CT scoring systems, airway size is often compared with the adjacent artery. This comparison assumes that the arterial diameter is not changed in relation to the disease process. The increased airway/artery ratio observed in our study and in the study by Long and coworkers [5] might be in part the result of hypoxia-induced vasoconstriction [24, 31]. If arterial size is changed in CF, it cannot be used as the reference structure to define bronchiectasis or airway wall thickening as is done both in the scoring systems and in quantified ratios. If the arterial size is reduced in CF, this would result in an overestimation of the degree of dilatation and airway wall thickening. Although we believe that this is unlikely to be a full explanation for our finding, it could contribute to the difference in airway/arterial ratio. In theory, comparing the mean absolute arterial size of all vessels in the infants and children with CF and control infants and children could test this assumption. However, because the vessels for analysis were selected based on the identification of airways and the identification of airways is dependent on them being big enough to be reliably measured on CT, this approach is flawed in this study. Future studies may want to compare absolute values for airway lumen and airway wall directly at well-defined, specific locations of the airway tree without use of the accompanying pulmonary artery.

A second important finding in our study was a 45% higher WA/AA ratio in the subjects with CF compared with the control subjects. This ratio did not increase with age and remained unchanged from CT_{cf1} to CT_{cf2}. This could be because of relatively low inflation, exclusion of mucus-plugged airways, or differences in airway sampling between infants and children and control children and CF children. However, AWT as a function of airway size was higher for CT_{cf2} compared with CT_{cf1}, reflecting a mean increase in AWT over the 2-year follow-up period. The reason why this change

from CT_{cf1} to CT_{cf2} was not reflected in the WA/AA ratio might be because the WA/AA ratio is more variable than AWT since the ratio includes variation in the measurement of airways and arteries. Long and coworkers found an increase in the WA/AA ratio in infants with CF from 1.05 at 1 month to 1.46 at 5 years, which was not significant. Therefore, their data correspond well to our data, which showed a mean value of 1.45 at the age of 5 years. The increase in AWT from CT_{cf1} to CT_{cf2}, although significant, was only 0.03 mm. A 0.03 mm increase in AWT is modest as is its potential effect on airway resistance. Despite this, the change in AWT correlated significantly with the change in $FEF_{25–75}$ predicted, a lung function test believed to be sensitive to abnormalities in the peripheral airways [32, 33]. This could be because only modest changes in CT-measured AWT reflect modest changes in small airway caliber [34] that could have a striking effect on airflow. Alternatively, or in addition, the modest increase in AWT could be a surrogate for other pathologic abnormalities, including, for example, obliteration of small airways. It could also be that the 0.03 mm is an underestimation of the real difference between CT_{cf1} and CT_{cf2} because more mucus plugged airways were excluded on CT_{cf2}. The quantitative analysis of AWT was more sensitive to change than the semiquantitative scoring of AWT. The semiquantitative evaluation of AWT as done in the scoring systems is subjective and not very reproducible. The fact that, in this study, AWT in the scoring systems was not progressive, but quantitatively assessed AWT increased over 2 years, may suggest an added value of quantitative analysis of AWT to scoring in children with CF.

The PFT findings in a larger sample of this cohort have previously been described [4]. The significant improvement in RV/TLC seen in this study was also observed in the larger cohort. This increase could be from a learning effect because this cohort includes many young patients. In the larger sample, both bronchiectasis score and mucus-plugging score worsened significantly. There are a number of potential reasons for dissociation between changes in structure and function: PFTs are a measure of global lung function, they depend on patient cooperation, and they are expressed as percent predicted using equations derived from a large population sample. In contrast, CT can detect (small) localized areas of bronchiectasis and individual mucus plugs, which may, over the short term, have little influence on lung function [4].

There are several limitations of our study. First, for ethical reasons, we used control scans that were performed for a clinical indication. However, none of the clinical indications would be expected to cause changes in airway wall or vascular dimensions. In addition, the airway/arterial ratio in the control subjects was very comparable to the published normal values in adults [35–37]. However, even if our control scans were not completely normal, any bias would likely result in an underestimation of true difference between patients with CF and control subjects.
A second limitation is that children with CF and control subjects were scanned using different CT scanners and protocols. However, the CT scanners were made by the same manufacturer and a high-enough beam current was used to provide good

quality images. Although differences in scanners and scanning technique might affect quantitative measurements of airway dimensions, such as AWT, it is unlikely that it will affect the ratio between dimensions. Therefore, we restricted our between group analyses to comparisons of ratios rather than absolute airway dimensions versus age. Differences in protocols also meant that airways were sampled differently in the various groups. Infants were scanned at only four levels, older children with CF were scanned at approximately 25 levels, and for older control subjects, full-lung scans were analyzed. Although we sampled a similar number of airways per CT in the older children with CF and control children, there were fewer airways per subject for infants with CF and control infants. Despite these sampling differences, there was no offset of the regression lines for age versus LA/AA and WA/AA between the infants and children for both control subjects and patients with CF. Another important difference between this study and that of Long and coworkers [5] is that we did not control for lung volume during scanning. Lung volume is an important determinant of airway lumen [38] and arterial dimensions. The differences in the slopes of the relationships between age and LA/AA and WA/AA between our children and the infants of Long and coworkers could be explained by differences in inflation level between the studies. To overcome the potential for such differences, future studies should be done using CT scanning with spirometer gating [39, 40].

A third limitation is that we could have introduced a selection bias because a higher percentage of airways on CT_{cf2} were excluded from the analysis because of mucus plugging. The exclusion of these occluded (possibly more severely affected) airways might have led to an underestimation of the progression of AWT as a function of airway size and an underestimation of the changes in the LA/AA and WA/AA ratios of CT_{cf2} relative to CT_{cf1}. In addition, it may be that fewer airways were excluded in the infants with CF compared with the children with CF, which might have led to an underestimation of the difference in the slopes of age versus WA/AA and LA/AA ratios in children with CF relative to infants with CF.

A fourth limitation is that some of the patients were too young to perform PFTs or were excluded from comparisons because their age was younger than the specified age for Wang and coworkers' [29] predicted equations for $FEF_{25–75}$ results, and therefore some comparisons were made with a smaller number of subjects, which reduced the power of our statistical analysis.

To conclude, quantitative measurements of airways are highly reproducible. In children with CF, the ratio between airway LA and AA and between airway WA and AA is increased and the airway walls are thickened. AWT, but not the ratio between airway WA and airway LA and AA, increased over 2 years of follow-up. Although lung function did not change significantly over the 2-year follow-up period, there were significant changes in quantitative airway wall thickening and qualitative CT scores as estimates of airway structure. Some of our findings are potentially influenced by differences in airway sampling between the groups, by differences in lung inflation during the CT procedure, and by the possibility of changes in arterial size in patients with CF. Future quantitative studies should address these issues by

measuring absolute values for airway wall, airway lumen, and artery at specified locations of the airway tree using volumetric CT scanning at a standardized well-inflated lung volume. Our data extend previous findings regarding CT imaging and quantitative assessment of CT findings in CF [5, 11, 41], and further indicate that CT scanning and quantitative CT measures may provide valuable information on the presence and progression of lung disease in CF.

References

1. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **168**(8)**:** 918-51.
2. Tiddens HA, Koopman LP, Lambert RK, et al. Cartilaginous airway wall dimensions and airway resistance in cystic fibrosis lungs. *Eur Respir J* 2000; **15**(4)**:** 735-42.
3. Sobonya RE, Taussig LM. Quantitative aspects of lung pathology in cystic fibrosis. *Am Rev Respir Dis* 1986; **134**(2)**:** 290-5.
4. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1)**:** 93-7.
5. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2)**:** 154-61.
6. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**(3)**:** 783-8.
7. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**(10)**:** 731-5.
8. Helbich TH, Heinz-Peer G, Fleischmann D, et al. Evolution of CT findings in patients with cystic fibrosis. *AJR Am J Roentgenol* 1999; **173**(1)**:** 81-8.
9. Santamaria F, Grillo G, Guidi G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest Be obtained? *Pediatrics* 1998; **101**(5)**:** 908-13.
10. Brody AS, Molina PL, Klein JS, Campbell JD, Millard SP, Quan J. High-Resolution CT is more sensitive to longitudinal decline in lung status in young children with CF than pulmonary function tests. *Pediatr Pulmonol* 2003; supplement 25**:** A388.
11. de Jong PA, Ottink MD, Robben SG, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2)**:** 434-9.
12. Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. *J Thorac Imaging* 1996; **11**(1)**:** 27-38.
13. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34**(3)**:** 228-31.
14. Hansell DM, Strickland B. High-resolution computed tomography in pulmonary cystic fibrosis. *Br J Radiol* 1989; **62**(733)**:** 1-5.
15. Lynch DA, Brasch RC, Hardy KA, Webb WR. Pediatric pulmonary disease: assessment with high-resolution ultrafast CT. *Radiology* 1990; **176**(1)**:** 243-8.
16. Stiglbauer R, Schurawitzki H, Eichler I, Vergesslich KA, Gotz M. High resolution CT in children with cystic fibrosis. *Acta Radiol* 1992; **33**(6)**:** 548-53.
17. Santis G, Hodson ME, Strickland B. High resolution computed tomography in adult cystic fibrosis patients with mild lung disease. *Clin Radiol* 1991; **44**(1)**:** 20-2.
18. Taccone A, Romano L, Marzoli A, Girosi D, Dell'Acqua A, Romano C. High-resolution computed tomography in cystic fibrosis. *Eur J Radiol* 1992; **15**(2)**:** 125-9.

19. Shah RM, Sexauer W, Ostrum BJ, Fiel SB, Friedman AC. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation. *AJR Am J Roentgenol* 1997; **169**(2)**:** 375-80.
20. Robinson TE, Leung AN, Northway WH, et al. Spirometer-triggered high-resolution computed tomography and pulmonary function measurements during an acute exacerbation in patients with cystic fibrosis. *J Pediatr* 2001; **138**(4)**:** 553-9.
21. Tiddens H, Silverman M, Bush A. The role of inflammation in airway disease: remodeling. *Am J Respir Crit Care Med* 2000; **162**(2 Pt 2)**:** S7-S10.
22. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000; **162**(3 Pt 1)**:** 1102-8.
23. Nakano Y, Whittall KP, Kalloger SE, Coxson HO, Paré PD, English JC. Development and Validation of Human Airway Analysis Algorithm Using Multidetector Row CT. *Proceedings of SPIE* 2002; **4683:** 460-469.
24. de Jong PA, Nakano Y, Hop WC, et al. Computed tomography (CT) show reduced pulmonary arterial size in children with cystic fibrosis (CF). *Pediatr Pulmonol* 2004; **38**(s27)**:** A 351.
25. de Jong PA, Nakano Y, Lequin MH, et al. Estimation of lung growth using computed tomography. *Eur Respir J* 2003; **22**(2)**:** 235-8.
26. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; **159**(3)**:** 851-6.
27. Zapletal A, Samanek M, Paul T. Lung Function in Children and Adolescents. Methods, Reference Values. Basel: Karger, 1987.
28. Quanjer PH, Borsboom GJ, Brunekreff B, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995; **19**(2)**:** 135-42.
29. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**(2)**:** 75-88.
30. Johnson C, Butler SM, Konstan MW, Morgan W, Wohl ME. Factors influencing outcomes in cystic fibrosis: a center-based analysis. *Chest* 2003; **123**(1)**:** 20-27.
31. Ryland D, Reid L. The pulmonary circulation in cystic fibrosis. *Thorax* 1975; **30**(3)**:** 285-92.
32. McFadden ER, Jr., Linden DA. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. *Am J Med* 1972; **52**(6)**:** 725-37.
33. Landau LI, Hill DJ, Phelan PD. Factors determining the shape of maximum expiratory flow-volume curves in childhood asthma. *Aust N Z J Med* 1973; **3**(6)**:** 557-64.
34. Nakano Y, Buzatu L, Wong JC, et al. Small Airway Dimensions in Human Lungs: Comparison of CT to Histology. *Am J Respir Crit Care Med* 2003; **167**(7)**:** A 585.
35. Kim JS, Muller NL, Park CS, Grenier P, Herold CJ. Cylindrical bronchiectasis: diagnostic findings on thin-section CT. *AJR Am J Roentgenol* 1997; **168**(3)**:** 751-4.
36. Woodring JH. Pulmonary artery-bronchus ratios in patients with normal lungs, pulmonary vascular plethora, and congestive heart failure. *Radiology* 1991; **179**(1)**:** 115-22.
37. Kim JS, Muller NL, Park CS, et al. Bronchoarterial ratio on thin section CT: comparison between high altitude and sea level. *J Comput Assist Tomogr* 1997; **21**(2)**:** 306-11.
38. Brown RH, Mitzner W. Effect of lung inflation and airway muscle tone on airway diameter in vivo. *J Appl Physiol* 1996; **80**(5)**:** 1581-8.
39. Robinson TE, Leung AN, Moss RB, Blankenberg FG, al-Dabbagh H, Northway WH. Standardized high-resolution CT of the lung using a spirometer-triggered electron beam CT scanner. *AJR Am J Roentgenol* 1999; **172**(6)**:** 1636-8.
40. Kalender WA, Rienmuller R, Seissler W, Behr J, Welke M, Fichte H. Measurement of pulmonary parenchymal attenuation use of spirometric gating with quantitative CT. *Radiology* 1990; **175:** 265-268.
41. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123**(5)**:** 1655-63.

Supplement (full methods)

Study population

Children with cystic fibrosis (CF): The Cystic Fibrosis Team Rotterdam (CFTR) in Sophia Children's Hospital (Rotterdam, the Netherlands) adapted in 1996 a clinical protocol of biennial computed tomography (CT) scans in combination with pulmonary function tests (PFTs). CT scans and PFTs evaluations were done during a clinically stable period. Clinical stability was determined by clinical evaluation; patients who were on treatment for an exacerbation with intravenous antibiotics were considered unstable and the CT scan was postponed. Children with CF who had two biennial CT scans (CT_{cf1} and CT_{cf2}) in combination with two PFTs (PFT_{cf1} and PFT_{cf2}) within one month from the CT scan were included in this study. CF was diagnosed by a positive sweat test and/or genotyping for known CF mutations and/or an abnormal potential difference measured across the rectal mucosa.

Control subjects: Control subjects were all patients who had a thin-slice thoracic CT scan ($CT_{controls}$) between 1999 and 2003 at Columbus Children's Hospital performed for various clinical indications as shown in Table 1. Scans that were reported by the radiologist as normal were re-evaluated by a second radiologist. Children diagnosed with heart or chronic lung disease such as asthma and children with abnormal CT scans reported in the radiologist report were excluded for further analysis. Scans that were considered normal at the second evaluation were included. The ethical review boards of Erasmus MC-Sophia (Rotterdam, Netherlands) and Columbus Children's Hospital (Ohio, USA) approved this study.

Table 1 Diagnosis of control subjects

Clinical diagnosis	Question of CT	Findings	Number
Osteochondrosarcoma (1), rhabdomyosarcoma (1), hepatoblastoma (1)	Lung metastasis?	No metastasis	3
Recovered spontaneous pneumothorax	Subpleural blebs?	No blebs	3
Solitary nodule	Follow-up scan	No nodule	3
Chest pain (later diagnosed as reflux)	Lung abnormalities?	Normal lungs	2
Chest wall mass: undefined (1) and osteochondritis (1)	Exact localization and extension	Extra pulmonary mass	2
Recurrent sinusitis	Lung involvement?	Normal lungs	2
Mitochondrial disease	Lung abnormalities?	Normal lungs	1
Aspiration	Foreign body?	No foreign body	1
	Vascular ring?	No vascular ring	1
Lupus like syndrome	Lung involvement?	Normal lungs	1
Pneumonia's in history	Bronchiectasis?	Normal lungs	1
Small pulmonary hemorrhage	Follow-up scan	No hemorrhage	1

CT scans

Children with CF: CT scanning was done from lung apex to lung base in the supine position after a breath hold instruction using a GE Prospeed SX scanner (General Electric Medical Systems, Milwaukee, WI). One-mm thick slices were obtained at 10-mm intervals using a potential of 120 kV and a beam current of 160 mAs (under nine years of age 120 mAs). Scans were reconstructed with a high-resolution algorithm (detail) and a standard reconstruction algorithm. Scans were archived in DICOM format and printed on film blinded for patient name, age and date of the scan (window level –600 HU, window width 1500 HU).

Control subjects: Volumetric scanning was done from lung apex to base after a breath hold instruction using a GE light speed 8-slice CT scanner (General Electric Medical Systems, Milwaukee, WI) using a potential of 120 kV and a beam current ranging from 30 to 120 mAs. Scans were reconstructed with a high-resolution algorithm (bone) and a standard algorithm at 1.25-mm thick slices.

CT scoring

Children with CF: All printed scans were scored using scoring systems published by Bhalla et al [1], Brody et al [2], Helbich et al [3] and Santamaria et al [4] in random order by a single experienced observer (PAdJ) [5]. The observer was blinded to the date of the scan, patient identification, and the PFTs. The results of these scoring systems in a larger group of patients were previously published [6].

Inspiration during CT scanning

Children with CF and control subjects: Lung volume during CT scanning was estimated from the standard-reconstructed images using a previously described method [7, 8] and expressed as percentage of predicted total lung capacity using the equations of Zapletal et al [9].

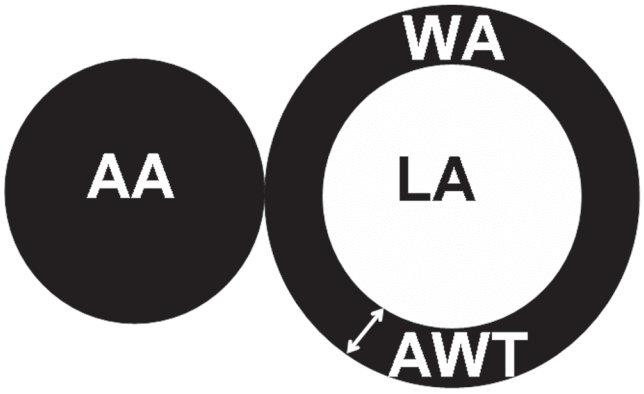
Quantitative analysis of airways and arteries

Airways and the accompanying pulmonary artery are measured on high-resolution reconstructed scans as follows [10, 11]. First a cross-sectional cut airway or artery is identified and enlarged. Next, the computer requests the observer to point with the mouse in the center of the airway or arterial lumen. From this point 64 rays are automatically cast from the lumen into the parenchyma. The computer allows the observer to delete rays that are evidently too long or too short. The borders of inner and outer airway wall or outer arterial wall are then determined using the full-with at half maximum principle [12]. The following dimensions are automatically computed from the selected rays: airway wall area (WA), airway lumen area (LA), airway lumen perimeter (Pi) and arterial area (AA) (see Figure 1). From these measurements airway wall thickness (AWT) and WA/AA as markers of airway wall thickening and LA/AA as a marker of bronchial dilatation can be calculated. AWT was calculated under the assumption that the airways were a perfect circle (AWT = 2 * square root ((LA + WA) / pi) - 2 * square root (LA / Pi)). Two observers (PAdJ and YN) measured 86

randomly selected airways and one observer (PAdJ) remeasured those 86 randomly selected airways after three months in order to determine intra- and interobserver variability. Those 86 airways were not included in the matched airways.

Children with CF and control subjects: Two observers (PAdJ and YN) matched identical looking cross-sectioned airway-artery pairs on CT_{cf1} and CT_{cf2}. Intrapulmonary markers, like small vessels, airway branching points and fissures were used to confirm that the same airway-artery pairs were being measured. Matched airways that contained mucus plugs on one of the scans were recorded but excluded for further measurements. The selected matched airway-artery pairs in children with CF and all visible cross-sectioned airway-artery pairs in control subjects were measured by one observer (PAdJ) using the described semi-automated method.

Figure 1 Airway-artery dimensions



AA = arterial area
LA = airway lumen area
WA = airway wall are
AWT = airway wall thickness (AWT = 2 * square root ((LA + WA) / pi) - 2 * square root (LA / pi))

Pulmonary function tests

Children with CF: PFTs were done using a Jäeger diagnostic system (MasterLab, Jäeger, Germany). The following lung function parameters were measured: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of expiratory vital capacity (FEF_{25-75}), airway resistance (Raw), residual volume (RV) and total lung capacity (TLC). The parameters were expressed as percentage of predicted using the equations of Quanjer and coworkers (FEV_1, FVC) [13], Wang and coworkers (FEF_{25-75}) [14] and Zapletal and coworkers (Raw, RV, TLC) [9]. Two ratios were calculated and expressed as a percentage: RV/TLC% and FEV_1/FVC%. Two patients were too young for spirometry at the time of the first scan. In addition the reference equations of Wang and coworkers can only be used for children older than seven years of age and therefore 6 additional patients had to be excluded for the FEF_{25-75} measurement.

Finally, Raw, RV and TLC were measured in 18 out of 23 children. Therefore, for the statistical analysis of FEF_{25-75} 15 patients could be included, for FEV_1, FVC and FEV_1/FVC 21 patients, and for Raw, RV, TLC and RV/TLC 18 patients.

Statistical analysis

Lung volume during CT scanning was compared between CT_{cf1}, CT_{cf2} and $CT_{controls}$ with the Mann Whitney U test.

Intra- and interobserver variability of automated airway measurements was calculated by expressing the difference of the first and second measurement as a percentage of the average of both measurements. This percentage was plotted against Pi to detect systematic errors depending on airway size [15]. In addition we calculated the intraclass correlation coefficients as a determinant of the intra- and interobserver variation.

Repeated Measurements analysis of variance (RMANOVA) is a statistical method that allows for differences between and within patients and for multiple observations per patient. Linear relationships were obtained for WA/AA, LA/AA, AWT and Pi by transformation to a 10-logaritmic scale. Next, RMANOVA was used to assess the relationships between airway-artery ratio's (logWA/AA and logLA/AA) and age for CT_{cf1}, CT_{cf2} and $CT_{controls}$ and between logAWT and logPi for CT_{cf1} and CT_{cf2}.

The differences between the groups for WA/AA, LA/AA and AWT were expressed as a ratio. For children with CF changes over time were calculated by subtracting CT_{cf1} from CT_{cf2} (ΔlogWA/AA, ΔlogLA/AA, ΔlogAWT, ΔBhalla-score, ΔBrody-score, ΔHelbich-score, ΔSantamaria-score, ΔBronchiectasis-score and ΔAirway wall thickness-score) and PFT_{cf1} from PFT_{cf2} (ΔFEV_1, ΔFVC, ΔFEF_{25-75}, ΔRaw, ΔRV, ΔTLC, ΔFEV_1/FVC, ΔRV/TLC).

Relationships between log (airway-artery dimensions) and PFTs and CT-scores and between Δlog (airway-artery dimensions), ΔPFTs and ΔCT-scores were assessed with RMANOVA. In addition, the Spearman correlation coefficients between ΔBronchiectasis-score or ΔAirway wall thickness-score and ΔFEF_{25-75} or ΔFEV_1 was calculated.

Changes over time (ΔPFTs and ΔCT-scores and Δcomponent scores) were analyzed using Wilcoxon Signed Rank tests.

SPSS 11.0 statistical package (SPSS Inc. Chicago, Il, USA) and SAS statistical package (SAS Institute Inc. Cary, NC, USA) were used for statistical analysis. Statistical significance was considered at a P-value < 0.05 and data are presented as mean ± SD (range) unless indicated otherwise.

Comparison with published data

In order to compare our result with published infant data by Long et al [16], we re-measured their data using our method. The details of their cohort have previously been described. Basically the cohort includes 34 infants with CF and 20 control infants who were scanned for a variety of indications and received 4 additional slices through the lung following an ethical approved protocol. RMANOVA statistics were done for the ratios of airway lumen to artery and airway wall to artery against age as described above.

References

1. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**(3)**:** 783-8.
2. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**(10)**:** 731-5.
3. Helbich TH, Heinz-Peer G, Fleischmann D, et al. Evolution of CT findings in patients with cystic fibrosis. *AJR Am J Roentgenol* 1999; **173**(1)**:** 81-8.
4. Santamaria F, Grillo G, Guidi G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest Be obtained? *Pediatrics* 1998; **101**(5)**:** 908-13.
5. de Jong PA, Ottink MD, Robben SG, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2)**:** 434-9.
6. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1)**:** 93-7.
7. de Jong PA, Nakano Y, Lequin MH, et al. Estimation of lung growth using computed tomography. *Eur Respir J* 2003; **22**(2)**:** 235-8.
8. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; **159**(3)**:** 851-6.
9. Zapletal A, Samanek M, Paul T. Lung Function in Children and Adolescents. Methods, Reference Values. Basel: Karger, 1987.
10. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000; **162**(3 Pt 1)**:** 1102-8.
11. Nakano Y, Whittall KP, Kalloger SE, Coxson HO, Paré PD, English JC. Development and Validation of Human Airway Analysis Algorithm Using Multidetector Row CT. *Proceedings of SPIE* 2002; **4683:** 460-469.
12. Amirav I, Kramer SS, Grunstein MM, Hoffman EA. Assessment of methacholine-induced airway constriction by ultrafast high-resolution computed tomography. *J Appl Physiol* 1993; **75**(5)**:** 2239-50.
13. Quanjer PH, Borsboom GJ, Brunekreff B, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995; **19**(2)**:** 135-42.
14. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**(2)**:** 75-88.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**(8476)**:** 307-10.
16. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2)**:** 154-61.

