Monitoring Cystic Fibrosis lung disease: Chest imaging and patient-related outcome measures.

Leonie Tepper

The work presented in this thesis was conducted at the Department of Pediatric Pulmonology and Radiology of the Erasmus MC Sophia Children's hospital in close collaboration with the Department of Medical Informatics and Child and Adolescent Psychiatry/Psychology.

The studies performed in this thesis were supported by Gilead Sciences, Inc and the Sophia Foundation for Medical Research (SSWO – "steun door Zeevaart").

The print and reproduction of this thesis were kindly supported by Ipskamp Drukkers

Cover design: A.W.Everaers
Layout: A.W.Everaers

ISBN

©2014 Leonie Tepper
All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without prior written permission from the copyright owner.

Monitoring Cystic Fibrosis lung disease: Chest imaging and patient-related outcome measures

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. J. Verweij

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
Woensdag 5 november 2014 om **11.30 uur**

door

Leonie Anke Tepper

geboren te Groningen

Promotiecommissie

Promotoren:	Prof. dr. H.A.W.M. Tiddens
	Prof. dr. G.P. Krestin
Co-promotoren:	Mw. dr. M. de Bruijne
	Mw. dr. E.M.W.J. Utens
Overige Leden:	Prof. dr. I.K.M. Reiss
	Prof. Dr. E. Steyerberg
	Prof. Dr. A.J. van der Heijden
	Prof. Dr. F.C. Verhulst
	Prof. Dr. C. De Boeck

CONTENTS

Chapter 1

General introduction

Cystic Fibrosis

Cystic Fibrosis (CF) is a severe, life-shortening genetic disease with a wide spectrum of clinical manifestations, affecting 70,000 patients in the EU and USA. The most prevalent clinical manifestation is structural lung disease. Structural lung disease is the main cause of morbidity in CF and accounts for 85% of the deaths in CF patients (1). Important for the pathogenesis of structural lung disease are genetic mutations on chromosome 7 encoding for the CF transmembrane conductance regulator (CFTR) (2-4). The most prevalent mutation is the dF508 deletion, but nowadays over 1926 mutations of the CFTR gene have been described not all resulting in CF and accounting for different disease severities (5). The wild type CFTR protein resides in the membrane of epithelial cells, and regulates the airway surface liquid by ion flux through the chloride channels at the epithelial surface (2,4). Due to CFTR gene mutations a dysfunctional CFTR protein is produced. Dysfunctional CFTR results in reduced or absent chloride secretion and increased sodium absorption, leading to an increase in mucus viscosity and impaired mucociliary clearance (6). As a result there is poor clearance of inhaled microorganisms. Chronic endobronchial infection by these microorganisms provokes an exaggerated inflammatory response leading eventually to structural lung damage (7,8). Despite extensive research many questions related to the pathophysiology of CF lung disease remain unanswered (7). It is well recognized that genetic and environmental modifiers can alter outcome. Importantly, prognosis is nowadays still primarily determined by the severity of CF lung disease (7). Therefore, in order to improve prognosis, CF lung disease should be prevented.

CF lung disease

The lungs of a CF patient are thought to be normal at birth. However, structural lung damage can already be observed at the age of 10 weeks (9-15). The most prominent components of CF lung disease are bronchiectasis and trapped air (16). Bronchiectasis is an irreversible dilatation of an airway, which develops over time as a consequence of chronic inflammation and infection leading to destruction of structural components of the bronchial wall. Using chest computed tomography (CT) it has been shown that 50 to 70% of children with CF develop bronchiectasis within the first 5 years of life (9,11,17). Trapped air on chest CT represents small airway disease. End-expiratory chest CT is the best modality to visualize the volume and distribution of trapped air (18). Two-thirds of the newly diagnosed infants with CF already have trapped air at the age of 1 year (9). It is therefore considered to be an important marker of early CF lung disease (9-11,16,19). Other important components of CF lung disease are mucus plugging, airway wall thickening and consolidation or atelectasis (16).

Monitoring CF lung disease

In order to prevent structural changes in the lungs, early detection and good monitoring are important. To detect and monitor structural changes in the lungs, several diagnostic modalities are used in clinical practice and in clinical trials. These diagnostic modalities can be categorized into: imaging techniques to visualize lung structure and measures of the function of the lung, which can be measured by a wide array of lung function tests. The most important imaging techniques for monitoring CF lung disease are nowadays chest Computed Tomography (CT) and chest Magnetic Resonance Imaging (MRI). Another method to monitor CF lung disease is related to patient's symptoms, which can be measured with the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Finally physical examination still plays an important role in the day to day monitoring of CF lung disease.

Lung function tests

To measure the function of the lung, spirometry and in particular the forced expiratory volume in one second (FEV_1), has been used as the primary outcome measure for both disease management and clinical trials (20-22). Although spirometry is widely used, it has several limitations. Firstly, FEV_1 is a relatively insensitive outcome measure for detecting and monitoring early stages of CF lung (23). Considerable structural lung damage can be present even with a normal FEV_1 (20). Secondly, spirometry requires active cooperation and can therefore only be reproducibly performed in most children of 6 years and older. Pre-school spirometry has been developed for children below the age of 6 years. In children aged 3 to 5 years, spirometry is based on computer-incentive games. Success rates between 45-75% have been reported (24-26). In children below 3 years of age infant pulmonary testing can be used but it requires sedation, is time consuming, and is technically difficult (27,28). A promising outcome measure in young children is the lung clearance index (LCI) derived from multiple breath washout techniques, which can be performed without sedation. The LCI has shown to be associated with structural lung disease, however it is not clear whether LCI is as sensitive as chest CT to monitor disease progression (19,22,29,30).

Chest imaging: CT and MRI

Chest CT is the most sensitive method to detect and monitor structural changes, like bronchiectasis and trapped air in the lungs (20,31-34). A disadvantage of CT is ionizing radiation (35). To minimize radiation exposure, low-radiation-dose CT scanning protocols have been developed. Furthermore, chest MRI has been suggested as a radiation free alternative for the diagnosis and monitoring of CF lung disease (36-39). The sensitivity of chest MRI to detect morphological changes such as bronchiectasis and trapped air is considered to be inferior to that of chest CT. This is especially true for early CF lung disease (36-39). However,

in the assessment of functional characteristics of the lung such as lung perfusion assessed by MRI or CT angiography and lung ventilation assessed by hyperpolarized helium MRI or Xenon CT, MRI is considered to be the established modality. To quantify changes in lung structure semi-quantitative scoring methods for chest CT and MRI have been developed and validated (40-43). In addition automated quantitative measurements of structural lung disease for chest CT are under development.

Quality of life measurements

To quantify a patient's symptoms, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) has been developed. The CFQ-R is a reliable and well-validated health-related quality of life measure, which meets the Food and Drug Administration (FDA) criteria for patient-reported outcome measures. According to the FDA a patient-reported outcome measure is the most sensitive method to measure quality of life (44).

For clinical management and clinical trials the CFQ-R has been translated and validated in multiple languages, including Dutch (44,45). There are three age-specific versions of the CFQ-R: 1) the CFQ-R Child version for ages 6-13 years; 2) the CFQ-R Teen/Adult version for ages 14 years and older; and 3) the CFQ-R Parent version, for parents of the children aged 6-13 years. All versions consist of several domains (e.g. Physical functioning, Vitality, Health perceptions, Respiratory symptoms scale), but the CFQ-R Respiratory Symptoms scale (CFQ-R RSS) is the most commonly used domain as it is impacted most by CF lung disease (46-51). The scores within each domain are standardized into scores ranging from 0 to 100, with higher scores indicating better health-related quality of life. Furthermore, the minimal important clinical difference for the CFQ-R RSS has been established, providing a systematic way to interpret changes in clinical status and to evaluate treatment response (44,52).

Validation of outcome measures

Currently, the most widely used outcome measure for CF lung disease is FEV_1 derived from spirometry. FEV_1 is well validated, however it is a relatively insensitive measure for diagnosing and monitoring CF lung disease. Therefore it has become less suitable over the last decades as a primary outcome in clinical trials, especially when studying early stages of CF lung disease (20-22). To detect and monitor CF lung disease in clinical practice and in clinical trials it is crucial to use sensitive, reproducible and feasible outcome measures.

Chest CT is a more direct and sensitive method than spirometry to study structural lung changes in CF lung disease, like bronchiectasis and trapped air. CT derived scores for

bronchiectasis and trapped air are relatively well validated as outcome measures in CF (9,16,20,23,31,40,53-60). Studies have shown that chest CT is 4-8 times more sensitive than FEV_1 for detecting disease progression (20-22). Furthermore, CT derived bronchiectasis score is associated with pulmonary exacerbations (56,61), is high in end-stage lung disease (16), and is associated with mortality (16). The importance of CT derived trapped air score, as an outcome measure has been less well established than bronchiectasis. Nevertheless it is considered to be an important component of CF lung disease, since it is the earliest structural abnormality on CT, preceding the occurrence of bronchiectasis, and in end-stage disease it makes up to 80% of the total lung volume (9,10,16,19).

Although extensive validation of chest CT related outcome measures has been performed, there are some important steps in the validation portfolio of chest CT missing. Firstly, the link between structural lung damage as established by CT and their impact on quality of life has not been established.

Secondly, the relation between trapped air and pulmonary exacerbations has not been well established (62). Thirdly, risk factors for progression of structural lung damage on chest CT have not been well established. Fourthly, whether early reversible stages of bronchiectasis can be identified is not clear.

For chest MRI, in contrast to chest CT, the validation process is at an early stage. Only few studies have validated MRI derived outcome measures for CF lung disease (36,38,39). Importantly, MRI should be validated against established outcome measures of CF lung disease such as FEV_1, pulmonary exacerbations and quality of life, measured with the CFQ-R.

The CFQ-R is well validated and has been utilized successfully in both controlled trials and longitudinal studies (46-51). The CFQ-R RSS was used as an outcome measure in several clinical trials showing responsivity to inhaled tobramycin (49), dornase alfa (50), hypertonic saline (51), and ivacaftor (47). It was used as primary outcome in a phase III study for FDA approval of aztreonam lysine for inhalation. In this study, a significant improvement in CFQ-R RSS was observed in the treated versus placebo group, with continued efficacy documented in an 18 month open-label follow up study (46,63).

Although a minimal clinical important difference has been established for the CFQ-R RSS, it is not clear how changes in respiratory symptoms measured with the CFQ-R RSS are related to the extent and progression of bronchiectasis and trapped air (52).

Aim of the study

In this thesis, 5 studies are presented. The aims of these studies were to further validate CT, MRI and the CFQ-R as outcome measures for the diagnosis and monitoring of CF lung disease.

To further validate chest CT as an outcome measure we:

- study the impact of bronchiectasis and trapped air on CT and pulmonary exacerbations and quality of life (Chapter 2).
- assess the associations between structural lung damage on CT and quality of life (Chapter 2 and 3).
- determine the risk factors for progression of structural lung damage on CT (Chapter 4).
- evaluate the development of bronchiectasis using consecutives CTs (Chapter 5).

To further validate chest MRI as an outcome measure we:

- study the relation between structural lung damage on MRI and FEV_1, pulmonary exacerbations and quality of life (Chapter 6).

To further validate CFQ-R as an outcome measure we:

- assess if a change in respiratory symptoms reflects the extent of bronchiectasis and trapped air on CT (Chapter 2,3).
- assess if a change in respiratory symptoms reflects the extent of bronchiectasis and trapped air on MRI (Chapter 6).

Outline of this thesis

Chapter 1 Contains the introduction to the studies that are described in this thesis.

Chapter 2 Describes a cross-sectional study in which CT scores for bronchiectasis and trapped air were correlated with quality of life scores and with pulmonary exacerbations.

Chapter 3 Describes a longitudinal study evaluating associations between changes in bronchiectasis, trapped air and patient-reported respiratory symptoms.

Chapter 4 Identifies predictors for bronchiectasis and trapped air severity over a 6 year follow up in children ages 6-13 years.

Chapter 5 Describes the development of bronchiectasis in CF on chest CT and identifies determinants for rapid progression of bronchiectasis.

Chapter 6 Describes the associations between MRI scores for bronchiectasis and trapped air and clinical markers of disease severity.

Chapter 7 Provides a general discussion on the results of the studies performed in this thesis.

References

1 Cystic Fibrosis Foundation. Patient registry annual report 2010. Bethesda, MD: Cystic Fibrosis Foundation 2010.

2 Ratjen F. Restoring airway surface liquid in cystic fibrosis. N Engl J Med 2006 Jan 19;354(3):291-293.

3 Flume PA. Pneumothorax in cystic fibrosis. Curr Opin Pulm Med 2011 Jul;17(4):220-225.

4 Mogayzel PJ,Jr, Flume PA. Update in cystic fibrosis 2009. Am J Respir Crit Care Med 2010 Mar 15;181(6):539-544.

5 Cystic Fibrosis Mutation Database. Available from: http://www.genet.sickkids.on.ca/StatisticsPage.html accessed December 15 2013.

6 Boucher RC. Evidence for airway surface dehydration as the initiating event in CF airway disease. J Intern Med 2007 Jan;261(1):5-16.

7 Ramsey BW, Banks-Schlegel S, Accurso FJ, Boucher RC, Cutting GR, Engelhardt JF, et al. Future directions in early cystic fibrosis lung disease research: an NHLBI workshop report. Am J Respir Crit Care Med 2012 Apr 15;185(8):887-892.

8 Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. Am J Respir Crit Care Med 1994 Aug;150(2):448-454.

9 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

10 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

11 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

12 Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003 Oct 15;168(8):918-951.

13 Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1133-1138.

14 Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med 2013 May 23;368(21):1963-1970.

15 Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. J Pediatr 2004 Feb;144(2):154-161.

16 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

17 Wainwright CE, Vidmar S, Armstrong DS, Byrnes CA, Carlin JB, Cheney J, et al. Effect of bronchoalveolar lavage-directed therapy on *Pseudomonas aeruginosa* infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA 2011 Jul 13;306(2):163-171.

18 Bonnel AS, Song SM, Kesavarju K, Newaskar M, Paxton CJ, Bloch DA, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. Pediatr Pulmonol 2004 Nov;38(5):396-405.

19 Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. PLoS One 2011;6(8):e23932.

20 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 Jan;23(1):93-97.

21 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

22 Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. Thorax 2011 Jun;66(6):481-488.

23 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.

24 Marostica PJ, Weist AD, Eigen H, Angelicchio C, Christoph K, Savage J, et al. Spirometry in 3- to 6-year-old children with cystic fibrosis. Am J Respir Crit Care Med 2002 Jul 1;166(1):67-71.

25 Vilozni D, Barker M, Jellouschek H, Heimann G, Blau H. An interactive computer-animated system (SpiroGame) facilitates spirometry in preschool children. Am J Respir Crit Care Med 2001 Dec 15;164(12):2200-2205.

26 Kozlowska WJ, Aurora P. Spirometry in the pre-school age group. Paediatr Respir Rev 2005 Dec;6(4):267-272.

27 Gappa M, Ranganathan SC, Stocks J. Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. Pediatr Pulmonol 2001 Sep;32(3):228-245.

28 Gappa M. The infant with cystic fibrosis: lung function. Paediatr Respir Rev 2004;5 Suppl A:S361-4.

29 Gustafsson PM, De Jong PA, Tiddens HA, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax 2008 Feb;63(2):129-134.

30 Ellemunter H, Fuchs SI, Unsinn KM, Freund MC, Waltner-Romen M, Steinkamp G, et al. Sensitivity of Lung Clearance Index and chest computed tomography in early CF lung disease. Respir Med 2010 Dec;104(12):1834-1842.

31 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 Jul 15;172(2):218-224.

32 Tiddens HA, Brody AS. Monitoring cystic fibrosis lung disease in clinical trials: is it time for a change? Proc Am Thorac Soc 2007 Aug 1;4(4):297-298.

33 Tiddens HA, de Jong PA. Update on the application of chest computed tomography scanning to cystic fibrosis. Curr Opin Pulm Med 2006 Nov;12(6):433-439.
34 Tiddens HA, Stick SM, Davis S. Multi-modality monitoring of cystic fibrosis lung disease: The role of chest computed tomography. Paediatr Respir Rev 2013 Jul 2.
35 Sodickson A. CT radiation risks coming into clearer focus. BMJ 2013 May 21;346:f3102.
36 Eichinger M, Heussel CP, Kauczor HU, Tiddens H, Puderbach M. Computed tomography and magnetic resonance imaging in cystic fibrosis lung disease. J Magn Reson Imaging 2010 Dec;32(6):1370-1378.
37 Altes TA, Eichinger M, Puderbach M. Magnetic resonance imaging of the lung in cystic fibrosis. Proc Am Thorac Soc 2007 Aug 1;4(4):321-327.
38 Puderbach M, Eichinger M, Haeselbarth J, Ley S, Kopp-Schneider A, Tuengerthal S, et al. Assessment of morphological MRI for pulmonary changes in cystic fibrosis (CF) patients: comparison to thin-section CT and chest x-ray. Invest Radiol 2007 Oct;42(10):715-725.
39 Puderbach M, Eichinger M. The role of advanced imaging techniques in cystic fibrosis follow-up: is there a place for MRI? Pediatr Radiol 2010 Jun;40(6):844-849.
40 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 May;231(2):434-439.
41 Brody AS. Scoring systems for CT in cystic fibrosis: who cares? Radiology 2004 May;231(2):296-298.
42 Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging 2006 Mar;21(1):14-21.
43 Eichinger M, Optazaite DE, Kopp-Schneider A, Hintze C, Biederer J, Niemann A, et al. Morphologic and functional scoring of cystic fibrosis lung disease using MRI. Eur J Radiol 2012 Jun;81(6):1321-1329.
44 US Food and Drug Administration. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Center for Biologics Evaluation and Research, US dept of Health and Human Services 2009.
45 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005 Oct;128(4):2347-2354.
46 Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest 2009 May;135(5):1223-1232.
47 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011 Nov 3;365(18):1663-1672.
48 Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011 Jan;46(1):36-44.

49 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. Pediatr Pulmonol 2002 Apr;33(4):269-276.

50 Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. Pharmacotherapy 2000 Oct;20(10):1167-1174.

51 Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006 Jan 19;354(3):241-250.

52 Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. Chest 2009 Jun;135(6):1610-1618.

53 Loeve M, Hop WC, de Bruijne M, van Hal PT, Robinson P, Aitken ML, et al. Chest computed tomography scores are predictive of survival in patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med 2012 May 15;185(10):1096-1103.

54 Loeve M, Krestin GP, Rosenfeld M, de Bruijne M, Stick SM, Tiddens HA. Chest computed tomography; a validated surrogate endpoint of cystic fibrosis lung disease? Eur Respir J 2012 Dec 20.

55 Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, et al. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009 Oct;253(1):223-229.

56 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

57 de Jong PA, Mayo JR, Golmohammadi K, Nakano Y, Lequin MH, Tiddens HA, et al. Estimation of cancer mortality associated with repetitive computed tomography scanning. Am J Respir Crit Care Med 2006 Jan 15;173(2):199-203.

58 de Jong PA, Tiddens HA. Cystic fibrosis specific computed tomography scoring. Proc Am Thorac Soc 2007 Aug 1;4(4):338-342.

59 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 Jul;145(1):32-38.

60 Mott LS, Graniel KG, Park J, de Klerk NH, Sly PD, Murray CP, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. Chest 2013 Oct;144(4):1193-1198.

61 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

62 Quittner AL, Alpern AN, Kimberg CI. Integrating Patient-Reported Outcomes into Research and Clinical Practice. Kending & Chernick's Disorders of the respiratory tract in children. 8th edic-tion:251-60.

63 Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010 Nov;45(11):1121-1134.

PART 1

Impact of cystic fibrosis on health related quality of life

Chapter 2

Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis

Tepper LA
Utens EMWJ
Caudri D
Bos AC
Gonzalez-Graniel K
Duivenvoorden HJ
van der Wiel ECW
Quittner AL
Tiddens HAWM

Eur Respir J. 2013 Aug;42(2):371-9.

ABSTRACT

Background. Cystic fibrosis (CF) is primarily characterized by bronchiectasis and trapped air on chest computed tomography (CT). The Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale (CFQ-R RSS) measures health-related quality of life.

Objective. To validate bronchiectasis, trapped air and CFQ-R RSS as outcome measures, we investigated correlations and predictive values for pulmonary exacerbations.

Methods. CF patients (6-20 years) had a CT, CFQ-R RSS and 1 year follow-up. Bronchiectasis and trapped air were scored using the CF-CT scoring system. Correlation coefficients and backward multivariate modeling were used to identify predictors of pulmonary exacerbations.

Results. 40 children and 32 adolescents were included. CF-CT bronchiectasis ($r=-0.38$, $p<0.001$) and CF-CT trapped air ($r=-0.35$, $p=0.003$) correlated with CFQ-R RSS. Pulmonary exacerbations were associated with: bronchiectasis (rate ratio (RR) 1.10, 95% Confidence Interval ($CI_{95\%}$) 1.02 to 1.19, $p=0.009$), trapped air (RR 1.02, $CI_{95\%}$ 1.00 to 1.05, $p=0.034$), and CFQ-R RSS (RR 0.95, $CI_{95\%}$ 0.91 to 0.98, $p=0.002$). The CFQ-R RSS was an independent predictor of pulmonary exacerbations (RR 0.96, $CI_{95\%}$ 0.94 to 0.97, $p<0.001$).

Conclusion. Bronchiectasis, trapped air and CFQ-R RSS were associated with pulmonary exacerbations. The CFQ-R RSS was an independent predictor. This study further validated bronchiectasis, trapped air and CFQ-R RSS as outcome measures.

INTRODUCTION

Cystic Fibrosis (CF) is a severe, life-shortening genetic disease affecting 70,000 patients in the EU and USA. The most prominent components of CF lung disease are bronchiectasis and trapped air. Bronchiectasis reflects irreversible widening of the airways and trapped air assesses small airway disease. Both bronchiectasis and trapped air typically begin in early childhood and progress slowly throughout life, eventually leading to end-stage lung disease (1,2).

Bronchiectasis and trapped air are important indicators of prognosis (3-5). Therefore accurate and sensitive monitoring of these indicators is needed for optimal clinical management and as potential outcome measures in clinical trials. To date, forced expiratory volume in one second (FEV_1), derived from pulmonary function tests (PFT), has been the central outcome measure for disease management and clinical trials. However, FEV_1 is a relatively insensitive measure for detecting and monitoring disease progression (6). Bronchiectasis, assessed with chest computed tomography (CF-CT bronchiectasis score), is more sensitive and accurate than chest radiograph (6). Literature suggests that the CF-CT bronchiectasis score is a valuable outcome measure since it is associated with pulmonary exacerbations (7,8), is an important component of end-stage lung disease (9), and is associated with mortality (9). It is not known whether the presence of bronchiectasis correlates with standardized, patient-reported outcome measures (10). In adults with chronic obstructive pulmonary disease, bronchiectasis is associated with reduced health-related quality of life, as measured by the symptoms scale of the St George Quality of Life Questionnaire (11). We hypothesized that a similar association may exist for bronchiectasis in CF.

The importance of trapped air as an outcome is less well-established than bronchiectasis. The volume and distribution of trapped air can be visualized well on end-expiratory chest CT (12). Trapped air is observed in approximately two-thirds of newly diagnosed infants, it is also an important component of end-stage lung disease (1,4,9). Hence, trapped air is considered a potential marker of early CF lung disease (2-4,9). To date, as an outcome measure for clinical management and trials, trapped air has not yet been validated against other clinical markers of disease severity, such as pulmonary exacerbations and patient-reported respiratory symptoms on a health-related quality of life measure.