Chapter 5

Radiation risks associated with computed tomography scanning in cystic fibrosis

Chapter 5.1 Estimation of cancer risks associated with repetitive computed tomography scanning

Low-dose radiation from computerized tomography (CT) may increase the risk of certain cancers, especially in children. We sought to estimate the excess all-cause and cancer-specific mortality, which may be associated with CT scanning of cystic fibrosis (CF) patients. The radiation dose was calculated for a published CF surveillance CT scanning protocol of biennial CT scans and the risk per scan was estimated using atom-bomb survivor data. A computational model was developed to calculate the excess mortality in a CF cohort associated with radiation from the CT scan and to evaluate the effects of background survival, scanning interval and level of CT radiation used. The average radiation dose for the published surveillance CT scanning protocol was 1 milli-Sievert. Survival reduction associated with annual scans from age 2 years until death using this protocol was approximately 1 month and 1 year for CF cohorts with a median survival of 26 years and 50 years, respectively. Corresponding cumulative cancer mortality was approximately 1% and 6% at age 40 and 65, respectively. Biennial CT scanning reduced the survival reduction and cumulative cancer mortality by half. In conclusion, routine lifelong annual CT scans carry a low risk of radiation-induced mortality in CF. However, as the overall survival increases for CF patients, the risk of radiation-induced mortality becomes greater. These data indicate that radiation dose must be considered in routine CT imaging strategies for CF patients, to ensure that benefits outweigh the risks.

Based on:

Pim A. de Jong, John R. Mayo, Kamran Golmohammadi, Yasutaka Nakano, Maarten H. Lequin, Harm A.W.M. Tiddens, John Aldrich, Harvey O. Coxson, Don D. Sin. Estimation of Cancer Mortality Associated with Repetitive Computed Tomography Scanning.

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Introduction

For the justification of clinical protocols and research proposals that include computed tomography (CT) the absolute risk associated with radiation from CT scans has to be weighed against potential or proven benefits. The risk associated with the low dose radiation delivered during chest CT scanning is chromosomal damage that can cause haematological cancers within 5 years [1, 2] and solid cancers more than 30 years [3] after the exposure. Firm data determining the absolute cancer mortality risk of CT radiation dose do not exist [1, 4], however, recent data derived from atom-bomb survivors enables an estimate of cancer mortality after exposure to low-dose radiation [2, 3, 5, 6]. Because of the substantial impact of CT imaging on patient management, CT utilization is increasing [4, 7], even in children and infants who have been shown to be more sensitive to radiation compared with adults [1-3, 7]. Therefore, concerns have been raised regarding the routine use of surveillance CT scans to document disease progression in children with cystic fibrosis (CF) [8-12].

Briefly, CF patients develop progressive irreversible structural lung damage early after birth leading to a reduced life expectancy [13-20]. Traditionally, chest radiographs, along with spirometric measurements and clinical assessment have been used to monitor disease progression and interventions in CF patients. More recently, studies have shown that the structural lung damage in these patients could be detected earlier using chest CT compared to chest radiographs [21, 22]. Therefore some CF centres have replaced the routine annual chest radiograph for a CT scan every second or third year [8-10]. Those centers have reported that CT is more sensitive than the current gold standard examination, pulmonary function parameters such as forced expiratory volume in 1 second (FEV_1), to monitor CF lung disease [9, 23]. This finding may stimulate the use of routine chest CT examinations in CF. The argument in favour of routine CT scanning in CF is that earlier and more sensitive disease detection would lead to more aggressive treatment [15, 24-26] and to prolonged longevity. Premised on this logic, together with the idea that CF patients have a reduced life expectancy, and therefore less time to develop cancers associated with the radiation exposure of CT scanning, it was assumed that increases in longevity would outweigh the radiation risk of routine CT scans when obtained biennially instead of annually.

However, with rapid medical progress over the past half century, the median survival of CF patients has increased linearly from one year in 1940 to 35 years in 2004. Further improvements in life expectancy are expected over the next three decades [15, 27]. Since the risk of radiation-associated cancers increases with increased longevity, the potential harm from routine CT scanning is likely to be amplified in the future for CF patients. To date, however, there are no studies that have determined the risk associated with routine CT scanning in CF.

The aim of our study was to develop a computational model to estimate the excess risk for all-cause mortality and cancer-specific cause of mortality associated with lifelong protocol based routine chest CT scanning in CF. We hypothesised that the risk associated with lifelong routine CT scanning in CF would be low, but that with continued improvements in survival in CF patients over the coming decades, the risk associated with routine CT scanning would increase.

Methods

CT dose calculation

The radiation dose per CT scan was calculated using parameters from a published CF protocol [9, 10]. Briefly, high-resolution CT scans were obtained on a GE Prospeed SX scanner (General Electric Medical Systems, Milwaukee, WI, USA) from lung apex to lung base as 1.0-mm thick images at 10-mm intervals using 120 kV and 160 mAs (children below nine years of age 120 mAs). The radiation dose per scan was calculated in milli Sievert (mSv) using imPACT CT Dosimetry Calculator [28] and corrected to paediatric values [29].

Computational model

We designed a simulation model to estimate the risk of exposure to CT scans in terms of survival reduction and cumulative cancer mortality in CF patients (Figure 1). Each model included two female and two male cohorts of CF patients. In each model one male and one female cohort was exposed to routine CT scans (intervention) and the other male and female cohort was not exposed to CT scans (control). The mortality in the control cohort was all-cause CF mortality obtained from published data [15, 30, 31]. The mortality in the intervention cohort was broken down to all-cause CF mortality and mortality due to radiation associated hematological cancers [2], and solid cancers [3]. We developed seven variations of the model. The first five models used a 38-year time horizon (cohorts followed from age 2 to 40) and the next two models used a 63-year time horizon (cohorts followed from age 2 to 65). In the first model we assumed that all patients in the intervention group received annual CT scans for the whole follow-up period. In the second model the interval between CT scans was increased to two years. In the third model we assumed that the estimated dose per CT scan was 5 times higher than the first model. In the fourth model we assumed that the dose per CT scan was five times lower than the first model. In these first four models we used survival CF data from 1990, when the median survival was approximately 26 years [31]. Model 5 was the same as model 1 except different CF survival data were used from 1999 when the median survival was approximately 32 years [30]. In the sixth model we followed patients up to the age of 65 and exposed them to annual CT scans for their whole life. In addition we extrapolated the linear increase in CF survival to 2030 when the median survival is expected to reach 50 years [15, 32]. The seventh model was the same as the sixth, except we used CT scans

only for early detection and stopped CT scanning at the age of 18. An overview of the models is provided in Table 1.

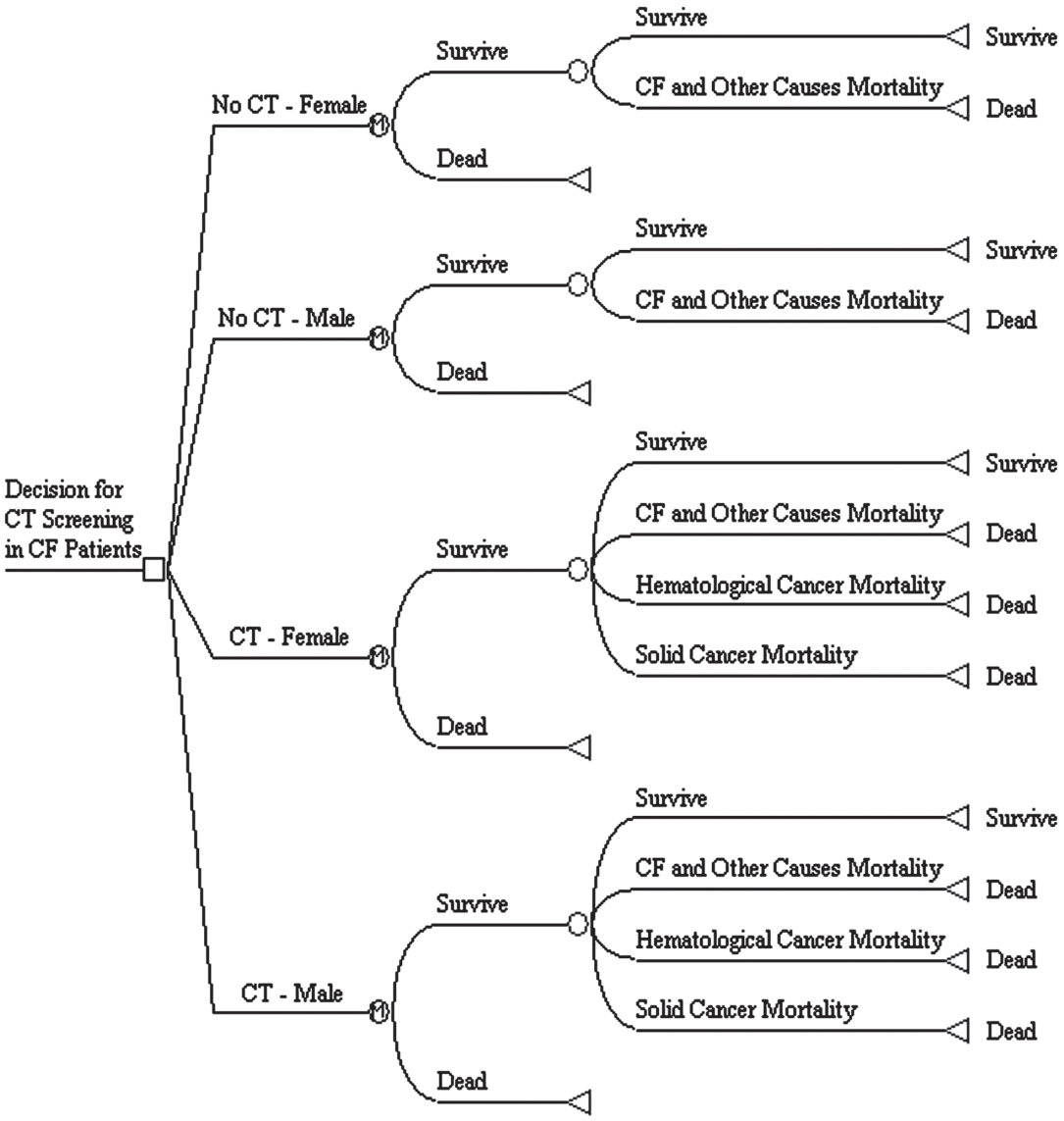
We used 6-month increments or cycle lengths to establish accurate transitional state probabilities. For each 6-month period, new probabilities of death were imputed into the models. Patients who died during each 6-month cycle were censored from further analysis. Survivors of each cycle were passed through another 6-month cycle wherein a new set of probabilities of death were applied. To determine the robustness of our data, multivariate sensitivity analyses were performed in which simultaneous clinically plausible adjustments for the relevant covariates for each of the strategies was made. We subjected all probabilities to a 10 percent variation around the probabilities of death using a triangular distribution. We sampled all variables based on their distribution and produced 100,000 sample sets in a Monte Carlo simulation. All modeled simulations were conducted using Data Pro (TREEAGE software Inc; Williamstown, MA).

Table 1 Computational models to estimate radiation associated cancer mortality

Model	Dose per CT scan (mSv)	CT scan interval (years)	Median male CF survival (years)	Median female CF survival (years)	Time horizon (years)	Consideration
1	1	1	±27.5	±24	2-40	Annual CT
2	1	2	±27.5	±24	2-40	Biennial CT
3	5	1	±27.5	±24	2-40	5-times higher dose
4	0.2	1	±27.5	±24	2-40	5-times lower dose
5	1	1	±34.5	±29.5	2-40	Current CF survival [30]
6	1	1	±52	±46	2-65	Future CF survival
7	1	1, stop at age 18	±52	±46	2-65	Future CF survival, early detection CT

Model one was based on survival data of 1990 [31] when the median cystic fibrosis (CF) survival was about 26 years. The model was based on annual computed tomography (CT) scans from the age of 2 till the age of 40. In model 5 survival data from 1999 were used [30] when the median CF survival was about 32 years. In model 6 and 7 CF survival was extrapolated to a median survival of 50 years that is assumed to occur in 2030 [15]. Since the main purpose in CF is early disease detection CT scans were done from age two till age 18, thereafter no CT scans were done. The assumption of the models was that there is no benefit from CT scanning.

Figure 1 Computational model to study the potential lethal cancer risk associated with radiation from computed tomography in cystic fibrosis patients



In this model the effect on lethal cancer development potentially associated with computed tomography (CT) radiation in cystic fibrosis (CF) was studied by changing the dose per scan, the interval between scans, the number of scans per patient and the life expectancy (annual mortality rate) in CF males and females.

Results

Dose calculation

CT dose was calculated for 58 CF-children aged 9.9±3.9 (3.5-17.3) years [9]. Their height and weight was 1.4±0.2 (1.0-1.8) meter and 32.1±12.3 (14.8-61.9) kilogram, respectively. The number of images per CT scan was 24±4 (16-34). The calculated dose per CT scan was 1.0±0.3 (0.5-1.9) mSv. For model one, we therefore used 1 mSv per CT scan.

Survival and cancer mortality after repetitive CT scanning

The reduction in median survival was less than one month in CF patients who had a median survival of 26 years and received annual CT scans (1 mSv) from age 2 and on. An increased median survival to 32 years resulted in a survival reduction of less than 1.5 months. However, when the median CF survival increased to 50 years the survival reduction increased to over a year for both males and females. If CT scans in these patients were used only for early disease detection until the age of 18 years, the survival reduction was more than half a year (Figure 2). When the time interval between the CT scans was increased to two years, the risk decreased by a factor of 2. A five-fold decrease and increase in the dose per CT scan (0.2 mSv and 5 mSv) resulted in approximately a five-fold decrease and increase in the survival reduction, respectively. For all situations modelled, males had a larger reduction in survival than females (Table 2).

The survival reduction was driven by excess number of deaths from haematological and solid cancers (Table 3). When the median CF survival was relatively low (model 1-5), most of the excess deaths in males were from haematological cancers while in females solid cancers predominated. The sum of all cancer deaths, however, remained below 1% at age 40 for both sexes at 1 mSv. However, when CF survival increased to a median of 50 years (models 6 & 7), the combined cumulative mortality from haematological and solid cancers was >6% for males and <6% for females when annual CT scans were used from the age of 2 and on. The risk decreased to 3.5% for males and 3.3% for females when CT scans were discontinued at age 18 years of age.

Table 2 Survival reduction of cystic fibrosis patients exposed to computed tomography radiation

		Male		Female	
Model		Median (months)	SD	Median (months)	SD
1	Annual CT	1.09	0.017	0.542	0.011
2	Biennial CT	0.56	0.009	0.276	0.005
3	5-times higher dose	5.36	0.080	2.672	0.051
4	5-times lower dose	0.22	0.003	0.109	0.002
5	Current CF survival	1.38	0.015	0.715	0.011
6	Future CF survival	15.02	0.208	12.41	0.188
7	Future CF survival, early detection CT	8.13	0.117	6.65	0.108

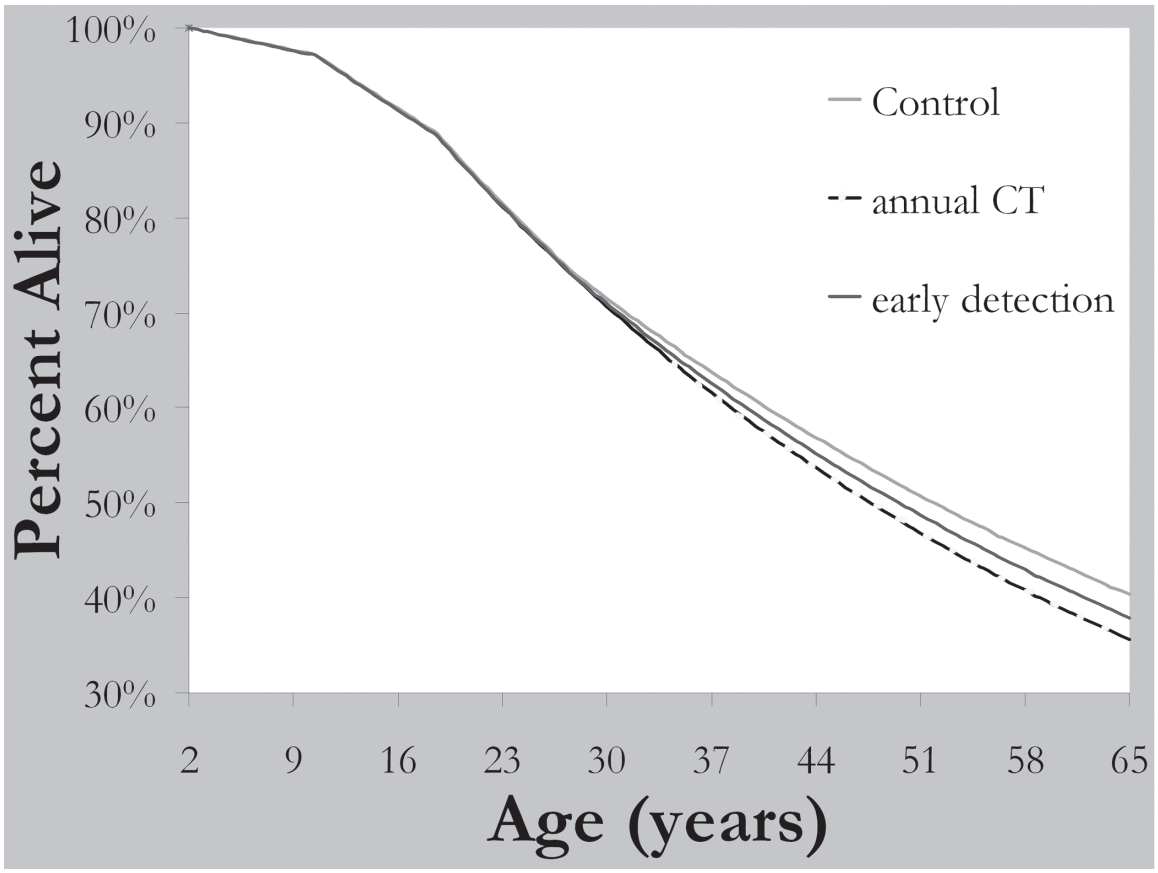
Data given are months based on haematological and solid cancers together
SD is standard deviation, which was based on a 10% variation
The assumption was no benefit from computed tomography (CT) scans and therefore these numbers represent the estimated risks associated with CT scanning and not a survival reduction in the real situation where there will be a benefit from the CT scans

Table 3 Cumulative mortality from cystic fibrosis (controls) and haematological and solid cancers after repeated computed tomography scanning

		Follow-up period in the modelled cohort	Solid cancer	Haematological cancer		All other causes mortality including CF	
			Male and female	Male	Female	Male	Female
Model		Years	%	%	%	%	%
1	Annual CT	Age 2 to 40	0.30	0.51	0.22	74	79
2	Biennial CT	Age 2 to 40	0.15	0.26	0.11	74	79
3	5-times higher dose	Age 2 to 40	1.43	2.52	1.10	74	79
4	5-times lower dose	Age 2 to 40	0.06	0.10	0.05	74	79
5	Current CF survival	Age 2 to 40	0.42	0.57	0.25	57	66
6	Future CF survival	Age 2 to 65	5.29	1.00	0.49	60	64
7	Future CF survival, early detection CT	Age 2 to 65	3.11	0.42	0.20	60	64

CT is computed tomography, CF is cystic fibrosis, % is percentage of cohort

Figure 2 Survival curves for cystic fibrosis patients exposed to radiation from computed tomography



Assumed was no survival benefits from the computed tomography (CT) scans and these data are only demonstrating and estimated magnitude of risk. The light gray line represents the controls, the dark gray line represents the early detection group and the black dotted line represents the annual CT group. The median cystic fibrosis background survival in these models was 50 years, which is expected to be in 2030.
The dose per scan was 1 mSv. Scans were acquired annually from age 2 till death (annual) or till age 18 (early detection). In the annual lifelong group the median survival reduction was 15 and 12 months for males and females, respectively. In the early detection group the median survival reduction was 8 and 7 months for males and females respectively. The cumulative prevalence of solid cancers at age 65 was more than 5% and 3% in the annual and early detection group, respectively. The cumulative prevalence of haematological cancers ranged from 0.5-1% and 0.2-0.4% in the annual and early detection group, respectively. Data are given for males.

Discussion

In this study we estimated the excess mortality associated with low-dose radiation from routine lifelong chest CT scanning in CF patients. We used a cohort of CF patients and varied the radiation dose per scan, scanning interval and background CF survival to determine the effects of using different strategies for CT scanning. An

important assumption in our model was that CT scans would not provide clinical benefits that would improve survival in CF patients. We made this assumption for two reasons. First, there is a paucity of studies with estimates of survival benefits related to routine CT scanning in CF. Second, the major objective of our study was to estimate the risk posed by low-dose radiation related to CT scanning, which has not been previously studied in the CF population. This question has both clinical and public health policy importance as a growing number of CF centres [8,9] have adopted a strategy to use routine CT scans every second or third year at least in managing CF patients during childhood.

We found that in the models in which the radiation per CT dose was low (1 mSv) and in which the overall expected median CF survival was 32 years or less, the risks imposed by low-dose radiation from routine CT scanning were low. However when the expected survival of the non-scanned (control) population increased to a median of 50 years the risk associated with lifelong routine CT scans became substantial. For instance, in model 6, the difference in median survival between those scanned and non-scanned was more than 1 year. This reduction was driven largely by a 5% excess mortality from solid cancers. When CT scanning was used only for early disease detection (model 7) the excess mortality from solid cancers was more than 3%. According to the latest projections based on data from USA [15, 32] the median CF survival is expected to improve to 50 years by 2030. Under this scenario, CF patients born today may be expected to live to age 50 years and beyond, which makes the current study highly relevant. Given the potential reduction in survival associated with radiation exposure from routine CT scans, it would be important to further demonstrate the clinical benefits related to this approach in order to justify the use of routine lifelong CT scanning in CF patients. Our data may also be germane and applicable to other clinical settings in which routine CT scanning is used. In our models the minimum number of CT scans per patients was 17 (model 7) and at age 65 the cumulative cancer mortality was about 3% in that model.

Notably, in the present study, we showed that biennial CT scanning could reduce the risk by half compared to annual CT scans. Moreover, by reducing the radiation dose five-fold, the risks can also be reduced five-fold. This shows that it is important to consider the dose and frequency of CT scanning for routine clinical purposes. A full-lung volumetric CT scan of the chest would expose the subject to approximately 5 mSv (model 4). Three inspiratory and 3 expiratory images would expose the subject to 0.2 mSv (model 3). A five-fold reduction in the milli Amperes per second (mAs) would be another option to reduce the radiation dose to approximately 0.2 mSv. Clearly, the model results stress the importance that lifelong routine imaging strategies can only be used when imaging strategies can be developed that will reduce lifelong radiation exposure below acceptable risk levels that are outweighed by the benefits.

There are several limitations to our study. Firstly, our data may have overestimated the mortality risks related to low-dose radiation since the atom-bomb survivor data, which we used to model the risks, were obtained before the advent of newer therapies to treat haematological cancers and improve survival of such patients [33]. Secondly, for largely unexplained reasons the atom-bomb survivor data showed a larger risk for haematological cancer in men than in women [2]. The data on solid cancers was not sex-specific, but it may be that the effect on mortality reduction of solid cancer is greater in women because of the development of breast cancer which could not be included in our model [3]. Thirdly, we did not consider the negative effects of radiation on non-cancer mortality like heart and blood vessel disease since there is no evidence of an increased risk for such diseases at the doses employed with CT scanning [3]. Fourthly, we did not take costs or potential benefits of CT into account since we aimed to model only the potential mortality risks associated with low-dose radiation exposure from routine CT scanning. Consideration of costs, in addition to safety issues, will be important in formulating a coherent public health policy in the use of routine CT scans in CF. Fifthly, the data we used to model cancer risks were obtained from the general population, not from the CF population. It is however re-assuring that several studies have shown that the cancer risks in CF are comparable to the normal population [34, 35]. Sixthly, our data should be interpreted in the context of other sources of radiation. In a Swiss survey the dose of a lateral plus antero-posterior chest radiograph was about 0.17 mSv and of a volumetric chest CT scan 9.0 mSv [36]. The dose for this scan is 10 times the dose of a high-resolution CT scan (HRCT) [7]. Therefore the dose for a HRCT would be 5 times the dose of chest radiographs. Interestingly, 140-350 transatlantic flying hours with a subsonic aircraft or 60-150 transatlantic flying hours with a Concorde results in a radiation exposure of 1 mSv [37]. Finally, natural background radiation in the USA due to cosmic radiation, natural radioactivity and domestic radon results in an average exposure of ~3 mSv / year.