Standardized, well-validated measures of health-related quality of life in CF, such as the disease-specific Cystic Fibrosis Questionnaire-Revised (CFQ-R) have been developed (13). The CFQ-R consists of several domains (e.g. Physical Functioning, Vitality, Health Perceptions, Respiratory Symptoms Scale (CFQ-RSS)). The CFQ-R Physical Functioning scale, CFQ-R Vitality scale, CFQ-R Health Perceptions and CFQ-R RSS have been shown to correlate to FEV_1 (14). The CFQ-R RSS has been utilized successfully in both controlled trials and longitudinal studies (15-20). The CFQ-R RSS was used as an outcome measure in several clinical trials showing responsivity to inhaled tobramycin (18), dornase alfa (19), hypertonic saline (20), and ivacaftor (16). CFQ-R RSS was used as primary outcome in a phase III study

for Food and Drug administration (FDA) approval of aztreonam lysine for inhalation. A significant improvement in CFQ-R RSS was found in the treated versus placebo group, with continued efficacy documented in an 18 month open-label follow up study (15,21).

Although a minimal important difference has been established for the CFQ-R RSS, it is not clear what change in respiratory symptoms reflects the extent of bronchiectasis and trapped air (22).

The objectives of this study were to further validate bronchiectasis and trapped air as outcome measures by correlating them with CFQ-R RSS and pulmonary exacerbations. Furthermore we aimed to validate bronchiectasis, trapped air, and CFQ-R RSS by investigating their predictive value for pulmonary exacerbations in the following year.

METHODS

Study population

Patients (aged 6-20 years) were diagnosed as having CF by a positive sweat test and/or genotyping for known CF mutations. We included clinically stable children and adolescents with CF, monitored at the Erasmus MC-CF Center Rotterdam, who had a CFQ-R and CT performed on the same day, at the annual check-up and at 1 year follow-up. If CT and the CFQ-R were not completed on the same day, a maximal time difference of 3 months was considered acceptable (n=1). Patients in need of intravenous antibiotics for respiratory signs or symptoms at the time of the annual examination were considered unstable and excluded. This retrospective cohort study was approved by the Institutional Review Board of the Erasmus MC-CF Center Rotterdam (MEC-2011-250).

Chest-CT evaluation of bronchiectasis and trapped air

All volumetric CTs were acquired using a 6-slice multi-detector CT scanner (Siemens Medical Solutions, Germany). Each CT consisted of a volumetric inspiratory and expiratory acquisition. Instructions for voluntary breath holds were given before scanning. kV tube voltages of 80 (patients < 35 kg) or 110 (patients > 35 kg) were used with a 0.6-sec rotation time. Scanning was done from apex to base at 1.5 pitch and 6x2 mm collimation. Images were reconstructed with a 3.0 mm slice thickness, 1.2 mm increment and kernel B60s. For the inspiratory protocol a modulating current was used (Siemens) with a reference tube current-time product of 20 mAs, for optimal image quality. For expiratory CTs a tube current fixed at 25 mA with an effective tube current-time product of 10 mAs (the typical value for a 5-year-old child) was used. This produced a lower radiation dose than the inspiratory protocol with sufficient image quality. Total radiation dose was in the order of 1 mSv.

All CTs were scored using the CF-CT scoring system, a modified version of Brody II scoring, evaluating the 5 lung lobes and the lingula as a sixth lobe for severity, extent of central and peripheral bronchiectasis, airway wall thickening, central and peripheral mucus plugging, opacities (atelectasis, consolidation, ground glass pattern) and cysts and bullae on inspiratory CTs and the pattern and extent of trapped air on expiratory CTs (7,23). The maximal possible composite CT score is 207 points. For statistical analysis, composite and component CT scores were expressed as a percentage of the maximum possible score (0-100). All scans were de-identified, using *Myrian Ò intrasense France*, and scored in random order by an observer blinded to clinical background (7).

Table 1. Baseline characteristics of the study cohort.

Characteristic	**Total group**		**Children**		**Adolescents**	
Number of patients	72		40		32	
Gender (Males)	35	(48.6)	20	(50)	15	(46.9)
Age, year	13.4	(6-20)	11.5	(6-14)	16.5	(14-20)
FEV_1, % predicted	83.4	(22-110)	85.7	(31-110)	75.9	(22-110)
FVC, % predicted	91.9	(32-119)	97.9	(53-119)	85.9	(32-112)
FEF_{75} % predicted	48.5	(6-95)	48	(7-95)	49.2	(6-92)
Positive *Pseudomonas aeruginosa* culture*	26	(36)	10	(25)	16	(50)
Chronic infection with *Pseudomonas aeruginosa***	19	(26)	5	(13)	14	(44)
CF-CT total score, %	7.8	(0-33)	5.2	(0-20)	11.8	(0-33)
Bronchiectasis score, %	0.0	(0-26)	0	(0-19)	2.6	(0-26)
Airway wall thickening score, %	8.3	(0-37)	4.9	(0-33)	14.8	(0-37)
Mucus plugging score, %	8.3	(0-50)	5.6	(0-50)	16.7	(0-42)
Opacities, %	5.6	(0-19)	4.6	(0-13)	7.4	(0-19)
Trapped air, %	36.7	(0-97)	33.3	(0-70)	43.3	(7-97)

Data are presented as no. (%) or median (range), unless otherwise indicated. FEF_{75} = forced expiratory flow at 75% of vital capacity.

* includes all positive Pseudomonas aeruginosa cultures positive in the year previous to the CT and CFQ-R.

** defined as ≥ 3 consecutive positive respiratory cultures for Pseudomonas aeruginosa.

To test the intra-observer agreement, observer 1 rescored 25 random scans after one month. A second observer scored 25 random scans to assure a good inter-observer agreement. Both observers were trained in CF-CT scoring and began scoring the study CTs after establishing good intra- and inter-observer agreement.

CFQ-R

Three age-appropriate versions of the Dutch CFQ-R were administered, using a multi-informant approach (Table 2): 1) the CFQ-R Child Version (ages 6-13; 35 items covering 8 domains); 2) CFQ-R Parent Version (caregivers of children 6-13; 43 items covering 11 domains) 3) CFQ-R Teen/Adult Version (ages > 14 years; 47 items covering 12 domains) (13). In addition to analyzing the CFQ-R RSS, we analyzed 3 health-related secondary domains; CFQ-R Physical Functioning, CFQ-R Vitality and CFQ-R Health Perceptions scale. Unfortunately, the CFQ-R Vitality and CFQ-R Health Perceptions do not exist for younger children (CFQ-R Child Version).

Table 2. Selected CFQ-R scores for children, their parents and adolescents.

Selected domain of the CFQ-R	Children (6-13 years)				Adolescents (≥14 years)	
	CFQ-R Child version n=40		CFQ-R Parent version n=37		CFQ-R Teen/Adult version n=32	
CFQ-R RSS	83	(50-100)	89	(50-100)	77	(11-100)
Physical Functioning	83	(39-100)	93	(52-100)	90	(38-100)
Vitality	-		73	(47-93)	67	(25-100)
Health Perceptions	-		78	(22-100)	67	(22-100)

CFQ-R scale scores for the different versions of the CFQ-R. CFQ-R RSS was the primary target. Physical Functioning, Vitality and Health Perceptions were secondary domains correlating with FEV_1. For each domain, a score between 0-100 is calculated. Higher scores indicate better health-related quality of life. Data are presented as median (range).

All scale scores were standardized on a 0-100 scale, with higher scores indicating better health-related quality of life (13).

PFT and pulmonary exacerbations

PFT results (diagnostic system: Jaeger AG) were expressed as percentages of predictive values, according to Stanjonevic for Forced vital capacity (FVC) and FEV_1, and Zapletal for the forced expiratory flow at 75% (FEF_{75}) (24,25).

Because there is no consensus on the definition of pulmonary exacerbations, they were conservatively defined as: episodes of treatment with IV antibiotics for pulmonary indications in the year following administration of CT and CFQ-R (7,8). *Pseudomonas aeruginosa* positivity as defined as: presence of ≥ 1 and <3 positive respiratory cultures in the year previous to the CT scan. Chronic colonization with *Pseudomonas aeruginosa* as defined as: ≥ 3 consecutive positive respiratory cultures.

Statistical analysis

Inter- and intra-observer agreement of CF-CT scores were calculated using intraclass correlation coefficients (ICC) (ICC 0.40 - 0.60= moderate, 0.60 - 0.80 = good, and ≥ 0.80= very good agreement). In case of low or moderate agreement between the observers Bland-Altman plots were calculated and for visualizing whether one over- or underestimated the CT scores on the different indices (26). Spearman's correlation coefficients were used to correlate CF-CT bronchiectasis and CF-CT trapped air scores with CFQ-R RSS, CFQ-R Physical Functioning, CFQ-R Vitality and CFQ-R Health Perceptions scale scores. Negative binomial regression models were used to investigate the association between CF-CT bronchiectasis, CF-CT trapped air and CFQ-R RSS and the number of pulmonary exacerbations in the subsequent year. A multivariate model was evaluated (backward, stepwise approach) to identify independent predictors of pulmonary exacerbations in the subsequent year. In order to reach sufficient power the univariate and multivariate regression analyses were performed on the complete study population (n=72). Analyses were repeated using the CFQ-R Child Version and CFQ-R Parent Version in children aged 6-13 years. In our final model the CFQ-R Child Version was used, because it is better to use the patients own report on his/her symptoms as recommended by the Food and drug administration (FDA) and European Medicines Agency (EMA). To interpret our results in clinical terms, we used a logistic model.

Statistical analyses were performed using SAS version 9.2. Results are displayed as median (range) unless otherwise defined. Two tailed-testing was performed. P-values < 0.05 were considered to be significant.

RESULTS

Study population

Seventy two patients (40 children, 32 adolescents) had 72 CTs and PFTs completed. Baseline characteristics are shown in Table 1. A total of 109 CFQ-Rs were collected: 40 CFQ-R Child, 37 CFQ-R Parent, and 32 CFQ-R Teen/Adult measures. Three parents did not return the CFQ-R (see Table 2). ICCs for within-observer agreement ranged from 0.68 (CF-CT trapped air score) to 0.98 (CF-CT bronchiectasis score), whereas between-observer agreement ranged from 0.50 (CF-CT trapped air score) to 0.91 (CF-CT total score).

Correlations between CT and CFQ-R (see Table 3)

In children the CF-CT Airway wall thickening ($p<0.001$), mucus plugging ($p<0.001$) and opacities ($p=0.007$) were significantly correlated with the CFQ-R RSS. Similarly, CF-CT airway wall thickening and mucus plugging were significantly correlated with the CFQ-R RSS

Table 3. Correlations between the CF-CT scores and the selected CFQ-R scaled scores across versions.

	Children (6-13 years)						Adolescents (≥14 years)				Children and adolescents	
	CFQ-R Child Version (n=40)		CFQ-R Parent Version (n=37)				CFQ-R Teen/Adult Version (n=32)				Total group (n=72)	
	CFQ-R RSS	CFQ-R Physical	CFQ-R RSS	CFQ-R Physical	Vitality	CFQ-R HP	CFQ-R RSS	CFQ-R Physical	Vitality	CFQ-R HP	CFQ-R RSS	CFQ-R Physical
CF-CT bronchiectasis score	-0.22	0.09	-0.35*	-0.26	0.01	-0.02	-0.46**	-0.50**	-0.23	-0.28	-0.38**	-0.09
CF-CT airway wall thickening score	-0.51**	-0.13	-0.42*	-0.41*	-0.19	-0.18	-0.49**	-0.53**	-0.22	-0.37*	-0.51**	-0.17
CF-CT mucus plugging score	-0.63**	-0.15	-0.43**	-0.14	-0.09	-0.03	-0.49**	-0.49**	-0.25	-0.36*	-0.56**	-0.25*
CF-CT opacities scores	-0.42**	0.17	-0.31	0.14	0.07	0.20	-0.50**	-0.42*	-0.28	-0.30	-0.47**	-0.04
CF-CT trapped air scores	-0.26	0.08	-0.14	0.03	0.03	0.09	-0.40*	-0.37*	-0.26	-0.18	-0.35**	-0.09

Correlations between CF-CT scores and the selected CFQ-R scale scores of the CFQ-R Child, Parent, Teen/Adult Version. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). CFQ-R RSS: CFQ-R respiratory symptoms scale. CFQ-R Physical: CFQ-R physical functioning. CFQ-R HP: CFQ-R health perceptions.

scores in the parent, but also the CF-CT bronchiectasis score (p=0.033). Similar associations were found among adolescents: CF-CT bronchiectasis score (p=0.007), airway wall thickening (p=0.005), mucus plugging (p=0.004), and opacities (p=0.004) all significantly correlated with the CFQ-R RSS scores.

No significant correlations were found between the CF-CT scores and the Physical Functioning scale in children, whereas in adolescents all of the CF-CT scores correlated.

In the other health-related secondary domains (Vitality and Health Perceptions), only CFQ-R Health Perceptions in adolescents was significantly associated with CF-CT airway wall thickening (p=0.038), and CF-CT mucus plugging (p=0.041).

Across ages (n=72), CF-CT bronchiectasis scores were significantly correlated with CFQ-R RSS (r=-0.38, p<0.01), with more structural changes associated with worse respiratory symptoms (Figure 1). This relationship was also present between CF-CT trapped air scores and CFQ-R RSS (r=-0.35, p<0.01) (Figure 2).

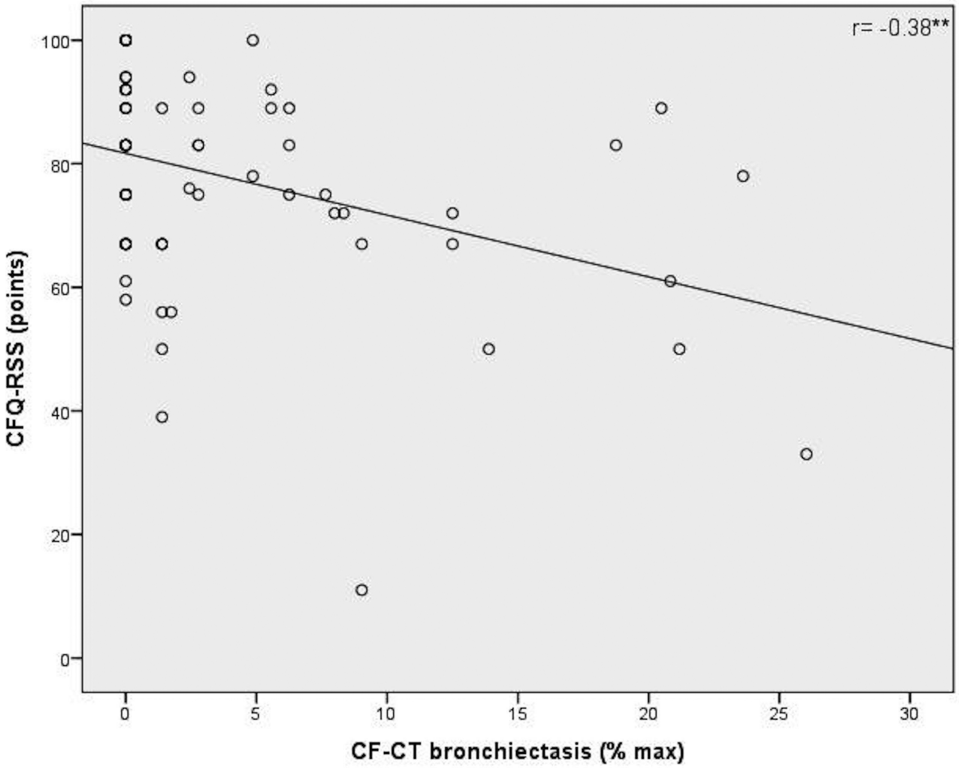


Figure 1. Correlation between CFQ-R RSS and CF-CT bronchiectasis score across ages (n=72) ** p < 0.01.

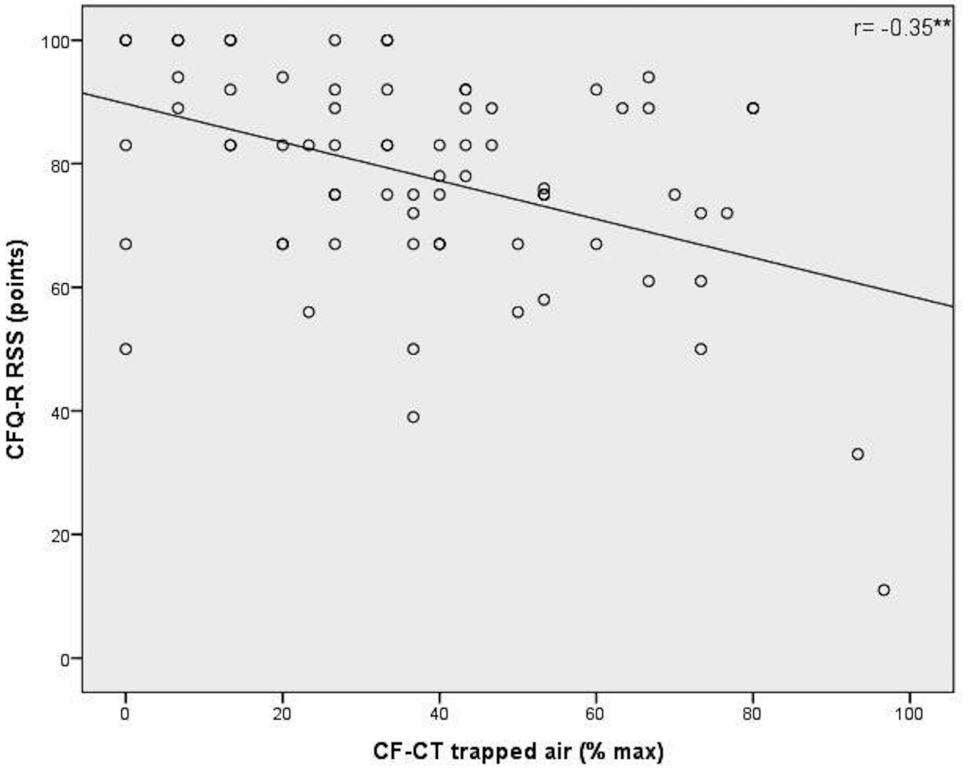


Figure 2. Correlation between CFQ-R RSS and CF-CT trapped air score across ages (n=72) ** $p < 0.01$.

Associations between CT, CFQ-R RSS and pulmonary exacerbations in the following year (Table 4)

CF-CT bronchiectasis scores were significantly associated with the number of pulmonary exacerbations in the following year, rate ratio of 1.10 (95% Confidence Interval ($CI_{95\%}$) 1.02 to 1.19, p=0.009). This indicates that the expected number of pulmonary exacerbations increased 10% in the following year ($CI_{95\%}$ 2.4 to 19%) for each 1 point increase in a patient's CF-CT bronchiectasis score. The rate ratio for CF-CT trapped air on pulmonary exacerbations in the following year was smaller, but also significant, 1.02 ($CI_{95\%}$ 1.00 to 1.05, p=0.034). CFQ-R RSS were associated with pulmonary exacerbations in the following year, rate ratio of 0.95 ($CI_{95\%}$ 0.91 to 0.98, p=0.002). Thus, the expected number of pulmonary exacerbations decreased 5% for each 1 point increase in CFQ-R RSS scores.

Prediction model for pulmonary exacerbations

Seventy-two patients had complete longitudinal data for the multivariate prediction model. Due to the relatively small sample size, a limited number of predictors were tested: gender, age, CF-CT bronchiectasis score, CF-CT trapped air score, CFQ-R RSS and positive culture for *Pseudomonas aeruginosa* in the year before the CT. In the final model, significant predictors of subsequent pulmonary exacerbations were: age (p=0.001), CFQ-R RSS (p<0.001), and positive cultures for *Pseudomonas aeruginosa* (p=0.008) (Table 4). A decrease of one point in CFQ-R RSS scores predicted a 4.7% ($CI_{95\%}$ 3.0 to 6.3 %) increase of pulmonary exacerbations in the following year. *Quittner et al*. showed that a 4-point reduction in CFQ-R RSS scores was clinically meaningful (22). According to the logistic model used in our study, this would equate to a 20% (4.7^4) increase in the number of pulmonary exacerbations in the following year. To determine whether CFQ-R scores were merely a reflection of the number of pulmonary exacerbations in the previous year, we performed a sensitivity analysis adding the number of pulmonary exacerbations in the previous year to the multivariate model. Interestingly, CFQ-R RSS scores continued to add predictive value for number of pulmonary exacerbations in the following year (2.6% decrease per point in CFQ-R, $CI_{95\%}$ 0.4 to 4.8, p=0.014). CF-CT bronchiectasis and trapped air did not remain significant in the multivariate model. No meaningful differences were present when the analysis were performed, using the CFQ-R Parent Version in place of the CFQ-R Child Version.

Table 4. Univariate and multivariate associations with pulmonary exacerbations in the following year.

Predictor	Univariate associations			Multivariate prediction model*		
	Rate Ratio†	$CI_{95\%}$	P-value	Rate Ratio†	$CI_{95\%}$	P-value
CF-CT bronchiectasis score	1.10	1.02-1.19	0.009			ns
CF-CT trapped air score	1.02	1.00-1.05	0.034			ns
CFQ-R RSS	0.95	0.91-0.98	0.002	0.96	0.94-0.97	<0.001
Positive culture *Pseudomonas aeruginosa* ‡	1.98	1.22-3.23	0.006	1.72	1.10-2.69	0.008
Age (years)	1.21	1.02-1.44	0.030	1.52	1.00-2.30	0.001
Gender	1.03	0.38-2.80	0.951			ns

N=72. In young children (6-13 years) the CFQ-R Child Version was used. *: Only variables significant at p=0.05 level in multivariable model are included. †: Rate Ratio for scores calculated per point increase in score. ‡: defined as ≥ 1 positive respiratory cultures for Pseudomonas aeruginosa in the past 12 months.

DISCUSSION

This is the first study to investigate the relationship between bronchiectasis and trapped air, assessed by chest CT and CFQ-R RSS scores. The most important finding was that more severe bronchiectasis was significantly associated with worsening respiratory symptoms. Bronchiectasis, trapped air and CFQ-R RSS were all significantly associated with pulmonary exacerbations in the following year.

The importance of bronchiectasis in CF lung disease has been well established (1,3-5,7-9), however the impact of bronchiectasis on patient-reported outcome measures in CF had not previously been examined (10). Our finding that bronchiectasis and CFQ-R RSS are negatively associated supports the validity of bronchiectasis as a clinically relevant outcome measure. Previous studies have shown that bronchiectasis was associated with pulmonary exacerbations in the following two years (7,8), while our data showed a similar association over a 1 year time period. Unfortunately, in our multivariate model, CF-CT bronchiectasis did not remain a significant predictor for pulmonary exacerbations, probably because we have a patient population with very mild CF, reflected by a median bronchiectasis score of 0.00.

Although trapped air has been less well validated as an outcome measure, we found a significant, independent correlation between trapped air and CFQ-R RSS. Although the associations between CF-CT trapped air scores and both CFQ-R RSS and pulmonary exacerbations were significant, they were not as strong as the associations with bronchiectasis. This may be because trapped air has less impact on patient functioning than bronchiectasis and can be reversible to some extent (1,2). A recent study showed that patients with severe advanced lung disease, such as bronchiectasis, had a higher mortality risk compared to patients who predominantly had trapped air (9). Our results suggested that trapped air can also be considered as a valuable CT-related surrogate outcome measure in CF.