In conclusion, our model indicated that the risk of routine lifelong annual CT scanning in CF is low but will increase when survival further improves. Our data urge caution in using CT scans for lifelong surveillance purposes in any disease unless there is a clear understanding of the benefits. Ways to reduce the dose per CT scan are available and more investigation in dose reduction as well as the optimal timing of routine CT scans is needed. The radiation dose related to routine CT scanning is likely to be reduced in the near future due to technical improvements. Our computational model can help to determine whether protocol improvements are sufficient to keep life-time exposure within acceptable limits.

References

1. Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. *Pediatr Radiol* 2002; 32(4): 228-3; discussion 242-4.
2. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. *Radiat Res* 1996; **146**(1): 1-27.
3. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 2003; **160**(4): 381-407.
4. Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004; **363**(9406): 345-51.
5. Puskin JS, Nelson NS, Nussbaum RH, Pierce DA, Preston DL. Risks from Low Doses of Radiation. *Science* 1996; **272**(5262): 631-635.
6. Pierce DA, Preston DL. Risks from low doses of radiation. *Science* 1996; **272**(5262): 632-3.
7. Mayo JR, Aldrich J, Muller NL. Radiation exposure at chest CT: a statement of the Fleischner Society. *Radiology* 2003; **228**(1): 15-21.
8. Dakin CJ, Pereira JK, Henry RL, Wang H, Morton JR. Relationship between sputum inflammatory markers, lung function, and lung pathology on high-resolution computed tomography in children with cystic fibrosis. *Pediatr Pulmonol* 2002; **33**(6): 475-82.
9. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1): 93-7.
10. de Jong PA, Ottink MD, Robben SG, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2): 434-9.
11. de Jong PA, Lequin MH, Mayo JR, Paré PD, Tiddens H. Re: Progressive damage on high-resolution computed tomography. *Eur Respir J* 2004; **dec**: 1071-72.
12. Rawlings D, Tennant D, Furness J. Progressive damage on high-resolution computed tomography. *Eur Respir J* 2004; **dec**: 1071.
13. Bedrossian CW, Greenberg SD, Singer DB, Hansen JJ, Rosenberg HS. The lung in cystic fibrosis. A quantitative study including prevalence of pathologic findings among different age groups. *Hum Pathol* 1976; **7**(2): 195-204.
14. Chow CW, Landau LI, Taussig LM. Bronchial mucous glands in the newborn with cystic fibrosis. *Eur J Pediatr* 1982; **139**(4): 240-3.
15. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **168**(8): 918-51.
16. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34**(3): 228-31.
17. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2): 154-61.
18. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: Distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr* 2004; **145**(1): 32-38.
19. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123**(5): 1655-63.
20. Bonnel AS, Song SM, Kesavarju K, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. *Pediatr Pulmonol* 2004; **38**(5): 396-405.
21. Hansell DM, Strickland B. High-resolution computed tomography in pulmonary cystic fibrosis. *Br J Radiol* 1989; **62**(733): 1-5.
22. Stiglbauer R, Schurawitzki H, Eichler I, Vergesslich KA, Gotz M. High resolution CT in children with cystic fibrosis. *Acta Radiol* 1992; **33**(6): 548-53.

23. de Jong PA, Nakano Y, Hop WC, et al. Changes In Airway Dimensions on Computed Tomography Scans of Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 2005.
24. Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993; **328**(24): 1740-6.
25. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995; **332**(13): 848-54.
26. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994; **331**(10): 637-42.
27. Fiel SB, FitzSimmons SC, Schidlow DV. Evolving Demographics of Cystic Fibrosis. *Am J Respir Crit Care Med* 1994; **15**(5): 349-355.
28. Jones D, Shrimpton PC. Survey of CT practice in the UK: normalised organ doses for x-ray computed tomography calculated using Monte Carlo techniques: National Radiological Protection Board. Harwell UK 1991. Available at: www.impactscan.org/ctdosimetry.htm. Accessed at: March 15 2005.
29. Khursheed A, Hillier MC, Shrimpton PC, Wall BF. Influence of patient age on normalized effective doses calculated for CT examinations. *Br J Radiol* 2002; **75**(898): 819-30.
30. Kulich M, Rosenfeld M, Goss C, Wilmott RW. Improved survival among young patients with cystic fibrosis. *J Pediatr* 2003; **142**: 631-636.
31. Rosenfeld M, Davis R, FitzSimmons SC, Pepe M, Ramsey B. Gender Gap in Cystic Fibrosis Mortality. *Am J Epidemiol* 1997; **145**: 794-803.
32. Fogarty A, Hubbard R, Britton J. International Comparison of Median Age at Death From Cystic Fibrosis. *Chest* 2000; **117**: 1656-1660.
33. Sporn M. The war on cancer. *Lancet* 1996; **347**(9012): 1377-1381.
34. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. *N Engl J Med* 1995; **332**(8): 494-9.
35. Padua RA, Warren N, Grimshaw D, et al. The cystic fibrosis delta F508 gene mutation and cancer. *Hum Mutat* 1997; **10**(1): 45-8.
36. Aroua A, Bize R, Buchillier-Decka I, Vader JP, Valley JP, Schnyder P. X-ray imaging of the chest in Switzerland in 1998: a natiowide survey. *Eur Radiol* 2003; **13**: 1250-1259.
37. Bottollier-Depois JF, Chau Q, Bouisset P, Kerlau G, Plawinski L, Lebaron-Jacobs L. Assessing Exposure to Cosmic Radiation on Board Aircraft. *Adv Space Res* 2003; **32**(1): 59-66.

5.2 Dose reduction of computed tomography in children with cystic fibrosis: Is it feasible to reduce the number of images per scan?

We aimed to determine whether it would be feasible to reduce the number of computed tomography (CT) images in children with cystic fibrosis (CF). One-mm thick CT images at 10-mm intervals were obtained biennially in CF-children. CT scans (20 baseline, 10 follow-up) were scored as sets including all, every second, every third, three selected, or five selected images. CT score (mean±SD) of every second image (15±2.6) was lower than that of all images (18±2.3, p=0.002). CT score worsened only when all or every second image was included (p=0.02). Significant information is lost when the interval between CT images is extended to >10-mm.

Based on:

P.A. de Jong, Y. Nakano, M.H. Lequin, H.A.W.M. Tiddens. Dose reduction of computed tomography in children with cystic fibrosis: Is it feasible to reduce the number of images per scan?

Accepted for publication in Pediatric Radiology

Introduction

In children with cystic fibrosis (CF) thin-section computed tomography (CT) scanning was shown to be useful to detect onset and progression of CF related lung disease [1-6]. CT scanning can detect CF related lung disease even before chest radiography [7-9] and pulmonary function testing [1, 3-5]. In addition, repeated CT scanning is more sensitive than pulmonary function testing to monitor progression of CF related lung disease [3]. A disadvantage of repeated CT scanning is the higher cumulative radiation exposure for the patients [10-12]. This, together with the prolonged survival of CF patients [13-15], increases the risk of radiation associated cancers [16, 17].

Reducing the dose per CT scan to the absolute minimum with acceptable diagnostic quality is a general and important radiologic principle. Several strategies for dose reduction of thin-section CT are available [12, 18-22]. One option is reducing the number of images per CT scan. Adequate sampling of the lung may be feasible using fewer images than commonly used in high-resolution CT protocols with 1-mm thick images at 10-mm intervals [3, 4]. However, CF related lung disease being heterogeneous in its presentation and therefore such reduction carries the risk that relevant abnormalities remain undetected. The relation between number of images and sensitivity to detect lung abnormalities has not been studied in CF to date.

The aim of this study was to investigate the relation between number of images per CT scan and severity of lung abnormalities as determined by an established CT scoring system [23].

Methods

Subjects

Twenty subjects were randomly selected from a published cohort of children diagnosed with CF [3]. All children underwent routine biennial CT scanning as part of their annual check-up during a clinically stable period. Clinical stability was determined by clinical evaluation; patients treated with intravenous antibiotics for an exacerbation were considered unstable, in which case scanning was postponed. CF was diagnosed by a positive sweat test and/or genotyping for known CF mutations and/or an abnormal potential difference measured across the rectal mucosa.

CT scanning protocol

CT scans were obtained using a single slice CT scanner (Prospeed SX; GE Medical Systems, Milwaukee, Wisconsin) in the supine position. The children were instructed to take a deep breath and hold it for at least 5 seconds. During each breath holding, two 1-mm thick images were obtained at 10-mm intervals from the lung apex to the

lung base. Scanning parameters were as follows: 120 kV, 160 mA (120 mA in children younger than 9 years), 1-second scanning time, and field of view 350 mm (250 mm in children younger than 9 years). Scans were reconstructed using a high-spatial frequency reconstruction algorithm (Detail; GE Medical Systems, Milwaukee, Wisconsin).

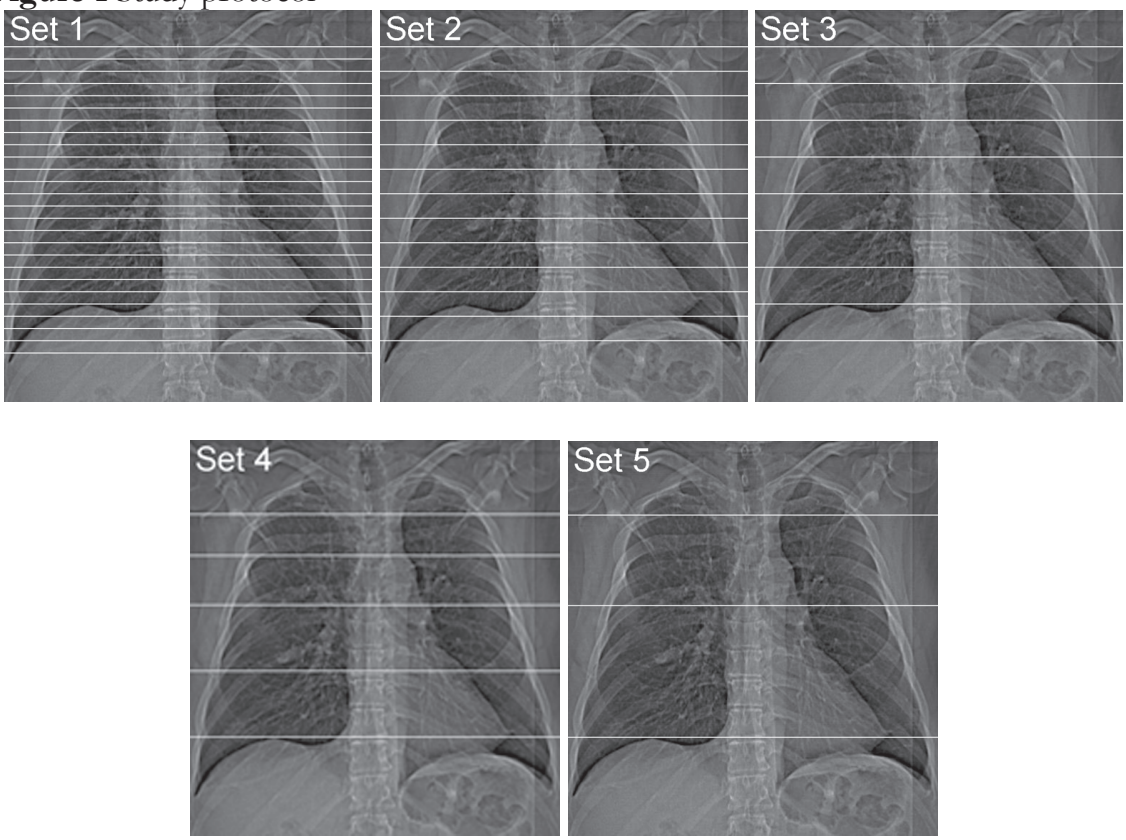
Evaluation of CT scans

The first CT scans from all 20 children (CT_1) and the second CT scans (CT_2) from 10 randomly selected children were used to compose five different sets of images (Figure 1). Set 1 contained all images for each scan (interval between images 10 mm), Set 2 contained every second image (interval 20 mm), Set 3 contained every third image (interval 30 mm), Set 4 contained a selection of five images and Set 5 contained a selection of only three images. The selected images were taken at the following anatomical positions: between the lung apex and the top of the aortic arch (Set 4 and Set 5); at the top of the aortic arch (Set 4); below the carina (Set 4 and Set 5); between the carina and the top of the diaphragm (Set 4) and at the top of the diaphragm (Set 4 and Set 5). The resulting 150 sets were blinded for patient characteristics, assigned a random number and scored [23] in random order by an experienced observer known to be able to score with low intra- and interobserver variability [4]. The scoring system used evaluates the 5 lobes and the lingula as a sixth lobe for the severity and/or extent of bronchiectasis, airway wall thickening, mucous plugging, alveolar consolidations, collapse and bulla or cysts [23].

Statistical analysis

For each set of images a score on a scale from 0 (no abnormalities) to 100 (worst possible) was calculated. CT scores from CT_1 (n=20) were compared between the five different sets using unpaired sample T-tests. Changes in CT scores from CT_1 to CT_2 (n=10) were calculated using paired sample T tests for each of the five sets. Significance level was set at $p<0.05$. Data are presented as mean ± standard deviation (range) unless indicated otherwise.

Figure 1 Study protocol



These scout films show the levels of the computed tomography (CT) images used (white lines) in the five sets of this study. Set 1 contained all images for each scan (interval between images 10 mm), Set 2 contained every second image (interval 20 mm), Set 3 contained every third image (interval 30 mm), Set 4 contained a selection of five images and Set 5 contained a selection of only three images.

Results

Subjects

Subjects (6 girls, 14 boys) were 10.0 ± 4.1 (3.7-17.6) years of age and had body height 1.4 ± 0.2 (1.0-1.8) meters and body weight 32.2 ± 15.1 (16.7-70.1) kilograms. The number of CT images in Set 1 for CT_1 was 25 ± 5 (18-34).

CT findings at baseline

The CT score in Set 1 for CT_1 was significantly higher than that in the other sets with larger intervals (Table 1). The incidence of CT abnormalities decreased for each set relative to Set 1. For example, the decrease from Set 1 to Set 2 was for bronchiectasis 85% to 65%, airway wall thickening 100% to 95%, alveolar consolidations 70% to 50%, collapse 55% to 40%, mucous plugging 90% to 75% and bulla and cysts 10% to 5%, respectively.

CT changes over two years

CT_2 worsened relative to CT_1 only for Set 1 and Set 2 ($p=0.02$). No significant changes were detected for the other sets with larger intervals ($p>0.31$) (Table 2).

Table 1 CT score at different intervals between CT images in children with cystic fibrosis

		CT score		
Set number	**Set description**	Mean	Standard deviation	Range
1	All images (every 10 mm)	18	2.3	6 – 38
2	Every second image	15*	2.6	0 – 42
3	Every third image	15*	2.1	1 – 34
4	Five selected images	11*	2.4	0 – 38
5	Three selected images	12*	2.1	1 – 30

Results are based on 20 CT scans obtained from 20 subjects
CT scores were obtained using a validated scoring system [23]
CT scores are lower in Set 2, 3, 4 and 5 compared to Set 1 ($p<0.002$, unpaired sample T test)

Table 2 Change in CT score over two years at different intervals between CT images

	Mean change	**95% confidence interval**	**P-value**
All slices	6.8	1.4 – 12.1	0.02
Every second image	5.5	1.1 – 9.8	0.02
Every third image	1.4	-1.5 – 4.3	0.31
Five selected images	1.6	-2.2 – 5.5	0.37
Three selected images	0.4	-4.7 – 3.8	0.83

Results are based on 10 baseline and 10 follow-up CT scans obtained from 10 subjects
CT scores were obtained using a validated scoring system [23]
Results were obtained using paired sample T tests

Discussion

Repeated CT scanning in CF is gaining importance as a clinical and research outcome measure. However, CT scanning involves radiation and therefore a risk to the patient, especially when repeated CT scanning is started in childhood. In this study we investigated whether radiation dose in children with CF could be reduced by reducing the number of images per CT examination.

Our results clearly show that CT scores and numbers of cases with CT abnormalities decreased with reduction of number of images per CT scan. In addition, over a time interval of two years we were able to detect significant worsening on images taken every 10-mm or every 20-mm, but not at greater intervals. Reducing the number of images per CT scan to less than 1 image every 10-mm does not seem to be a valid option for dose reduction in CF. Our results can be explained by the heterogeneous nature of CF related lung disease. For this reason, the fewer the number of images in

children with CF, the higher the risk that localized structural abnormalities remain undetected. Our results also suggest that full-lung volumetric CT scans would be an even more sensitive method than the thin-section sequential CT protocol used in this study and other studies. However, this needs to be investigated in further studies. Whether our results are applicable to more advanced CF in adults or other chest diseases is unknown and will depend on the heterogeneity of the abnormalities in those situations.

It is unfortunate that reducing the number of images per CT scan in CF children does not seem to be a valid strategy to reduce radiation dose. Fortunately, there are other options for dose reduction in this disease. For example, at the time of our study our CT scanning protocol was a relatively high-dose protocol, which dose, however, could be substantially reduced over the last years. Suggestions for dose reduction by lowering the milli Amperes per second based on patients' body weight have been published [21].

At the time of the study we did not include expiratory CT scans. Gas trapping in CF has recently gained much attention [24-27]. A similar approach as used in our study could be used to determine the optimal number of expiratory images needed to adequately estimate the severity of gas trapping.

A limitation of our study is that all images were scored by a single observer. However, this observer is known to be able to score with a low intra- and interobserver variability using the scoring system applied in the present study [4]. In addition all images were scored in random order. Another limitation is that the follow up scan was done in only 10 of the 20 patients in order to reduce the work load from the time consuming CT scoring. For the present study design 150 sets had to be scored at approximately 10 to 15 minutes per set. It is unlikely that a larger number of follow up scans would change the conclusions of our study.

In conclusion, the sensitivity of inspiratory CT scans to determine the severity of CF related lung disease is higher when images are taken at 10-mm intervals rather than at larger intervals. Therefore, reducing the radiation dose in CF by reducing the number of inspiratory images per CT scan is not an attractive strategy. Other methods to further reduce the radiation dose should be investigated.

References

1. Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. *J Thorac Imaging* 1996; **11**(1)**:** 27-38.
2. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2)**:** 154-61.

3. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1)**:** 93-7.
4. de Jong PA, Ottink MD, Robben SG, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2)**:** 434-9.
5. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: Distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr* 2004; **145**(1)**:** 32-38.
6. de Jong PA, Nakano Y, Hop WC, et al. Changes In Airway Dimensions on Computed Tomography Scans of Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 2005.
7. Hansell DM, Strickland B. High-resolution computed tomography in pulmonary cystic fibrosis. *Br J Radiol* 1989; **62**(733)**:** 1-5.
8. Lynch DA, Brasch RC, Hardy KA, Webb WR. Pediatric pulmonary disease: assessment with high-resolution ultrafast CT. *Radiology* 1990; **176**(1)**:** 243-8.
9. Santis G, Hodson ME, Strickland B. High resolution computed tomography in adult cystic fibrosis patients with mild lung disease. *Clin Radiol* 1991; **44**(1)**:** 20-2.
10. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001; **176**(2)**:** 289-96.
11. Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. *Pediatr Radiol* 2002; **32**(4)**:** 228-3; discussion 242-4.
12. Mayo JR, Aldrich J, Muller NL. Radiation exposure at chest CT: a statement of the Fleischner Society. *Radiology* 2003; **228**(1)**:** 15-21.
13. Fogarty A, Hubbard R, Britton J. International Comparison of Median Age at Death From Cystic Fibrosis. *Chest* 2000; **117:** 1656-1660.
14. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **168**(8)**:** 918-51.
15. Rosenfeld M, Davis R, FitzSimmons SC, Pepe M, Ramsey B. Gender Gap in Cystic Fibrosis Mortality. *Am J Epidemiol* 1997; **145:** 794-803.
16. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. *Radiat Res* 1996; **146**(1)**:** 1-27.
17. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 2003; **160**(4)**:** 381-407.
18. Linton OW, Mettler FA, Jr. National conference on dose reduction in CT, with an emphasis on pediatric patients. *AJR Am J Roentgenol* 2003; **181**(2)**:** 321-9.
19. Haaga JR, Miraldi F, MacIntyre W, LiPuma JP, Bryan PJ, Wiesen E. The effect of mAs variation upon computed tomography image quality as evaluated by in vivo and in vitro studies. *Radiology* 1981; **138**(2)**:** 449-54.
20. Frush DP. Strategies of dose reduction. *Pediatr Radiol* 2002; **32**(4)**:** 293-7.
21. Donnelly LF, Emery KH, Brody AS, et al. Minimizing radiation dose for pediatric body applications of single-detector helical CT: strategies at a large Children's Hospital. *AJR Am J Roentgenol* 2001; **176**(2)**:** 303-6.
22. Ambrosino MM, Genieser NB, Roche KJ, Kaul A, Lawrence RM. Feasibility of high-resolution, low-dose chest CT in evaluating the pediatric chest. *Pediatr Radiol* 1994; **24**(1)**:** 6-10.
23. Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. *Pediatr Radiol* 1999; **29**(10)**:** 731-5.
24. Dorlochter L, Nes H, Fluge G, Rosendahl K. High resolution CT in cystic fibrosis--the contribution of expiratory scans. *Eur J Radiol* 2003; **47**(3)**:** 193-8.
25. Bonnel AS, Song SM, Kesavarju K, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. *Pediatr Pulmonol* 2004; **38**(5)**:** 396-405.

26. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123**(5)**:** 1655-63.
27. Robinson TE, Leung AN, Northway WH, et al. Composite spirometric-computed tomography outcome measure in early cystic fibrosis lung disease. *Am J Respir Crit Care Med* 2003; **168**(5)**:** 588-93.

Chapter 6

Monitoring of lung growth using computed tomography

6.1 Estimation of lung growth using computed tomography

Anatomical studies suggest that normal lungs grow by rapid alveolar addition until about 2 yrs of age followed by a gradual increase in alveolar dimensions. The aim of this study was to examine the hypothesis that normal lung growth can be monitored by computed tomography (CT). Therefore, the gas volume per gram of lung tissue was estimated from measurements of lung density obtained from CT scans performed on children throughout the growth period. CT scans were performed on 17 males and 18 females, ranging in age from 15 days–17.6 yrs. CT-measured lung weight was correlated with predicted *post mortem* values and CT measured gas volume with predicted values of functional residual capacity. The median value for lung expansion was 1.86 mL*g-1 at 15 days, decreased to 0.79 mL*g-1 by 2 yrs and then increased steadily to 5.07 mL*g-1 at 17 yrs. Computed tomography scans can be used to estimate lung weight, gas volume and expansion of normal lungs during the growth period. The increase in the lung expansion after the age of 2 yrs suggests progressive alveolar expansion with increasing lung volume.

Based on:

P.A. de Jong, Y. Nakano, M.H. Lequin, J.R. Mayo, R. Woods, P.D. Paré, and H.A. Tiddens. 2004. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* **23**(1):93-7.

Introduction

Several reports have shown that only between one-third and one-half of the number of alveoli in the human lung are present at birth [1–3]. This number increases rapidly after birth by a process of septation of the primary saccules and reaches adult values between 1.5–2 yrs of age, and is certainly finished by 8 yrs [1–3]. After this process is completed, the number of alveoli remains constant and the lung continues to grow by increasing the dimensions of all of the lung structures. The small conducting airways that are completely surrounded by alveoli increase their dimensions in a similar fashion, resulting in a substantial increase in peripheral airway conductance around 2 yrs because flow increases in proportion to the fourth power of the change in their radius [4]. Direct measurement of airway conductance suggests a rapid increase in peripheral airway conductance at ~5 yrs of age when alveolar addition slows down and linear dimensions of the lung begin to increase. Lung distension after the period of rapid alveolar addition also increases due to changes in the mechanical properties of the chest wall. These changes result in a relative underdistension of the lung at <8 yrs of age and a relative overdistension thereafter [5, 6].

The present study was designed to determine if quantitative measurements of computed tomography (CT) scans could measure normal lung development. Furthermore, if CT scans can be used to monitor normal lung growth they may be useful in assessing the effect of chronic lung disease on lung growth.

Methods

Subjects

All thoracic CT scans performed at Sophia Children's Hospital (Rotterdam, the Netherlands) between 1998–2001 that were reported as normal by radiologists were included in the study. The study was approved by the ethical committee of Sophia Children's Hospital (Rotterdam, the Netherlands).

Computed tomography scans

The examinations were all performed on a GE Prospeed SX CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) and the images were archived in DICOM (Digital Imaging and Communications in Medicine) format. The CT scans were performed in the supine position at full-suspended inspiration from age 6 yrs and during quiet breathing for the younger children. Three subjects had axial CT scans with 1-mm thick slices at 10-mm intervals (ages of 11, 12 and 17 yrs). The other subjects had spiral CT scans with slice thicknesses ranging 3–10 mm. Field of view ranged 25–35 cm, and beam current and potential 130–250 mA and 120–140 kV. The images were reconstructed with a standard reconstruction algorithm.