Interestingly, we also found significant associations in other CT indices: CF-CT airway wall thickening, mucus plugging, and opacities were significantly associated with the CFQ-R RSS in children and adolescents. Airway wall thickening and mucus plugging are considered to be early indicators of developing disease, in contrast to bronchiectasis, which is considered to be a last stage of structural damage in the larger airways. Therefore, it is not surprising that these early indicators, and not bronchiectasis, were significantly associated with the CFQ-R RSS in the younger age group. Note that this was a young population with very mild CF lung disease. This further validates the CFQ-R RSS as a sensitive measure of structural lung damage in the early stages of CF lung disease.

We found that the lower the CFQ-R RSS score, the higher the risk for pulmonary exacerbations, irrespective of other predictors. This innovative result is consistent with the research of *Britto et al.* (27). They concluded that pulmonary exacerbations have a profound, nega-

tive impact on health-related quality of life in CF-children, using a generic instrument (Child Health Questionnaire). Furthermore, our data suggested that the CFQ-R RSS is sensitive to early, minor respiratory symptoms preceding pulmonary exacerbations. Therefore the CFQ-R RSS may allow earlier detection of disease progression.

In our multivariate model, after including CFQ-R RSS, CT had no added value to predict the frequency of pulmonary exacerbations. It is important to realize that the CFQ-RSS and CT provide different information. The CFQ-R RSS focuses exclusively on the frequency and severity of respiratory symptoms, whereas CT provides critical information about structural lung changes like the extent of bronchiectasis and trapped air. CT also provides information about airway wall thickening and mucus plugging, which can be considered as early leading indicators of developing disease. Consequently, aggressive treatment to prevent structural lung damage should be considered if either indicator is present on CT. Therefore, both CT and CFQ-R RSS are considered important outcome measures.

Limitations

This was a retrospective study. Therefore, we selected a robust, conservative definition of pulmonary exacerbations that were unlikely to be missed (7,8,28,29). Data were collected from a single center, which may reduce the generalizability of the results. Furthermore, we used an age-range of 6 to 20 years; whether similar correlations exist in infant or adult CF populations requires further study. Considering the progressive nature of CF, we would expect a higher rate of pulmonary exacerbations in adults and thus, stronger associations.

In conclusion, we showed that in children with CF, more severe bronchiectasis and trapped air were associated with worse CFQ-R RSS scores. Bronchiectasis, trapped air and the CFQ-R RSS were significantly associated with pulmonary exacerbations in the following year. Our findings validate the importance of CT measures of bronchiectasis and trapped air and the CFQ-R RSS as clinically relevant outcome measures for CF.

REFERENCES

1 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

2 Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. PLoS One 2011;6(8):e23932.

3 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

4 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

5 Pillarisetti N, Linnane B, Ranganathan S, AREST CF. Early bronchiectasis in cystic fibrosis detected by surveillance CT. Respirology 2010 Aug;15(6):1009-1011.

6 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.

7 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

8 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

9 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

10 Quittner AL, Alpern AN, Kimberg CI. Integrating Patient-Reported Outcomes into Research and Clinical Practice. Kending & Chernick's Disorders of the respiratory tract in children. 8th edic-tion:251-60.

11 Garcia MAM, Tordera MP, Sanchez PR, Cataluna S. Internal consistency and validity of the spanish version of the St. George Respiratory questionnaire for use in patients with clinically stable bronchiectasis. Archivos de Bronchoneumologia 2005(41):110-117.

12 Bonnel AS, Song SM, Kesavarju K, Newaskar M, Paxton CJ, Bloch DA, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. Pediatr Pulmonol 2004 Nov;38(5):396-405.

13 Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Erratum to: Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national, US sample. Qual Life Res 2012 Sep;21(7):1279-1290.

14 Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. Chest 2010 Mar;137(3):642-650.

15 Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest 2009 May;135(5):1223-1232.

16 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011 Nov 3;365(18):1663-1672.

17 Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011 Jan;46(1):36-44.

18 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol 2002 Apr;33(4):269-276.

19 Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. Pharmacotherapy 2000 Oct;20(10):1167-1174.

20 Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006 Jan 19;354(3):241-250.

21 Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010 Nov;45(11):1121-1134.

22 Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest 2009 Jun;135(6):1610-1618.

23 Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging 2006 Mar;21(1):14-21.

24 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008 Feb 1;177(3):253-260.

25 Zapletal A, Naidr J, Pohunek P. A brief description of methods for studying pulmonary function in children and adolescents. Cesk Pediatr 1992 Sep;47(9):520-523.

26 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-310.

27 Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002 Jan;121(1):64-72.

28 Ortiz JR, Neuzil KM, Victor JC, Wald A, Aitken ML, Goss CH. Influenza-associated cystic fibrosis pulmonary exacerbations. Chest 2010 Apr;137(4):852-860.

29 Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, et al. Return of FEV1 after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol 2010 Feb;45(2):127-134.

Chapter 3

Tracking CF disease progression with CT and respiratory symptoms in a cohort of children aged 6-19 years

Tepper LA
Caudri D
Utens EMWJ
van der Wiel ECW
Quittner AL
Tiddens HAWM

Accepted Ped.Pulmonology

ABSTRACT

Background. Cystic fibrosis (CF) lung disease is characterized by bronchiectasis and trapped air on chest Computed Tomography (CT).

Objective. We aim to validate bronchiectasis and trapped air as outcome measures by evaluating associations between changes in bronchiectasis, trapped air and patient-reported respiratory symptoms.

Methods. A longitudinal cohort study has been conducted. CF patients (aged 6-19 years) who had two routine CTs and completed twice a Cystic Fibrosis Questionnaire-Revised within 2 years (referred to as T_1 and T_2), in the period of July 2007 to January 2012 were included. Bronchiectasis and trapped air were scored using the CF-CT scoring system. Correlation coefficients and student's paired t-tests were performed.

Results. In total 40 patients were included with a median age at T_1 of 12.6 years (range 6-17 years), and at T_2 14.5 years (range 8-19 years). At T_1, bronchiectasis ($r=-0.49$, $p<0.01$) and trapped air ($r=-0.34$, $p=0.04$) correlated with CFQ-R Respiratory Symptoms Scores (CFQ-R RSS). At T_2 similar correlations were found with the CFQ-R RSS. Over two years, there was significant progression in bronchiectasis ($p=0.03$) and trapped air ($p=0.03$), but not in CFQ-R RSS. Changes in bronchiectasis and trapped air were not associated with changes in CFQ-R RSS.

Conclusion. Our results indicate that bronchiectasis and trapped are sensitive outcome measures in CF lung disease, showing a significant association with CFQ-R RSS at two-time points. However, progression of bronchiectasis and trapped air over two year does not necessarily correlate to changes in quality of life.

INTRODUCTION

Cystic Fibrosis (CF) is a severe genetic disease affecting approximately 70,000 patients in Europe and the United States. Prognosis is primarily determined by the severity of lung disease. To improve treatment and prognosis, it is critical to conduct clinical trials using sensitive, reproducible and feasible outcome measures (1,2). Many outcome measures have been evaluated in prior studies, leading to the identification of new endpoints.

There are currently two endpoints considered to be measures of clinical status: 1) assessment of pulmonary exacerbations, and 2) standardized questionnaires assessing respiratory symptoms, e.g. the Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale (CFQ-R RSS). Other endpoints, such as bronchoalveolar lavage, markers of inflammation, spirometry, and imaging, are considered surrogate outcomes (1,2).

Currently, the most widely used surrogate outcome measure is Forced Expiratory Volume in one second (FEV_1) derived from spirometry. However, FEV_1 is a relatively insensitive measure for monitoring early CF lung disease (3-5). Studies have shown that chest Computed Tomography (CT) is 4-8 times more sensitive than FEV_1 for detecting disease progression and therefore, a potential promising outcome measure (3).

Given that progression of CF lung disease is primarily characterized by the development of bronchiectasis and trapped air, chest CT may offer advantages over other outcome measures. Bronchiectasis is a bronchial dilatation that begins early in life (6-8) and has been validated against other clinically meaningful outcomes. It correlates with mortality (9), is an important component of end stage lung disease (9), is strongly associated with pulmonary exacerbations (10-12), and correlates cross-sectionally to patient-reported outcomes (12).

Trapped air represents small airways disease. The volume and distribution of trapped air can be visualized on end-expiratory chest CT (13), but it is not as well-validated as an outcome measure as bronchiectasis. Trapped air is the earliest structural abnormality on CT, preceding the occurrence of bronchiectasis (7,8,14). In end-stage disease, it is present in up to 40% of the total lung volume (9), and correlates with health-related quality of life (12). Bronchiectasis and trapped air are promising outcome measures, however further validation is needed.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R), is a reliable and well validated health-related quality of life measure that meets the FDA criteria for patient-reported outcome development and has been translated and validated in Dutch and other languages (15,16). The CFQ-R consists of several domains, some of which have been significantly associated with FEV_1 (17); Respiratory Symptoms, Physical Functioning, Vitality, and Health Perceptions. *Sawicki et al.* showed that the CFQ-R RSS was sensitive to changes in respiratory symptoms over a 9-15 month study period (18), an independent predictor of pulmonary

exacerbations (12) and responsive to the effect of different kind of medications: inhaled tobramycin (19), dornase alfa (20), hypertonic saline (21), and ivacaftor (22). Less is known about the extent to which patient-reported respiratory symptoms reflect the progression of bronchiectasis and trapped air over longer time periods. For example, the CFQ-R has a two-week recall window whereas changes on a CT scan may be detectable over a longer time scale.

Contributing to the validation of bronchiectasis and trapped air as new outcome measures, we evaluated the associations between bronchiectasis, trapped air, and CFQ-R scores cross-sectionally at two time periods (T_1 and T_2) and longitudinally over two years. We hypothesized that progression of bronchiectasis and trapped air would be associated with a worsening of CFQ-R RSS scores over a two-year time period.

MATERIALS AND METHODS

Study population

This longitudinal cohort study used clinical data from the annual evaluation of all children and adolescents with CF, treated in the Erasmus MC-CF Center (Rotterdam, the Netherlands) from July 2007 to January 2012, who completed a CT and CFQ-R twice (performed on the same day as part of their annual examination) and gave their consent to use their data. The included children and adolescents (aged 6-17 years) were clinically stable and diagnosed with CF by a positive sweat test and/or genotyping for known CF mutations. According to the routine annual examination of the Erasmus MC-CF center every child with CF completes a CFQ-R. A routine chest CT is performed biennially. Therefore the time between two CTs is approximately two years. T_1 defines completion of the first CT and CFQ-R. T_2 defines their completion at the second time point. Children and adolescents receiving intravenous antibiotics for respiratory symptoms at their annual examination were considered unstable and were therefore excluded. This study was approved by the Institutional Review Board of the Erasmus MC-CF Center (MEC-2011-460).

Chest CT evaluation and spirometry

All volumetric CTs were acquired using a 6-slice multi-detector CT scanner (Siemens Medical Solutions, Germany). Each CT consisted of a volumetric inspiratory and expiratory acquisition. If the CT was not spirometry controlled, instructions for breath holds were given before scanning. The total radiation dose was approximately 1 mSv (on-line supplement).

All CTs were scored using the CF-CT scoring system, evaluating the 5 lung lobes and the lingula for our primary outcomes: severity, extent of central and peripheral bronchiectasis

(CF-CT bronchiectasis score), on inspiratory CTs, and the pattern and extent of trapped air (CF-CT trapped air score) on expiratory CTs (10,23). Other components of the CF-CT scoring system that were evaluated are the severity and extent of airway wall thickening, central and peripheral mucus plugging, opacities (atelectasis, consolidation, ground glass pattern), cysts and bullae.

For statistical analysis, the component CT scores (expressed as a percentage of the maximum possible score (0-100%)) of one observer were used. All scans were anonomyzed, using *MyrianÒ (intrasense Montpelier, France)*, and scored in random order by observer 1 blinded to clinical background (10). To assess intra-observer agreement, observer 1 re-scored 25 scans after one month. A second random set of 25 scans was selected for observer 2 to evaluate inter-observer agreement (9,10,24). Both observers were trained in CF-CT scoring.

Spirometry was performed using a diagnostic system (Jaeger AG, Germany). Spirometry results (FEV_1, FVC) were expressed as percentages of predictive values, according Stanojevic (25).

CFQ-R

The CFQ-R has different versions based on age: 1) the CFQ-R Child Version for ages 6-13 years; 2) the CFQ-R Teen/Adult Version for ages 14 years and older, and 3) the CFQ-R Parent Version, completed by parents of the children aged 6-13 years. We did not include the CFQ-R Parent scores in our analyses, because it is better to use the patient's own report, according to both the FDA and European Medicines Agency (16).

Several domains of the CFQ-R have been shown to correlate with FEV_1 (17): Respiratory Symptoms Scale, Physical Functioning scale, Vitality scale, and Health Perceptions. CFQ-R Vitality and Health Perceptions only appear in the Teen/Adult Version and given our sample size they were excluded from analysis. Our primary goal was to evaluate the CFQ-R RSS because it most directly reflects lung disease. Responses to items on each scale were standardized into scores ranging from 0 to 100, with higher scores indicating better health-related quality of life.

Statistical analysis

Inter- and intra-observer agreement of component CF-CT scores were calculated using intraclass correlation coefficients (ICC). Although no universally accepted standards are available for what constitutes good reliability, ICC values between 0.4 and 0.6, 0.6 and 0.8, and ≥ 0.8 are considered to represent moderate, good and very good agreement. According to

Cohen's criteria (1988) associations between 0.10 and 0.29 are considered weak, between 0.30 and 0.49 intermediate and above 0.50 are considered strong associations. Systematic errors in component scores were evaluated using Bland-Altman plots, expressing the differences between two observers as a function of their mean (26).

Spearman's correlation coefficients were used to correlate CF-CT bronchiectasis, trapped air, airway wall thickening, mucus plugging and opacities scores with CFQ-R RSS and Physical Functioning at T_1 and T_2. Student's paired t-tests were used to determine whether there were significant changes over time in: CF-CT scores, FEV_1, CFQ-R RSS, and Physical Functioning. Changes in scores were calculated by taking the difference between the values at T_2 and T_1. Statistical analyses were performed using SPSS version 20.0 for windows. Continuous variables are displayed as medians (ranges). P-values less than 0.05 (two tailed) were considered statistically significant.

RESULTS

Study population

Forty patients (Figure 1) completed the CT and CFQ-R protocol twice (T_1: 29 children and 11 adolescents). The median time interval between T_1 and T_2 was 2.0 years (range 0.9-4.0). In 4 of the included patients the time interval was less than 1.5 years and 1 patient had a four-year time interval between CTs. Baseline Characteristics of this cohort are shown in Table 1.

At T_1 we collected: 29 CFQ-R Child measures and 11 CFQ-Rs Teen/Adult measures (Table 2). At T_2, 12 children had reached 14 years of age and therefore switched from the Child to the Teen/Adult Version. At T_2 we collected: 17 CFQ-R Child measures and 23 Teen/Adult measures. The CFQ-R scale scores at T_1 and T_2 are shown in Table 2.

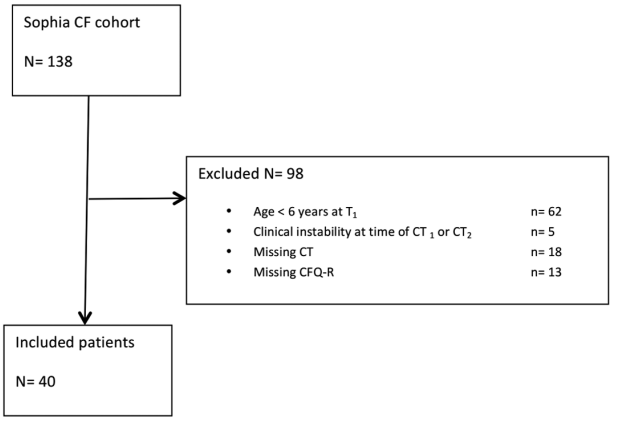


Figure 1. Flowchart.

The ICC's for intra-observer agreement for bronchiectasis and trapped air were respectively 0.86 and 0.75, ranging from 0.72 (CF-CT opacities) to 0.86 (CF-CT bronchiectasis). Inter-observer agreement for bronchiectasis and trapped air were respectively 0.89 and 0.69, ranging from 0.69 (CF-CT trapped air) to 0.95 (CF-CT mucus plugging).

Table 1. Baseline and two year follow up characteristics of the whole study cohort.

Characteristic		T_1		T_2		p-value	Mean difference ($CI_{95\%}$)
Number of patients		40		40			
Gender (Males)		19	47.5				
Age, year		12.6	(6;17)	14.5	(8;19)	<0.01**	-1.9 (-2.1;-1.7)
	Children	29	72.5	17	42.5		
	Adolescents	11	27.5	23	57.5		
SES[#]							
	Low	6	16.7				
	Average	13	36.1				
	High	12	33.3				
	Scientific	5	13.9				
Genetics							
	Homozygous dF508	25	62.5				
	Heterozygous dF508	13	32.5				
	Heterozygous other mutation	2	5.0				
Presence of co-morbidities							
	Pancreatic insufficient	35	87.5				
	CFRD	3	7.5				
	Asthma	2	5.0				
	ABPA	1	2.5				
	Chronic colonization *Pa*	5	12.5				
BMI		17.1	(13;31)	18.7	(13;30)	<0.01**	-1.0 (-1.5;-0.5)
FEV_1, % predicted (n=37)		82.4	(31;114)	84.0	(37;117)	0.14	-6.5 (-15.2;2.3)
FVC, % predicted (n=37)		93.3	(22;118)	92.3	(56;128)	0.06	-9.2 (-18.9;0.4)
CF-CT bronchiectasis score, %		1.6	(0;22)	2.1	(0;24)	0.03*	-0.7 (-1.4;-0.1)
CF-CT airway wall thickening score, %		2.8	(0;26)	3.7	(0;26)	0.21	-0.7 (-1.8;0.4)
CF-CT mucus plugging score, %		2.8	(0;39)	4.2	(0;56)	0.06	-1.9 (-3.9;0.1)
CF-CT opacities score, %		3.7	(0;15)	5.6	(0;13)	0.83	0.1 (-0.8;1.0)
CF-CT trapped air score, %		26.9	(0;76)	32.4	(7;78)	0.03*	-6.6 (-12.6;-0.6)

Data are presented as no. (%) or median (range). T_1 and T_2 indicate the 2 time moments. CFRD: CF-related diabetes. ABPA: Allergic Bronchopulmonary Aspergillose. Chronic colonization Pseudomonas aeruginosa (Pa) is defined as ≥ 3 consecutive positive respiratory cultures for Pseudomonas aeruginosa.. [#] SES: socio-economic status based on the highest level of education of the parents (n=36) * Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

Table 2. Scale scores of the CFQ-R at T_1 and T_2.

	T_1		T_2		Change two years	
	CFQ-R Child Version (6-13 years) (n=29)	CFQ-R Teen/ Adult Version (≥14 years) (n=11)	CFQ-R Child Version (6-13 years) (n=17)	CFQ-R Teen/Adult Version (≥14 years) (n=23)	P-value	Mean difference ($CI_{95\%}$)
CFQ-R RSS	83 (50;100)	89 (61;100)	83 (52;92)	89 (56;100)	0.84	-0.4 (-4.4;3.6)
CFQ-R Phys.	83 (61;100)	96 (67;100)	89 (61;100)	92 (62;100)	0.26	-2.8 (-7.6;2.1)
CFQ-R Vital.#	-	67 (50;100)	-	67 (50;100)	n/a	
CFQ-R H.P.#	-	67 (11;100)	-	78 (11;100)	n/a	

Data are presented as median (range). T_1 and T_2 indicate the two time points.
The selected scale scores of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) are the CFQ-R Respiratory Symptoms scale (CFQ-R RSS), CFQ-R Physical Functioning (CFQ-R Phys.), CFQ-R Vitality (CFQ-R Vital.), and CFQ-R Health Perceptions (CFQ-R H.P.). #The sample size was too small (n=11) to analyse the change in CFQ-R Vitality and CFQ-R Health Perceptions over a two-year time period.

Correlations between CT and CFQ-R at T_1 and T_2 (Table 3)

At T_1, all CT indices were significantly associated with CFQ-R RSS. Furthermore, CF-CT opacities were associated with Physical Functioning.

Table 3. Associations between CT indices and CFQ-R scale scores at T_1 and T_2.

	T_1		T_2	
	CFQ-R RSS(n=40)	CFQ-R Physical Functioning (n=40)	CFQ-R RSS (n=40)	CFQ-R Physical Functioning (n=40)
CF-CT bronchiectasis score, %	-0.49**	-0.17	-0.41**	-0.12
CF-CT trapped air score, %	-0.34*	-0.23	-0.37*	-0.04
CF-CT airway wall thickening score, %	-0.43**	-0.19	-0.45**	-0.14
CF-CT mucus plugging score, %	-0.47**	-0.24	-0.46**	-0.12
CF-CT opacities score, %	-0.37*	-0.39*	-0.36*	-0.10

Associations between CT indices, CFQ-R RSS and CFQ-R Physical Functioning at T_1 and T_2. The CFQ-R RSS and CFQ-R Physical Functioning Scale are included in the CFQ-R Child Version and in the Teen/ Adult Version. The CFQ-R Vitality scale and CFQ-R Health Perceptions scale are excluded because of the sample size. **Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Similar correlations were found at T_2: all CT indices were significantly associated with CFQ-R RSS. No significant associations were found between CT indices and Physical Functioning.

Change over time

There was a significant increase in CF-CT bronchiectasis and CF-CT trapped air scores, indicating a significant progression of bronchiectasis and trapped air over a two-year time period (Table 1, Figure 2). Over two years, the mean progression of bronchiectasis was 0.7%, and progression of trapped air was 6.6%.

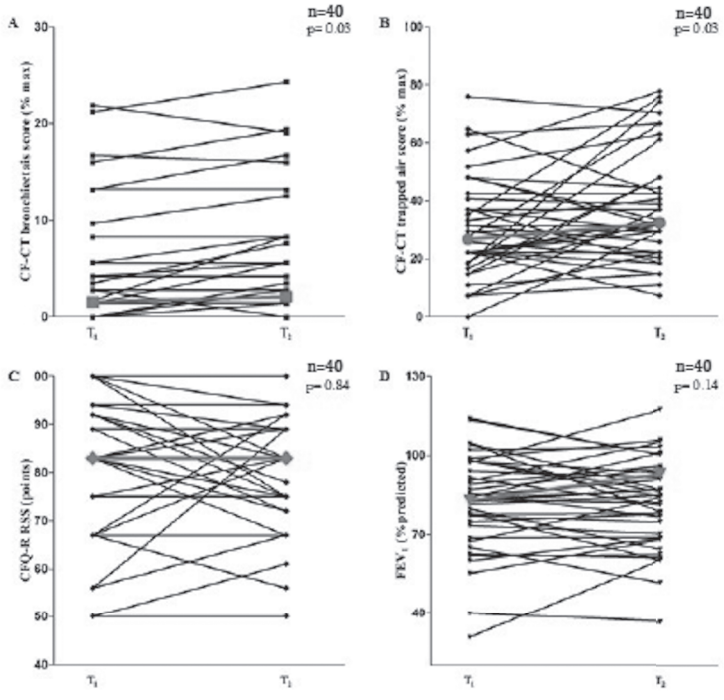


Figure 2. This figure shows over a two year time period in: a) a significant progression in CF-CT bronchiectasis score (p=0.03); b) a significant progression of CF-CT trapped air score (p=0.03); c) no significant change in CFQ-R RSS (p=0.84), and d) no significant change in FEV1 (p=0.14). T1 and T2 indicate the two time points with a time interval of two years. The red line represents the median.