Computed tomography analysis

The CT scans were transferred to the iCAPTURE Centre/McDonald Research Laboratory (Vancouver, BC, Canada) and analysed using a method described previously [6, 7]. Briefly, this program uses the voxel dimensions to calculate lung volume and the x-ray attenuation values of the lung to estimate lung density. Lung weight, in grams, is calculated by multiplying the lung density by the volume. Lung expansion, in millilitres of gas per gram of tissue, is calculated by sub-tracting the inverse of the density of tissue (assumed to be 1.065 $g*mL^{-1}$) from the inverse of the CT-measured lung density [7, 8]. CT-estimated lung weight was compared to previously reported *post mortem* values from children with normal lungs [9]. CT-determined gas volume was compared to predicted normal values for functional residual capacity (FRC) using equations for children of various body lengths. FRC was measured in the supine position in children aged 0–6 yrs [10] and in the sitting position in the children aged 6 yrs [11]. CT-determined gas volume was also compared to published values of total lung capacity (TLC) for children with a body length <115 cm [3] and to predicted values for children with a body length >115 cm [11]. The values for alveolar number at each body length, calculated separately for both males and females using data from Thurlbeck [3], were compared to the CT-determined lung expansion in mL $gas*g^{-1}$ tissue at the same body length.

Statistics

Spearman's correlation was used to compare CT-measured lung weight to predicted lung weight and CT-measured gas volume to predicted FRC and TLC.

Results

The CT scans from 17 male and 18 female children, ranging in age from 15 days–17.6 yrs were examined in this study. Twenty-three had primary tumours outside the lung (lymphoma (n=9), Wilms tumour (n=3), osteosarcoma (n=4), rabdomyosarcoma (n=3), hepatoblastoma (n=2), Ewing sarcoma (n=1), melanoma (n=1)), where the scans were performed to rule out lung metastasis. The remaining scans were performed for suspected malignancies (n=2), dysphagia (n=1), haemoptysis (n=2), to assess lung damage following infections (n=3) and for a variety of other reasons (n=4). Sex, age, height, weight of the subjects and the CT estimates of gas volume, weight, mean volume of $gas*g^{-1}$ tissue and predicted alveolar numbers of the subjects' lungs are shown in Table 1.

The CT-measured lung weight compares favourably to published *post mortem* values for children with a body length of ≤140 cm, which corresponds to 12 yrs of age [9]; both are shown as a function of body length in Figure 1. There was a positive correlation (Spearman's correlation coeficient=0.91, $p<0.0001$) between the CT-measured lung weight and published *post mortem* values. CT-measured gas volume

compared favourably to predicted values for FRC, especially for children <10 yrs (body length of 135 cm). The gas volume of the older children tended to be above FRC during the scanning procedure (Figure 2). The Spearman's correlation coefficient for the relationship between CT-measured gas volume and predicted values for FRC over the total age range was 0.90 ($p<0.0001$). A comparison of published values for the total number of alveoli to the mean values of lung expansion*g^{-1} lung at the same body length, for both males and females, is shown in Figure 3. These data show an initial decrease of the lung volume*g^{-1} tissue between birth and the first year (body lengths <85cm), followed by a plateau and then a progressive increase. The gas volumes of the two youngest cases (both female) were 47 and 59% of TLC, respectively.

Table 1 Patient characteristics

	Subjects n	Min	Max	Mean±SD
Patient characteristics:				
Age (years)	35	0.04	17.6	8.9±5.7
Height (cm)	35	54	179	132.7±37.5
Weight (kg)	35	2.7	91.5	35.2±22.7
CT estimates:				
Gas volume (mL)	35	86	5061	1489±1289
Lung expansion (mL*gram^{-1})	35	0.79	5.07	2.65±1.23
Lung weight (g)	35	45	1001	452±272
Alveolar number male (*10^6)#	17	112.15	491.29	419.19±86.22
Alveolar number female (*10^6)#	18	93.49	428.55	364.83±76.20

Min.: minimum; Max.: maximum; CT: computed tomography. n=35, 17 males and 18 females.
: alveolar numbers shown are predicted *post mortem* data from ref [3].

Figure 1 Computed tomography estimated normal lung weight (●, ----) compared with published *post mortem* normal lung weight (○, —).

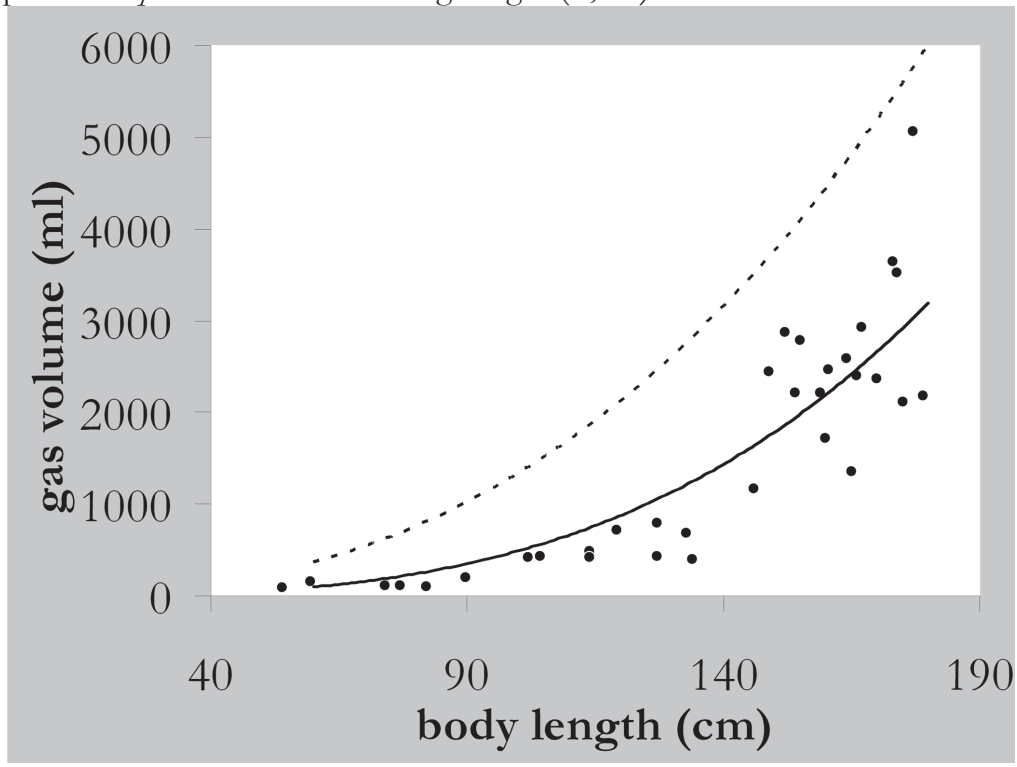


Figure 2 Computed tomography estimated gas volume of the lung (●) compared with predicted functional residual volume (—) and predicted total lung capacity (----).

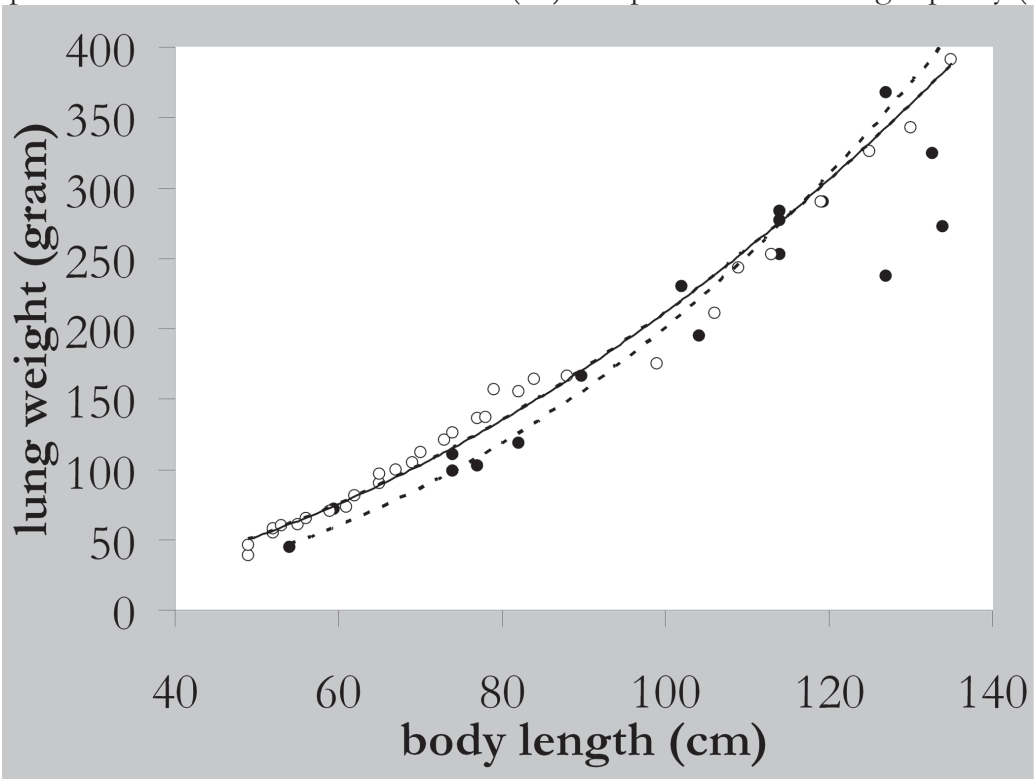
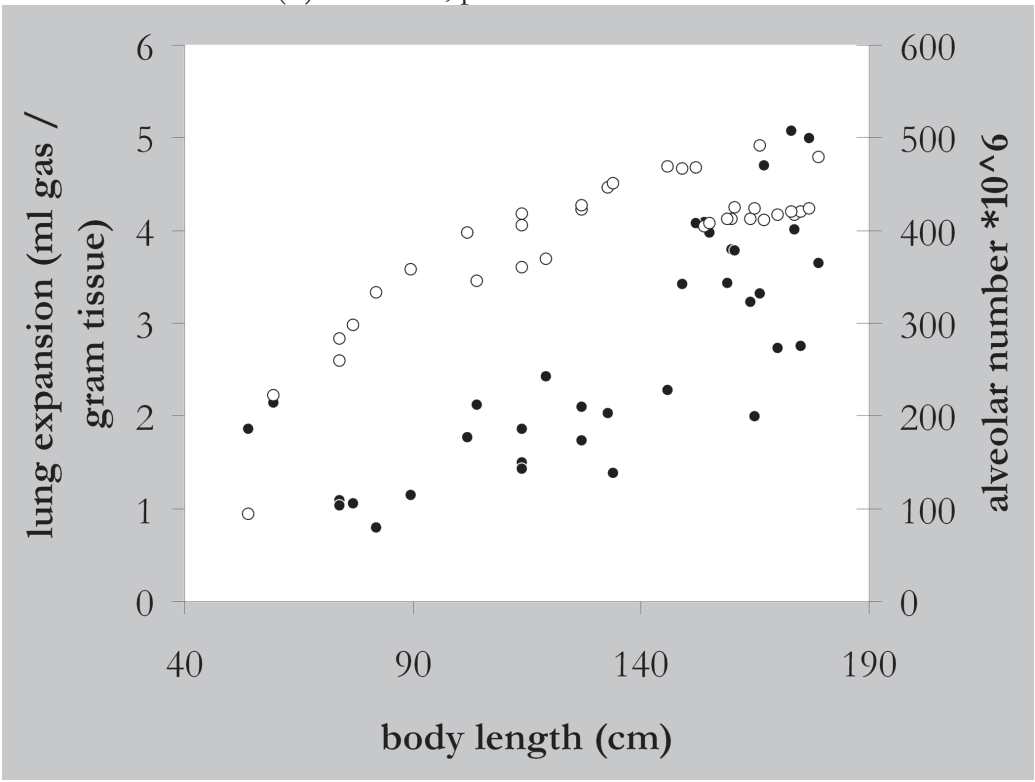


Figure 3 Computed tomography estimated lung expansion (●) and published *post mortem* alveolar numbers (○). R^2=0.43, p=0.01.



Discussion

Previous studies have shown that quantitative measurements of CT scans can quantify the changes in lung tissue associated with chronic lung disease. The present study shows that the CT scan can be used to estimate the lung weight and gas volume in children with normal lungs.

The CT measurements of total lung weight, volume and expansion reported here compare favourably to published values of *post mortem* lung weight [9] and predicted gas volume at FRC in children. Previous anatomical studies have shown that the number of alveoli increase rapidly following birth. As the added alveoli are a uniform size the current authors postulated that the divisions of existing airspace into smaller units would cause the gas volume*g^{-1} of tissue to fall. This hypothesis is supported by the data showing a decline in gas volume*g^{-1} tissue from birth to 2 yrs of age. This decrease in lung expansion between birth and 2 yrs of age is consistent with the rapid addition of alveolar tissue by septation of growing alveoli and larger structures (possibly primary saccules) to form mature respiratory bronchioles, alveolar ducts and sacs [3]. In the current study, since there is only data on two very young patients, the

initial decline could be due to other reasons such as relatively large airspaces in these subjects or chance. However, since there is no pathological verification of the lung structure and since the data is consistent with published results, the current authors think that this initial decline in lung expansion is due to the septation process. The subsequent increase in gas volume*g^{-1} of tissue from age 2–8 yrs probably results from a combination of increased alveolar size and increased outward recoil of the chest wall, which leads to an increased FRC [5, 6]. While it has been shown that young males have more alveoli than young females (Figure 3) [3], the increase in alveolar number with age follows the same trend in both sexes and, therefore, it is unlikely that sex differences are responsible for the initial decline in lung expansion.

In this study, the CT measurements of lung weight for the subjects were compared to predicted values derived from the autopsy studies of Coppoletta and Wolbach [9]. These investigators measured the weight of the vital organs of children between birth and 12 yrs of age in relation to body length using >1,000 autopsy records. Comparison of the CT measurements of lung weight for the present subjects to the values predicted for their body length show excellent agreement, indicating that lung weight can be accurately measured using a CT scan performed during the growth period. Although it can be argued that it is hard to compare the results of data on children obtained in the 1930s with children of today, these are the only values that are available for analysis.

The results presented here also show that CT scans performed on children ≤10 yrs are obtained at gas volumes that are close to FRC. Older children appear to have inflation levels somewhere between FRC and TLC, indicating that their CT scans were performed after a breath of variable size. The fact that the CT scans were consistently performed close to FRC ≤10 yrs indicates that the observed decline in lung expansion between birth and 2 yrs of age can be attributed to an addition of new alveoli. After the period of rapid alveolar addition is complete the gradual expansion in gas volume*g^{-1} lung is consistent with expansion in the size of alveoli in combination with a gradual increase in FRC due to changes in the mechanical properties of the lung and chest wall [5, 6].

This study has some limitations. As mentioned above, the authors do not have any direct pathological validation of the measurements in these subjects. They have, therefore, had to rely on published data to compare results. However, the current data did correlate well with the other previously published data and the authors propose that while this may weaken the study it does not invalidate it. The measurement of lung expansion from CT is critically dependent on the lung volume at which the scan is performed. Therefore, in this study, lung volume was measured on the scans and this volume was related to the predicted values for FRC. The technique used to make the prediction equations is different for the children aged <6 yrs [10] compared to the older children [11]. Bar-Yishay *et al.* [10] measured FRC in the supine position, Zapletal *et al.* [11] measured FRC in the sitting position. This results in

higher values for FRC in the older children. In addition, the CT scanning technique was different for the children aged <6 yrs compared to the older children and the big breath method in the older children results in higher long volumes during the scanning procedure compared to the quiet breathing of the younger children. The exact effect of these errors are not known, however, the observed decline in lung expansion before the 2 yrs cannot be contributed to these errors since the scanning technique and FRC prediction is similar for children aged <6 yrs.

In conclusion, it has been shown that quantitative measurements of normal lung development can be made using computed tomography scans. The authors propose that the computed tomography scan can be used as a relatively non-invasive tool to provide valuable information about normal lung growth and the pathogenesis of lung disease.

References

1. Zeltner TB, Caduff JH, Gehr P, Pfenninger J, Burri PH. The postnatal development and growth of the human lung. I. Morphometry *Respir Physiol* 1987; **67**: 247–267.
2. Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. *Early Hum Dev* 1986; **13**: 1–11.
3. Thurlbeck WM. Postnatal human lung growth. *Thorax* 1982; **37**: 465–571.
4. Hogg JC, Williams J, Richardson JB, Macklem PT, Thurlbeck WM. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. *N Engl J Med* 1970; **282**: 1283–1287.
5. Taussig LM, Helms PJ. Basic Physiology. In: Stocks J, Sly PD, Tepper RS, Morgan WJ, eds. Infant Respiratory Function Testing. New York, Wiley-Liss, 1996; pp. 2–15.
6. Mansell AL, Bryan AC, Levison H. Relationship of lung recoil to lung volume and max expiratory flow in normal children. *J Appl Physiol* 1977; **42**: 817–823.
7. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; **159**: 851–856.
8. Coxson HO, Mayo JR, Behzad H, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol* 1995; **79**: 1525–1530.
9. Coppoletta JM, Wolbach SB. Body length and organ weights of infants and children. *J Path* 1933; **9**: 55–70.
10. Bar-Yishay E, Shulman DL, Beardsmore CS, Godfrey S. Functional residual capacity in healthy preschool children lying supine. *Am Rev Respir Dis* 1987; **135**: 954–956.
11. Zapletal A, Samanek M, Paul T. Lung function in children and adolescents: methods, reference values. First ed. Basel, Karger, 1987.

6.2 Estimation of lung dimensions throughout the growth period using computed tomography

We aimed to use computed tomography (CT) to estimate airway wall and lumen, arterial and parenchyma dimensions in children throughout the growth period and to provide normative data to study alterations caused by pulmonary disease. Clinical CT scans reported as normal that were performed in children for non-pulmonary and non-cardiac reasons were analyzed for lung weight; gas volume; lung expansion; lung surface to volume ratio; airway wall area; airway lumen area; airway lumen perimeter; arterial area and airway surface to volume ratio. Ages of the 85 subjects ranged from 0 to 17.6 years. The data show only little increase in lung expansion throughout childhood. There was substantial variability in lung expansion between subjects (R^2 = 0.51 and 0.45 for males and females, respectively). Airway wall and lumen and arterial area were exponentially associated with subjects' height. Airway surface to volume ratio (cm^{-1}) was linearly associated to lung surface to volume ratio (cm^{-1}, R^2=0.46-0.66, $p<0.001$). Our data provide normative CT estimates of airway wall and lumen, arterial and parenchyma dimensions throughout the growth period that may be useful to study alterations in disease.

Based on:

Pim A de Jong, Frederick R Long, Jonathan C Wong, Peter J Merkus, Harm A Tiddens, James C Hogg, Harvey O Coxson. Computed Tomographic Estimation of Lung Dimensions throughout the Growth Period

Resubmitted to *Eur Resp J*

Introduction

Between one-third and one-half of the adult number of alveoli are present in the human lung at birth [1]. This number increases rapidly by a process of septation of the primary saccules and probably reaches adult values between 1.5–2 years of age and certainly by 8 years [1-5]. After the phase of rapid alveolar addition is completed, the number of alveoli remains constant and the lung continues to grow by increasing the dimensions of all of the lung structures [1, 4, 5]. In contrast to alveoli, the number of conducting airways and pulmonary arteries is complete at birth and they increase only in size during postnatal growth [6, 7]. Whether airway sizes and airway growth patterns differ between sexes in infancy [8-17] or later in childhood [18-25] remains controversial.

Alterations in the growth of lung structures occurs secondary to a wide variety of congenital [26] and developmental insults [27-29] yet little normative data exists regarding how lung structure changes with age or height. Therefore, a better understanding of lung growth in health and disease in needed. Computed tomography (CT) scanning has made it possible to study lung structure *in vivo* [21, 30-34] and provides a useful tool for evaluation of both lung disease [28, 29, 35, 36] and normal lung parenchyma (lung weight, gas volume and expansion) [37].

Previously we estimated lung parenchyma dimensions in a cohort of children ranging from birth through adolescence [37]. In the present study we estimated airway wall and lumen dimensions of the conducting airways and dimensions of the accompanying pulmonary artery in addition to the lung parenchyma in a different cohort of children and compare our findings to the previous study. The aim of this study was to use CT to estimate airway wall and lumen, arterial and parenchyma dimensions in children throughout the growth period and to provide normative data to study alterations caused by pulmonary disease.

Methods

Subjects

Only CT scans initially reported as normal with confirmation of this opinion by a second radiologist were included in the study. The questions of the CT scan, the clinical diagnoses or the findings were the following: Pulmonary haemorrhage (minimal bleeding, n=2); cystic fibrosis (n=6, all stable <1 yrs of age); cystadenomatous malformation of the lung (n=1); tumours with no metastasis including brain tumour not specified (n=1), lymphoma (n=9), Ewing sarcoma (n=1), ovarian teratoma (n=1), unknown (n=3), wilms tumour (n=5), hepatoblastoma (n=4), rhabdomyosarcoma (n=4), neuroblastoma (n=2), osteochondrosarcoma (n=4), testis tumour (n=1) and melanoma (n=1); vascular ring excluded (n=3); haemangioma (n=1); foreign body excluded (n=2); sternal cleft (n=1);

laryngotracheomalacia (mild, n=1); aspiration or reflux (n=4); respiratory distress (n=2); meckel diverticulum (n=1); langerhans cell histiocytosis (n=1); mitochondrial disease (n=2); follow-up small cyst (n=1); recurrent infections (n=4); seroma (n=1); recovered pneumothorax (n=3); solitary nodule follow up (n=3); chest wall mass (n=2); recurrent sinusitis (n=2); haemoptysis (n=2); lupus like syndrome (n=1); chest pain (n=1); uveitis (n=1); and dysphagia (n=1).

We included 35 subjects from Rotterdam and 50 subjects from Columbus. All 35 of the CT scans performed at Erasmus MC-Sophia (Rotterdam, The Netherlands) were included in a previous report [37]. Nineteen of the 50 CT scans obtained at Columbus Children's Hospital (Columbus, Ohio, USA) have been previously reported [28]. In that report airway wall and lumen and arterial dimensions were measured using a different measurement program and in that study the normal dimensions were compared with cystic fibrosis patients. The ethical review boards of Erasmus MC-Sophia and Columbus Children's Hospital approved the study.

Computed tomography scans

The CT examinations performed in Columbus were obtained on a GE lightspeed Ultra 8-slice CT scanner (General Electric Healthcare, Milwaukee, WI) using a potential of 120 kV and a beam current ranging from 30 to 120 mAs. Volumetric inspiratory scanning was performed from lung apex to base after a breath-hold instruction in the children from 5 years and on. A previously described method of volume controlled CT was used in children younger than five years of age [38-40]. Briefly, the infants were sedated and an apnoea was briefly induced to allow lungs to be inflated to an airway pressure of 25-cm H_2O using a facemask during the CT scanning. The 19 infants previously reported were scanned on the same scanner using the same scanning technique but only at 4 selected levels [28]. Those 19 CT scans could therefore only be used to estimate airway wall and lumen and arterial dimensions and not to estimate lung parenchyma. The other 31 CT scans from Columbus could be used to measure airway wall and lumen, arterial and parenchyma dimensions. All scans were reconstructed using both a high-resolution ("Bone") and an intermediate ("Standard") reconstruction algorithm at 1.25-mm slice thickness. No contrast was used for the CT scanning.

The scanning protocol of the Rotterdam subjects has previously been described [37]. Volumetric CT scans (3-10 mm collimation) were performed after a breath-hold instruction or while quiet breathing on a GE single slice scanner and reconstructed using an intermediate ("Standard") algorithm. Because of the thick slices only lung parenchyma and not airway and arterial dimensions could be estimated and therefore no additional measurements were done on those CT scans. Only the data were re-analysed as described later. The reason to show these 35 subjects again is to demonstrate the differences of parenchyma dimensions between Rotterdam and Columbus subjects and to explain these differences [37].

Computed tomography parenchyma analyses

The CT scans were transferred to the James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research (Vancouver, BC, Canada). The lung parenchyma was analysed using the "Standard" reconstruction algorithm as previously described [33, 34]. Briefly, the lung was segmented from the chest wall and surrounding structures. The gas volume is calculated by summing the voxels within the lung and density is calculated from the x-ray attenuation values. Lung weight, in grams, is calculated by multiplying the lung density by volume. Lung expansion, in millilitres of gas per gram of tissue, is calculated by subtracting the inverse of the density of tissue (assumed to be 1.065 $g*mL^{-1}$) from the inverse of the CT-measured lung density [33, 34]. Lung surface area to volume ratio (S/V) is calculated using the lung expansion values at TLC as previously described; S/V lung = $e^{6.84-(0.32*\text{lung expansion at TLC})}$ Ref 34.

CT-estimated lung weight was compared to previously reported post mortem values from children with normal lungs [41]. The CT-determined gas volume was compared to predicted normal values for functional residual capacity (FRC) and total lung capacity (TLC) using standard prediction equations based on body length [1, 4, 42-44]. CT-estimated lung expansion was compared between Columbus and Rotterdam subjects and between males and females. To overcome the problem of different inflation levels between subjects during the CT procedure, lung expansion at full lung inflation was calculated by dividing the predicted TLC by the CT-estimated lung weight (hereafter: lung expansion at TLC).