There was no statistical difference between the patients with a worsening in CF-CT bronchiectasis scores (n=13) and the ones with stable or improved CF-CT bronchiectasis scores (n=27) in: SES (p=0.27), genetics (p=0.24), pancreatic insufficiency (p=0.52), CFRD (p=0.19), asthma (p=0.59), ABPA (p=0.14), chronic colonization with *Pseudomonas aeruginosa* (p=0.16), FEV_1 percent predicted at T_2 (p=0.19), and CFQ-R RSS scores at T_2 (p=0.30). Nineteen patients with a worsening in CF-CT trapped air scores and 21 patients with stable or improved CF-CT trapped air scores were included in the trapped air subgroup analyses. Similar results were found in this subgroup analyses with respect to baseline characteristics: SES (p=0.93), genetics (p=0.51), pancreatic insufficiency (p=0.19), CFRD (p=0.49), asthma (p=0.13), ABPA (p=0.29), chronic colonization with *Pseudomonas aeruginosa* (p=0.55), FEV_1 percent predicted at T_2 (p=0.65), and CFQ-R RSS scores at T_2 (p=0.84).

Furthermore, we did not find a significant change over time in airway wall thickening (Table 1), mucus plugging (Table 1), opacities (Table 1), CFQ-R RSS (Table 2, Figure 2), Physical Functioning (Table 2), or FEV_1 (Table 1, Figure 2). No significant correlations were found between changes in CF-CT scores, CFQ-R RSS and Physical Functioning (Table 4).

Table 4. No significant correlation between changes in CF-CT scores, CFQ-R RSS and Physical Functioning scores.

	Delta CFQ-R RSS (n=40)	**Delta CFQ-R Physical Functioning (n=40)**
Delta CF-CT bronchiectasis score, %	0.11	0.15
Delta CF-CT trapped air score, %	-0.03	0.16

DISCUSSION

To our knowledge, this is the first study to evaluate associations between bronchiectasis, trapped air and CFQ-R scores, by both cross-sectional and longitudinal analysis. The most important findings of this study were that CT indices correlated significantly with CFQ-R RSS at T_1 and T_2. Although we found a significant progression of bronchiectasis and trapped air over two-years, this was not reflected by lower CFQ-R RSS scores or lower FEV_1.

The cross-sectional association between CT and CFQ-R indices at T_1 is consistent with our previous study (12). Although, this longitudinal study has a considerable overlap in patient population with our previous study, we now show that after two-year follow up of this cohort, the associations between CT and CFQ-R indices remain similar in strength and significance.

Also consistent with a previous study is the observed progression of bronchiectasis (3). *De Jong et al*. found an average progression of bronchiectasis scores of 1.7% per year in children (3). In the current study, we found a substantially lower mean progression of bronchiectasis score of 0.7% over two years. Considering the 10 year time difference between study periods (1997-2004 versus 2007-2012), it seems likely that less severe progression of bronchiectasis is a result of improved treatment and monitoring starting earlier in life.

We expected that patients with progression of CF lung disease on CT would experience more respiratory symptoms. However we did not observe this. There are several possible explanations. One possibility is that patients adapt to their worsening of pulmonary disease. Several previous studies have shown that patients with a chronic disease tend to adapt to their disabilities (27). However, an 18-month open-label study of Aztreonam inhalation with monthly measurements of CFQ-R and lung function did not show any evidence of response shift (28). In addition, a recent study of *Sawicki et al.* showed that the CFQ-R

RSS was sensitive to changes in respiratory symptoms over a shorter time period of 9-15 months (18). Our sample size was much smaller and may not have been adequately powered to detect these changes. Also the variability in CF-CT bronchiectasis scores was lower than the variability in CFQ-R RSS (SDS 2.0, SDS 12.4, respectively), indicating that the bronchiectasis score was more sensitive than the CFQ-R RSS at detecting a change in this small cohort. There was more separate variance than common variance between CT and CFQ-R, suggesting that the CFQ-R provides different information than CT. Another possibility is that in our study population, progression of bronchiectasis was less severe than the *Sawicky et al.* population and therefore, patients did not perceive a worsening of their symptoms.

In addition to progression of bronchiectasis, we found a significant progression of trapped air. This is consistent with previous studies showing that trapped air progresses over time and eventually contributes importantly to severe advanced lung disease (9). In our study, progression of trapped air did not result in lower CFQ-R RSS scores. It is possible that the extent and progression of irreversible trapped air was small and therefore, did not cause more respiratory symptoms. Furthermore, the CFQ-R has a two-week recall window, whereas changes on a CT may be detectable over a longer time scale (15,29). An alternative explanation is that trapped air does not have a negative impact on symptoms.

In contrast to bronchiectasis and trapped air no significant progression was found in airway wall thickening, mucus plugging or opacities. This is partly in concordance with a previous longitudinal study performed in our CF cohort including data between 1996 and 2002 (3). *De Jong et al.* also observed no progression in airway wall thickening and opacities over two years. However, they did observe a significant progression of mucus plugging (3). That we did not observe progression of mucus plugging is likely related to changes in therapy over the last decade by our CF team, focusing now more on effective mucociliary clearance (30).

A disadvantage of CT that should always be taken into account is its ionizing radiation exposure. The radiation exposure related to our protocol is in the order of one third of the annual background radiation exposure in the USA, which is considered low risk. Similar to previous studies, we observed that chest CT is more sensitive to detect progression of CF lung disease than FEV_1 (5,31). A significant worsening in bronchiectasis and trapped air was detected, while FEV_1 didn't change significantly over time. Similar findings were observed by *de Jong et al.* (3) and more recently by *Owens et al.* (5). Our current study adds further support that CT is more sensitive for monitoring disease progression than FEV_1.

Limitations

The data for this longitudinal, retrospectively analyzed study were collected from a single center, which may reduce the generalizability of the results. Furthermore, we used an

age-range of 6 to 19 years and considering the progressive nature of CF, an association between progression in CT and progression in CFQ-R RSS scores may become apparent with increasing age. Additionally, the observation period of two years might have been too short to detect change in symptoms. Furthermore, two different versions (child and adolescent) of the CFQ-R were used at different ages and the sample might have been too small to detect changes over time. Data were collected as part of the annual examination. During this study period the annual evaluation protocol was changed, to structure the follow up schedule for routine chest CTs, so that every child with CF has a CT at the same age (6/8/10/12/14/16/18 years). Therefore we had to exclude 18 patients who did not have two CTs between 2007 and 2012. Furthermore data on CFQ-Rs in 13 patients were lost due to technical problems. We consider these missing data as completely at random and it is very unlikely that this has biased our results.

Conclusion

Our results indicate that bronchiectasis and trapped are sensitive outcome measures in CF lung disease. Bronchiectasis and trapped air were significantly correlated with CFQ-R RSS at two time points. However, the observed progression of bronchiectasis and trapped air in two years was not necessarily associated with changes in quality of life.

REFERENCES

1 Davis SD, Brody AS, Emond MJ, Brumback LC, Rosenfeld M. Endpoints for clinical trials in young children with cystic fibrosis. Proc Am Thorac Soc 2007 Aug 1;4(4):418-430.

2 Rosenfeld M. An overview of endpoints for cystic fibrosis clinical trials: one size does not fit all. Proc Am Thorac Soc 2007 Aug 1;4(4):299-301.

3 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 Jan;23(1):93-97.

4 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

5 Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. Thorax 2011 Jun;66(6):481-488.

6 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

7 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

8 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

9 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

10 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

11 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

12 Tepper LA, Utens EMW, Quittner AL, Gonzalez-Graniel K, Duivenvoorden HJ, Tiddens HAWM. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis. Eur Respir J. 2013 Jan11. [Epub ahead of print] .

13 Bonnel AS, Song SM, Kesavarju K, Newaskar M, Paxton CJ, Bloch DA, et al. Quantitative air-trapping analysis in children with mild cystic fibrosis lung disease. Pediatr Pulmonol 2004 Nov;38(5):396-405.

14 Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. PLoS One 2011;6(8):e23932.

15 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005 Oct;128(4):2347-2354.
16 US Food and Drug Administration. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Center for Biologics Evaluation and Research, US dept of Health and Human Services 2009.
17 Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socio-economic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. Chest 2010 Mar;137(3):642-650.
18 Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011 Jan;46(1):36-44.
19 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol 2002 Apr;33(4):269-276.
20 Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. Pharmacotherapy 2000 Oct;20(10):1167-1174.
21 Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006 Jan 19;354(3):241-250.
22 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011 Nov 3;365(18):1663-1672.
23 Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging 2006 Mar;21(1):14-21.
24 Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, et al. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009 Oct;253(1):223-229.
25 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008 Feb 1;177(3):253-260.
26 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-310.
27 Postulart D, Adang EM. Response shift and adaptation in chronically ill patients. Med Decis Making 2000 Apr-Jun;20(2):186-193.
28 Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010 Nov;45(11):1121-1134.
29 Loeve M, Krestin GP, Rosenfeld M, de Bruijne M, Stick SM, Tiddens HA. Chest computed tomography; a validated surrogate endpoint of cystic fibrosis lung disease? Eur Respir J 2012 Dec 20.

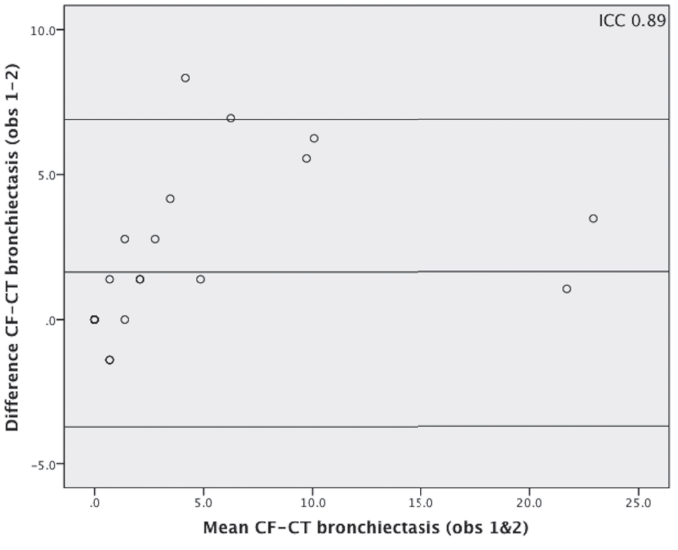
30 Bakker EM, Volpi S, Salonini E, Mullinger B, Kroneberg P, Bakker M, et al. Small airway deposition of dornase alfa during exacerbations in cystic fibrosis; a randomized controlled clinical trial. Pediatr Pulmonol 2013 Jul 3.

31 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.

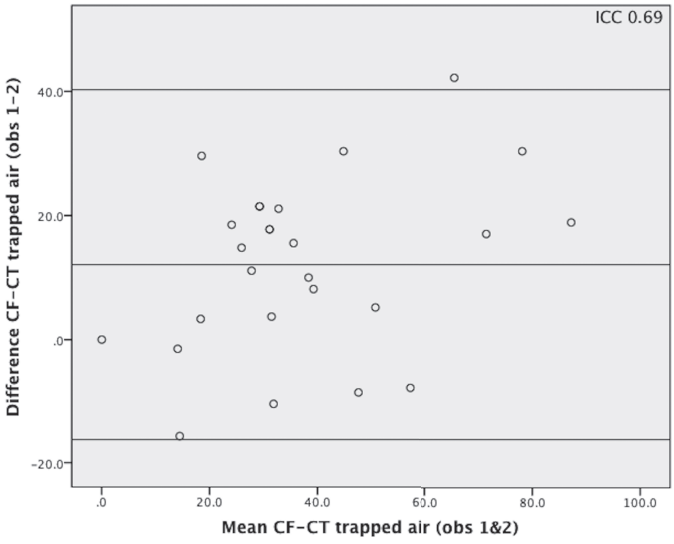
ONLINE SUPPLEMENT

CT scanning

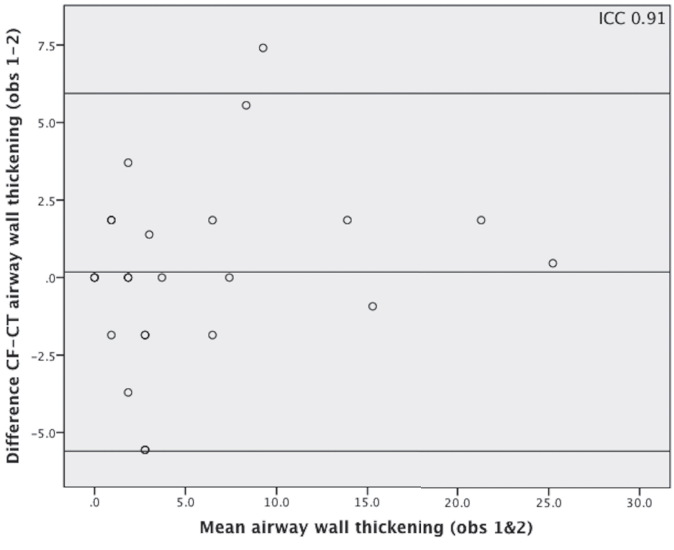
All volumetric CTs were acquired using a 6-slice multi-detector CT scanner (Siemens Medical Solutions, Germany). Each CT consisted of a volumetric inspiratory and expiratory acquisition. Instructions for voluntary breath holds were given before scanning. kV tube voltages of 80 (patients < 35 kg) or 110 (patients > 35 kg) were used with a 0.6-sec rotation time. Scanning was done from apex to base at 1.5 pitch and 6x2 mm collimation. Images were reconstructed with a 3.0 mm slice thickness, 1.2 mm increment and kernel B60s. For the inspiratory protocol a modulating current was used (Siemens) with a reference tube current-time product of 20 mAs, for optimal image quality. For expiratory CTs, a tube current fixed at 25 mA with an effective tube current-time product of 10 mAs was used. This yielded a lower radiation dose than the inspiratory protocol, with sufficient image quality. Total radiation dose was approximately 1 mSv.



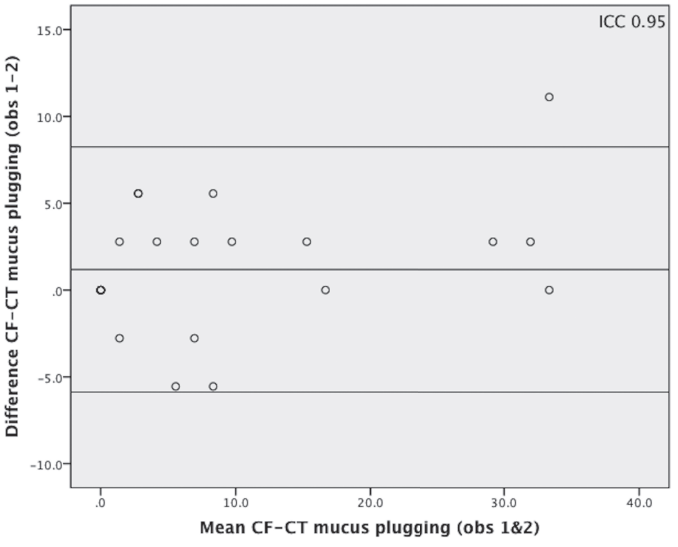
e-Figure 1.1. Bland Altman of the CF-CT bronchiectasis score. The horizontal lines represent mean and ±2 SD.



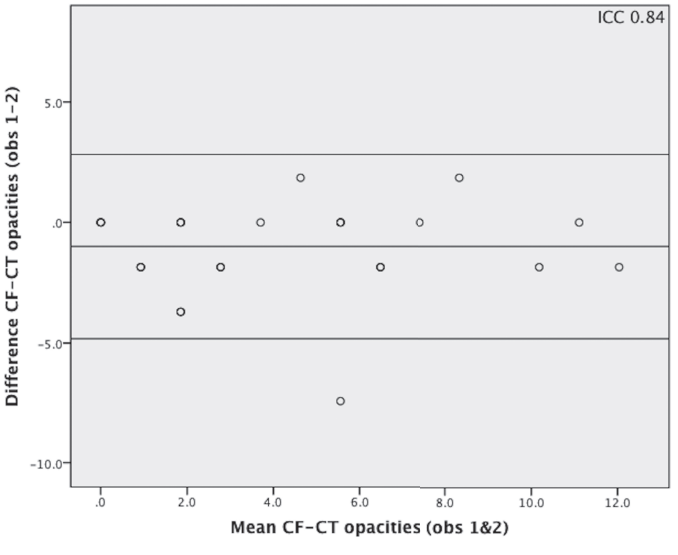
e-Figure 1.2. Bland Altman of the CF-CT trapped air scores. The horizontal lines represent mean and ±2 SD.



e-Figure 1.3. Bland Altman of the CF-CT airway wall thickening scores. The horizontal lines represent mean and ±2 SD.



e-Figure 1.4. Bland Altman of the CF-CT mucus plugging scores. The horizontal lines represent mean and ±2 SD.



e-Figure 1.5. Bland Altman of the CF-CT opacities scores. The horizontal lines represent mean and ±2 SD.

PART 2

Further validating CT as an outcome measure in CF

Chapter 4

Early predictors of bronchiectasis and trapped air severity in cystic fibrosis

Tepper LA
Caudri D
Rosenfeld M
Tiddens HAWM

Submitted to Journal of Cystic Fibrosis

ABSTRACT

Background. CT-detected bronchiectasis and trapped air are important determinants of cystic fibrosis (CF).

Objective. To identify predictors of bronchiectasis and trapped air severity after 6 years follow up among children ages 6-13 years with CF.

Methods. Single centre longitudinal study. Inclusion: CF patients with two routine volumetric CTs obtained 6 years apart, aged 6-13 years at CT_1. Predictors tested in univariate and stepwise multivariate modelling included: gender, age, socio-economic status, FEV_1, *Pseudomonas aeruginosa* infection, pulmonary exacerbations, bronchiectasis and trapped air at CT_1.

Results. Twenty-three patients were included; age at CT_1 was 9.4 (range 7-13) years. Significant predictors for bronchiectasis were: FEV_1 ($p=0.02$); *Pseudomonas aeruginosa* infection ($p<0.01$); bronchiectasis at CT_1 ($p<0.01$). Significant predictors for trapped air were: bronchiectasis at CT_1 ($p=0.05$); pulmonary exacerbations ($p=0.03$); gender ($p=0.02$). Bronchiectasis at CT_1 was the strongest predictor for bronchiectasis at CT_2; a 1% higher score resulted in a 1.03 % higher bronchiectasis score at CT_2 ($p<0.01$). Gender remained predictive for trapped air at CT_2; females had a 26.9% higher score than males ($p=0.02$).

Conclusion. Bronchiectasis at CT_1 was the strongest predictor for bronchiectasis severity at CT_2, supporting the clinical importance of bronchiectasis. We found female gender to be the strongest predictor for trapped air severity.

INTRODUCTION

In cystic fibrosis (CF), the main cause of morbidity and mortality is progressive obstructive lung disease, characterized by bronchiectasis and trapped air detectable by chest-computed tomography (CT) (1-3).

Bronchiectasis and trapped air develop early in life (4-9). Recent studies have shown that by the age of 3 to 5 years, 50-70% of children with CF have developed bronchiectasis (4,6,10). In 75% of young children with CF, progression of bronchiectasis on serial CTs is detected by 5 years (4,6,10). The average progression of CF-CT bronchiectasis scores in these young children was 1.7% per year (11). Preventing bronchiectasis progression is vital because bronchiectasis has a negative impact on lung function (11); pulmonary exacerbations (12,13); mortality (14); quality of life (15), and is an important component of end-stage lung disease (14).

Another important component of end-stage lung disease is trapped air (14). Trapped air was present in 67% of infants with CF by the age of 3 months (4). Furthermore, trapped air is associated with reduced quality of life (15) and mortality (14).

To prevent progression of CF lung disease it is important to identify early predictors of progression of bronchiectasis and trapped air. Several cross-sectional studies have identified clinical characteristics associated with bronchiectasis and trapped air (4-6). However, longitudinal associations have only been studied in the AREST CF studies including children up to 6 years of age (4,16). In infants <3 years of age, *Sly* et al. identified meconium ileus, respiratory symptoms, free neutrophil elastase activity in bronchoalveolar lavage fluid and trapped air as predictors of bronchiectasis (16). *Mott* et al. identified similar predictors for bronchiectasis in children in this cohort up to six years of age (4). Furthermore, severe CFTR genotype and worsening in the BAL inflammatory response score were identified as predictors for trapped air (4). To date no predictors of bronchiectasis and trapped air severity have been studied in a cohort of children over 6 years of age. The aim of our study is to identify longitudinal predictors of bronchiectasis and trapped air severity in children ages 6-13 who underwent two CT scans 6 years apart.

METHODS

Study population

In this retrospective, single centre study we included longitudinally collected data from children diagnosed with CF undergoing biennial volumetric CT scans at 6-13 years of age (CT_1) and approximately 6 years later (CT_2) as part of routine clinical care between January 2004 and February 2012 at the Erasmus MC - CF Centre.

Children were diagnosed with CF by a positive sweat test and/or genotyping for known CF mutations. Children and adolescents receiving intravenous antibiotics for respiratory symptoms at their annual examination were considered unstable and were excluded. All included patients gave their informed consent for data use. The Institutional Review Board of our centre gave approval for the study (MEC-2013-593).

CT acquisition and spirometry

CTs were performed on different CT scanners due to the introduction of newer and faster CT scanners and the introduction of low dose CT protocols. In addition, spirometer-controlled CT scanning to optimize inspiratory and expiratory volume, was introduced in our hospital in 2007, after all CT_1's were performed (17). Consequently, only CT_2 scans were performed with spirometer-control. Details about CT acquisition are provided in the on-line supplement.

Spirometry was performed using the Jaeger clinical spirometer (Jaeger AG, Würzburg, Germany). The spirometry parameter analysed was forced expiratory volume in 1 sec (FEV_1), expressed as a percentage of predicted values (% predicted), according to *Stanojevic* et al. (18).

Outcomes and covariates

CTs were de-identified using MyrianÒ (intrasense Montpelier, France), and scored in random order. Similar to previous studies, CTs were scored by one observer (observer 1: D.Z.) with two years of experience in analyzing CTs with the validated CF-CT scoring system (12,14,19). This scoring system evaluates the 5 lung lobes and the lingula for the main outcome measures: severity, extent of bronchiectasis (CF-CT bronchiectasis score) on inspiratory CTs, and pattern and extent of trapped air (CF-CT trapped air score) on expiratory CTs (12,14,19). Other evaluated components of the CF-CT scoring system were: the severity and extent of airway wall thickening; mucus plugging; and opacities (atelectasis, consolidation). The maximum possible score was 207 points. Sub-scores for bronchiectasis and trapped air were expressed as percentages of maximal scores on a 0-100 scale. To

test scoring reliability of observer 1 (D.Z.), a second observer with two years of experience in CF-CT scoring (A.B.), scored a random subset of 25 CTs. For intra-observer agreement, observer 1 (D.Z.) rescored 25 scans after one month in a blinded fashion.

The following covariates were evaluated as possible predictors of bronchiectasis and trapped air severity at CT_2: gender; age at CT_1; socio-economic status (defined as the highest level of education of either parent); FEV_1 % predicted at CT_1; *Pseudomonas aeruginosa* infection (defined as ≥ 1 positive respiratory cultures for *Pseudomonas aeruginosa* from birth to $CT_{1)}$; pulmonary exacerbations (defined as the number of courses of intravenous antibiotics in the year prior to CT_1 (12,20,21)); and CF-CT bronchiectasis and trapped air scores at CT_1.

Statistical analysis

Characteristics at time points CT_1 and CT_2 were compared using Student's paired t-tests (continuous variables) and Chi-square test (categorical variables).