Computed tomography airway and artery analysis

Airway wall and lumen and arterial dimensions were estimated using the 50 Columbus subjects at specified locations of the bronchial tree (Figure 1) as previously described [31, 32]. If in the 19 Columbus subjects with 4 slices a given airway branch could not be found this branch was excluded. The measurement locations were: trachea (T), right bronchus intermedius (RBI), right apical bronchus (RAB) and the first, second and third branch after the right apical bronchus (RAB1, RAB2 and RAB3 respectively). Airway lumen area (LA) and perimeter (Pi) and airway wall area (WA) were measured from T through RAB2, since RAB3 was too small to be measured. Arterial area (AA) was measured from RAB through RAB3, since T and RBI do not have a measurable pulmonary artery. A seed point is manually placed in the lumen of the airway or artery and 64 rays are cast from this point into the parenchyma. The borders of inner and outer airway wall or outer arterial wall are determined using the full-width at half maximum principle [45]. Rays that are too long or too short are manually edited and the dimensions calculated by connecting the ends of the rays using a spline function. Lumen area (LA) is defined as the area internal to the inner wall in airways and the internal perimeter (Pi) is the length of the inner boundary of the rays. Airway wall area (WA) is the area between the inner and outer boundaries. Arterial area (AA) is the area internal to the outer wall of the artery.

Trachea lumen area was compared to previously published values of CT estimated trachea lumen area [46, 47]. Airway lumen perimeter was divided by airway lumen area to estimate airway surface to volume ratio (airway S/V-ration = Pi/LA). The airway surface to volume ratio was compared to the lung surface to volume ratio.

Figure 1 sites at the bronchial tree of airway-artery measurements

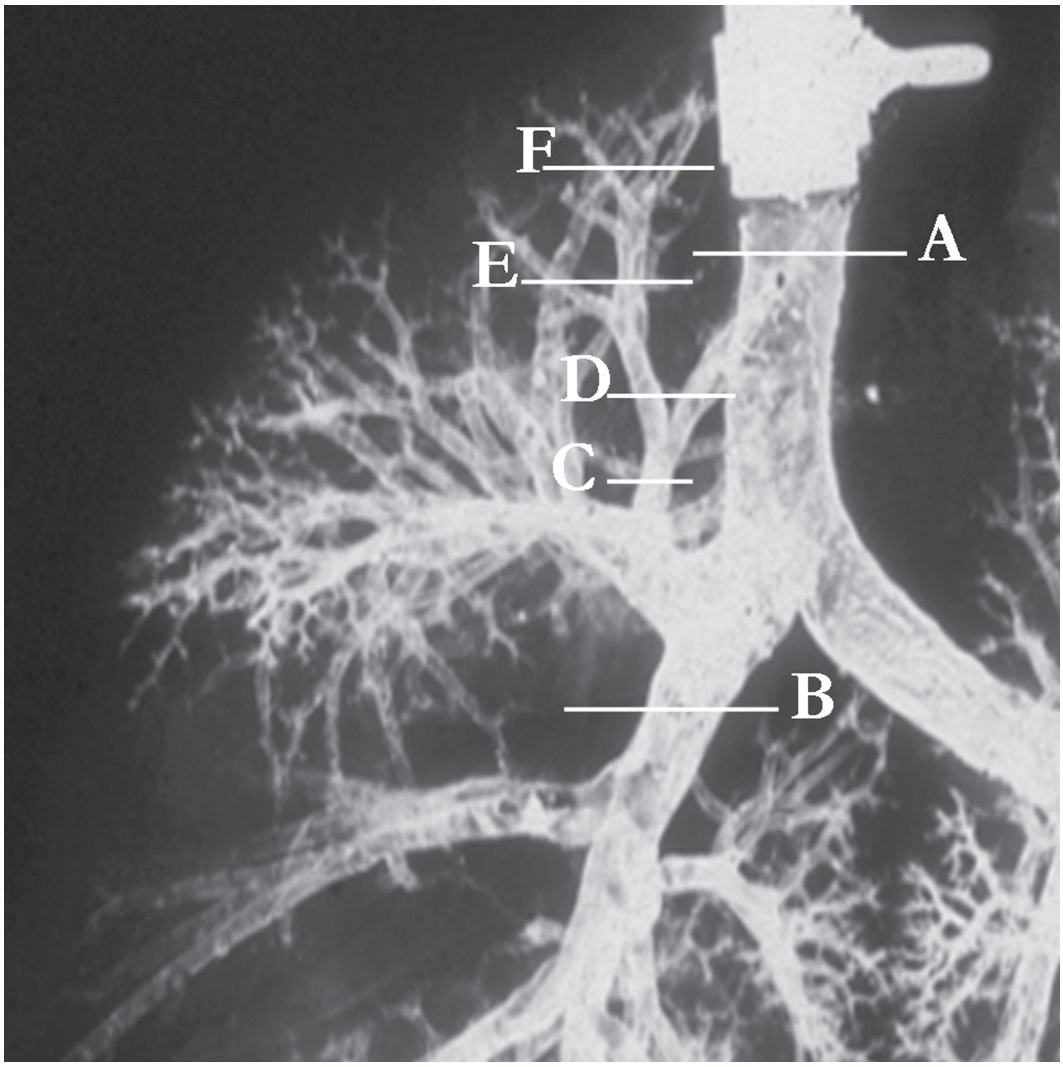


Figure shows a bronchogram that clearly demonstrates the divisions of the airway tree where the measurements were performed on CT for the present study.

A: trachea (T):	lumen area and wall area
B: right bronchus intermedius (RBI):	lumen and wall area
C: right apical bronchus (RAB):	lumen and wall area and arterial area
D: first branch after RAB:	lumen and wall area and arterial area
E: second branch after RAB:	lumen and wall area and arterial area
F: third branch after RAB:	arterial area

Statistical analysis

Parenchyma dimensions were estimated in 66 subjects (35 Rotterdam, 31 Columbus. Airway wall and lumen and arterial dimensions were estimated in 50 subjects (all Columbus). Comparison between airway and arterial dimensions and parenchyma dimensions was possible in 31 subjects (all Columbus). Those data were analysed using a software package (SPSS version 10.0; SPSS, Chicago, Ill). Significance level was set as $p<0.05$. For all variables mean ± SD (range) were calculated. Exponential, power, linear and logistic curve fitting with 95% confidence intervals was performed to correlate airway wall and lumen area, arterial area, lung weight, lung expansion at TLC with subject height. The best fitting curve is reported. Spearman correlation was used to determine the relationships between LA of the trachea and the other measured airways, between the AA of the right apical bronchus and the other measured arteries and between the lung S/V-ratio and the airway S/V ratio (Pi/LA).

Results

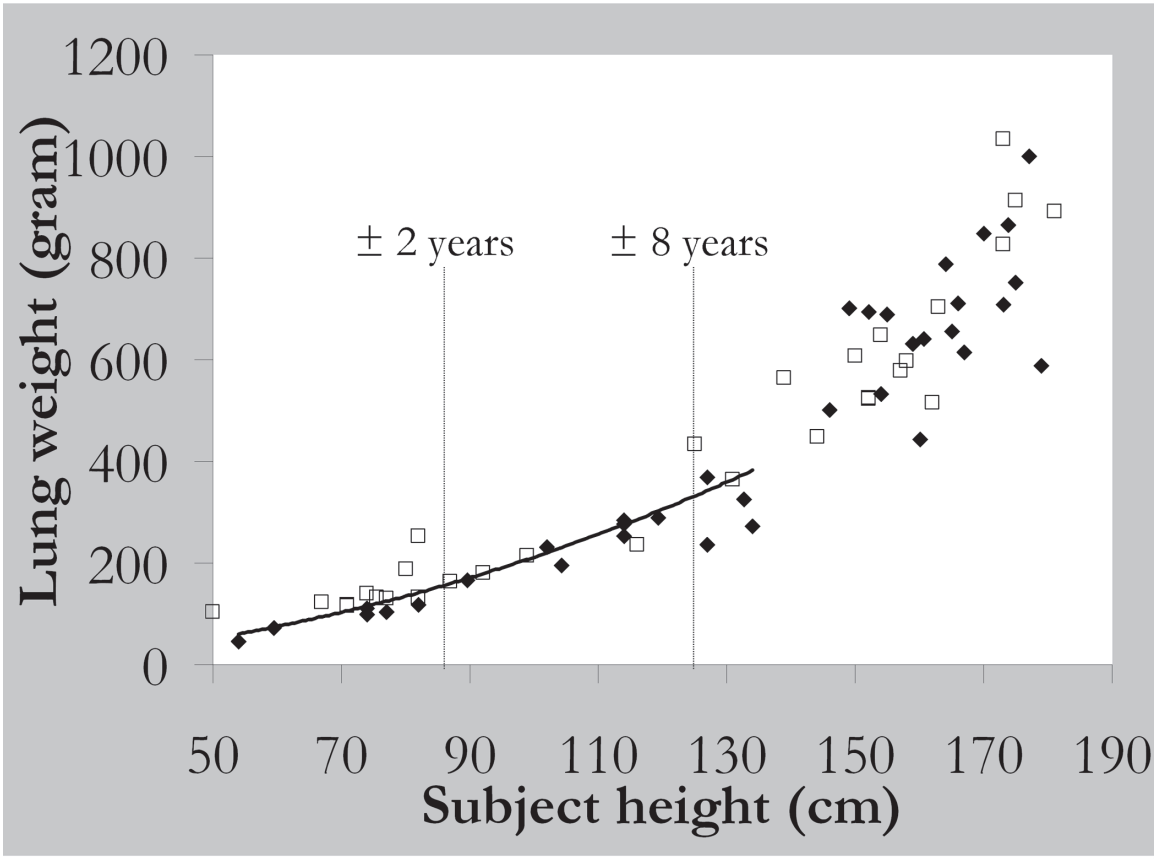
Study population

Table 1 shows the subjects' age, sex and height and results from CT parenchyma analysis. The calculated mean (SD) lung expansion at TLC was 6.53 (1.37) (female) and 6.18 (1.94) (male) ml gas/g tissue.

Parenchyma

Lung weight (CT measured and predicted published values) was compared to subjects' height (Figure 2) and the regression equation for the line of best fit is shown in Table 2. CT measured gas volume was compared to predicted TLC and predicted FRC in Figure 3. CT measured lung expansion is shown in Figure 4a for Rotterdam and Columbus subjects and lung expansion at TLC is shown in Figure 4b for males and females. The corresponding regression equations of lung expansion at TLC for males and females are shown in Table 2.

Figure 2 CT measured lung weight and predicted lung weight (line) against subjects' height



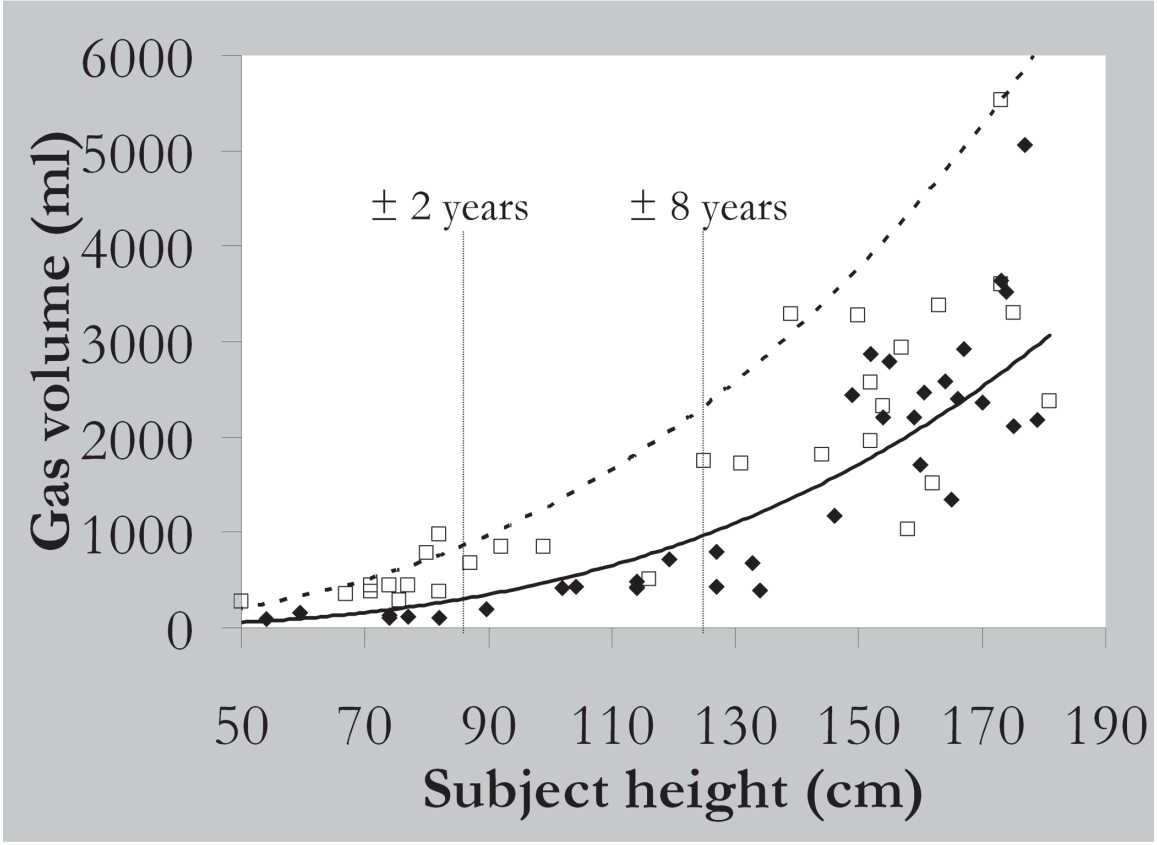
Closed diamonds represent Rotterdam data and open squares represent Columbus data. Solid line represents predicted lung weight from published data on autopsy specimens [41]. CT measured lung weight = 29.167 * EXP $^{\text{subject height} * 0.0192}$ (R^2=0.94, p<0.0001).

Table 1 Patient characteristics and CT estimates given per age

Age (yrs)	N (male)	Subject height (cm)		CT weight (g)		CT gas volume (ml)		Predicted TLC (ml)		Pred TLC / CT weight (ml/g)	
		mean	SD	mean	SD	Mean	SD	mean	SD	mean	SD
0	17 (11)	65.1	9.8	99	27	225	128	423	173	4.4	1.4
1	12 (9)	79.4	3.9	146	26	472	241	729	106	5.3	1.1
2	6 (3)	88.7	3.4	200	47	674	414	998	108	5.2	1.8
3	5 (4)	101.6	1.8	213	18	565	244	1345	47	6.2	0.3
4	2 (2)	114.5	0.7	277	0	433	0	1837	184	6.2	0.0
5	4 (3)	116.0	7.7	258	23	445	36	1825	485	7.5	2.7
6	2 (1)	123.0	5.7	329	55	758	52	2292	349	7.0	0.1
7	2 (1)	120.5	6.4	335	141	1125	875	2170	378	6.9	1.8
8	1 (1)	133.0	0.0	324	0	680	0	2842	0	8.8	0.0
9	2 (2)	132.5	2.1	319	66	1060	942	2832	117	9.1	2.3
10	1 (0)	144.0	0.0	449	0	1818	0	3320	0	7.4	0.0
11	2 (0)	146.5	10.6	548	23	2750	768	3489	648	6.4	1.4
12	7 (4)	153.0	6.8	619	82	2490	715	4010	399	6.6	0.9
13	4 (0)	160.3	2.6	616	141	1887	672	4373	188	7.4	1.7
14	6 (2)	168.3	12.5	727	159	2557	489	5114	1057	7.2	1.7
15	5 (2)	171.8	3.9	795	147	3247	1611	5352	376	6.8	0.8
16	3 (0)	165.0	10.6	740	228	3489	1382	4731	804	6.6	0.9
17	4 (2)	166.5	5.9	711	163	2649	875	4976	594	7.2	1.1

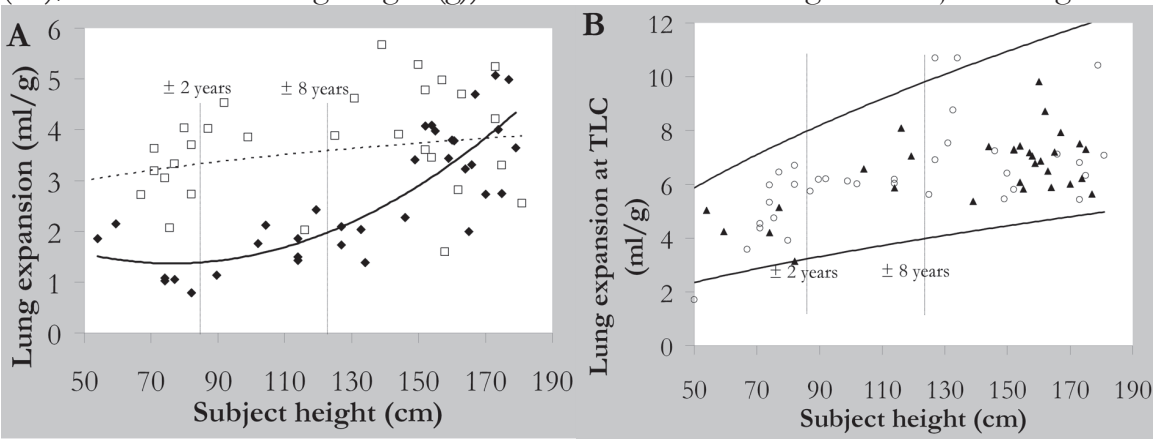
N is number. SD is standard deviation. CT weight, CT gas volume and predicted total lung capacity divided by CT weight were obtained in 66 out of 85 subjects.

Figure 3 CT measured gas volume and predicted TLC and FRC against subjects' height



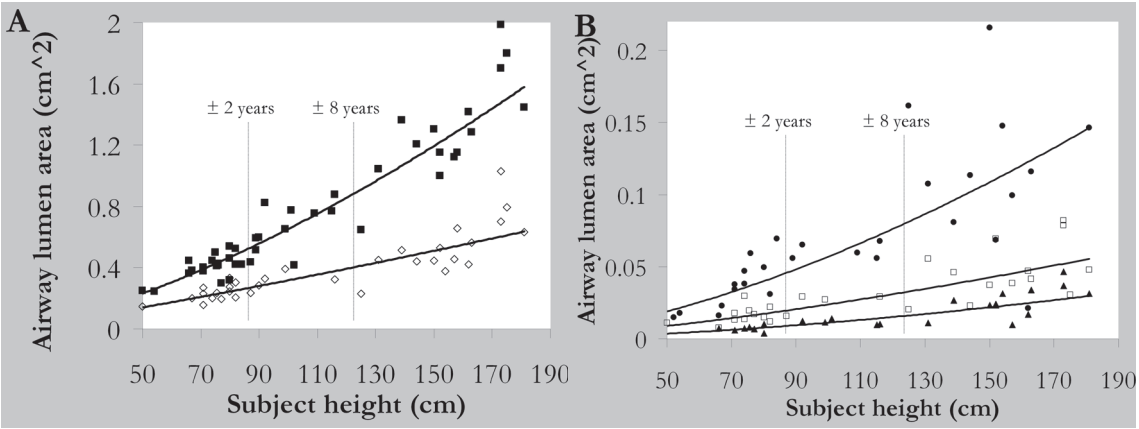
Closed diamonds represent Rotterdam data and open squares represent Columbus data.
Dashed line represents predicted total lung capacity (TLC) and solid line represents predicted functional residual capacity (FRC). Subjects' height for approximately 2 years and 8 years of age is given.

Figure 4 A. CT measured lung expansion for Rotterdam and Columbus subjects against subjects' height. B. Lung expansion at total lung capacity (Predicted TLC (ml)/ CT measured lung weight (g)) for males and females against subjects' height



A: Closed diamonds represent Rotterdam data, open squares represent Columbus data. Dashed line represents best fit through Columbus data and solid line represents best fit through Rotterdam data. Subjects' height for approximately 2 years and 8 years of age is given. Note the marked differences in lung expansion between Rotterdam and Columbus infants caused by differences in lung inflation during the CT scanning procedure. B: Closed triangles represent females and open circles represent males. Lines represent 95% confidence interval through data for males and females together. Data were grouped for males and females due to small sample size.

Figure 5 The relationship between airway lumen area (cm^2) and subject height (cm)



A. The left panel shows data for trachea and right bronchus intermedius. Solid squared represent trachea, open diamonds represent right bronchus intermedius. B. The right panel shows data for right apical bronchus (RAB), first branch after RAB (RAB1) and second branch after RAB (RAB2). Solid circles represent RAB, open squares represent RAB1, closed triangles represent RAB2. Regression lines are provided for each generation and corresponding equations are given in Table 2. 95% confidence intervals are not shown. Data were grouped for males and females due to small sample size.

Table 2 Regression equations for CT estimated lung structures versus subject height

Y	Number	Sex	A	B	Correlation (R^2)	P-value
Lung weight (g)	66	Both	29.167	0.0192	0.94	<0.001
Lung expansion (ml/g)	31	Female	0.652	0.466	0.45	<0.001
Lung expansion (ml/g)	35	Male	0.2374	0.6867	0.51	<0.001
Lumen area (cm^2)						
Trachea	48	Both	0.0003	1.6426	0.90	<0.001
Right bronchus intermedius	34	Both	0.0003	1.4572	0.85	<0.001
Right apical bronchus (rab)	29	Both	$2*10^{-6}$	2.0165	0.80	<0.001
First branch after rab	29	Both	$3*10^{-6}$	1.6847	0.75	<0.001
Second branch after rab	25	Both	$5*10^{-7}$	1.9444	0.77	<0.001
Wall area (cm^2)						
Trachea	48	Both	0.0016	1.2724	0.87	<0.001
Right bronchus intermedius	34	Both	0.0024	1.1099	0.86	<0.001
Right apical bronchus	29	Both	0.0004	1.3027	0.80	<0.001
First branch after rab	29	Both	0.0005	1.1278	0.83	<0.001
Second branch after rab	25	Both	$5*10^{-5}$	1.4132	0.85	<0.001
Arterial area (cm^2)						
Right apical bronchus	31	Both	0.0004	1.2099	0.76	<0.001
First branch after rab	30	Both	$5,6*10^{-5}$	1.5279	0.73	<0.001
Second branch after rab	46	Both	$1,9*10^{-5}$	1.6145	0.77	<0.001
Third branch after rab	47	Both	$4,5*10^{-6}$	1.7790	0.86	<0.001

Equations $Y=A*X^B$, except lung weight ($Y=A*EXP^{XB}$). All equations X=subject height (cm). Lung expansion is predicted total lung capacity (TLC) divided by CT measured lung weight, expressed as ml gas/g tissue

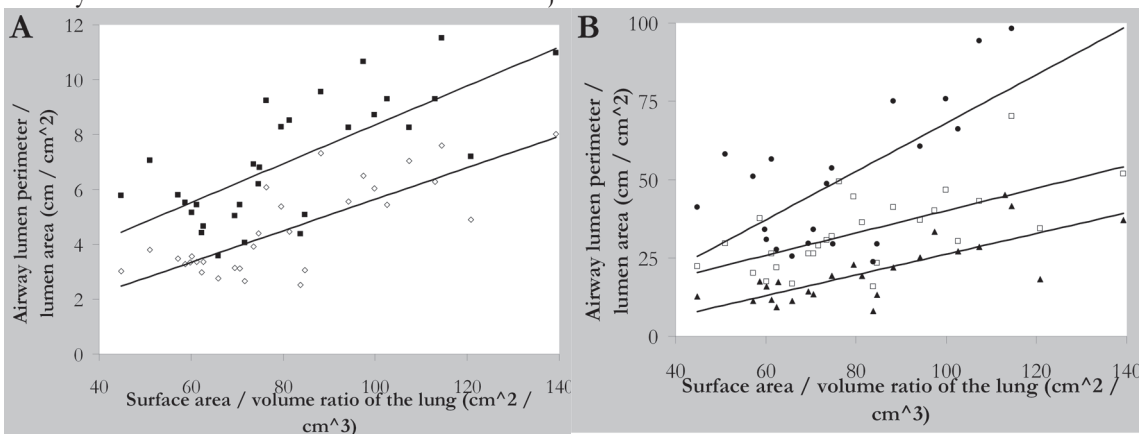
Airways and arteries

The $LA_{Trachea}$ of our subjects was compared to published normal values (data not shown) [46, 47]. There is a strong correlation between the trachea ($LA_{Trachea}$) and all the other measured airways (R^2: LA_{RBI}=0.93, LA_{RAB}=0.82, LA_{RAB1}=0.87 and LA_{RAB2} =0.91, all $p<0.0001$). There is also a strong correlation between the arterial dimension of the right apical bronchus (AA_{RAB}) and all the other measured arteries (R^2: AA_{RAB1} =0.85, AA_{RAB2}=0.87 and AA_{RAB3}=0.87 all $p<0.0001$). The relationship between LA and subject height for the various generations is shown in Figure 5 (95% confidence intervals are not shown). Equations for airway wall and lumen and artery area versus subjects' height are listed in Table 2.

Airway versus parenchyma

The relationship between surface to volume ratio of the lung and surface to volume ratio of the various airways is shown in Figure 6. The correlation between surface to volume of the lung and surface to volume of the trachea, RBI, RAB, RAB1 and RAB2 was 0.62, 0.51, 0.59, 0.42 and 0.44 respectively (all $p<0.0001$).

Figure 6 Lung surface area to lung volume ratio against airway lumen perimeter to airway lumen area for the Columbus subjects



A. The left panel shows data for trachea and right bronchus intermedius. Open diamonds represent trachea, solid squares represent right bronchus intermedius. B. The right panel shows data for right apical bronchus (RAB), open squares represent first branch after RAB (RAB1), closed circles represent second branch after RAB (RAB2). Solid triangles represent RAB, open squares represent RAB1, closed circles represent RAB2. Linear regression lines are provided for each generation. The linear dimensions of the lung (cm^{-1}) are linearly related to the linear dimensions of the airway (cm^{-1}).

Discussion

This study uses CT scans to estimate airway wall and lumen, arterial and parenchyma dimensions (lung weight, gas volume, lung expansion, surface to volume ratio) in children throughout the growth period. These data show that when lung expansion is corrected for predicted TLC, there is only a small gradual change in lung expansion at TLC. This suggests that even during the first two years of life when the septation process results in rapid alveolar addition, lung weight does not increase as rapidly as the gas volume. Using pathologic specimens, Thurlbeck found an increase in lung expansion from 3 millilitre of gas per gram tissue (ml/g) at birth to about 8 ml/g at age six [3]. These values correspond well to our values of approximately 4 ml/g at birth and 6 ml/g in adolescence obtained using CT. These findings are markedly different from our previous report where we found a decrease in lung expansion during the first two years of life, while in the present study lung expansion slightly increased during this period [37]. This difference can be explained by the difference in lung inflation techniques between Columbus and Rotterdam, which produced very different pulmonary gas volumes between Rotterdam and Columbus (Figure 3).

Therefore, expressing the lung expansion at TLC by dividing measured or predicted TLC by CT estimated lung weight may be a more appropriate method to present the data (Figure 4).

There was substantial variability in expansion at TLC during the growth period. Part of this variation could be caused by differences in scanning technique (slice thickness). Most of the variation however is likely to represent variation between individuals which might limit its usefulness to study small alterations in lung expansion at TLC in disease.

The tracheal lumen area compared favourably to previous CT estimates from Griscom et al [46, 47] and to post mortem studies, bronchographic studies and other CT studies [48]. In the present study we were also able to measure airways smaller than the trachea down to the limit that current CT scanners allow (approximately lumen diameter of 1 mm). We could not demonstrate differences in airway sizes between males and females, which contrast with functional studies in children and adults [8, 9, 11, 19, 20, 23, 43]. This suggests that the changes in function might be due to differences in smaller airways that cannot be measured by CT or to type II errors in our study due to the small sample size. In addition based on our data one can not determine if the conducting airways are relatively larger or smaller in infancy. Potentially (preferably longitudinal) CT studies can solve these controversial issues.

We found less variation in the airway wall and lumen and arterial estimates compared to lung expansion at TLC. For the variation in airway and arterial measurements at a given subject height that we found, there are several possible explanations. The measurement program is one source of some of this variation [32, 49] and differences in lung inflation between subjects are another [50]. But some of the variation likely represents the real variability between subjects. We speculate that this could have implications for the subsequent development of airway disease or respiratory symptoms in subjects with relatively narrow airways [24, 30], however this requires further study.

The surface to volume ratio of alveoli was linearly related to the surface to volume ratio of the airways suggesting that the growth of the airway and the alveolus is closely linked, but longitudinal studies of the same individuals would be required to establish this point. Such studies could address if airways grow isotropic or dysanaptic. However, the radiation exposure from current CT protocols currently limits this approach to subjects that require CT scans of the thorax for other reasons.

The major limitation of this study is that for the safety reasons mentioned above it only provides cross sectional information about lung growth. The second limitation is that we have neither pathologic validation of the measurements in these subjects, nor access to pulmonary function. The third limitation is that the number of subjects studied, which made it difficult to analyse differences between males and females.

Finally as we only measured airways in the right upper lobe we must assume that the growth patterns are the same in other lobes.

In conclusion, these data show that lung expansion is more stable than previously reported because lung volume, corrected to TLC, and lung weight increases in such a way that overall lung expansion increases surprisingly little between birth and 17 years of age. Also in the period of rapid alveolar addition there is only a slightly increase in lung expansion at TLC. This suggests that the increase in gas volume associated with alveolar addition requires a very limited increase in lung tissue. We did not find evidence that CT measured airways are larger in infants or in male subjects, which may be related to sample size. Nevertheless, our data provides useful normative estimates of airway, artery and maybe parenchyma growth, which may be applicable to study alterations in children with pulmonary diseases.

References

1. Thurlbeck WM. Postnatal human lung growth. *Thorax* 1982; **37**(8)**:** 564-71.
2. Dunnill M. Postnatal growth of the lung. *Thorax* 1962; **17:** 329-333.
3. Thurlbeck WM. Postnatal growth and development of the lung. *Am Rev Respir Dis* 1975; **111**(6)**:** 803-44.
4. Zeltner TB, Burri PH. The postnatal development and growth of the human lung. II. Morphology. *Respir Physiol* 1987; **67**(3)**:** 269-82.
5. Hislop A, Wigglesworth J, Desai R. Alveolar develoment in the human fetus and infant. *Early Hum Dev* 1986; **13**(1)**:** 1-11.
6. Reid L. 1976 Edward B.D. Neuhauser lecture: the lung growth and remodeling in health and disease. *AJR Am J Roentgenol* 1977; **129**(5)**:** 777-788.
7. Hislop AA. Airway and blood vessel interaction during lung development. *J Anat* 2002; **201**(4)**:** 325-34.
8. Jones M, Castile R, Davis S, et al. Forced expiratory flows and volumes in infants. Normative data and lung growth. *Am J Respir Crit Care Med* 2000; **161**(2 Pt 1)**:** 353-9.
9. Lambert RK, Castile RG, Tepper RS. Model of forced expiratory flows and airway geometry in infants. *J Appl Physiol* 2004; **96**(2)**:** 688-92.
10. Stocks J. The functional growth and development of the lung during the first year of life. *Early Hum Dev* 1977; **1**(3)**:** 285-309.
11. Tepper RS, Morgan WJ, Cota K, Wright A, Taussig LM. Physiologic growth and development of the lung during the first year of life. *Am Rev Respir Dis* 1986; **134**(3)**:** 513-9.
12. Hislop A, Muir DC, Jacobsen M, Simon G, Reid L. Postnatal growth and function of the pre-acinar airways. *Thorax* 1972; **27**(3)**:** 265-74.
13. Horsfield K, Gordon WI, Kemp W, Phillips S. Growth of the bronchial tree in man. *Thorax* 1987; **42**(5)**:** 383-8.
14. Cudmore R, Emery J, Mithal A. Postnatal growth of the bronchi and bronchioles. *Arch Dis Child* 1962; **Oct**(37)**:** 481-484.
15. Davies G, Reid L. Growth of the alveoli and pulmonary arteries in childhood. *Thorax* 1970; **25**(6)**:** 669-81.
16. Hogg JC, Williams J, Richardson JB, Macklem PT, Thurlbeck WM. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. *N Engl J Med* 1970; **282**(23)**:** 1283-7.

17. Mansell AL, Bryan AC, Levison H. Relationship of lung recoil to lung volume and maximum expiratory flow in normal children. *J Appl Physiol* 1977; **42**(6)**:** 817-23.
18. Hibbert M, Lannigan A, Raven J, Landau L, Phelan P. Gender differences in lung growth. *Pediatr Pulmonol* 1995; **19**(2)**:** 129-34.
19. Green M, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol* 1974; **37**(1)**:** 67-74.
20. Martin TR, Castile RG, Fredberg JJ, Wohl ME, Mead J. Airway size is related to sex but not lung size in normal adults. *J Appl Physiol* 1987; **63**(5)**:** 2042-7.
21. Pagtakhan RD, Bjelland JC, Landau LI, et al. Sex differences in growth patterns of the airways and lung parenchyma in children. *J Appl Physiol* 1984; **56**(5)**:** 1204-10.
22. Martin TR, Feldman HA, Fredberg JJ, Castile RG, Mead J, Wohl ME. Relationship between maximal expiratory flows and lung volumes in growing humans. *J Appl Physiol* 1988; **65**(2)**:** 822-8.
23. Briscoe W, Dubois A. The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. *J Clin Invest* 1958; **37:** 1279-1285.
24. Merkus PJ, Borsboom GJ, Van Pelt W, et al. Growth of airways and air spaces in teenagers is related to sex but not to symptoms. *J Appl Physiol* 1993; **75**(5)**:** 2045-53.
25. Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. *Pediatr Pulmonol* 1996; **21**(6)**:** 383-97.
26. Ijsselstijn H, Tibboel D, Hop WJ, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. *Am J Respir Crit Care Med* 1997; **155**(1)**:** 174-80.
27. Tiddens H, Silverman M, Bush A. The role of inflammation in airway disease: remodeling. *Am J Respir Crit Care Med* 2000; **162**(2 Pt 2)**:** S7-S10.
28. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2)**:** 154-61.
29. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23**(1)**:** 93-7.
30. Hislop AA. Lung growth and computed tomography. *Eur Respir J* 2003; **22**(2)**:** 195-6.
31. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000; **162**(3 Pt 1)**:** 1102-8.
32. Nakano Y, Whittall KP, Kalloger SE, Coxson HO, Paré PD, English JC. Development and Validation of Human Airway Analysis Algorithm Using Multidetector Row CT. *Proceedings of SPIE* 2002; **4683:** 460-469.
33. Coxson HO, Mayo JR, Behzad H, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol* 1995; **79**(5)**:** 1525-30.
34. Coxson HO, Rogers RM, Whittall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999; **159**(3)**:** 851-6.
35. de Jong PA, Ottink MD, Robben SG, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231**(2)**:** 434-9.
36. de Jong PA, Nakano Y, Hop WC, et al. Changes in Airway Dimensions on Computed Tomography Scans of Children With Cystic Fibrosis. *Am J Respir Crit Care Med* 2005.
37. de Jong PA, Nakano Y, Lequin MH, et al. Estimation of lung growth using computed tomography. *Eur Respir J* 2003; **22**(2)**:** 235-8.
38. Long FR, Castile RG. Technique and clinical applications of full-inflation and end-exhalation controlled-ventilation chest CT in infants and young children. *Pediatr Radiol* 2001; **31**(6)**:** 413-22.
39. Long FR. High-resolution CT of the lungs in infants and young children. *J Thorac Imaging* 2001; **16**(4)**:** 251-8.
40. Long FR, Castile RG, Brody AS, et al. Lungs in infants and young children: improved thin-section CT with a noninvasive controlled-ventilation technique--initial experience. *Radiology* 1999; **212**(2)**:** 588-93.

41. Coppoletta J, Wolbach S. Body length and organ weights of infants and children. *J Path* 1933; **9:** 55-70.
42. Bar-Yishay E, Shulman DL, Beardsmore CS, Godfrey S. Functional residual capacity in healthy preschool children lying supine. *Am Rev Respir Dis* 1987; **135**(4)**:** 954-6.
43. Castile R, Filbrun D, Flucke R, Franklin W, McCoy K. Adult-type pulmonary function tests in infants without respiratory disease. *Pediatr Pulmonol* 2000; **30**(3)**:** 215-27.
44. Zapletal A, Samanek M, Paul T. Lung Function in Children and Adolescents. Methods, Reference Values. Basel: Karger, 1987.
45. Amirav I, Kramer SS, Grunstein MM, Hoffman EA. Assessment of methacholine-induced airway constriction by ultrafast high-resolution computed tomography. *J Appl Physiol* 1993; **75**(5)**:** 2239-50.
46. Griscom NT, Wohl ME. Dimensions of the growing trachea related to body height. Length, anteroposterior and transverse diameters, cross-sectional area, and volume in subjects younger than 20 years of age. *Am Rev Respir Dis* 1985; **131**(6)**:** 840-4.
47. Griscom NT, Wohl ME, Fenton T. Dimensions of the trachea to age 6 years related to height. *Pediatr Pulmonol* 1989; **6**(3)**:** 186-90.
48. Effmann EL, Fram EK, Vock P, Kirks DR. Tracheal cross-sectional area in children: CT determination. *Radiology* 1983; **149**(1)**:** 137-40.
49. Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 2005; **171**(2)**:** 142-6.
50. Brown R, W. M. Effect of lung inflation and airway muscle tone on airway diameter in vivo. *J Appl Physiol* 1996; **80**(5)**:** 1581-1588.

Chapter 7

Summary, general discussion and future directions

7.1 Summary

For clinical management of CF related lung disease to be optimally effective, onset and progression of lung disease is commonly closely monitored. This can be done either indirectly by measuring lung function or more directly by imaging lung structure. Pulmonary function tests (PFTs), such as spirometry and body plethysmography, are considered the most important tools for measuring lung function routinely from the age of 5-6 years onwards. To image lung structure chest radiographs are routinely used. In many centers chest radiographs are made at least once yearly and often at times of exacerbations.

Longitudinal data have shown that PFTs are more sensitive than chest radiographs to monitor the progression of CF lung disease. Studies in the early nineties have shown that computed tomography (CT) scans are more sensitive than chest radiographs for the early detection of structural lung abnormalities in CF. In addition, CT scoring systems correlated moderately to good with PFTs and structural abnormalities on CT scans were detected in some CF patients with normal PFTs.

Many CT scoring systems for the quantification of structural lung abnormalities on CT scans of CF patients have been developed. Unfortunately, for several of these systems the between and within observer reproducibility was not tested or not described. As a comparative evaluation is lacking as well, it is hard to determine which system can be used best.

Apart from semi-quantitative scoring, CT scans enable quantitative measurements of airway wall and lumen dimensions. Quantitative CT analysis techniques have been validated for lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma but were not used to study CF.

Longitudinal studies in CF comparing changes in CT scores or quantitative CT measures with PFTs are still lacking.

Chapter 1 contains a general introduction to the thesis and states the aim of study.

Chapter 2 describes the rationale of our studies given the current practice of monitoring CF lung disease and its limitations. Chapter 2 specifically focuses on the benefits and limitations of monitoring lung function and lung structure with the use of PFTs, chest radiographs and CT scanning.

Chapter 3 describes the validation and use of CT scoring systems for CF.
Section **3.1** describes a study that compared thin-section CT scores obtained with five scoring systems for the assessment of pulmonary disease in children with cystic fibrosis. The additional value of bronchial and arterial dimension measurements was

determined as well. Scores obtained with five thin-section CT scoring systems were compared. A score of 0 indicates the absence of abnormalities; a higher score means that more structural abnormalities were seen. Three observers assigned scores and then reassigned scores after intervals varying from 1–2 weeks to 1–2 months of thin-section CT scans obtained in 25 children with CF. Interobserver and intraobserver reliability were calculated with intraclass correlation coefficients. Quantitative measurements of bronchial and arterial dimensions were obtained. Thin-section CT scores were correlated (Spearman correlation) with bronchial and arterial dimensions and with results of PFTs, such as forced expiratory volume in 1 second (FEV_1). Scores with all five scoring systems were reproducible, with intraclass correlation coefficients of 0.74 and higher ($P < 0.05$), and showed significant correlations with FEV_1 ($R = –0.73$ to $–0.69$, $P < 0.01$). Ratio of bronchial diameter to accompanying pulmonary arterial diameter was correlated with thin-section CT scores but not with FEV_1. Ratio of bronchial wall thickness to accompanying pulmonary arterial diameter was not correlated with thin-section CT scores or PFTs results. To conclude, thin-section CT scores were reproducible and were correlated with PFTs results. Measurements of bronchial dimensions were not significantly related to scores or PFTs results.

In **Chapter 4** we describe studies that compared the sensitivity of CT to standard PFTs for monitoring lung disease in children and adults with CF.
Section **4.1** describes the finding of progressive damage on high resolution CT (HRCT) despite stable PFTs in children with CF. The aim of the study was to investigate the ability of HRCT scoring systems and PFTs to detect changes in lung disease in CF children (n=48) who had two HRCT scans in combination with two PFTs 2 yrs apart. Their scans were scored using five scoring systems (Castile, Brody, Helbich, Santamaria and Bhalla). "Sensitivity" was defined as the ability to detect disease progression. In this group of children; HRCT scores worsened, whereas PFTs remained unchanged or improved. Of the HRCT parameters, mucous plugging and the severity, extent and peripheral extension of bronchiectasis worsened significantly. Relationships between changes in HRCT scores and PFTs were weak. Substantial structural lung damage was evident in some children who had normal lung function. These data show that HRCT is more sensitive than PFTs in the detection of early and progressive lung disease, and suggest that HRCT may be useful in the follow up of CF children and as an outcome measure in studies that aim to reduce lung damage.
In section **4.2** we describe the longitudinal evaluation of lung structure on CT scans and lung function in children and adults with CF. The first aim of this study was to investigate whether CT scores would be more sensitive than PFTs to monitor structural disease progression in adults with CF. The second aim was to investigate whether previous results in children with CF could be reproduced. CT scans and PFTs were retrospectively studied in a cohort of CF-patients aged 5 to 52 years for whom 2 or 3 CT scans in combination with PFTs (FEV_1, FVC, FEV_1/FVC, MEF_{25}, MEF_{50}, RV, TLC and RV/TLC) at a three-year interval between CT scans were available. All CT scans were scored by two observers. PFTs were expressed as

percentage predicted and Z-score. Of 119 patients included, 92 patients had two and 24 had three CT scans. CT scores (composite and components) and PFTs worsened significantly ($p<0.02$). However, peripheral bronchiectasis worsened most by 1.7% per year in children ($p<0.0001$) and by 1.5% per year in adults ($p=0.0003$). CT scores and PFTs showed similar worsening rates for adults and children ($p>0.09$). Therefore, it was concluded that peripheral bronchiectasis score was more sensitive than PFTs or composite CT score and other component scores for monitoring lung disease progression in this cohort of children and adults with CF.
In section **4.3** changes in quantitative airway dimensions on CT scans of children with CF over a two-year interval were studied. Children with CF (n=23) who had two CT scans (CT_{cf1} and CT_{cf2}) combined with PFTs at a two-year interval between measurements were compared to age-matched controls (n=21) who had one CT scan ($CT_{control}$). On cross-sectional cut airway-artery pairs, airway wall area (WA), airway lumen area (LA) and perimeter (Pi), and arterial area (AA) were quantified. LA/AA (=marker of bronchiectasis), airway wall thickness (AWT) and WA/AA (=markers of wall thickness) were calculated. CT scans were scored using 4 different scoring systems. PFTs were expressed as percent predicted. Airway wall area to arterial area ratio (WA/AA) was 1.45 ($p<0.001$) and airway lumen area to arterial area ratio (LA/AA) was 1.92 times higher ($p<0.001$) in CF compared to controls. LA/AA and WA/AA remained unchanged from CT_{cf1} to CT_{cf2} and did not increase with age. AWT as a function of airway size increased from CT_{cf1} to CT_{cf2} by 2% (0.03 mm; $p = 0.02$). The change in AWT was inversely related to the change in FEF_{25-75} ($p=0.002$). It was concluded, therefore, that in CF quantitative measurements of airways on CT scans show an increased ratio between airway lumen and arterial area and progressive airway wall thickening; scoring systems show progression of bronchiectasis but unchanged airway wall thickness and PFTs remain stable. In conclusion, in the three studies described above CT was more sensitive than PFTs to monitor CF related lung disease, both in children and in adults.

Chapter 5 focuses on radiation risks associated with CT scanning in CF.
In section **5.1** we stated that low-dose radiation from CT might increase the risk of certain cancers, especially in children. We sought to estimate the excess all-cause and cancer-specific mortality associated with serial lifelong CT scanning in CF patients. CT scanning dose was calculated for a published CF protocol and the risk per scan was estimated from atom-bomb survivor data. A computational model was developed to evaluate the effects of background survival, scanning interval and scanning doses on radiation-related excess mortality in a CF cohort. The average dose per CT scan was 1 milli-Sievert. Survival reduction associated with annual scans from age 2 years until death was 1 month and >1 year for CF cohorts with a median survival of 26 years and 50 years, respectively. Corresponding cumulative cancer mortality was <1% and 6% of the cohort. We concluded that routine lifelong annual CT scans carry a low risk of radiation-induced mortality in CF. However, as the overall survival for CF patients tend to increase, the risk of radiation-induced mortality will become much more meaningful. These data suggest that serial imaging

strategies can only be used when lifelong radiation exposure remains below acceptable risk levels that outweigh the benefit.
In section **5.2** we describe a study to determine whether the number of CT images and therefore the dose per CT scan could be reduced without any significant loss of information in children with CF. A cohort of children with CF was followed with biennial surveillance CT scans, obtained in inspiration after a voluntary breath-hold as 1-mm thick images at 10-mm intervals from lung apex to base. A random set of 20 baseline CT scans and 10 follow-up CT scans were blinded. Sets of every image (10-mm interval), every second image (20-mm interval), every third image (30-mm interval) and a selection of three and five images were scored randomly using a published CT scoring system by one experienced observer. The 20 subjects were 10 years of age with a range of 3.7-17.6 years at baseline. Fewer CT images resulted in significantly lower (less abnormal) CT scores and the number of patients positive for abnormalities decreased subsequently. At intervals greater than 20-mm no significant changes in CT score over two years could be detected, whereas CT scores at 10-mm ($p=0.02$) and 20-mm ($p=0.02$) intervals worsened significantly. We concluded that reducing the number of inspiratory CT images by increasing the interval between images to greater than 10-mm is not a valid option for radiation dose reduction in children with CF.

In **chapter 6** we examined whether lung growth could be monitored by CT.
In section **6.1** the gas volume per gram of lung tissue was estimated from measurements of lung density obtained from CT scans performed in children throughout the growth period. CT scans were performed in 17 boys and 18 girls, ranging in age from 15 days–17.6 yrs. CT-measured lung weight was correlated with predicted *post mortem* values and CT measured gas volume with predicted values of functional residual capacity. The median value for lung expansion was 1.86 $ml*g^{-1}$ at 15 days, decreased to 0.79 $ml*g^{-1}$ by 2 yrs and then increased steadily to 5.07 $ml*g^{-1}$ at 17 yrs. Therefore, CT scans can be used to estimate lung weight, gas volume and expansion of normal lungs during the growth period. The increase in lung expansion after the age of 2 yrs suggests progressive alveolar expansion with increasing lung volume.
In section **6.2** we aimed to estimate airway, arterial and parenchyma dimensions throughout the growth period using CT and to provide normative data to study alterations in disease. 'Normal' CT scans performed in children for non-pulmonary and non-cardiac reasons were included. CT scans were analyzed for lung weight; gas volume; lung expansion; lung surface to volume ratio; airway wall area (WA); airway lumen area (LA); airway lumen perimeter (Pi); and arterial area (AA) and airway surface to volume ratio (Pi/LA). Ages of the 85 subjects ranged from 0 to 17.6 years. We found a slight increase in lung expansion for a given subject height in the first years of life with little change thereafter. There was substantial variability in lung expansion between subjects. Airway and arterial sizes were exponentially associated with subjects' height, but the number of subjects was too small to detect differences between sexes. Airway surface to volume ratio (cm^{-1}) was linearly to lung surface to

volume ratio (cm^{-1}, R^2=0.46-0.66, $p<0.001$). Our data provide normative CT estimates of airway, arterial and parenchyma dimensions throughout the growth period that may be useful to study alterations in disease.

7.2 General discussion

The studies presented in this thesis demonstrated that chest CT is clearly more sensitive than PFTs to follow the progression of the lung disease in children and adults who have CF. In addition, CT enabled to detect focal areas of end-stage lung disease in many CF patients with normal PFTs. Hence, PFTs, the gold standard for monitoring CF patients, are less sensitive to detect early and progressive disease in CF children. These findings are likely to have important clinical implications. Firstly, the early detection of structural changes on CT allows earlier intervention. Adequate treatment might then perhaps prevent irreversible structural damage. There is increasing evidence that early and aggressive therapy reduces loss of lung function and pulmonary exacerbations and improves quality of life in patients with CF [1-6]. Therefore, a reasonable case could be made for regular routine CT scans to detect airway disease given the current reduced life-expectancy. However, the effect of CT on clinical decisions and the magnitude of its benefit remain to be determined. As infants or CF patients with end-stage lung disease were not included in our studies, we cannot tell whether CT is also more sensitive in these groups.