Inter- and intra-observer agreement of CF-CT bronchiectasis and trapped air scores were calculated using intraclass correlation coefficients (ICC). Although no universally accepted standards are available for what constitutes good reliability, ICC values between 0.4 and 0.6, 0.6 and 0.8, and ≥ 0.8 are generally considered to represent moderate, good and very good agreement. Systematic errors in component scores were evaluated using Bland-Altman plots, expressing the differences between two observers as a function of their mean (22).

As a rule of thumb, we did not include >1 variables per n=10 patients in our models. Given our sample size all associations were assumed linear, and interaction between predictors was not tested for. Linear regression model assumptions were tested in the final models and showed no evidence for violation of the assumptions of homoscedasticity and normality of the residuals.

All statistical analyses were performed using SPSS version 20.0..Continuous variables are reported as medians (ranges). P-values less than 0.05 (two tailed) were considered statistically significant. There was no adjustment for multiple comparisons.

Table 1. Characteristics of the study cohort (N=23) at baseline (CT_1) and follow up (CT_2).

Characteristic	CT_1		CT_2		p-value	Mean difference ($CI_{95\%}$)
Gender (Male)	17	73.9				
Age, years	9.4	(7; 13)	15.6	(14; 20)		6.5 (6.3; 6.8)
Socio economic status‡						
Low	4	17.4				
Average	8	34.8				
High	8	34.8				
Academic	3	13.0				
Genetics						
Homozygous dF508	11	47.8				
Heterozygous dF508	11	47.8				
Other	1	4.3				
Presence of co-morbidities						
Pancreatic insufficient	18	78.3				
CF-related diabetes	2	8.7				
Asthma	1	4.3				
ABPA	0	0				
Pseudomonas aeruginosa infection‡‡	12	52.2				
Pulmonary exacerbation (yes/no)#	5	21.7				
BMI	16.1	(13; 21)				
FEV_1, % predicted	84.0	(55; 117)	79.7	(47; 117)	0.07	-5.2 (-10.7; 0.3)
CF-CT bronchiectasis score, %	2.8	(0; 17)	5.6	(0; 29)	0.04*	2.6 (0.1; 5.0)
CF-CT trapped air score, %##	22.2	(0;50)	37.0	(0;89)	0.01*	22.2 (6.1; 38.3)

Data are presented as no. (%) or median (range). ABPA: Allergic Bronchopulmonary Aspergillosis. ‡ Based on the highest level of education of either parent. ‡‡ Presence of one or more positive respiratory cultures for Pseudomonas aeruginosa from diagnosis to CT_1 or from diagnosis to CT_2. # Pulmonary exacerbation (yes/no), represents the number of patient who had a pulmonary exacerbation requiring intravenous antibiotics in the year prior to the CT. ## n=13 (8 males) for trapped air analysis because not all subjects had an expiratory CT at time of CT_1. * Significance at the 0.05 level (2-tailed). ** Significance at the 0.01 level (2-tailed).

RESULTS

Study population

Twenty-three children (17 males) were included in this study. The median age at CT_1 was 9.4 (range 7-13) years and at CT_2 15.6 (range 14-20) years. The mean time interval between the two CTs was 6.5 (range 5.9-7.9) years. Baseline characteristics of the study population are shown in Table 1. All participants were eligible for the bronchiectasis analysis, assessed on

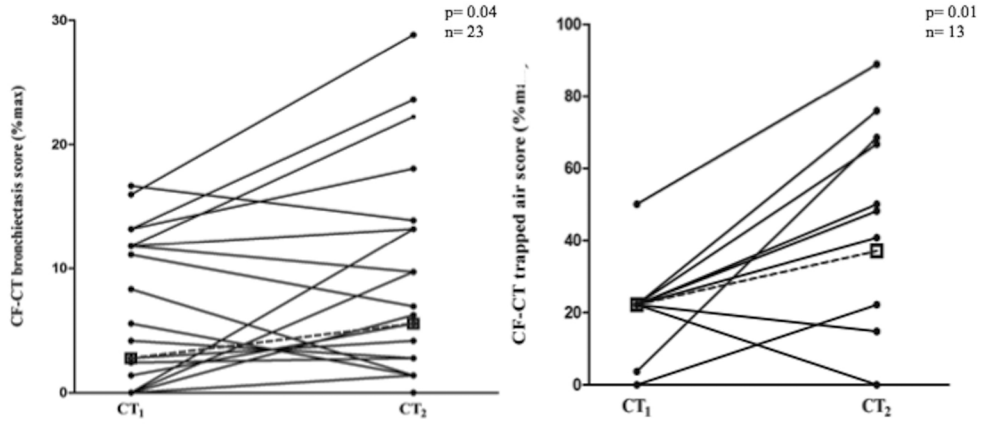


Figure 1. Individual changes in bronchiectasis scores (left panel, n=23) and trapped air scores (right panel, N=13) from CT1 to CT 2 (mean interval 6.5 years). The dashed line represents the median scores.

the inspiratory scans at CT_1 and CT_2. The inspiratory CT_2 was spirometer-controlled in 15 of the 23 children (e-Figure 1, on-line supplement). Thirteen children (8 males) were eligible for trapped air analysis, assessed on expiratory scans at CT_1 and CT_2. The expiratory CT_2 was spirometer-controlled in 6 of these 13 children (e-Figure 1, on-line supplement).

The ICC for inter-observer agreement for the bronchiectasis score was 0.86 and for trapped air 0.72 (e-Figure 2). The ICC for intra-observer agreement for the bronchiectasis score was 0.87 and for trapped air 0.73.

Change over time

At CT_2 significantly more patients had a *Pseudomonas aeruginosa* isolated from a respiratory culture since birth ($p<0.01$) and at least one pulmonary exacerbation in the year prior ($p<0.01$) to CT_1 (Table 1). We found significant progression of bronchiectasis (mean difference in bronchiectasis score 2.6, 95% CI 0.1, 5.0, p=0.04) and trapped air (mean difference in trapped air score 22.2, 95% CI 6.1, 38.3, p=0.01, Table 1, Figure 1) over 6.5-year follow-up. A trend was observed for the loss in FEV_1 % predicted during follow up (mean difference -5.2%, 95% CI -10.7, 0.3, p=0.07).

Prediction

Statistically significant predictors at CT_1 for bronchiectasis at CT_2 were (Table 2): FEV_1 % predicted (p=0.02), *Pseudomonas aeruginosa* infection before CT_1 ($p<0.01$) and bronchiectasis score ($p<0.01$). A decline of 1% in FEV_1 % predicted was associated with a 0.26% higher bronchiectasis score at CT_2 ($CI_{95\%}$ -0.47 to -0.04). Children with *Pseudomonas aeruginosa*

Table 2. Univariate predictors at CT_1 for bronchiectasis (BE) at CT_2 (n=23).

Predictor at CT_1	% increase in BE at CT_2	$CI_{95\%}$	P-value
Gender	6.1	-1.9; 14.1	0.13
Age	0.72	-1.5; 2.9	0.50
Socio economic status	-0.80	-2.9; 1.3	0.44
FEV_1 (% predicted)	-0.26	-0.47; -0.04	0.02*
Pseudomonas aeruginosa infection	8.8	2.4; 15.0	<0.01**
Pulmonary exacerbation in the year prior to CT_1	6.6	-2.0; 15.1	0.12
Bronchiectasis score	1.03	0.6; 1.4	<0.01**
Trapped air score#	0.15	-0.3; 0.6	0.45

n=13 (8 males) for trapped air analysis because not all subjects had an expiratory CT at time of CT_1. * Significance at the 0.05 level (2-tailed). ** Significance at the 0.01 level (2-tailed).

infection before CT_1 had an 8.8% higher bronchiectasis score at CT_2 ($CI_{95\%}$ 2.4 to 15.0). A 1% higher bronchiectasis score at CT_1 was associated with a 1.03% higher bronchiectasis score at CT_2 ($CI_{95\%}$ 0.6 to 1.4). These results predict that a patient with a bronchiectasis score at CT_1 of 3% would have a bronchiectasis score at CT_2 of 3.09%.

Table 3. Univariate predictors at CT_1 for trapped air (TA) at CT_2 (n=13).

Predictor at CT_1	% increase in TA at CT_2	$CI_{95\%}$	P-value
Female gender	26.9	4.7; 49.1	0.02*
Age	3.6	-2.9; 10.0	0.26
Socio economic status	-1.7	-8.0; 4.6	0.59
FEV_1 (% predicted)	-0.36	-1.1; 0.4	0.30
Pseudomonas aeruginosa infection	9.7	-12.1; 31.5	0.37
Pulmonary exacerbation in the year prior to CT_1	27.7	3.8; 51.5	0.03*
Bronchiectasis score	1.7	0.0; 3.4	0.05*
Trapped air score	0.80	-0.7; 2.3	0.28

* Significance at the 0.05 level (2-tailed). ** Significance at the 0.01 level (2-tailed).

Statistically significant predictors at CT_1 for trapped air at CT_2 were (Table 3): female gender (p=0.02), pulmonary exacerbations in the year prior to CT_1 (p=0.03), and bronchiectasis score at CT_1 (p=0.05). Females had on average a 26.9% higher trapped air score at CT_2 than males ($CI_{95\%}$ 4.7 to 49.1). Each pulmonary exacerbation in the year prior to CT_1 was associated with a 27.7% higher trapped air score at CT_2 ($CI_{95\%}$ 3.8 to 51.5). A 1% higher bronchiectasis score at CT_1 was associated with a 1.71% higher trapped air score at CT_2 ($CI_{95\%}$ 0.1 to 3.4).

In a backward stepwise multivariate model all the significant predictors from univariate analysis were initially included. The weakest predictors were taken out stepwise until only independently significant predictors remained. In this analysis the CF-CT bronchiectasis score at CT_1 was the strongest predictor for bronchiectasis severity at CT_2 (CI95% 0.6; 1.4, $p<0.01$) and female gender remained as strongest predictor for trapped air severity at CT_2 (CI95% 4.7;49.1,$p=0.02$).

DISCUSSION

This is the first longitudinal study in children with CF over age 6 evaluating risk factors for bronchiectasis and trapped air over a 6-year time period. We found that the bronchiectasis score at CT_1, FEV_1 % predicted at CT_1 and *Pseudomonas aeruginosa* infection before CT_1 were predictive of bronchiectasis severity at CT_2. However, the effect of the latter two characteristics appeared to be mediated through the bronchiectasis at CT_1, which was the only independent predictor for bronchiectasis severity 6 years later. The bronchiectasis score at CT_1, a pulmonary exacerbation in the year prior to CT_1, and female gender were identified as predictors for trapped air severity at CT_2. In backward stepwise multivariate analyses female gender was the strongest predictor of trapped air severity 6 years later.

FEV_1 % predicted at CT_1 was identified as a predictor for the severity of bronchiectasis at CT_2. This was expectated, because previous studies showed an association between FEV_1 and the CF-CT bronchiectasis score (12,13,23). Furthermore we showed that *Pseudomonas aeruginosa* infection was a predictor of bronchiectasis severity at CT_2, which is consistent with a longitudinal study performed in younger children (16). We indicate the CF-CT bronchiectasis score at CT_1 as the strongest predictor for bronchiectasis severity at CT_2. This was expected because bronchiectasis is considered to be irreversible (4). CF-CT bronchiectasis score at CT_1 could predict only 0.03% of the increase in bronchiectasis during the 6-year follow-up, and none of the other tested variables could add any predictive value in the multivariate model. The fact that we could not identify better predictors for bronchiectasis progression may partially be due to the limited sample size. Secondly, there was relatively little progression in bronchiectasis over the 6-year study period, which substantially reduced the power to detect significant predictors for bronchiectasis progression. We found an annual increase in the CF-CT bronchiectasis score of 0.4% in our current cohort, whereas previously in our centre in a similar aged cohort using an annual increase of 1.7% was found (11). These results suggest that in the 7-year time difference between the two study periods (1997-2004 versus 2004-2012) the efficacy of monitoring and treatment of CF lung disease may have substantially improved.

The bronchiectasis score at CT_1 was also predictive of trapped air severity 6 years later. This is not surprising, since bronchiectasis and trapped air are commonly reported together,

although their pathophysiological relationship remains unclear. In contrast to bronchiectasis scores, trapped air scores at CT_1 were not predictive of bronchiectasis or trapped air severity. A possible explanation for not identifying trapped air as a predictor might be that trapped air has shown to be reversible to some extent (14).

A pulmonary exacerbation in the year prior to CT_1 was identified as a predictor for trapped air severity at CT_2, which is consistent with findings from the AREST CF cohort performed in children aged 0-6 years (4-6). An interesting observation is that female gender was the strongest significant predictor of trapped air severity at CT_2. Given the small sample size, this could be a chance finding. However, gender differences in clinical outcomes have been previously reported (24,25), probably due to the role of sex hormones (25). It is an interesting finding that requires further investigation.

In our relative small cohort bronchiectasis and trapped air severity progressed significantly over 6 years. This progression was not accompanied by a significant decrease in FEV_1 % predicted. This is the third study showing that chest CT is a more sensitive outcome measure than FEV_1 for monitoring progression of lung disease in children, suggesting that chest CT could play an important role in clinical care and in clinical trials (11,26),

This study has several limitations. The longitudinal, retrospectively analysed data used in this study was collected from a single centre, which may reduce the generalizability of our results. Volumetric expiratory CT scanning is the most sensitive protocol for the detection of trapped air (27). Therefore we could only include the expiratory scans for trapped air analysis. During the study period CT protocol changes were made to improve image quality with lower radiation dose and to reduce scanning time. We cannot exclude that the use of different CT protocols and scanners might have introduced some noise and reduced the strengths of our associations. However, it is well recognized that scoring is relatively insensitive to changes in CT scanners and CT scanning protocols (28). Finally, we focussed on an age range of 7-20 years, because this is the period of the most rapid decline of lung function (29). Considering the progressive nature of CF, other predictors may become apparent with further increase in age.

The implications of our study in children over age 6 are that there was a reduced observed progression of bronchiectasis and trapped air, strongly suggesting that treatment improved substantially in the last decade, resulting in better interventions to prevent structural lung disease or arrest progression. Identifying bronchiectasis to be irreversible in 6 years suggests that randomized controlled trials in young children should focus on the prevention of bronchiectasis. Similar to previous studies, the observed significant progression of bronchiectasis and trapped air was not accompanied by a significant decrease in FEV_1 % predicted. This strongly indicates that CT is a sensitive modality to monitor progression of CF lung disease. Ongoing research is focussed on better volume control during CT acquisition, the use of more sensitive methods to quantify bronchiectasis, which will most likely further improve the sensitivity of CT.

In conclusion, bronchiectasis score at CT_1 was identified as the strongest predictor for bronchiectasis severity at CT_2, while female gender was the strongest predictor for trapped air severity 6 years later, supporting the clinical importance of early prevention of bronchiectasis.

REFERENCES

1 Beal RJ. Data from the USA CF registry plenary session NACFC 2009.

2 Loeve M, Hop WC, de Bruijne M, van Hal PT, Robinson P, Aitken ML, et al. Chest computed tomography scores are predictive of survival in patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med 2012 May 15;185(10):1096-1103.

3 Tiddens HA, Stick SM, Davis S. Multi-modality monitoring of cystic fibrosis lung disease: The role of chest computed tomography. Paediatr Respir Rev 2013 Jul 2.

4 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

5 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

6 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

7 Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1133-1138.

8 Davis SD, Fordham LA, Brody AS, Noah TL, Retsch-Bogart GZ, Qaqish BF, et al. Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis. Am J Respir Crit Care Med 2007 May 1;175(9):943-950.

9 Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. J Pediatr 2004 Feb;144(2):154-161.

10 Wainwright CE, Vidmar S, Armstrong DS, Byrnes CA, Carlin JB, Cheney J, et al. Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA 2011 Jul 13;306(2):163-171.

11 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 Jan;23(1):93-97.

12 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

13 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

14 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

15 Tepper LA, Utens EM, Caudri D, Bos AC, Gonzalez-Graniel K, Duivenvoorden HJ, et al. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis. Eur Respir J 2013 Aug;42(2):371-379.

16 Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med 2013 May 23;368(21):1963-1970.
17 Mott LS, Graniel KG, Park J, de Klerk NH, Sly PD, Murray CP, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. Chest 2013 Oct;144(4):1193-1198.
18 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008 Feb 1;177(3):253-260.
19 Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, et al. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009 Oct;253(1):223-229.
20 Ortiz JR, Neuzil KM, Victor JC, Wald A, Aitken ML, Goss CH. Influenza-associated cystic fibrosis pulmonary exacerbations. Chest 2010 Apr;137(4):852-860.
21 Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, et al. Return of FEV1 after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol 2010 Feb;45(2):127-134.
22 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-310.
23 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.
24 Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. Am J Epidemiol 1997 May 1;145(9):794-803.
25 Sutton S, Rosenbluth D, Raghavan D, Zheng J, Jain R. Effects of puberty on cystic fibrosis related pulmonary exacerbations in women versus men. Pediatr Pulmonol 2013 Mar 4.
26 Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. Thorax 2011 Jun;66(6):481-488.
27 Long FR, Williams RS, Adler BH, Castile RG. Comparison of quiet breathing and controlled ventilation in the high-resolution CT assessment of airway disease in infants with cystic fibrosis. Pediatr Radiol 2005 Nov;35(11):1075-1080.
28 Tiddens H, van Straten M, Ciet P. Computed tomography. . Ernst E, Midulla F, editors. Pediatric Respiratory Medicine: The European Respiratory Society; 2013. p. 166-76.
29 Welsh L, Robertson CF, Ranganathan SC. Increased rate of lung function decline in Australian adolescents with cystic fibrosis. Pediatr Pulmonol 2013 Oct 31.

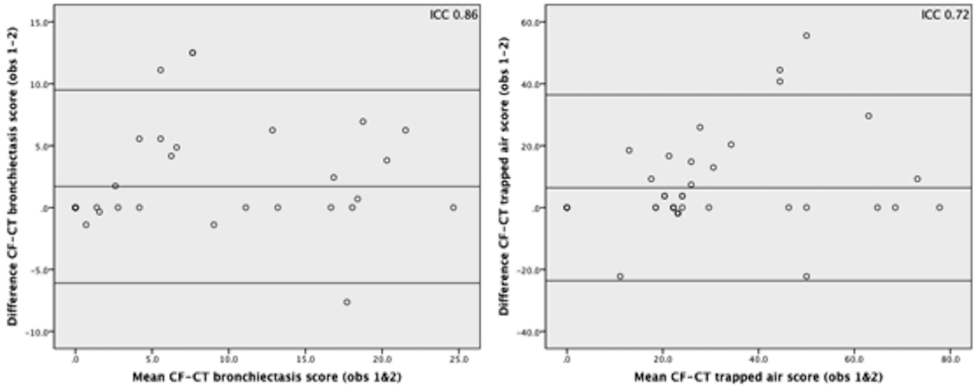
ONLINE SUPPLEMENT

CT acquisition and scoring

Volumetric CT was introduced in 2004 in our hospital. CTs were performed on different CT scanners, due to the introduction of new scanners and low dose CT protocols in the study period. CTs made from January 2004 until May 2004 were performed on the single slice Prospeed CT scanner (GE SCT Prospeed, General Electric Healthcare, United Kingdom). CTs were acquired using 1 mm thick images. Scanning parameters were 120kV, 160 mA (≤.9 years of age 120 mA), 1-s scanning time and a field of view of 350 mm (≤.9 years of age 250 mm) (1)

In June 2004 they were performed on the 16-slice multi-detector CT scanner (Siemens Sensation 16, Siemens Healthcare, Germany). CTs were acquired using 3 mm thick images. Scanning parameters were 100kV and the tube current was modulated based on tissue.

From July 2004 onwards on a 6-slice multi-detector CT scanner (Siemens Emotion 6, Siemens Healthcare, Germany) was used. All CTs made from 2004 onwards consists of a volumetric inspiratory acquisition, while only the expiratory CTs made on the GE SCT Prospeed scanner (GE SCT Prospeed, General Electric Healthcare, United Kingdom) were volumetric. In this study we only used volumetric CTs, therefore we did not include 13 limited cuts expiratory CTs at CT1 (e-Figure 1).

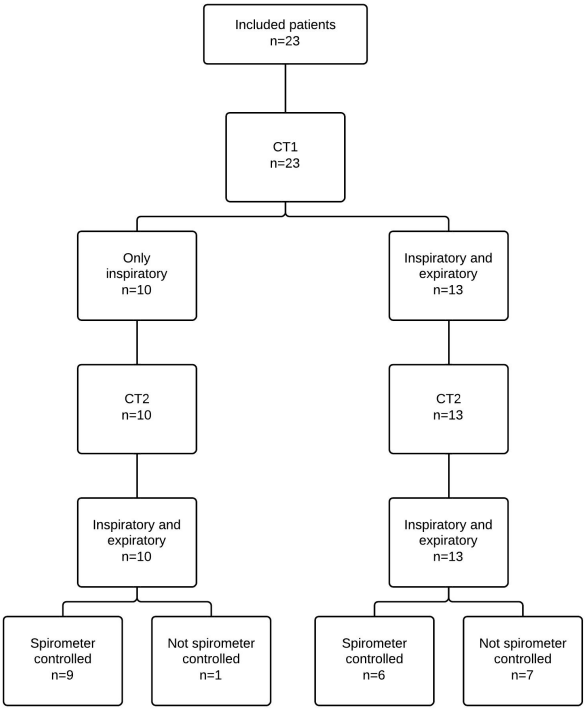


e-Figure 1. Flowchart of the included CTs, showing the number of patients who had and inspiratory and expiratory CT1 en CT2which acquisition was obtained at CT1 and CT2 and which CT2 was spirometer controlled.

In 2010, the Definition Flash scanner (SOMATOM Definition Flash, Siemens Healthcare, Germany) was introduced. At time of CT2, CTs were predominantly performed on the Definition Flash scanner or on the Emotion 6. Three CTs were at CT2 were made on the Definition AS+ (SOMATOM Definition AS+, Siemens Healthcare, Germany). Scanning parameters of the Emotion 6, Definition Flash and Definition AS+ are displayed in e-Table 1.

According to our volumetric CT scanning protocol instructions for voluntary breath holds were given prior to and during scanning. Patients were trained half an hour prior to the CT scan, to familiarise the patient with the breathing manoeuvres in supine position. Patients were first instructed to breath normally to ensure a tidal breathing pattern. Subsequently at inspiratory acquisition, the patient was instructed to fully expire to residual volume, followed by maximal inspiration to total lung capacity. After achieving a tidal breathing pattern at expiratory acquisition, the patient was instructed to fully inspire to total lung capacity, followed by a maximal expiration to residual volume. In 2007 spirometer controlled CT scanning was introduced to maximize inspiratory and expiratory volume. The majority (15/23) of the CT2 scans were spirometer controlled (e-Figure 1). However, if due to logistic reasons CT2 could not be spirometer controlled then instructions for breath holds were given prior to and during scanning.

CTs were scored using the CF-CT scoring system. Similar to previous studies, CTs were scored by one observer (observer 1) with two years of experience in analyzing CTs with the validated CF-CT scoring system (2-4). To test scoring reliability of observer 1, a second experienced observer with two years of experience in CF-CT scoring, scored a random subset of 25 CTs. For intra-observer agreement, observer 1 rescored 25 scans after one month. The agreement between the two observers is shown in e-Figure 2.



e-Figure 2. Bland-Altman expressing the inter observer agreement for the CF-CT bronchiectasis and CF-CT trapped air scores.

Chapter 5

The development of bronchiectasis on chest computed tomography in children with cystic fibrosis: Can pre-stages be identified?

Tepper LA
Caudri D
Perez Rovira A
Tiddens HAWM
de Bruijne M

Submitted to Radiology

ABSTRACT

Background. Bronchiectasis is the most prominent component of cystic fibrosis (CF) lung disease but little is known about its development.

Objective. To study the development of bronchiectasis on chest CT and to identify determinants for rapid progression of bronchiectasis.

Methods. In this single center longitudinal study we included 43 children and adolescents with CF who received at least four consecutive biennial volumetric CTs, made between January 2005 and July 2013. Areas with bronchiectasis were marked as a region of interest (ROI) on the most recent CT. Using deformable image registration the same ROIs were identified in preceding CTs. CTs were de-identified and ROIs were scored randomly. An observer indicated for all ROIs whether: bronchiectasis, mucus plugging, airway wall thickening, atelectasis/consolidation, or normal airways was present.

Results. Forty-three patients with 362 ROIs were included. In 187 out of 362 (51.7%) ROIs bronchiectasis was persistent in all CTs. For 175 ROIs showing development of bronchiectasis, in 79.4% bronchiectasis developed within 2 years. In 20.6% bronchiectasis was preceded by: mucus plugging (17.7%), airway wall thickening (1.7%), or atelectasis/consolidation (1.1%). Pancreatic insufficiency was more prevalent in patients showing rapid progression (n=21) compared to patients showing slow progression (n=18,p=0.05).

Conclusion. We studied the development of 175 bronchiectatic airways over a time interval of maximally 8 years. In 20.6% pre-stages of bronchiectasis could be identified, of which mucus plugging was observed most frequently. Most bronchiectatic airways developed within a time interval of 2 years without pre-stages, underlining the treacherous nature of CF lung disease.

INTRODUCTION

The most prominent component of cystic fibrosis (CF) lung disease is bronchiectasis (1). Bronchiectasis is a permanent and irreversible abnormal dilatation of the bronchial lumen and is most reliably detected by chest-computed tomography (CT) (2-5).

Bronchiectasis has been observed on chest CT in infants with CF as young as 10 weeks of age (6-11). At 3 to 5 years of age, 50-70% of children with CF already have bronchiectasis, which is the main cause of morbidity and mortality in CF (6,8,12). To prevent the development of bronchiectasis it is of great clinical importance to identify early pre-stages on CT with the aim to prevent further progression. Mucus plugging, airway wall thickening and atelectasis or consolidation have been shown to be important components of end-stage lung disease and might therefore be eligible pre-stages (1). Studies showed that if bronchiectases are present, they progressively develop (1,6,10,13,14). However, it remains unclear how bronchiectatic airways evolve and why progression is more rapid in some patients (15).

Therefore this study aims to identify pre-stages of bronchiectasis in CF on chest CT and to determine which patients are at risk for a rapid progression of bronchiectasis.

METHODS

Study population

This retrospective study used longitudinally collected clinical data from the routine annual evaluation of CF patients under treatment in the Erasmus MC-CF Center (Rotterdam, the Netherlands) from January 2005-May 2013. We included clinically stable CF patients who had at least four consecutive volumetric inspiratory CTs, to guarantee a minimum follow up period of six years. A routine chest CT is performed biennially as part of the annual evaluation program. During this study period the annual evaluation program was changed, to structure the follow up schedule for routine chest CTs, so that every child with CF has a CT at the same age (6/8/10/12/14/16/18 years).

Patients who had a lung transplant in the study period were excluded. Furthermore, if at time of CT scanning patients had a pulmonary exacerbation, defined as receiving intravenous antibiotics for respiratory symptoms, or had pulmonary complications (e.g. pneumothorax or hemoptysis) they were considered to be unstable and excluded.

We denoted the most recent available volumetric CT made during annual evaluation as $CT_{baseline}$. $CT_{minus1;minus4}$ are denoted as respectively the first, second, third, and fourth CT prior to $CT_{baseline}$. This study was approved by the Institutional Review Board of the Erasmus MC-CF Center (MEC-2013-593).

CT acquisition and spirometry

CTs were performed on different CT scanners using different protocols, due to the introduction of a new CT scanner and new low dose CT protocols in the study period. More details about the CT acquisition and CT scanners are given in the on-line supplement.

From 2007 onwards, most volumetric CTs were spirometer controlled. Spirometry controlled CT scanning was introduced in our hospital to optimize inspiratory and expiratory volume. If due to logistic reasons CT was not spirometer controlled, then training for breath holds prior to the scan and instructions during the scan were given by the lung function technician (on-line supplement). Spirometry was performed at the annual evaluation using a diagnostic system (Jaeger AG, Würzburg, Germany). The spirometry parameters included for analysis were Forced expiratory volume in 1 sec (FEV_1) and Forced Vital Capacity (FVC). FEV_1 and FVC were expressed as percentage of predictive values, calculated using the *Stanojevic* et al. reference equations (16).

CT analyses

According to the definition of the validated CF-CT scoring system (17-19), bronchiectasis is present if the bronchial lumen diameter is larger than the adjacent pulmonary artery outer diameter, or if there is a lack of tapering for at least 2 cm distal to a branching point. Based on literature about the pathophysiology of bronchiectasis and based on the expertise of a panel consisting of a pediatric pulmonologist (HT), a radiologist (PC), a biomedical imaging expert (MB), and a PhD student (LT), five mutually exclusive categories to classify pre-stages of bronchiectasis were identified. These categories were: 1) bronchiectasis, 2) mucus plugging, 3) airway wall thickening, 4) atelectasis or consolidation, and 5) normal airways. These categories are well defined as part of the CF-CT scoring system and are further explained in the on-line supplement (17-19).

CTs were de-identified and randomized. One observer (observer 2: DZ) encircled all areas with bronchiectasis (bronchial lumen diameter-pulmonary artery outer diameter ratio > 2 or saccular bronchiectasis) in the most recent volumetric inspiratory CT ($CT_{baseline}$). Those areas were marked as a region of interest (ROI) using tools in our image analysis platform (®Myrian Onco XL, *Intrasense, France*). By using deformable image registration, the same areas were automatically identified in the previous CTs ($CT_{minus1;minus4}$). All preceding ROIs were assessed by two experienced observers with respectively 1 and 2 years of experience (HO and DZ) and assigned to one of the five above-mentioned categories. ROIs were assessed in complete random order with respect to patients and order of CT-scans (minus1 to minus4). Therefore, the observers had no knowledge on the assigned category of the ROI's in previous or later scans.

Statistical analysis

To assess observer agreement kappa scores were calculated. For the inter-observer agreement, a random subset of 35 patients with a total of 1230 ROIs were scored by two observers (H.O. and D.Z.). For the intra-observer agreement, a subset of 20 patients with 194 ROIs were rescored by H.O. after one month. In the final analyses, only the scores of observer H.O. were used. Although no universally accepted standards are available for what constitutes good agreement, kappa scores of < 0.40, between 0.4 and 0.75, and ≥ 0.75 are considered to represent poor, moderate to good and excellent agreement, respectively (20).

Descriptive statistics were used to characterize the evolving patterns of bronchiectasis.

We calculated how often bronchiectasis was persistent in all CTs and how often it was directly preceded by mucus plugging, airway wall thickening, atelectasis/consolidation, or normal airways.

In order to distinguish patients who rapidly developed bronchiectasis from previously normal airways from the ones who were likely to have a pre-stage, we created two progression groups: a rapid progression group and a slow progression group. The number of ROIs in which bronchiectasis was directly preceded by normal airways in any two successive scans was calculated. The median number of these rapidly progressing ROIs per patient was calculated (median=3) and used as the cut-off point to define the groups of rapid and slow progressors. Patients who had more than 3 ROIs in which normal airways became bronchiectatic within two years were thus included into the rapid progression group (n=21); the others were included in the slow progression group (n=18). The two groups were compared with respect to baseline characteristics using Chi square tests.

SPSS version 13.0 was used for the analyses in this study. Values are shown as median (range) unless otherwise indicated. P-values < 0.05 (two tailed) are considered to be statistically significant.

RESULTS

Study population and CT data

Forty-three patients were included (Figure 1). Of those 43 patients, 39 patients had 4 consecutive CTs and 4 patients had 5 consecutive CTs. The median interval between two CTs was 2.0 years (range 0.8-3.9). Baseline characteristics of the study cohort are shown in Table 1.

In the $CT_{baseline}$ of the included 43 patients, 367 unique ROIs were identified. In 5/367 (1.4%) ROIs, bronchiectasis turned into a different category before being scored as bronchiec-

tasis in the baseline scan, In 3 of the 5 cases the following pathway was identified: bronchiectasis in which the CT immediately preceding the CT with bronchiectasis showed: normal airways; mucus plugging; bronchiectasis; normal airways. In 2 of the 5 cases the following pathway was identified: bronchiectasis in which the CT immediately preceding the CT with bronchiectasis showed: atelectasis/consolidation; bronchiectasis; normal airways.

Previous literature showed that bronchiectasis are irreversible and therefore we excluded those 5/367 cases from further analysis. An overview of the structural lung damage ($CT_{baseline}$;CT_{minus4}) in our study period is shown in Figure 2.

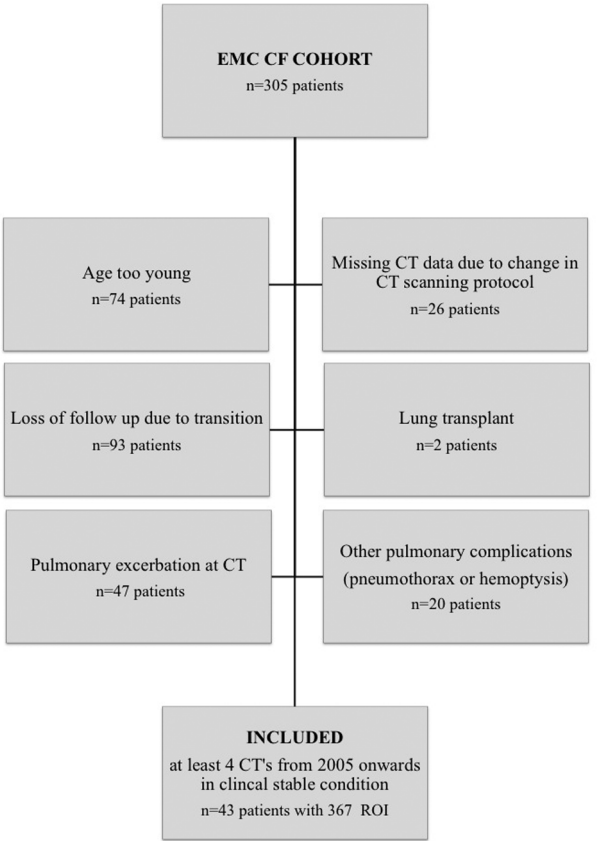


Figure 1. Flowchart of the study population.

The kappa for inter-observer agreement was 0.48 and for intra-observer agreement 0.77. The between and within observer agreement is displayed in Table 2.

Bronchiectasis and pre-stages (Figure 2)

In 187 of the 362 (51.7%) ROIs bronchiectasis was persistent in all available CTs. For the remaining 175 ROIs in which development of bronchiectasis could be observed, the CT immediately preceding the first CT with bronchiectasis showed: normal airways (139/175, 79.4%); mucus plugging (31/175, 17.7%); airway wall thickening (3/175, 1.7%), or atelectasis/consolidation (2/175, 1.1%).

The most commonly identified pre-stage of bronchiectasis was mucus plugging. In 23 ROIs mucus plugging turned into bronchiectasis within 1 CT (2 years, range 1.7-2.4). In the other 8 ROIs mucus plugging persisted for 2 CTs (4 years, range 3.7-5.9) before progression to

Table 1. Baseline characteristics of the study cohort.

Characteristic	$CT_{baseline}$	$CT_{minus\ 1}$	$CT_{minus\ 2}$	$CT_{minus\ 3}$	$CT_{minus\ 4}$
Number of patients	43	43	43	43	4
Number of regions of interest	367	367	367	367	46
Gender (Males)	18	18	18	18 (41.9)	3 (75.0)
Age, year	15.3 (9;24)	13.2 (6;22)	11.0 (4;18)	9.0 (2;16)	6.8 (2;10)
SES[#]					
Low	12 (29.3)	12 (29.3)	12 (29.3)	12 (29.3)	1 (25.0)
Average	15 (36.6)	15 (36.6)	15 (36.6)	15 (36.6)	1 (25.0)
High	13 (31.7)	13 (31.7)	13 (31.7)	13 (31.7)	2 (50.0)
Scientific	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	0 (0.0)
Genetics					
Homozygous dF508	30 (69.8)	30 (69.8)	30 (69.8)	30 (69.8)	3 (75.0)
Heterozygous dF508	9 (20.9)	9 (20.9)	9 (20.9)	9 (20.9)	1 (25.0)
Heterozygous other mutation	4 (9.3)	4 (9.3)	4 (9.3)	4 (9.3)	0 (0.0)
Presence of co-morbidities[‡]					
Pancreatic insufficient	40 (93.0)	40 (93.0)	40 (93.0)	40 (93.0)	3 (75.0)
CFRD	10 (23.3)	10 (23.3)	10 (23.3)	10 (23.3)	0 (0.0)
Asthma	3 (7.0)	3 (7.0)	3 (7.0)	3 (7.0)	0 (0.0)
ABPA	2 (4.7)	2 (4.7)	2 (4.7)	2 (4.7)	0 (0.0)
Chronic colonization *Pa*[‡‡]	8 (18.6)	8 (18.6)	8 (18.6)	8 (18.6)	1 (25.0)
BMI	19.2 (15;36)	18.0 (14;30)	17.0 (5;31)	16.5 (14;25)	15.7 (15;17)
FEV_1, % predicted	86.5 (33;106)	85.4 (37;112)	85.0 (40;113)	85.8 (42;126)	88.4 (85;92)
FVC, % predicted	94.0 (49;115)	92.3 (56;128)	95.2 (57;118)	93.2 (49;128)	99.0 (94;102)

Data are presented as no. (%) or median (range). $CT_{baseline}$-CT_{minus4} indicate the time moments on which the CTs were made, with $CT_{baseline}$ representing the most recent CT and $CT_{minus1-4}$ respectively representing the CT made 1,2,3 or 4 years before $CT_{baseline}$. [#] SES: socio-economic status based on the highest level of education of either parent (n=41 at $CT_{baseline}$-CT_{minus3} and n=4 at T_{-4}). [‡] Indicating the number of patients having co-morbidities; CFRD: CF-related diabetes; ABPA: Allergic Bronchopulmonary Aspergillosis; [‡‡]chronic colonization Pa: defined as ≥ 3 consecutive positive respiratory cultures for Pseudomonas aeruginosa (Pa) from birth to $CT_{baseline}$.

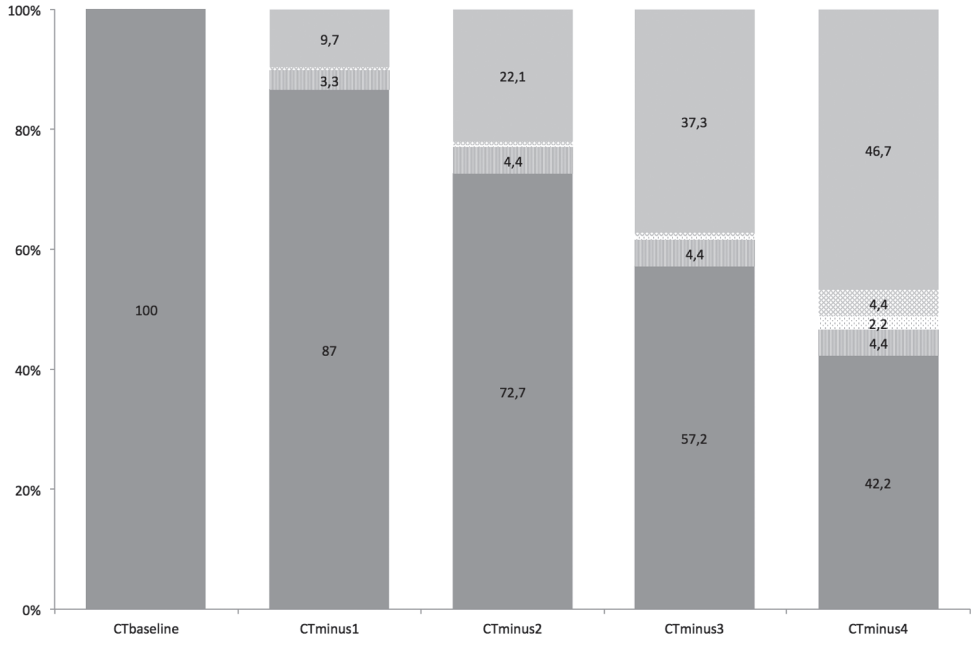


Figure 2. Structural lung damage over time (n=362 in 43 patients). bronchiectasis, mucus plugging, airway wall thickening, atelectasis/consolidation, normal airways. CTbaseline is the most recent CT. Percentages are only displayed if they are over 1% .

bronchiectasis. Mucus plugging never remained longer than 3 consecutive CTs, without progressing to bronchiectasis.

Progression to bronchiectasis

Based on the median number of 3 ROIs per patient that progressed from normal to bronchiectasis in two years, we included 21 patients in the rapid progression group and 18 patients in the slow progression group. There was no statistical difference between those groups in gender (p=0.47), socio-economic status (p=0.49), genetic defect (p=0.78), CF-related diabetes (CFRD, p=0.16), asthma (p=0.12), Allergic Bronchopulmonary Aspergillosis (ABPA, p=0.12) or chronic *Pseudomonas aeruginosa* infection (p=0.39). However, there was a borderline significant difference (p=0.05) for pancreatic insufficiency: all patients included in the rapid group were pancreatic insufficient, while 15 of the 18 patients in the slow progression group were pancreatic insufficient.

Table 2. Observer agreement.

		Observer 2				
		BE	MP	AWT	A/C	Normal
Observer 1	BE	866	25	10	17	58
	MP	8	24	1	1	5
	AWT	2	0	0	0	2
	A/C	4	1	0	2	0
	Normal	68	14	12	4	106

		Observer 1				
		BE	MP	AWT	A/C	Normal
Observer 1	BE	154	0	0	0	0
	MP	1	1	0	0	0
	AWT	0	0	0	0	0
	A/C	1	1	0	1	0
	Normal	10	0	1	0	25

Left: agreement between observer 1 and 2 over a random subset of 1230 regions of interest (kappa 0.48). Right: within-observer agreement of observer 1 over a random subset of 194 regions of interest (kappa 0.77). BE: bronchiectasis, MP: mucus plugging, AWT: airway wall thickening, A/C: atelectasis or consolidation, Normal: no abnormalities.

DISCUSSION

This is the first longitudinal study of CT diagnosed bronchiectasis aiming to identify CT detectable pre-stages of bronchiectasis in children with CF. We assessed the evolution of uniquely identified ROIs using a deformable image registration technique. Our observations provide a unique insight into the radiologic course of developing bronchiectasis.

Our most important findings are that most bronchiectases appeared within the 2-year timeframe between successive scans. Of the pre-stages that could be identified, mucus plugging was the most common predecessor of bronchiectasis.

Mucus plugging was identified as a pre-stage of bronchiectasis. Although no previous studies identifying pre-stages of bronchiectasis have been performed, a previous study from our group identified mucus plugging as an indicator for bronchiectasis 6 years later (21). Those results suggest that there might be an apparent transition from mucus plugging to bronchiectasis, implying that an optimal mucociliary clearance treatment in order to prevent bronchiectasis is important in the management of CF.

Development of bronchiectasis without clearly identifiable pre-stages two years earlier was commonly seen in this study, suggesting that the development of most bronchiectasis is an acute process and not caused by a slow continuous progressive transition. To identify risk factors for the acute development of bronchiectasis in our relatively small single center cohort, we divided our patients into a rapid and slow progression group. This sub-group analysis showed only borderline significant difference in baseline characteristics between the pancreatic status in the two groups. All patients in the rapid progression group were pancreatic insufficient, versus 80% of the patients in the slow progression group. The importance of pancreatic status as a marker of disease severity has been observed in other studies (6,22). Although we could not identify an association between severe CFTR genotype and progression of bronchiectasis in our cohort aged 9-24 years, we must acknowledge our small sample size, which may have resulted in inadequate power to detect this association. Previous research by *Mott et al.* did observe a significant association between genotype and bronchiectasis progression in children below the age of 6 years (6).

To gain further insight into the pathophysiology of bronchiectasis, it would be interesting to also include trapped air in the analyses; given that an association between trapped air and persistence or progression of bronchiectasis has recently been shown in young children with CF (6). The most sensitive method to detect trapped air is an expiratory spirometer-controlled CT (23). For our current study, we did not have sufficient spirometer controlled expiratory CTs to include this analysis.

There are some limitations to this study. The longitudinal, retrospectively analysed data used in this study were collected from a single centre, which may reduce the generalizability of our results. Data were collected as part of the annual evaluation. During the study period our annual evaluation protocol changed to improve the structure of the follow up schedule for routine chest CTs so that every child has a CT at the same age (2/4/6/8/10/12/14/16/18 years) resulting in a larger time range between two CTs for some patients. CTs were performed on different CT scanners, due to the introduction of newer and quicker CT scanners. Furthermore, CT protocols changed in our study period to low dose CT protocols and spirometer controlled CT scanning, to reduce radiation and improve image quality (23). We cannot exclude that the use of these different CT scanners and CT protocols may have reduced the strengths of our associations. Despite this, it is well recognized that the use of scoring systems is relatively insensitive to these changes (24). As our study is the first to identify ROIs and retrospectively assess the status of these regions in the years preceding bronchiectasis, this scoring method has not been used in other studies. The intra-observer variability of the scores obtained with this scoring method was moderate to good with a kappa of 0.77. This suggests that the scores are reproducible within one observer. A disadvantage of our scoring method is that we may have missed more subtle changes in airway wall thickening. Scoring is not considered a very sensitive and reproducible method to quantify airway wall thickening (19); in most CT scoring studies the kappa for airway wall thickening is low. It is well possible that when using more sensitive automated methods to

assess airway wall thickening, in the future subtle airway wall thickness might be picked up as a pre-stage of bronchiectasis.

Clinical implication

Our study shows the treacherous nature of CF lung disease in a cohort of patients who are receiving standards of treatment as in the majority of cases bronchiectasis developed within two years without identifiable pre-stages. The only pre-stage that was identified in 17.7% of bronchiectasis was mucous impaction. Hence, this observation in a patient warrants close attention by the CF team to further improve mucociliary clearance. Furthermore, our results suggest that in some patients the development of bronchiectasis can occur rapidly. The identification of pre-stages of bronchiectasis at an early time might create a treatment opportunity before irreversible bronchiectasis occurs. Therefore, an annual CT may be considered in children with a rapid progression of bronchiectasis. Nevertheless, additional studies are needed to identify the risk factors leading the sudden development of bronchiectasis. Next, clinical intervention studies are needed that aim to prevent this 'sudden' development of bronchiectasis.

REFERENCES

1 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

2 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 Jul 15;172(2):218-224.

3 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 Jan;23(1):93-97.

4 Tiddens HA, Brody AS. Monitoring cystic fibrosis lung disease in clinical trials: is it time for a change? Proc Am Thorac Soc 2007 Aug 1;4(4):297-298.

5 Barker AF. Bronchiectasis. N Engl J Med 2002 May 2;346(18):1383-1393.

6 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

7 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

8 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

9 Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1133-1138.

10 Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med 2013 May 23;368(21):1963-1970.