A second important finding of our studies is that CT scoring in CF for the systems tested is generally reproducible between and within observers. We demonstrated that five published CT scoring systems all showed good intra- and interobserver agreement in two centers. Our scoring system studies indicated that bronchiectasis is the most relevant parameter for following CF patients clinically. Bronchiectasis is irreversible, while mucous plugging and airway wall thickening can be reversible, which may make these parameters less relevant, both clinically and in trials. Bronchiectasis is a highly relevant treatment end-point for a clinical trial in CF. In order to detect changes the duration of such a trial should be at least one to two years. The use of sensitive CT outcome measures is likely to reduce trial costs since fewer patients are needed compared to PFT related end points, although the increased power remains to be demonstrated.

Third, we demonstrated that quantitative measurements of airway wall and lumen dimensions can be used in CF. These measurements revealed an increase in airway wall thickness over a two-year period that remained unnoticed in the five CT scoring systems. Airway wall thickening is an important CT feature in CF since it is related to airway inflammation. Our finding may therefore be relevant for trials that aim to reduce airway inflammation in CF.

We experienced several limitations in the quantitative studies. First, we used the accompanying pulmonary artery to define airway wall thickening and lumen dilatation. However, in CF patients the pulmonary artery dimensions themselves may have been changed by the disease progress. Secondly, several airways were excluded for analysis because of mucous plugging. This is likely to result in an underestimation of our findings. Thirdly, severely deformed airways were excluded for analysis since the accompanying artery could not be identified or the shape of the airway was too much distorted to allow measurement. Fourthly, we were unable to correct for inflation volume of the lungs during CT scanning and diseased airways may be more sensitive than healthy airways for variation in inflation. Finally, the HRCT protocol with 1-cm gaps between images greatly hampered matching of the same airway on follow-up CT scans. In spite of these limitations we were able to detect a progressive airway wall thickening that remained undetected with the scoring systems.

Our computational model showed that the survival reduction risk of routine lifelong CT scans every second year in the CF population was low given the current background survival. However, in a fictive cohort of CF patients with an average survival of 50 years (expected survival in 2030) the cumulative mortality of radiation induced cancers of *annual* lifelong CT scans was over 6%. It should be stressed that possible clinical benefits of the scans were excluded from the model because we were only interested in the magnitude of risk. Clearly, scanning protocols should be designed in such a way that lifelong radiation dose is within acceptable limits that are outweighed by the benefits for patients with CF. The model can help us to design such scanning strategies with the lowest risk/benefit ratio.

Finally we made the interesting observation that airway, parenchyma and arterial dimensions can be estimated from CT throughout the growth period. Therefore CT may enable the estimation of lung growth in health and disease in longitudinal studies. A condition for such studies is that their potential benefit must outweigh the radiation risks for the general or diseased population. Lung growth may be affected by CF lung disease early in life. Hence CT may have a role in studying abnormal lung growth patterns in CF.

7.3 Directions for Future Research

The studies described in this thesis followed some pioneer work that was published in the late eighties and early nineties. Our studies were a next step in this field of monitoring CF lung disease and their importance was discussed in the previous section. Still further research is needed to determine in more detail the role of CT scanning and to design better CT scanning strategies in CF patients clinically and in trials. CT provides the opportunity to improve our understanding of the pathogenesis of lung disease in CF and to study the impact of CF lung disease on lung growth.

Radiologists have the opportunity to move their specialty to the next level; from looking at images and providing descriptions of the abnormalities to a full exploit of the quantitative nature of their techniques with an evidence-based basis for their strategies. The following section aims to propose some directions for future research.

Clinical benefit of CT scanning: Future studies may want to study in more detail the potential benefit associated with repetitive CT scanning in CF. It will also be clinically relevant to extend our cohort studies to patient groups with less and more severe disease. The detection of the earliest stages of disease in infancy, especially with quantitative methodology, will be an exciting area and some cross-sectional work has already been done [7]. Although some studies [8, 9] addressed specifically acute versus chronic or reversible versus irreversible changes on CT, further studies in this area are required.

Use of CT in intervention trials: A challenge in CF lung disease is to determine which therapies change the course of structural lung disease progression. CT may provide the opportunity for improved power and therefore fewer patients in trials. Fewer patients per trial involve lower costs and in addition more therapies can be tested simultaneously in these patients, who almost all participate in trials. An additional opportunity is observation of the structural substrate that is changed by the therapeutic agent. As previously stated, it may be more meaningful to halt the progression of bronchiectasis rather than to reverse or halt mucous plugging or airway wall thickening. A relevant study would be investigating the relationship between bronchiectasis and quality of life or mortality.

Quantitative CT: More investigations in quantitative measurements of airway wall and lumen dimensions as well as air trapping in CF are needed. Some work has recently been done in this area in cross-sectional evaluations and a therapeutic trial with RhDNase [7, 10, 11]. Quantitative CT techniques possibly are able to detect minor abnormalities in airway tapering or in airway compliance (difference in airway lumen in inspiration and expiration) before bronchiectasis becomes visible. The use of the accompanying pulmonary artery as a reference for airway wall and lumen is troublesome. Future studies using volumetric full-lung scanning should be able to follow the same airway over time without the use of the artery as a size reference. Nevertheless the arterial dimension could in itself potentially be an interesting marker of lung disease in CF, although further studies are required to establish this point.

Gas trapping: There is an increasing interest in air or gas trapping [10-14]. Gas trapping is thought to be an early and sensitive measure in CF since it reflects small airway obstruction and this is where CF lung disease is thought to begin. Further studies demonstrating the variability in the amount of gas trapping within patients over time are needed. The optimal numbers of images per expiratory CT scans have to be determined.

Correlation with pathology: More studies are needed that correlate abnormalities (qualitative or quantitative) to the histopathologic abnormalities in explanted lungs or autopsy specimens of end-stage CF lungs. There are only few studies quantifying the pathology in CF lungs, and most of which are from an era before modern treatment became available. Pathology studies are hampered by their cross-sectional design and by the fact that they include mainly end-stage abnormalities. It is important to study the better preserved relatively normal areas of lung in these explanted or autopsy specimens, which will be possible because of the heterogeneous distribution of the disease. These studies will be important to validate CT scores and quantitative measurement techniques for CF.

Lung growth: CT could have a role as a research tool to determine the influence of CF lung disease on postnatal alveolar and lung growth.

CT scanning protocols: Optimization of CT scanning protocols and strategies with respect to dose, scanning technique and optimal interval between CT scans are needed in CF. Investigation should aim to determine the optimal dose per CT scan required to interpret and quantify the abnormalities and to determine the numbers of images needed for in- and expiratory CT scans. The introduction of multi-detector CT scanners in the nineties has provided the opportunity to scan the whole lung in a single breath hold and this is likely to become the future standard. CT protocols might include spirometer triggered CT scans [12, 15]. This method is more invasive and time-consuming. It seems that those protocols are able to detect more gas trapping although no study compared this technique with the conventional technique. It would be valuable to study the changes in airway lumen, airway wall and arterial dimensions at different lung inflation levels in health and disease. The risk of protocols at various doses and intervals can be studied, also with the use of computational modeling strategies.

Other modalities to monitor CF lung disease: Several other imaging and non-imaging modalities are available to potentially monitor the pulmonary status of CF patients. There is currently no use for chest radiographs in monitoring structural lung disease in CF patients. Chest radiographs have limited sensitivity to detect early disease and follow the progression. Neither is there a use currently for magnetic resonance imaging (MRI). MRI has the advantage that it involves no radiation. Nevertheless MRI visualization of airway wall, airway lumen and mucous plugging is presently limited even with the use of hyperpolarized gases. MRI may be more useful to study the perfusion, ventilation and diffusion of CF lungs in a research setting. Some investigators have used endobronchial ultrasound [16, 17] to measure subdivisions of the airway wall down to the right apical bronchus. We feel this technique is too invasive to become widespread in CF monitoring. In addition current probes cannot visualize smaller airways, which are of main interest. An area of major interest involves a non-imaging technique, the measurement of ventilation homogeneity with SF_6 in multiple breath washout tests [18]. These tests have received more attention

recently and seem a promising marker of early lung disease in CF. The comparison between CT and multiple breath washout tests is highly relevant. Other biomarkers of CF lung disease are likely to emerge in the future that may reduce the need for imaging lung structure. Such markers may be found in blood, sputum, urine or exhaled gas and offer an easily available measurement.

References

1. Quan JM, Tiddens H, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. 2001; **139**(6): 813-20.
2. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol* 2002; **34**(3): 228-31.
3. Kulich M, Rosenfeld M, Goss C, Wilmott RW. Improved survival among young patients with cystic fibrosis. *J Pediatr* 2003; **142**: 631-636.
4. Doring G, Hoiby N, Wagener JS, Headley AA, Littlewood JM. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. *J Cyst Fibros* 2004; **3**(2): 67-91.
5. Schidlow DV. "Maintaining the horizontal line": early intervention and prevention of CF lung disease. *J Cyst Fibros* 2004; **3**(2): 63-6.
6. Robinson PJ. Dornase alfa in early cystic fibrosis lung disease. *Pediatr Pulmonol* 2002; **34**(3): 237-41.
7. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr* 2004; **144**(2): 154-61.
8. Shah RM, Sexauer W, Ostrum BJ, Fiel SB, Friedman AC. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation. *AJR Am J Roentgenol* 1997; **169**(2): 375-80.
9. Robinson TE, Leung AN, Northway WH, et al. Spirometer-triggered high-resolution computed tomography and pulmonary function measurements during an acute exacerbation in patients with cystic fibrosis. *J Pediatr* 2001; **138**(4): 553-9.
10. Goris ML, Zhu HJ, Blankenberg F, Chan F, Robinson TE. An automated approach to quantitative air trapping measurements in mild cystic fibrosis. *Chest* 2003; **123**(5): 1655-63.
11. Bonnel AS, Song SM, Kesavarju K, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. *Pediatr Pulmonol* 2004; **38**(5): 396-405.
12. Robinson TE, Leung AN, Moss RB, Blankenberg FG, al-Dabbagh H, Northway WH. Standardized high-resolution CT of the lung using a spirometer-triggered electron beam CT scanner. *AJR Am J Roentgenol* 1999; **172**(6): 1636-8.
13. Robinson TE, Leung AN, Northway WH, et al. Composite spirometric-computed tomography outcome measure in early cystic fibrosis lung disease. *Am J Respir Crit Care Med* 2003; **168**(5): 588-93.
14. Dorlochter L, Nes H, Fluge G, Rosendahl K. High resolution CT in cystic fibrosis--the contribution of expiratory scans. *Eur J Radiol* 2003; **47**(3): 193-8.
15. Kalender WA, Rienmuller R, Seissler W, Behr J, Welke M, Fichte H. Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. *Radiology* 1990; **175**(1): 265-8.
16. Shaw TJ, Wakely SL, Peebles CR, et al. Endobronchial ultrasound to assess airway wall thickening: validation in vitro and in vivo. *Eur Respir J* 2004; **23**(6): 813-7.
17. Yamasaki A, Tomita K, Sano H, et al. Measuring subepithelial thickness using endobronchial ultrasonography in a patient with asthma: a case report. *Lung* 2003; **181**(3): 115-20.

18. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J* 2003; **22**(6): 972-9.

Monitoren van longziekte bij cystic fibrosis met computed tomografie

"Samenvatting, discussie en verder onderzoek"

Om de aan cystische fibrose (CF) gerelateerde longziekte zo goed mogelijk te behandelen moeten de start en het beloop van de longafwijkingen nauwkeurig worden gevolgd. Dit kan op een indirecte manier worden gedaan met behulp van longfunctietesten of op een meer directe manier door de longstructuur af te beelden met röntgentechnieken. Tot op heden worden longfunctietesten, zoals spirometrie en lichaamsplethysmografie metingen, gezien als de belangrijkste methode om longafwijkingen op te sporen in CF. Longfunctietesten kunnen routinematig gebruikt worden vanaf de leeftijd van 5 of 6 jaar. Om de longstructuur af te beelden wordt routinematig gebruik gemaakt van de thoraxfoto. In de meeste CF-centra wordt jaarlijks een thoraxfoto gemaakt en soms ook bij een acute verslechtering (exacerbatie) van de ziekte.

Onderzoek heeft aangetoond dat longfunctietesten gevoeliger zijn dan thoraxfoto's om de voortgang of verslechtering van de aan CF gerelateerde longziekte te vervolgen. In het begin van de jaren negentig werd aangetoond dat computed tomografie (CT) scans gevoeliger zijn in vergelijking met thoraxfoto's om afwijkingen in de longstructuur vroeg op te sporen in CF-patiënten.

Er werden diverse CT scoringssystemen ontwikkeld om de afwijkingen op een systematische wijze in een getal om te zetten. Deze CT scoringssystemen bleken een matig tot goed verband te tonen met longfunctietesten. Een opvallende bevinding was dat structurele afwijkingen op CT scans werden gevonden in sommige patiënten met CF die een normale longfunctie hadden. Welk CT scoringssysteem het beste was om de longafwijkingen te scoren was niet duidelijk omdat de scoringssystemen nooit met elkaar vergeleken waren. Het was ook niet duidelijk hoe herhaalbaar verschillende beoordelaars één CT scan konden boordelen en hoe herhaalbaar in de tijd één beoordelaar één CT scan kon beoordelen.

Naast het gebruik van CT scoringssystemen zijn er ook computersystemen ontwikkeld waarmee luchtwegen (wand en lumen) en bloedvaten gemeten kunnen worden. Deze computersystemen zijn ontwikkeld voor gebruik bij longziekten zoals chronisch bronchitis, longemfyseem, en astma. Deze systemen waren echter nog nooit gebruikt voor metingen van luchtwegen op CT scans van CF-patiënten.

Verder waren er geen studies gedaan waarbij over een langere tijd de veranderingen in de longafwijkingen zoals gemeten met CT scoringssystemen en luchtwegmetingen werden vergeleken met veranderingen in longfunctietesten.

Hoewel CT scans gevoeliger zijn dan de thoraxfoto om longafwijkingen bij CF op te sporen was er geen onderzoek bekend dat heeft bestudeerd in hoeverre de straling verbonden aan CT onderzoek de levensverwachting van CF-patiënten nadelig kon beïnvloeden.

Hoofdstuk 1 is een algemene introductie van dit proefschrift waarin ook het doel van de studies wordt beschreven.

Hoofdstuk 2 beschrijft de redenen van onze studies in het licht van de huidige praktijk van het vervolgen van de aan CF gerelateerde longziekte. Dit hoofdstuk is met name gericht op de voor- en nadelen van het bepalen van vroege afwijkingen en het vervolgen van afwijkingen met behulp van longfunctietesten, thoraxfoto's en CT scans.

Hoofdstuk 3 beschrijft de vergelijking van CT scoringssystemen in CF. Sectie **3.1** beschrijft een studie waarin de CT scores van vijf verschillende scoringssystemen worden vergeleken. Verder wordt de toegevoegde waarde van metingen van luchtwegen en longbloedvaten bepaald. CT score 0 betekende dat er geen afwijkingen aanwezig waren en een hogere score dat afwijkingen werden gezien. Drie beoordelaars scoorden 25 CT scans van kinderen met CF. Het scoren werd herhaald na intervallen van 1-2 weken tot 1-2 maanden. Luchtwegen en bloedvaten werden gemeten. De variatie tussen de beoordelaars en binnen één beoordelaar werd berekend. Het verband werd bepaald tussen CT scores en afmetingen van luchtwegen en bloedvaten en longfunctie parameters zoals uitademingvolume in de eerste seconde van de geforceerde uitademing (FEV_1). We vonden dat de CT scores betrouwbaar tussen en binnen beoordelaars konden worden gescoord met alle vijf de systemen. De CT scores toonden een duidelijk verband met de FEV_1. De ratio tussen luchtweglumen diameter en de diameter van de parallel lopende bloedvaten toonde ook een verband met CT scores, maar niet met FEV_1. De ratio tussen luchtwegwanddikte en de diameter van de parallel lopende bloedvaten toonde met beide de CT scores en de FEV_1 geen verband. Daarom concludeerden we dat CT scores reproduceerbaar waren en een verband toonden met longfunctietesten. Metingen van luchtwegdimensies toonden geen verband met CT scores of longfunctietesten.

In **Hoofdstuk 4** worden de studies beschreven waarin de gevoeligheid van CT vergeleken wordt met die van longfunctietesten voor het vervolgen van CF gerelateerde longziekte in kinderen en volwassenen.

Sectie **4.1** beschrijft de bevinding dat op CT scans van kinderen met CF longafwijkingen toenamen terwijl de longfunctie stabiel bleef. Het doel van deze studie was om de gevoeligheid van CT scoringssystemen en longfunctietesten te vergelijken om veranderingen in longziekte te vervolgen. De studie werd gedaan in 48 kinderen met CF die allemaal twee CT scans in combinatie met twee longfunctietesten hadden ondergaan met een interval van twee jaar tussen de CT scans. De CT scans werden gescoord met vijf CT scoringssystemen: Castile, Brody, Helbich, Santamaria en Bhalla. Gevoeligheid was gedefinieerd als de mogelijkheid om verslechtering vast te stellen. In de groep kinderen verslechterden de CT scores terwijl de longfunctietesten stabiel bleven of verbeterden. Op de CT scans was een toename van de hoeveelheid slijmproppen te zien. Verder was er een uitbreiding van het aantal en van de ernst van bronchiectasieën. Het verband tussen veranderingen in CT scores en longfunctietesten was zwak. Substantiële longafwijkingen werden gezien op de CT scans van sommige kinderen met een normale longfunctie. Dit onderzoek laat dus zien dat CT een gevoeligere test is in vergelijking met longfunctietesten om de start en de verslechtering van de longziekte in kinderen met CF op te sporen. Dit suggereert dat CT nuttig zou kunnen zijn om longafwijkingen bij CF-patiënten te vervolgen. Verder zou CT gebruikt kunnen worden als meetpunt in studies die als doel hebben om longschade in CF te verminderen.
In Sectie **4.2** beschrijven we een vervolgonderzoek van longstructuur en longfunctie in kinderen en volwassen patiënten met CF. Het eerste doel van deze studie was om te bepalen of CT scores gevoeliger zouden zijn dan longfunctietesten om bij volwassen CF-patiënten longafwijkingen te vervolgen. Het tweede doel was om te bepalen of de resultaten van de voorgaande studie in kinderen met CF kon worden herhaald. CT scans en longfunctietesten werden bestudeerd in een groep Zweedse CF-patiënten in de leeftijd van 5 tot 52 jaar. Van iedere patiënt waren 1, 2 of 3 CT-scans beschikbaar in combinatie met longfunctietesten met een interval van drie jaar tussen de CT scans. Alle CT scans werden gescoord door 2 beoordelaars. Longfunctietesten werden uitgedrukt als percentage voorspeld en Z-score. 119 patiënten werden opgenomen in de studie, 92 hadden twee en 24 hadden drie CT scans. De CT score (totale en losse componenten) en de longfunctietesten verslechterden. Echter, bronchiectasieën verslechterden het meest met 1,7% per jaar in kinderen en 1,5% per jaar in volwassenen. CT scores en longfunctietesten verslechterden even snel in kinderen als in volwassenen. De score van bronchiectasieën was dus gevoeliger dan de longfunctietesten, de totale CT score en de scores van de andere componenten van het scoringssysteem om longafwijkingen te volgen in deze groep kinderen en volwassen CF-patiënten.
In Sectie **4.3** werden veranderingen in luchtwegafmetingen op CT scans van kinderen met CF gemeten. Drieëntwintig kinderen met CF die twee CT scans (CT_{cf1} en CT_{cf2}) in combinatie met longfunctietesten met een interval van twee jaar tussen de metingen hadden werden vergeleken met 21 controles ($CT_{controles}$) van gelijke leeftijd. Deze controle-patiënten hadden allen één CT scan die door twee radiologen als normaal was beoordeeld. Van alle luchtweg-bloedvat paren werden luchtwegwandoppervlakte, luchtweglumenoppervlakte en omtrek, en

bloedvatoppervlakte gemeten. Met deze gegevens werden de verhouding tussen luchtweglumen- en bloedvatoppervlakte als maat voor bronchiectasieën berekend. Als maat voor luchtwegwanddikte werd de verhouding tussen luchtwegwanddikte en bloedvatoppervlakte berekend. Verder werden de CT scans met vier verschillende CT scoringssystemen gescoord. Resultaten van de longfunctietesten werden uitgedrukt als percentage voorspeld. De verhouding tussen luchtwegwanddikte en bloedvatoppervlakte was 1,45 en de verhouding tussen luchtweglumen- en bloedvatoppervlakte was 1,92 keer hoger in CF-patiënten in vergelijking met controles. Luchtwegwanddikte als een functie van luchtweggrootte nam toe van CT_{cf1} naar CT_{cf2} met 0,03 mm (2%). Deze verandering in luchtwegwanddikte toonde een duidelijk verband met de verandering in de longfunctie. In CF laten metingen van luchtwegen op CT-scans dus een toename zien van de verhouding tussen luchtweglumen- en bloedvatoppervlakte en een toename van de luchtwegwanddikte. De scoringssystemen laten een toename zien van de bronchiectasieën, maar onveranderde luchtwegwanddikte. Longfunctietesten waren stabiel. In de drie beschreven studies was CT dus gevoeliger dan longfunctietesten om longafwijkingen te vervolgen zowel in kinderen als in volwassen patiënten met CF.

Hoofdstuk 5 concentreert zich op het stralingsrisico dat samenhangt met het maken van CT scans in CF-patiënten.
In Sectie **5.1** stellen wij dat de lage stralingsdosis van CT scans het risico op bepaalde soorten kanker zou kunnen vergroten, met name als CT scans op de kindleeftijd worden gedaan. Ons doel was om met een rekenkundig computermodel een schatting te maken van de totale extra sterfte ten gevolge het doen van herhaalde CT scans in patiënten met CF. De stralingsdosis per CT scan werd berekend voor het CT-protocol dat gebruikt werd in CF-patiënten van het Erasmus MC - Sophia. In het computermodel werd gebruik gemaakt van stralingsrisico gegevens afkomstig van de Japanse bevolking die de atoombom overleefden. Computersimulaties werden gedaan waarin het effect van het interval tussen CT scans en de dosis per CT scan op de overleving van CF-patiënten werd berekend. In de simulaties werd er vanuit gegaan dat de informatie verkregen van de CT scans de levensverwachting niet veranderde. Het doen van een jaarlijkse CT scan vanaf de leeftijd van twee jaar bij een gemiddelde overleving van 26 jaar of van 50 jaar gaf een vermindering in overleving van respectievelijk een maand tot meer dan een jaar. De bijbehorende extra kankersterfte was minder dan 1% en ongeveer 6%. Onze conclusie was dat het doen van een CT scan om het jaar een laag risico geeft op stralinggeassocieerde kankersterfte in CF. Echter, aangezien de overleving van CF-patiënten lijkt toe te nemen zal dit stralingsrisico in betekenis toe nemen. Ons onderzoek suggereert dat herhaald röntgenonderzoek gebruikt kan worden om ziekte op te sporen, te vervolgen en te behandelen mits de levenslange stralingsbelasting onder een acceptabel risiconiveau blijft, waarbij het voordeel groter moet zijn dan het nadeel.
In Sectie **5.2** beschrijven we een studie om te bepalen of in kinderen met CF het aantal afbeeldingen per CT scan, en daarmee de stralingsdosis per CT scan, verminderd zou kunnen worden zonder belangrijk verlies van informatie. Met name

op de kinderleeftijd is het belangrijk om de stralingsdosis per CT-onderzoek tot het absolute minimum te beperken. Voor dit onderzoek werd gebruik gemaakt van een groep van CF-patiënten die werden gevolgd met tweejaarlijkse routine CT scans. CT scans werden gemaakt tijdens een adempauze bij maximale inademing. Hierbij werden 1-mm dikke plakjes gemaakt op intervallen van 10-mm tussen de plakjes van de longtop tot de onderkant van de longen. Uit de patiëntengroep werd een willekeurige selectie gemaakt van 20 CT scans met voor 10 patiënten ook de vervolg CT scan. Sets werden samengesteld van alle plakjes (10-mm interval), ieder tweede plakje (20-mm interval), ieder derde plakje (30-mm interval) en van drie en vijf plakjes op geselecteerde niveaus. Sets werden in willekeurige volgorde gescoord door een ervaren beoordelaar met behulp van een CT scoringssysteem. De 20 CF-patiënten waren 10 jaar oud bij het begin van de studie met een spreiding van 3,7 tot 17,6 jaar. Als er minder plakjes werden gescoord resulteerde dit in een vermindering van de CT score en het aantal patiënten met bepaalde afwijkingen nam af oftewel de longschade werd onderschat. Als het interval groter was dan 20-mm kon er geen verslechtering van de CT score over een periode van twee jaar worden gevonden. Bij intervallen van 10-mm en 20-mm werd wel een verslechtering van de CT score over twee jaar gevonden. We concludeerden daarom dat vermindering van het aantal plakjes per CT scan geen aantrekkelijke optie was om de stralingsdosis per CT scan te verminderen bij kinderen met CF.