11 Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. J Pediatr 2004 Feb;144(2):154-161.

12 Wainwright CE, Vidmar S, Armstrong DS, Byrnes CA, Carlin JB, Cheney J, et al. Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA 2011 Jul 13;306(2):163-171.

13 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.

14 Flume PA. Pulmonary complications of cystic fibrosis. Respir Care 2009 May;54(5):618-627.

15 Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J 2009 Oct;34(4):843-849.

16 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008 Feb 1;177(3):253-260.

17 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.
18 Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging 2006 Mar;21(1):14-21.
19 de Jong PA, Tiddens HA. Cystic fibrosis specific computed tomography scoring. Proc Am Thorac Soc 2007 Aug 1;4(4):338-342.
20 Fleiss JL(. Statistical methods for rates and proportions (2nd ed.). New York: John Wiley. ISBN 0-471-26370-2 .
21 Tepper LA, Utens EM, Caudri D, Bos AC, Gonzalez-Graniel K, Duivenvoorden HJ, et al. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis. Eur Respir J 2013 Aug;42(2):371-379.
22 Simanovsky N, Cohen-Cymberknoh M, Shoseyov D, Gileles-Hillel A, Wilschanski M, Kerem E, et al. Differences in the pattern of structural abnormalities on CT scan in patients with cystic fibrosis and pancreatic sufficiency or insufficiency. Chest 2013 Jul;144(1):208-214.
23 Mott LS, Graniel KG, Park J, de Klerk NH, Sly PD, Murray CP, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. Chest 2013 Oct;144(4):1193-1198.
24 Tiddens H, van Straten M, Ciet P. Computed tomography. . Ernst E, Midulla F, editors. Pediatric Respiratory Medicine: The European Respiratory Society; 2013. p. 166-76.

ONLINE SUPPLEMENT

CT acquisition

CTs were performed on 6 different CT scanners, due to the introduction of new and faster scanners that allowed reducing radiation dose for our clinical chest CT protocol in the study period.

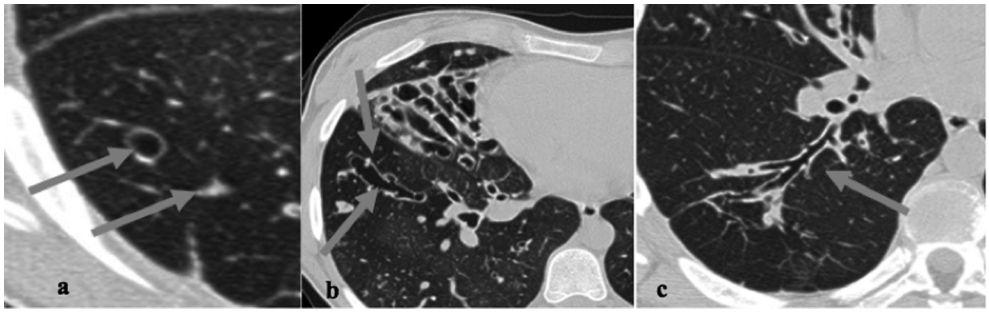
The included CTs (77.8%) were predominantly performed on the Emotion 6 (Siemens Emotion 6, Siemens Healthcare, Germany). In 2010, the Definition Flash scanner (SOMATOM Definition Flash, Siemens Healthcare, Germany) was introduced. In total 18.8% (33/176) of the included CTs were performed with the Definition Flash scanner (SOMATOM Definition Flash, Siemens Healthcare, Germany). The remaining 4% was performed on respectively the Definition AS+ (SOMATOM Definition AS+, Siemens Healthcare, Germany), the Definition Edge (SOMATOM Definition Edge, Siemens Healthcare, Germany), the Sensation 16 scanner (Siemens Sensation 16, Siemens Healthcare, Germany), and on the Biograph (Siemens Biograph, Siemens Healthcare, Germany).

Scanning parameters of the Definition Flash, Emotion 6, and Definition AS+ are displayed in e-Table 1. Regarding the other CT scanners, CTs were acquired using 3 mm thick images. Scanning parameters were 100kV and the tube current was modulated based on tissue.

For our spirometer controlled volumetric CT scanning protocol, patients were trained half an hour prior to the CT scan, to familiarise the patient with the spirometer and breathing manoeuvres in supine position. Patients were first instructed to breath normally to ensure a tidal breathing pattern. Subsequently for the inspiratory acquisition, the patient was instructed first to fully expire to residual volume, followed by maximal inspiration to total lung capacity. After the inspiratory manoeuvre the patient resumed tidal breathing. Next, the patient was instructed to fully inspire to total lung capacity, followed by a maximal expiration to residual volume. In 2007 spirometer controlled CT scanning was introduced, to optimize inspiratory and expiratory volume. In our study population, the majority (74.4%) of the included $CT_{baseline}$ scans were spirometer controlled. However, if due to logistic reasons $CT_{baseline}$ could not be spirometer controlled, then training for breath holds prior to scanning and instructions during scanning were given by the lung function technician.

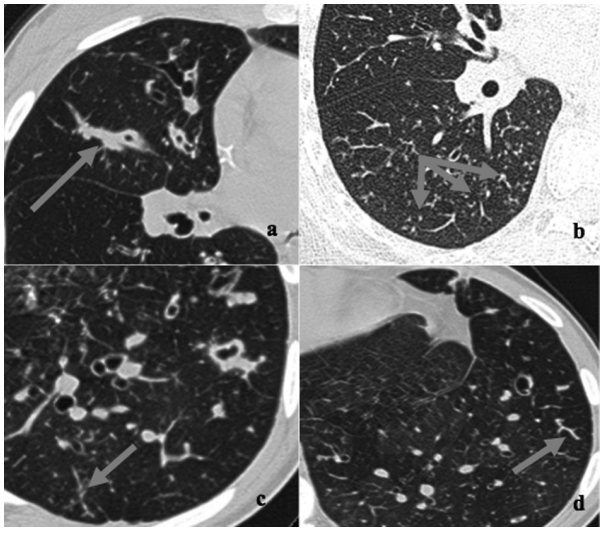
CT analyses

According to the definition of the well-validated CF-CT scoring system (18-20), bronchiectasis was present if the bronchial lumen diameter is larger than the adjacent pulmonary artery outer diameter, or if there was a lack of tapering for at least 2 cm distal to a branching point (e-Figure 1.1). Based on literature about the pathophysiology of bronchiectasis and based on the expertise of a panel consisting of a pediatric pulmonologist, a radiologist, a



e-Figure 1.1. Different features of bronchiectasis. Figure 1.1a shows cylindric bronchiectasis. The upper arrow indicates the bronchiectasis and the lower arrow indicates the corresponding vessel. Figure 1.1b shows saccular bronchiectasis. The upper arrow indicates the corresponding vessel and the lower arrow indicates the saccular bronchiectasis. Figure 1.1c shows a lack of normal bronchial tapering for at least 2 cm, as indicated by the arrow.

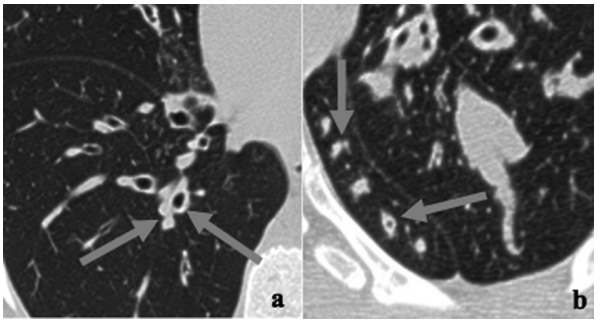
biomedical imaging expert and a PhD student (MD), we identified five mutually exclusive categories to classify pre-stages of bronchiectasis were identified. These categories were: 1) bronchiectasis, 2) mucus plugging, 3) airway wall thickening, 4) atelectasis or consolidation, and 5) normal airways (17-19).



e-Figure 1.2. Illustration of scoring category: mucus plugging. The arrow in image 1.2a indicates a mucus filled bronchus. In Figure 1.2b it indicates the rosette pattern. The arrow in Figure 1.2c indicates the tree-in-bud sign and in Figure 1.2d it indicates a small mucous filled branching structure.

The first category is the presence of bronchiectasis, defined according to the above-mentioned definition. The second category is mucus plugging. Mucus plugging is defined as complete or incomplete filling of clearly identifiable bronchi, resulting in abnormal branching structures or centrilobular nodules in a rosette pattern or tree-in-bud sign (e-Figure 1.2). The third category is the presence of airway wall thickening, which is defined as the ratio between the bronchial wall thickness and the outer diameter of the adjacent pulmonary artery being more than 33% (e-Figure 1.3). The fourth is the presence of atelectasis or consolidation. The last category includes normal airways.

CTs were de-identified and randomized. One observer (observer 2: D.Z.) encircled all areas with bronchiectasis in the most recent volumetric inspiratory CT ($CT_{baseline}$). Those areas were marked as a region of interest (ROI) using tools in our image analysis platform (®Myrian Onco XL, *Intrasense, France*). By using deformable image registration, the same areas were automatically identified in the previous CTs ($CT_{minus1;minus4}$). All preceding ROIs were assessed by two experienced observers with respectively 1 and 2 years of experience (HO and DZ) and assigned to one of the 5 above-mentioned categories. In case in a particular ROI more than one of the above mentioned categories was present, the following rating was applicable: bronchiectasis and mucus plugging were rated as bronchiectasis; bronchiectasis and airway wall thickening were rated as bronchiectasis; and if in our region of interest mucus plugging and airway wall thickening were present, this was rated as mucus plugging. ROIs were assessed in complete random order with respect to patients and order of CT-scans (minus1 to minus4). Therefore, the observers had no knowledge on the assigned category of the ROI's in previous or later scans.



e-Figure 1.3. Illustration of scoring category: airway wall thickening. In e-Figure 1.3a the left arrow indicates a vessel and the right arrow indicates airway wall thickening of a central airway. In e-Figure 1.3b the left arrow indicates a vessel and the right arrow indicates peripheral wall thickening.

PART 3

Validating MRI as an outcome measure in CF

Chapter 6

Validating chest MRI to detect and monitor cystic fibrosis lung disease in a pediatric cohort

Tepper LA
Ciet P, Caudri D
Quittner AL
Utens EMWJ
Tiddens HAWM

Submitted Ped. Pulmonol.

ABSTRACT

Background. Computed Tomography (CT) is the gold standard to assess bronchiectasis and trapped air in cystic fibrosis (CF) lung disease, but has the disadvantage of radiation exposure. Magnetic Resonance Imaging (MRI) is a radiation free alternative.

Objective. To validate MRI as outcome measure by; correlating MRI scores for bronchiectasis and trapped air with clinical parameters, and by comparing those MRI scores with CT scores.

Methods. In patients with CF (aged 5.6-17.4 years), MRI and CT were alternated annually during routine annual check-ups between July 2007 and January 2010. Twenty-three children had an MRI performed one year prior to CT, 34 children had a CT one year prior to MRI. Bronchiectasis and trapped air were scored using the CF-MRI and CF-CT scoring system. CF-MRI scores were correlated with clinical parameters: FEV_1, *Pseudomonas aeruginosa*, pulmonary exacerbations and patient-reported respiratory symptoms measured on the Cystic Fibrosis Questionnaire-Revised (CFQ-R), using Spearman's correlation coefficient. MRI and CT scores were compared using intra-class correlation coefficients (ICC) and Bland-Altman plots.

Results. Fifty-seven patients who had an MRI, CT and CFQ-R during the study period were included. CF-MRI bronchiectasis correlated with FEV_1, *Pseudomonas aeruginosa*, pulmonary exacerbations and patient-reported respiratory symptoms. CF-MRI trapped air only correlated with FEV_1 and *Pseudomonas aeruginosa*. ICCs between MRI and CT bronchiectasis and trapped air were 0.41 and 0.35 respectively. MRI tended to overestimate bronchiectasis compared to CT.

Conclusion. The associations between CF-MRI scores and several important clinical parameters further contributes to the validation of MRI. MRI provides different information than CT.

INTRODUCTION

Cystic fibrosis (CF) is a common hereditary disease, found mainly in Caucasian populations, and has a broad spectrum of disease severity (1). Life expectancy is limited to approximately 38 years, primarily due to end stage lung disease which is characterized by bronchiectasis and trapped air (1,2). Bronchiectasis reflects irreversible widening of the airways and trapped air is indicative for small airway disease. Both can already be observed in early childhood (3-5) and despite intensive treatment, bronchiectasis and trapped air progress slowly throughout life (1). Accurate and sensitive monitoring of bronchiectasis and trapped air is important for clinical management and research (6).

Chest Computed Tomography (CT) is considered to be the gold standard to detect and monitor bronchiectasis and trapped air in CF (7,8). Despite the development of low-radiation-dose volumetric CT scanning protocols, the repeated use of CT is restricted due to ionizing radiation (9,10). Therefore it is desirable to develop chest Magnetic Resonance Imaging (MRI) as a radiation free alternative for monitoring CF lung disease (11).

Many studies have been conducted to improve the image quality of MRI (12). Unfortunately, despite those improvements, MRI is still considered less sensitive than CT for detecting and monitoring bronchiectasis and trapped air (17). More importantly, in contrast to CT, only a few studies have validated bronchiectasis and trapped air as assessed by MRI as an outcome measure for CF lung disease. It has been shown that bronchiectasis and trapped air, assessed by CT, are associated with: FEV_1 (13), pulmonary exacerbations (14,15), and patient-reported respiratory symptoms measured with the standardized, well-validated Cystic Fibrosis Questionnaire-Revised (CFQ-R) (16,17).

We aim to further validate MRI as an outcome measure by: 1) investigating the associations between MRI scores for bronchiectasis and trapped air and clinical parameters as FEV_1, *Pseudomonas* aeruginosa, pulmonary exacerbations and patient-reported respiratory symptoms; 2) comparing MRI scores for bronchiectasis and trapped air with CT scores.

METHODS

Study population

Clinically stable CF patients (aged 6-20 years) who were treated in the Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands) and had a chest MRI or chest CT, spirometry and CFQ-R performed as part of their annual evaluation between July 2007 and January 2010 were included. In this annual evaluation, a chest MRI is alternated with a chest CT, resulting in a CT and MRI in all children within a one-year interval. Children in need of intravenous antibiotics for respiratory signs or symptoms at the time of the annual examination were considered unstable and excluded. This analysis of prospectively collected, routine data on the Sophia Children's cohort was approved by the ethical review board of the Erasmus MC-Sophia Children's Hospital (MEC 2011-460).

Imaging protocols - MRI and CT

According to our protocol, at the annual evaluation, a MRI was performed at ages 7/9/11/13/15/17 years. All MRI scans were performed using a 1.5T unit (Excite HD, software release 12, General Electric Healthcare, Milwaukee, WI). Six breath-hold scans of maximum 10 s were done in all orthogonal planes (axial, coronal, and sagittal), covering the whole lung region, during full inspiration and end-expiration.

According to our imaging protocol, at the annual evaluation, a CT was made at ages 6/8/10/12/14/16/18. All volumetric inspiratory and expiratory CTs were acquired using a 6-slice multi-detector CT scanner (Somaton Emotion, Siemens Medical Solutions, Erlangen, Germany). Instructions for voluntary breath holds were given before scanning or the CT was spirometry controlled. A detailed scanning protocol for MRI and CT is displayed in the on-line supplement.

Imaging analysis – MRI and CT scans

All MRI and CT scans were anonymized and scored in random order by 1 observer blinded to clinical background, using *MyrianÒ (intrasense Montpelier, France)* (14). A different observer scored MRI and CT scans because they were not specifically trained for the MRI.

The CF-MRI scoring system was used to analyze the MRI images. This scoring system was set up using the same methodology as the CF-CT scoring system (see below). This scoring system has been used in previous studies and shown to be applicable to MRI (11,18). The severity and extent of central and peripheral bronchiectasis and extent of trapped air were scored. The pattern of trapped air with the CF-MRI scoring system was not scored, because this was previously shown to be unreliable (18). A composite score for bronchiectasis was

calculated, expressing bronchiectasis as a percentage of a maximum score, on a 0-100 scale. A sum score for trapped air was calculated by summing up the trapped air scores of the 5 lobes and lingula. Higher scores indicated more trapped air.

CTs were scored using the CF-CT scoring system; an upgraded scoring system originally derived from the Brody II scoring system (14,19,20). This scoring system evaluates the 5 lung lobes and lingula as the sixth lobe. In this study we scored the severity and extent of central and peripheral bronchiectasis on inspiratory CTs and the pattern and extent of trapped air on expiratory CTs. CF-CT composite scores for bronchiectasis and trapped air were calculated and expressed as a percentage of the maximum possible score, on a 0-100 scale.

Cystic Fibrosis Questionnaire-Revised (CFQ-R)

CFQ-R questionnaires were completed at every annual evaluation. The Dutch CFQ-R comprises three different versions: 1) the CFQ-R Child Version, for children aged 6-13 years; 2) the CFQ-R Adolescent/Adult Version, for ages 14 and older; and 3) the CFQ-R Parental Version, for parents of children aged 6-13 years. We did not include the CFQ-R Parent Version in our analyses because the FDA and European Medicines Agency prefer use of the patient's *own* report on his/her symptoms (21).

Several domains of the CFQ-R have been shown to correlate with FEV_1 (13, 21) (e.g. Respiratory Symptoms scale, Physical Functioning scale, Vitality scale, and Health Perceptions), but for sample size reasons and because the Respiratory Symptoms scale most specifically reflects lung disease we only included this scale in our analysis. Responses to items on the Respiratory Symptoms scale were standardized into a score ranging from 0 to 100, with higher scores indicating better health-related quality of life.

Spirometry and pulmonary exacerbations

Spirometry was performed at every annual evaluation using a diagnostic system (Jaeger AG, Würzburg, Germany). Results were expressed as percentages of predictive values, according *Stanjonevic et al.* for FEV_1 and the forced vital capacity (FVC) (22).

Because there is no consensus on the definition of pulmonary exacerbations, they were conservatively defined as: episodes of treatment with IV antibiotics for pulmonary indications in the year following administration of CT/CFQ-R or MRI/CFQ-R. *Pseudomonas aeruginosa* ever was defined as the presence of one or more positive respiratory cultures previous to the MRI or CT scan.

Statistical analysis

To validate MRI, we correlated CF-MRI bronchiectasis and trapped air with clinical parameters assessed at the same time using Spearman's correlation coefficient: FEV_1; pulmonary exacerbations; *Pseudomonas aeruginosa* ever or never before MRI; and patient-reported respiratory symptoms. Correlations with these clinical parameters were also calculated for CF-CT bronchiectasis and trapped air. According to Cohen's criteria (1988) correlations with a R_2 between 0.10 and 0.29 are considered weak, between 0.30 and 0.49 moderate and above 0.50 as strong. Intra-observer agreement of CF-MRI scores and CF-CT scores were calculated using intraclass correlation coefficients (ICC). ICC values between 0.40 and 0.60, 0.60 and 0.80, and ≥ 0.80 are considered to represent moderate, good and very good agreement, respectively.

For the comparison of MRI and CT, these investigations were performed within one year. The order in which MRI and CT were performed was expected to be random. To assess this, the two groups (MRI-CT vs. CT-MRI) were compared with respect to baseline characteristics using Chi-square and unpaired t-tests. Spearman's correlation coefficient and ICC were then used to compare CF-MRI and CF-CT bronchiectasis scores and trapped air scores, and agreement was visually inspected using Bland-Altman plots (23).

Statistical analyses were performed using SPSS version 20.0 for windows and SAS version 9.2. Continuous variables are displayed as median (range) unless defined otherwise. P-values less than 0.05 (two tailed) were considered statistically significant.

Table 1. Baseline characteristics of the study population.

	N (%) or median (range)
Number of patients	57 (100%)
MRI in first year – CT in second (%)	23 (40.4%)
Male gender (%)	29 (50.9%)
Pulmonary exacerbation (%)	18 (31.6%)
Pseudomonas aeruginosa (%)	42 (73.7%)
Age baseline, years	13.0 (5.6-17.4)
Age at CT scan, years	13.2 (5.6-17.7)
Age at MRI scan, years	13.5 (6.6-18.6)
FEV_1, % predicted	86.2 (30.3-111.5)
FVC, % predicted	95.1 (53.9-119.4)
Respiratory symptoms on CFQ-R (n=57)	83.0 (39-100)
Respiratory symptoms on child CFQ-R (n=36)	83.0 (58-100)
Respiratory symptoms on adolescent CFQ-R (n=21)	78.0 (39-100)

A pulmonary exacerbation was present if treated with intravenous antibiotics in the year before baseline imaging. *Pseudomonas aeruginosa,* refers to the presence of *Pseudomonas aeruginosa* ever in a sputum culture before imaging was performed.

RESULTS

Study population

We included 57 patients (29 male, 28 female) who had a MRI and CT during the study period. Baseline characteristics of the study population are shown in Table 1. Twenty-three patients had an MRI performed prior to CT (MRI-CT group), the MRI was performed (median) one year (range 0.9-2.0 years) prior to CT. In 34 patients a CT was performed prior to the MRI (CT-MRI group) with a median time interval of 1.0 year, (range 0.9-3.0 years). There were no statistical difference between the MRI-CT group and the CT-MRI group with respect to clinical variables at baseline scan, but there was a trend for more male patients in the MRI-CT group (Table 2).

Table 2. Comparison of baseline characteristics between children with MRI prior to CT compared with CT prior to MRI.

	MRI - CT	**CT - MRI**	**p-values**
Number of patients	23	34	
Male gender (%)	15 (65.2)	14 (41.2)	0.08
Pulmonary exacerbation (%)	7 (30.4)	11 (32.4)	0.74
Pseudomonas aeruginosa (%)	16 (69.6)	26 (76.5)	0.57
Age at first scan, years	13.3 (6.6-16.5)	12.5 (5.6-17.4)	0.39
FEV_1, % predicted	86.8 (30.3-111.5)	86.2 (39.8-110.1)	0.45
FVC, % predicted	94.1 (53.9-119.2)	94.4 (56.9-119.4)	0.43
Respiratory symptoms on CFQ-R	83.0 (58-100)	76.5 (39-100)	0.42

Data are presented as n (%) or as median (range). A pulmonary exacerbation was present if treated with intravenous antibiotics in the year before baseline imaging. *Pseudomonas aeruginosa*, refers to the presence of *Pseudomonas aeruginosa* ever in a sputum culture before imaging was performed.

Imaging analysis – observer agreement

The intra-observer agreement in the MRI group was 0.82 and 0.51, for bronchiectasis and trapped air (sum score) respectively. In the CT group, intra-observer variability for bronchiectasis 0.98 and for trapped air 0.68.

MRI and CT correlations with clinical parameters (Table 3)

CF-MRI bronchiectasis correlated significantly with FEV_1, *Pseudomonas aeruginosa*, pulmonary exacerbations and patient-reported respiratory symptoms. CF-CT bronchiectasis was significantly, but less strongly correlated with FEV_1, pulmonary exacerbations and patient-reported respiratory symptoms. The correlation with *Pseudomonas aeruginosa* was weaker and did not reach significance (p=0.051).

The CF-MRI trapped air sum score correlated significantly with FEV_1 % predicted and *Pseudomonas aeruginosa*. CF-CT trapped air sum score was significantly correlated with FEV_1 and patient-reported respiratory symptoms, but not with *Pseudomonas aeruginosa*. Scatter plots showing those correlations are displayed in the on-line supplement.

Table 3. Correlations between sub-scores for MRI and CT and clinical outcome measures.