Hoofdstuk 6 gaat over hoe longgroei gemeten kan worden met CT scans.
In Sectie **6.1** werd het volume aan gas in de longen per gram longweefsel geschat (longuitzetting) door het meten van de longdensiteit op CT scans van kinderen in de groeiperiode. CT scans werden gemaakt in 17 jongens en 18 meisjes in de leeftijd van 15 dagen tot 17,6 jaar. Longgewicht geschat met de CT scan was min of meer hetzelfde als het longgewicht van overleden kinderen zoals beschreven in de literatuur. Het volume aan gas in de longen was min of meer gelijk aan de voorspelde functionele residuale capaciteit. De longuitzetting nam af van 1,85 milliliter gas per gram longweefsel op de leeftijd van 15 dagen tot 0,79 milliliter gas per gram longweefsel op de leeftijd van 2 jaar. Hierna nam de longuitzetting weer toe tot 5,07 milliliter gas per gram longweefsel op 17 jaar. CT scans lijken daarom geschikt om schattingen te kunnen doen van de groei van longen gedurende de groeiperiode. De toename van de longuitzetting na de leeftijd van 2 jaar suggereert een toenemende uitzetting van de kleinste longblaasjes (alveoli) als het longvolume toeneemt.
Het doel van de studie beschreven in sectie **6.2** was om afmetingen van luchtwegen, bloedvaten en longblaasjes te schatten op CT scans gemaakt gedurende de groeiperiode. Verder om normaalwaarden te bepalen die gebruikt kunnen worden om afwijkingen in de groei op te kunnen sporen als gevolg van ziekte. De normale CT scans waren afkomstig van kinderen die een CT scan van de longen hadden ondergaan zonder dat er sprake bleek te zijn van hart- of longafwijkingen. Op deze normale CT scans werden longgewicht; volume aan gas in de longen; longuitzetting; de ratio tussen longoppervlakte en longvolume; luchtwegwandoppervlakte; luchtweglumenoppervlakte; luchtweglumenomtrek; bloedvatoppervlakte; en de ratio

luchtwegomtrek en luchtweglumenoppervlakte gemeten. De leeftijd van de 85 kinderen varieerde tussen de 0 en 17,6 jaar. We vonden een geringe toename in de longuitzetting in de eerste levensjaren die daarna maar weinig meer veranderde. Er was een aanzienlijke variatie in longuitzetting tussen de individuen van een bepaalde leeftijd. Luchtweg en bloedvatenafmetingen toonden een verband met de lichaamslengte. De afmeting van longblaasjes toonde een verband met de afmetingen van luchtweglumen. Onze gegevens verschaffen normaalwaarden voor afmetingen van luchtwegen, bloedvaten en longblaasjes gedurende de groeiperiode die nuttig kunnen zijn bij het bestuderen van afwijkende groei bij ziekte.

Discussie

De belangrijkste bevinding van de studies in dit proefschrift is dat CT gevoeliger is dan longfunctietesten om de toename van longafwijkingen aan te tonen in kinderen en volwassen patiënten met CF. Verder bleek CT in staat om gebiedjes met ernstige longafwijkingen aan te tonen in patiënten met normale longfunctietesten. CT scans zijn dus gevoeliger dan longfunctietesten om de start en de verslechtering van de longziekte in CF aan te tonen. Deze bevindingen hebben waarschijnlijk belangrijke gevolgen voor de kliniek. Ten eerste, het vroeg ontdekken van structurele afwijkingen op de CT scan maakt het mogelijk om patiënten met CF in een vroege fase en gerichter te behandelen. Zo kan geprobeerd worden om onherstelbare schade in de longen te voorkomen. Het wordt steeds duidelijker dat vroege en agressieve behandeling van patiënten met CF de snelheid van achteruitgang in longfunctie en het aantal acute verslechteringen (exacerbaties) vermindert en de levenskwaliteit verbetert. Het routinematig maken van CT scans lijkt een goede strategie om de verminderde levensverwachting van CF-patiënten verder te verbeteren. Hoe CT scans klinische beslissingen beïnvloeden en wat hiervan de invloed is op de levensverwachting van de patiënt moet nog verder worden onderzocht. In onze studies zoals beschreven in dit proefschrift zijn geen kinderen jonger dan vier jaar en slechts enkele patiënten in het eindstadium van de ziekte onderzocht. Daarom kunnen we geen uitspraken doen over de gevoeligheid van CT scans in deze patiëntengroepen.

Een tweede belangrijke bevinding van ons onderzoek is dat het scoren van CT scans met de vijf geteste scoringssystemen betrouwbaar gedaan kan worden. Er bleek weinig variatie te zijn tussen verschillende waarnemers die één CT scan scoren en in een waarnemer die het scoren van één CT scan na een periode herhaalt. Verder bleek dat met name bronchiectasieën op CT scans de meeste relevante afwijking is om patiënten met CF te vervolgen in de kliniek. Bronchiectasieën zijn onherstelbaar verwijde luchtwegen. Afwijkingen zoals slijmproppen en luchtwegwandverdikking zijn daarentegen afwijkingen die nog omkeerbaar kunnen zijn. Bronchiectasieën zijn daarom ook meer geschikt dan slijmproppen en luchtwegwandverdikking om als

meetpunt te gebruiken in geneesmiddelenonderzoek gericht op de longafwijkingen in CF. Door het gebruik van CT scans in geneesmiddelenonderzoek kunnen waarschijnlijk de kosten verminderd worden doordat met deze gevoeligere test minder patiënten nodig zijn.

Ten derde hebben we aangetoond dat het mogelijk is om met beeldanalysetechnieken de luchtwegwanddikte en luchtweglumendiameter te meten in CF. Met dergelijke metingen hebben we in 2 jaar tijd een toename in de luchtwegwandverdikking kunnen vaststellen. De vijf scoringssystemen bleken niet gevoelig genoeg om deze toename op te sporen. Luchtwegwandverdikking is een belangrijk kenmerk in CF-patiënten omdat dit een maat is voor de ernst van de luchtwegontsteking. Deze methode kan daarom belangrijk zijn voor toekomstig onderzoek naar geneesmiddelen die er op gericht zijn om de luchtwegontsteking in CF te verminderen. Er waren echter nog wel een aantal problemen om met deze technieken de luchtwegen te meten. Sommige luchtwegen konden bijvoorbeeld niet gemeten worden omdat er slijmproppen in zaten. Andere luchtwegen waren zo ernstig vervormd dat ze niet meer gemeten konden worden. Ook is het waarschijnlijk dat het inademingniveau tijdens het maken van de CT scan van invloed is op de metingen. Het verder ontwikkelen van deze gevoelige beeldanalysetechnieken is aantrekkelijk omdat deze in de toekomst geautomatiseerd kunnen worden.

Een vierde belangrijke bevinding kwam uit ons rekenkundig computermodel naar de stralingsrisico's van CT. Dit onderzoek liet zien dat met de huidige overleving van CF-patiënten het risico van het maken van CT scans iedere twee jaar laag is. Als we in de simulaties echter uitgingen van jaarlijkse scans vanaf de peuterleeftijd en van een overleving van 50 jaar nam de sterfte ten gevolge van de met stralen samenhangende kanker toe tot 6%. Het moet benadrukt worden dat we in ons model net deden alsof er geen behandelingsvoordeel zou zijn door de CT scans. Het is duidelijk dat CT-protocollen op een dusdanige manier ontwikkeld moeten worden dat de risico's van de totale levenslange stralenbelasting van een patiënt onder een acceptabele grens blijven. Het voordeel van het maken van scans voor patiënten met CF lijkt dus groter dan de nadelen. Computermodellen kunnen ons helpen om veilige protocollen te ontwikkelen.

Ten slotte deden we de interessante observatie dat met behulp van CT scans de longgroei gemeten kan worden in gezonde kinderen. Het is niet onwaarschijnlijk dat de longgroei bij CF-patiënten gestoord is. CT zou een rol kunnen spelen om de invloed van ziekte op longgroei te bestuderen.

Verder onderzoek

Onze studies zoals beschreven in dit proefschrift waren een vervolg op CT-onderzoek uit eind jaren '80 en begin jaren '90. Onze studies waren een logische volgende stap om de aan CF gerelateerde longziekte beter te kunnen vervolgen. Verder onderzoek is nodig om de rol van het maken van CT scans in CF-patiënten nader te bepalen. Verder moeten betere strategieën voor het maken van CT scans worden ontwikkeld. CT geeft ons de mogelijkheid om onze kennis en begrip van het ziekteproces te verdiepen en om de invloed van de aan CF gerelateerde longziekte op de longgroei te bepalen. De volgende paragraaf heeft als doel om een aantal grote lijnen aan te geven voor verder vervolgonderzoek.

Klinisch voordeel van CT scans: Toekomstig onderzoek zou in nog meer detail het voordeel van routinematige CT scans bij CF kunnen bestuderen. Het is belangrijk om onze studies uit te breiden naar patiëntengroepen met vroegere en latere afwijkingen. Met name het meten van de vroege afwijkingen in hele jonge CF-patiënten kan tot belangrijke nieuwe inzichten leiden. Verder onderzoek naar de omkeerbaarheid van de op CT gevonden afwijkingen is wenselijk. Als laatste is het belangrijk om de relatie te bestuderen naar de ernst van de afwijkingen op CT en de kwaliteit van leven en overleving van de patiënten.

CT scans en geneesmiddelenonderzoeken: Het is een grote uitdaging in CF om te onderzoeken welke behandelingen de toename van de longschade kunnen vertragen. Met behulp van CT scans kan worden bepaald of een therapie effectief is. Bovendien kan dit worden gedaan met minder patiënten en tegen lagere kosten. Op dit moment zijn er veel nieuwe geneesmiddelen voor CF-patiënten in ontwikkeling. Het wordt hierdoor steeds moeilijker om voldoende patiënten te vinden om al deze nieuwe geneesmiddelen te testen. Door CT scans als meetpunt te gebruiken kan dit probleem (deels) opgelost worden. Bovendien kunnen we het effect van behandelingen op de longafwijkingen met CT beter bestuderen. Zoals we eerder schreven is het vooral belangrijk om het ontstaan en de toename van bronchiectasieën te vertragen.

CT metingen: Verder onderzoek is nodig om beeldanalyse technieken te verbeteren voor het opmeten van luchtwegen en van de luchthoudendheid van de longen op CT scans. Belangrijk is vooral om technieken te ontwikkelen waarmee subtiele afwijkingen opgespoord kunnen worden die kunnen leiden tot afwijkingen zoals bronchiectasieën. Toekomstige studies kunnen het beste geen gebruik meer maken van bloedvatafmetingen om luchtwegen mee te vergelijken. Met nieuwe CT scanners kan de hele long in één adempauze gescand worden. Met deze techniek is het eenvoudiger om luchtwegwand dimensies te vervolgen zonder gebruik te hoeven maken van de met de luchtwegen meelopende bloedvaten. Op zichzelf zijn de afmetingen van de bloedvaten interessant omdat veranderingen in bloedvaten een

maat zouden kunnen zijn van de ernst van de aan CF gerelateerde longziekte. Aanvullende studies zijn echter nodig om deze veronderstelling te onderbouwen.

Luchthoudendheid: Er is een toenemende interesse in veranderingen in luchthoudendheid van de longen in relatie tot de ademhaling. In CF beginnen de afwijkingen vooral in de kleine luchtwegen. Als gevolg hiervan kan lucht in bepaalde gebieden van de long minder snel of helemaal niet uitgeademd worden. Deze gebieden worden 'trapped gas' genoemd en zien er extra zwart uit op de CT scan. Het is aannemelijk dat metingen van luchthoudendheid in CF-patiënten een vroege en gevoelige ziektemaat zou kunnen zijn. Verder onderzoek is nodig om de variabiliteit in de hoeveelheid 'trapped gas' over een bepaalde periode te bepalen. Verder moet het aantal uitademing CT plakjes dat nodig is om 'trapped gas' goed aan te tonen nog bepaald worden.

Relatie CT en pathologie: Het is nodig om de relatie te bestuderen tussen de afwijkingen op CT scans en de afwijkingen van de longen onder de microscoop. Dit kan door bij transplantatiepatiënten de CT van voor de operatie te vergelijken met de uitgenomen long. Op dit moment zijn er maar weinig zulke studies en de studies die er zijn stammen vaak nog uit het tijdperk voordat de huidige antibiotica beschikbaar waren. Zulke studies zijn helaas altijd tot op zekere hoogte beperkt om het een dwarsdoorsnede betreft van longen in een eindstadium van de ziekte. Een mogelijke oplossing is om in zulke longen ook de meer normale gebieden te bestuderen. De longafwijkingen in CF zijn immers door de hele long ongelijk in ernst. Studies zijn belangrijk om scoringssystemen en CT metingen te verbeteren voor het gebruik in CF.

Longgroei: CT kan een rol spelen om de invloed van de aan CF gerelateerde longziekte op de groei van longen na de geboorte te bestuderen.

CT protocollen: Verder onderzoek is nodig naar het optimaliseren van CT scanning protocollen met betrekking tot de stralendosis, de techniek en het tijdsinterval tussen CT scans. Dit onderzoek moet tot doel hebben om met een minimaal aantal CT plakjes zoveel mogelijk relevante informatie te verzamelen. Verder is het nodig om technieken te ontwikkelen waarmee betere controle kan worden verkregen over het longvolume waarbij de CT scan gedaan wordt. Het lijkt erop dat CT scans gemaakt met speciale protocollen 'trapped gas' beter kunnen aantonen dan wanneer een eenvoudig in- en uitademingcommando wordt gegeven. Deze methode vraagt echter meer van de patiënt en is meer tijdrovend. Met deze techniek moet het ook mogelijk zijn om veranderingen in luchtweg- en bloedvatafmetingen in relatie tot het longvolume te bestuderen in zowel gezonde als zieke personen. De stralingsrisico's van de verschillende protocollen kan worden ingeschat met de rekenkundige computermodellen

Overige testen om longziekte vroeg te ontdekken en te vervolgen in CF: Verschillende andere methoden zijn beschikbaar die mogelijk de aan CF gerelateerde longziekte zouden kunnen vervolgen. Op dit moment is er geen plaats meer voor het gebruik van thoraxfoto's om CF-patiënten te vervolgen. Deze techniek is te ongevoelig om vroege afwijkingen op te sporen en om veranderingen in longafwijkingen te vervolgen. Er is op dit moment ook (nog) geen plaats voor MRI (magnetic resonance imaging) in het afbeelden van de longen van CF-patiënten. MRI heeft als grote voordeel dat er geen röntgenstralen bij betrokken zijn. Echter de afbeeldingen van luchtwegen met MRI is op dit moment minder goed dan die van CT. MRI zou wel een plaats kunnen hebben om bijvoorbeeld longdoorbloeding te besturen. Ook is echografie gebruikt om de luchtwegwand te bestuderen. Deze techniek is echter te ingrijpend om op grote schaal toegepast te kunnen worden. De echokop moet namelijk via de luchtpijp in de luchtwegen gebracht worden om metingen te kunnen doen. Verder zijn de echokoppen op dit moment nog te groot om met name kleine luchtwegen af te beelden welke het meest relevant zijn in CF. Een ander veelbelovend onderzoeksgebied is het meten van inhomogeniteit van de ventilatie met uitademingtesten van bepaalde gassen. Deze functionele testen lijken gevoelig te zijn om vroege longafwijkingen in CF op te kunnen sporen. De uitkomsten van deze testen moeten vergeleken gaan worden met CT scans.

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De schrijver

Pim de Jong werd geboren op 11 juni 1979 in het Groene Hart Ziekenhuis te Gouda en groeide op in Groot-Ammers. In 1997 legde hij met succes zijn VWO-examen af aan de Driestar te Gouda en hij begon in datzelfde jaar met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Als student was hij actief o.a. als trainer studievaardigheden, als manager van een Happietaria studentenvrijwilligers restaurant (35.000,- Euro werd in 17 dagen verdient voor een infrastructuur project in Soedan), als voorzitter van de studentenvereniging R.E.S.V. Ichthus, als organisator van het derde jaarlijkse congres van Christian Medical Fellowship Nederland voor studenten, en als vrijwilliger in een Dabar-campingteam gedurende verschillende zomervakanties te Stavenisse. In februari 2001 begon het afstudeerproject naar computed tomografie en cystic fibrosis op de afdeling Kinderlongziekten van het Erasmus MC – Sophia onder begeleiding van Dr. Harm A Tiddens (hoofd: Prof.dr. Johan C de Jongste). Het onderzoek werd uitgevoerd in nauwe samenwerking met de afdeling Kinderradiologie in het Erasmus MC (Dr. Maarten H Lequin) en de afdeling Radiologie in het Academisch Ziekenhuis te Maastricht (Dr. Simon G Robben). Na het afleggen van het doctoraalexamen in september 2001 werd het onderzoek voortgezet gedurende een stage van zes maanden aan de Universiteit van British Columbia te Vancouver, Canada onder begeleiding van Dr. Yasutaka Nakano (hoofd: Prof. Peter D Paré). Financiële steun kwam via een Gerrit Jan Mulder Stichting-fellowship. Pim liep co-schappen tussen april 2002 en mei 2004 en legde in juni 2004 zijn artsenexamen af met lof. Tussen de co-schappen door werkte hij verder aan zijn onderzoek op de afdeling Radiologie van het Columbus Children's Hospital te Ohio, VS (Dr. Fred R Long) en het Queens Silvia Hospital te Göteburg, Zweden (Dr. Anders Lindblad). Van juli 2004 tot en met juni 2005 was hij onderzoeksfellow aan de Univeriteit van British Columbia te Vancouver, Canada onder begeleiding van Dr. Harvey O Coxson (hoofd: Dr. Robert D Levy). Financiële steun voor deze periode kwam van de Michael Smith Foundation/Canadian Institute of Health Research en de BC Lung Association. Zijn onderzoek leverde uiteindelijk promotie op tot doctor op 14 december 2005. Van juli tot december 2005 was hij assistent geneeskunde niet in opleiding op de afdeling Kindergeneeskunde van het MCRZ - Zuiderziekenhuis te Rotterdam. Hij ziet uit naar een spannende en uitdagende loopbaan in de Radiologie en is inmiddels begonnen met de opleiding tot radioloog in het Universitair Medisch Centrum te Utrecht (hoofd: Prof.dr. W.P. Mali, opleider: Dr. J.P. van Schaik). Hij is dankbaar voor en geniet van het gewone dagelijkse leven, de mogelijkheid om nuttig te zijn binnen de geneeskunde, en het pasbegonnen huwelijk met zijn vrouw Rianne.

About the author

Pim de Jong was born on June 11th, 1979 in the 'Groene Hart' Hospital in Gouda and raised at Groot-Ammers village. He completed pre-university education (VWO) at 'het Driestar College' in Gouda in 1997 and enrolled at Erasmus University Medical School in Rotterdam in the same year. As a student he was a teacher of first year medical students; he run his own student volunteers restaurant (35,000 Euro was gained in 4 weeks for a project in Sudan); he was president of the students' association R.E.S.V. Ichthus; he organised the 3rd annual Christian Medical Fellowship Netherlands-students conference; and he with his friends was volunteering in the summer holidays on a camping site in Stavenisse. In February 2001 he started his research project 'Computed tomography and cystic fibrosis' at the department of Respiratory Medicine at Erasmus MC-Sophia, Rotterdam (supervisor: Dr. Harm A Tiddens, head: Prof. Johan C de Jongste) in close collaboration with the department of Pediatric Radiology, Erasmus MC-Sophia (Dr. Maarten H Lequin) and the department of Radiology, Academic Hospital Maastricht (Dr. Simon G Robben). He received his masters in medicine from Erasmus University Medical School in September 2001 and continued his research as a visiting scholar at the University of British Columbia, Vancouver, Canada (head: Prof. Peter D Paré, supervisor: Dr. Yasutaka Nakano) from October 2001 till April 2002 supported by a 'Gerrit Jan Mulder Stichting' fellowship. He did his medical internships between April 2002 and May 2004 and obtained his medical degree in June 2004. In the meantime he continued his research at the department of Radiology at Columbus Children's Hospital, Ohio, USA (Dr. Fred R Long) and at Queens Silvia Hospital, Göteborg, Sweden (Dr. Anders Lindblad). From July 2004 till June 2005 he was a research fellow at the Departments of Medicine and Radiology at the University of British Columbia, Vancouver, Canada (head: Dr. Robert D Levy, supervisor: Dr. Harvey O Coxson) supported by the Michael Smith Foundation/Canadian Institute of Health Research and the BC Lung Association. His research resulted in a PhD on December 14th, 2005. From July till December 2005 he was an intern at the department of Pediatrics of the MRCZ-Zuider Hospital, Rotterdam. He is looking forward to an exciting career in Radiology and started his residency program at the University Medical Center in Utrecht in December 2005 (head: Prof. W P Mali, trainer: Dr. J.P. van Schaik). He will continue to be thankful and joyful for the gift of life, for the opportunity to work in Medicine and for his relationship with his wife Rianne in the marriage that was just begun.

Publicaties (publications)

1. Brody AS, Tiddens HA, Castile RG, Coxson HO, de Jong PA, Goldin J, et al. Computed Tomography in the Evaluation of Cystic Fibrosis Lung Disease. *Am J Respir Crit Care Med* 2005.
2. de Jong PA, Muller NL, Pare PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. *Eur Respir J* 2005; **26(1)**: 140-52.
3. de Jong PA, Nakano Y, Hop WC, Long FR, Coxson HO, Pare PD, et al. Changes in airway dimensions on computed tomography scans of children with cystic fibrosis. *Am J Respir Crit Care Med* 2005; **172(2)**: 218-24.
4. Nakano Y, Wong JC, de Jong PA, Buzatu L, Nagao T, Coxson HO, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 2005; **171(2)**: 142-6.
5. de Jong PA, Ottink MD, Robben SG, Lequin MH, Hop WC, Hendriks JJ, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. *Radiology* 2004; **231(2)**: 434-9.
6. de Jong PA, Nakano Y, Lequin MH, Mayo JR, Woods R, Pare PD, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J* 2004; **23(1)**: 93-7.
7. de Jong PA, Nakano Y, Lequin MH, Merkus PJ, Tiddens HA, Hogg JC, et al. Estimation of lung growth using computed tomography. *Eur Respir J* 2003; **22(2)**: 235-8.
8. Pim A de Jong, Yastaka Nakano, Harm A Tiddens. Computed Tomography Dose Reduction in Children with Cystic Fibrosis: Reducing the number of images per scan? *Ped Rad* accepted

Not peer reviewed

9. Pim A de Jong, Maarten H Lequin, Peter D Paré, Harm AWM Tiddens. Re. Dr. Papaioannou. *Radiology* accepted (letter to the editor)
10. Pim A de Jong, Maarten H Lequin, John Mayo, Peter D Paré, Harm AWM Tiddens. Re: Re: progressive damage on high resolution computed tomography. *Eur Resp J* Dec 2004 (letter to the editor)

Submitted

11. Pim A de Jong, Frederick R Long, Jonathan C Wong, Peter J Merkus, Harm A Tiddens, James C Hogg, Harvey O Coxson, Estimation of Lung Growth Using Computed Tomography. Resubmitted to *Eur Resp J*
12. Pim A. de Jong, Anders Lindblad, Lorenzo Rubin, Johan C de Jongste, Mela Brink, Harm A.W.M. Tiddens. Computed Tomography is more sensitive than pulmonary function tests for monitoring lung disease progression in children and adults with cystic fibrosis. Resubmitted to *Thorax*

13. Pim A. de Jong, John R. Mayo, Kamran Golmohammadi, Yasutaka Nakano, Maarten H. Lequin, Harm A.W.M. Tiddens, John Aldrich, Harvey O. Coxson, Don D. Sin. Cancer Mortality Associated with Repetitive CT Scanning. Resubmitted to *Am J Resp Crit Care Med*
14. Pim A de Jong, Jonathan D Dodd, Harvey O Coxson, Claudine Storness-Bliss, Peter D Paré, John R Mayo and Robert D Levy. Bronchiolitis Obliterans Following Lung Transplantation: Early Detection Using Computed Tomography. Submitted
15. Pim A de Jong, Frederick R Long. The influence of beam current on quantitative measurements of airway wall and lumen in a piglet model. In progress
16. Jonathan D Dodd, Pim A de Jong Harvey O Coxson, John R Mayo and Robert D Levy. Diagnosis of Bronchiolitis Obliterans Using Volumetric Computed Tomography. In progress
17. Harvey O Coxson, Pim A de Jong, Jonathan D Dodd, Claudine Storness-Bliss, Peter D Paré, John R Mayo and Robert D Levy. Quantitative analysis of air trapping for diagnosis of Bronchiolitis Obliterans Following Lung Transplantation: Early Detection Using Computed Tomography. In progress
18. Lorenzo Rubin, Pim A. De Jong, Maarten H. Lequin, Wim C. Hop, B. Assael, Harm A. Tiddens. Cystic Fibrosis Related Pulmonary Disease: More Structure than Function? In progress
19. Lindblad A, de Jong P, Brink M, Tiddens H, Gustafsson P. Comparison of lung clearance index and high-resolution computed tomography in cystic fibrosis. In Progress
20. Pim A de Jong, Frederick R Long, Harm A Tiddens, Alan S Brody, and the Consenus CF CT study group. A Consensus Scoring System for Cystic Fibrosis (CT_{CF}-score) Lung Disease. In progress