		FEV_1	Pseudomonas aeruginosa	Exacerbation	Respiratory Symptoms
MRI	CF-MRI bronchiectasis score	-0.59**	0.31*	0.45**	-0.38**
	CF-MRI trapped air sum score	-0.52**	0.32*	0.24	-0.18
CT	CF-CT bronchiectasis score	-0.38**	0.26		-0.36**
	CF-CT trapped air sum score	-0.34*	0.15*		-0.34**

A pulmonary exacerbation (in table called exacerbation) was present if treated with intravenous antibiotics in the year before baseline imaging. *Pseudomonas aeruginosa*, refers to the presence of *Pseudomonas aeruginosa* ever in a sputum culture before imaging was performed. Respiratory symptoms are the patient-reported respiratory symptoms on the CFQ-R. *significant, p-value < 0.05 (2-tailed). **significant, p-value < 0.01 (2-tailed).

MRI and CT comparison for bronchiectasis and trapped air (Table 3, Figure 1,2)

CF-MRI bronchiectasis correlated with CF-CT bronchiectasis (r=0.67, p<0.001). The identity plot (Figure 1) shows that compared to CT, MRI tends to overestimate bronchiectasis across the whole range of disease severity. A lower correlation was found between CF-MRI and CF-CT trapped air scores (r=0.33, p=0.014, Figure 1). The ICC for CF-MRI bronchiectasis and CF-CT bronchiectasis was 0.41 (95% confidence interval ($CI_{95\%}$) -0.09-0.71). Figure 2 expresses the agreement between MRI and CT for bronchiectasis in a Bland-Altman plot; the average CF-MRI scores were 10 percentage points higher than CF-CT scores, but this difference appeared to increase as the average scores increase.

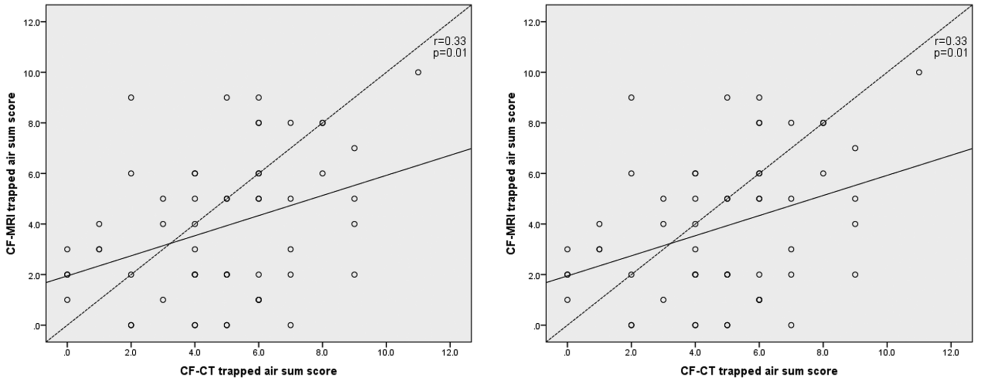


Figure 1. Identity plots of CF-MRI vs. CF-CT bronchiectasis score (Figure 1.1) and CF-MRI vs. CF-CT trapped air sum score (Figure 1.2). Dashed line represents the line of identity (y=1*X).

Weaker correlations were found between CF-MRI trapped air and CF-CT trapped air (r=0.33, p=0.014). For trapped air the ICC was 0.35 ($CI_{95\%}$ 0.11-0.55). The Bland-Altman plot does not show a systematic difference (Figure 2). The limits of agreement are wide (-7.0 to +5.1) in comparison to the range of average trapped air sum scores.

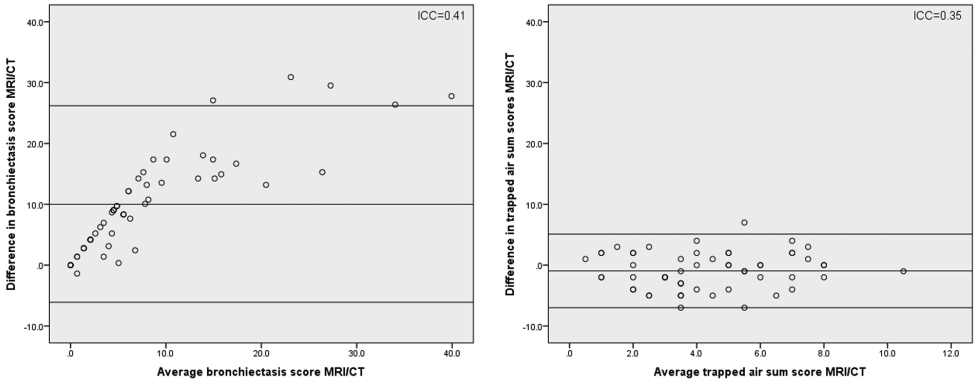


Figure 2. Bland-Altman plots of MRI versus CT for bronchiectasis and trapped air. The x-axis shows the average bronchiectasis (Figure 2.1) or the average trapped air score (Figure 2.2). The y-axis displays the differences between bronchiectasis scores on MRI and CT (Figure 2.1), or the differences between trapped air scores on MRI and CT (Figure 2.2). The middle line in both graphs is the mean and the two outer lines are the ±2SD.

DISCUSSION

To our knowledge this is the first study validating chest MRI as an imaging modality to detect and monitor CF lung disease in the pediatric population by correlating bronchiectasis and trapped air scores with clinical parameters as FEV_1, *Pseudomonas aeruginosa*, pulmonary exacerbations and patient-reported respiratory symptoms. We also compared CF-MRI scores with CF-CT scores with respect to the detection of bronchiectasis and trapped air (12,18).

Our most important findings were the observed significant correlations between CF-MRI bronchiectasis scores and all investigated clinical parameters. It correlated well with FEV_1 % predicted, which is the most commonly used outcome parameter for CF-lung disease in clinical research. This finding is consistent with data from *McMahon et al.* who observed a similar correlation between bronchiectasis assessed by MRI and FEV_1 in a small group of adults (24). Interestingly the observed association between CF-MRI bronchiectasis and FEV_1 % predicted was stronger than the association between the CF-CT bronchiectasis and FEV_1 % predicted. Significant correlations between CT bronchiectasis and FEV_1 have been observed in several cross-sectional studies (13,14,16). Since CT is considered to be a sensitive monitoring tool for CF lung disease and considering the observed associations,

our results suggest that MRI could play a similar role in monitoring progression of bronchiectasis. The next step is to compare the sensitivity of MRI to CT in tracking the progression of bronchiectasis over longer periods of time.

Our results report the first data on the associations between the CF-MRI bronchiectasis scores and other clinically relevant parameters, such as pulmonary exacerbations, *Pseudomonas aeruginosa,* and patient-reported respiratory symptoms. In contrast to CF-MRI bronchiectasis, no significant correlation was found between CF-CT bronchiectasis and *Pseudomonas aeruginosa*. This is consistent with the findings of *Puderbach et al.*, who concluded that MRI is able to detect small pulmonary changes and that inflammation can be well characterized by MRI (11). Thus, these findings suggest that MRI is able to detect inflammation before bronchiectatic changes appear on CT. Although the correlation between CT score and *Pseudomonas aeruginosa* was not statistically significant, the magnitude of the correlation was only slightly smaller than the correlation between the MRI score and *Pseudomonas aeruginosa*.

Another new finding is the association between CF-MRI bronchiectasis and patient-reported respiratory symptoms on the CFQ-R. A similar association was found between CF-CT bronchiectasis patient-reported respiratory symptoms, as previously reported by our group (16). Taking into account that the larger central bronchi are better visualized on MRI compared to the smaller peripheral bronchi (18), this result suggests that these major bronchiectatic changes have an important, negative effect on respiratory symptoms. We did not find a correlation between CF-MRI trapped air and patient-reported respiratory symptoms, while CF-CT trapped air was significantly associated with patient-reported respiratory symptoms, which is consistent with our previous study (16). A possible explanation for this might be that the pattern of trapped air can not yet be scored reliably on MRI (18).

In our cross-sectional comparison of MRI and CT, we did not find any significant differences in baseline characteristics between the twenty-three patients who underwent the MRI a year before the CT and the 34 patients who underwent the CT a year before the MRI. Consistent with the results of *Ciet et al,* we found that MRI generally overestimates bronchiectasis compared with CT (18). Despite the use of the bSSFP sequence the spatial resolution of MRI was lower compared to the spatial resolution of CT, making the recognition of decreased attenuation of the pulmonary parenchyma (trapped air) more difficult. Other factors that could influence the image quality in the MRI are motion artifacts due to heart and vessel pulsation; by using the bSSFP sequence, we would expect less influence from motion artifacts (25).

Implications

Our cross-sectional analysis showed that CF-MRI bronchiectasis was associated with clinically relevant outcomes, some even stronger than CT, which is currently considered the gold standard for monitoring bronchiectasis and trapped air. MRI and CT assess bronchiectasis and trapped air in a different way, as shown in the low correlations and ICCs between the two. This suggests that MRI may be able to detect other aspects of CF lung disease than CT. These findings support of our current strategy of alternating MRI and CT in following our CF patients.

Limitations

An important limitation in this comparison of MRI with CT is the fact that these scans were not performed on the same day, but were separated by a median interval of one year. In theory, differences between MRI and CT may therefore be explained by disease progression rather than differences in sensitivity and specificity of the MRI. However it is unlikely that this is the case. First, the order in which the MRI and CT were performed was random and on average, there was no difference between the patients' age at time of MRI and CT. Second, on average not much disease progression is expected over a one-year period (13). Furthermore, bronchiectasis is a stable and irreversible condition. Finally, we found bronchiectasis to be overestimated on MRI compared to CT, irrespective of the order of the two scans. Therefore, it is unlikely that our results can be explained by the time lag between the two scans.

The fact that we used data collected from a single center reduces the generalizability of our results. In addition, chest MRI protocols are poorly standardized between centers and the protocol, selected, may greatly influence the sensitivity of MRI to detect changes related to CF lung disease. A multi-sequence protocol might further improve MRI sensitivity (26). Although the CF-MRI scoring system has been used in a previous study, the CF-MRI scoring system was adapted from the CF-CT scoring method and not specifically designed for MRI. A more sophisticated scoring method could improve the sensitivity of the MRI (11,18).

Further, the fact that we included patients who ranged from 6 to 20 years, with relatively mild CF disease, limits the generalizability of our findings to this younger age group and those with less severe disease. Finally, because the MRIs were scored by a different observer than the CTs, we cannot exclude the possibility that this may have introduced a systematic difference between the two imaging modalities. However, it is unlikely that this affects the general conclusion of our study since the observers were experienced and well trained in scoring MRIs and CTs. Furthermore the intra-observer variability in both MRI and CT were good.

Conclusion

The observed associations between MRI and clinical parameters further validates chest MRI as a method to monitor CF lung disease. Our results suggest that the MRI provides different information than CT. Next, longitudinal studies are needed to compare the sensitivity of CT and MRI to track disease progression.

REFERENCES

1 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

2 Beal RJ. Data from the USA CF registry plenary session NACFC 2009.

3 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

4 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

5 Pillarisetti N, Linnane B, Ranganathan S, AREST CF. Early bronchiectasis in cystic fibrosis detected by surveillance CT. Respirology 2010 Aug;15(6):1009-1011.

6 Loeve M, Krestin GP, Rosenfeld M, de Bruijne M, Stick SM, Tiddens HA. Chest computed tomography; a validated surrogate endpoint of cystic fibrosis lung disease? Eur Respir J 2012 Dec 20.

7 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

8 Tiddens HA, de Jong PA. Update on the application of chest computed tomography scanning to cystic fibrosis. Curr Opin Pulm Med 2006 Nov;12(6):433-439.

9 Sodickson A. CT radiation risks coming into clearer focus. BMJ 2013 May 21;346:f3102.

10 Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, et al. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009 Oct;253(1):223-229.

11 Puderbach M, Eichinger M, Haeselbarth J, Ley S, Kopp-Schneider A, Tuengerthal S, et al. Assessment of morphological MRI for pulmonary changes in cystic fibrosis (CF) patients: comparison to thin-section CT and chest x-ray. Invest Radiol 2007 Oct;42(10):715-725.

12 Puderbach M, Eichinger M. The role of advanced imaging techniques in cystic fibrosis follow-up: is there a place for MRI? Pediatr Radiol 2010 Jun;40(6):844-849.

13 de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax 2006 Jan;61(1):80-85.

14 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

15 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

16 Tepper LA, Utens EMW, Quittner AL, Gonzalez-Graniel K, Duivenvoorden HJ, Tiddens HAWM. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis. Eur Respir J. 2013 Jan11. [Epub ahead of print] .

17 Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Erratum to: Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national, US sample. Qual Life Res 2012 Sep;21(7):1279-1290.
18 Ciet P, Wielopolski P, Lever S, van der Wiel E, Lequin M, Tiddens H. Comparison of proton-MRI (MRI) and contrast enhanced MRI (CE-MRI) in Cystic Fibrosis (CF) to detect small airways disease? Presented at RSNA 2011, ECR 2011, NACFC 2010.
19 Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging 2006 Mar;21(1):14-21.
20 de Jong PA, Tiddens HA. Cystic fibrosis specific computed tomography scoring. Proc Am Thorac Soc 2007 Aug 1;4(4):338-342.
21 US Food and Drug Administration. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Center for Biologics Evaluation and Research, US dept of Health and Human Services 2009.
22 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008 Feb 1;177(3):253-260.
23 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-310.
24 McMahon CJ, Dodd JD, Hill C, Woodhouse N, Wild JM, Fichele S, et al. Hyperpolarized 3helium magnetic resonance ventilation imaging of the lung in cystic fibrosis: comparison with high resolution CT and spirometry. Eur Radiol 2006 Nov;16(11):2483-2490.
25 Failo R, Wielopolski PA, Tiddens HA, Hop WC, Mucelli RP, Lequin MH. Lung morphology assessment using MRI: a robust ultra-short TR/TE 2D steady state free precession sequence used in cystic fibrosis patients. Magn Reson Med 2009 Feb;61(2):299-306.
26 Wild JM, Marshall H, Bock M, Schad LR, Jakob PM, Puderbach M, et al. MRI of the lung (1/3): methods. Insights Imaging 2012 Aug;3(4):345-353.

ONLINE SUPPLEMENT

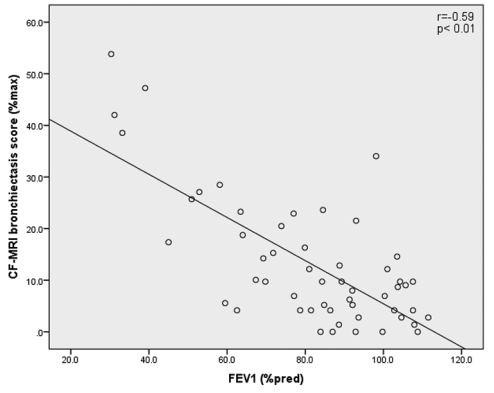
MRI and CT acquisition

All MRI scans were performed using a 1.5T unit (Excite HD, software release 12, General Electric Healthcare, Milwaukee, WI). The body coil provided radiofrequency excitation. An eight-channel phased-array receive cardiac coil was used for larger, more compliant subjects, a four channels smaller flexible one for smaller subjects. The system had a gradient hardware capable of a maximum gradient strength of 40 mT/m with a rise time of 266 s to maximum. The scan protocol started with two three-plane orthogonal localizers collected first in expiration and next in inspiration (4 s). For the inspiratory localizer, shimming was performed and the resulting images served as base localizers for all subsequent scans. These shim settings were maintained throughout scanning. Instructions for voluntary breath holds were given before scanning. Six breath-hold scans of maximum 10 s were done in all orthogonal planes (axial, coronal, and sagittal), covering the whole lung region, in full inspiration and end-expiration using an ultra-short TR/TE 2D SSFP with TR/TE = 2.2/0.7 ms and flip angle 35°. The flip angle was chosen upon testing on healthy volunteers to obtain adequate signal from lung parenchyma and, subjectively, a good intensity balance between blood and fat signals. The in-plane resolution was kept constant with a field-of-view of 360 mm using a scan matrix 128 x 180 (frequency/phase-encodings) resulting in 2.8 x 2.0 mm2 in-plane resolution and a section thickness of 8 mm and no gap. To evaluate the airways and permit comparison with CT, scans were performed in inspiration using 6-mm slices with no gap and 2.3 x 1.4 mm2 in-plane resolution with TR/TE/flip angle = 2.6/0.9/20°. All sequences used are generally available in the imaging protocols on the GE system. The scan was divided in two 10-s breath-holds to cover the entire chest. The complete MRI scan time lasted no more than 15 min(1).

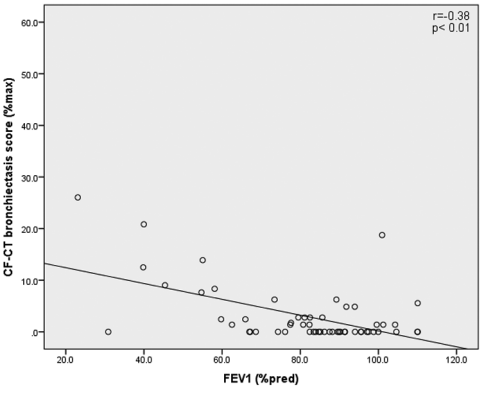
All volumetric CTs were acquired using a 6-slice multi-detector CT scanner (Somaton Emotion, Siemens Medical Solutions, Erlangen, Germany). Each chest-CT consisted of a volumetric inspiratory and expiratory acquisition. Instructions for voluntary breath holds were given before scanning or the CT was spirometry controlled. kV tube voltages of 80 (patients < 35 kg) to 110 (patients > 35 kg) were used with a 0.6-sec rotation time. Scanning was done from apex to base at 1.5 pitch and 6x2 mm collimation. Images were reconstructed with a 3.0 mm slice thickness, 1.2 mm increment and kernel B60s. For the inspiratory protocol a modulating current was used (CareDose4D, Siemens Medical Solutions) with a reference tube current-time product of 20 mAs, for an optimal image quality. For expiratory CTs, image quality was considered sufficient using a tube current fixed at 25 mA with an effective tube current-time product of 10 mAs; producing a lower radiation dose than the inspiratory protocol. Total radiation dose was in the order of 1 mSv.

MRI and CT correlations with clinical parameters (Figures 1-4)

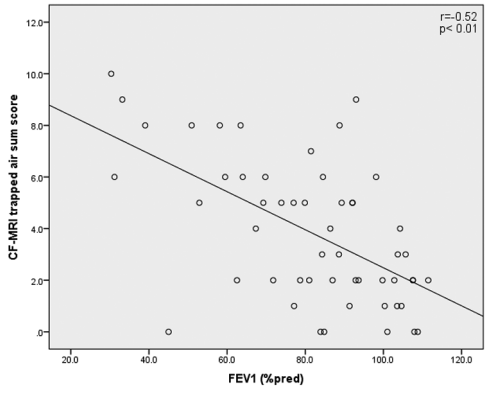
The significant associations between MRI and CT assessments of bronchiectasis and trapped air scores and FEV_1 % predicted (%pred) are shown in Figure 1.1-1.4.



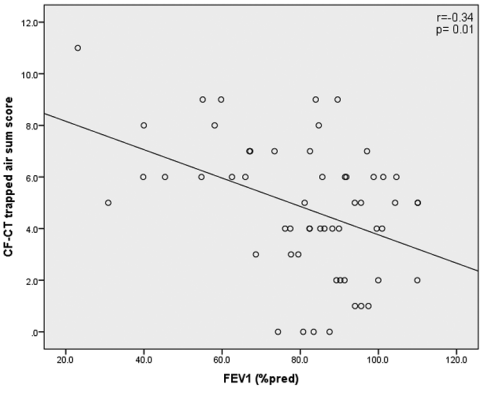
e-Figure 1.1 The significant association between CF-MRI bronchiectasis scores and FEV1 % predicted (%pred).



e-Figure 1.2 The significant association between CF-CT bronchiectasis scores and FEV1 % predicted (%pred).



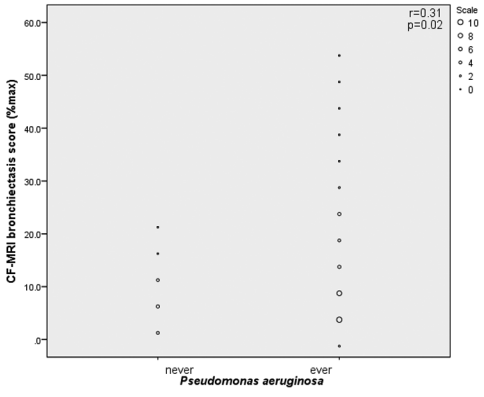
e-Figure 1.3 The significant association between CF-MRI trapped air scores and FEV1 % predicted (%pred).



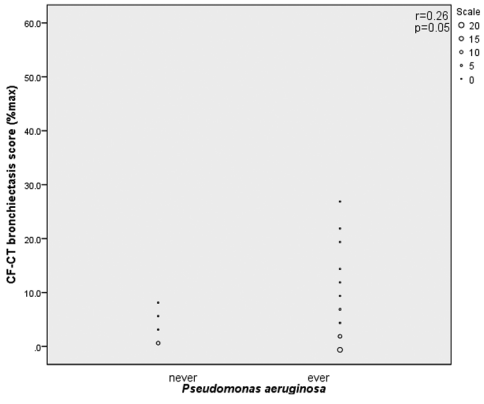
e-Figure 1.4 The significant association between CF-CT trapped air scores and FEV1 % predicted (%pred).

CF-MRI (Figure 2.1), CF-CT bronchiectasis score (Figure 2.2) CF-MRI trapped air scores (Figure 2.3) were significantly associated with *Pseudomonas aeruginosa*, whereas no association was found between the CF-CT trapped air score and *Pseudomonas aeruginosa* (Figure 2.4).

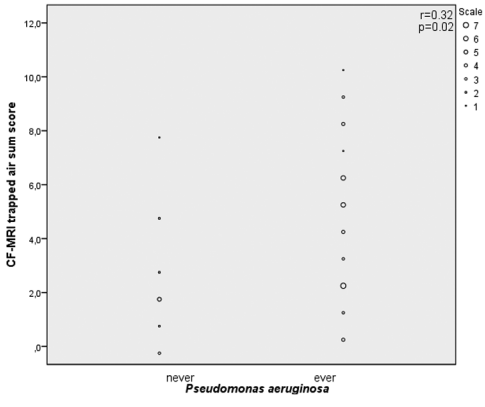
There was a significant association between CF-MRI bronchiectasis (Figure 3.1), CF-CT bronchiectasis (Figure 3.2) and pulmonary exacerbations in the year prior to MRI or CT. No association was found for CF-MRI trapped air (Figure 3.3) or CF-CT trapped air (Figure 3.4) and pulmonary exacerbations in the year prior to MRI or CT.



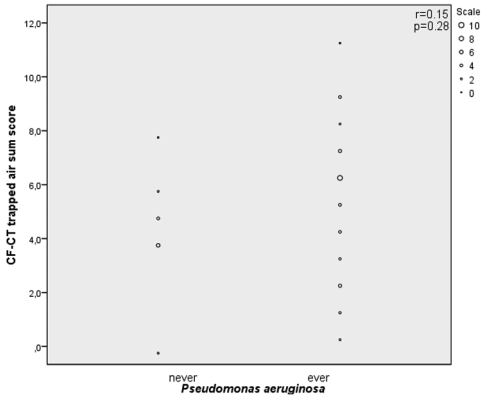
e-Figure 2.1 The significant association between CF-MRI bronchiectasis and Pseudomonas aeruginosa.



e-Figure 2.2 The significant association between CF-CT bronchiectasis and Pseudomonas aeruginosa.

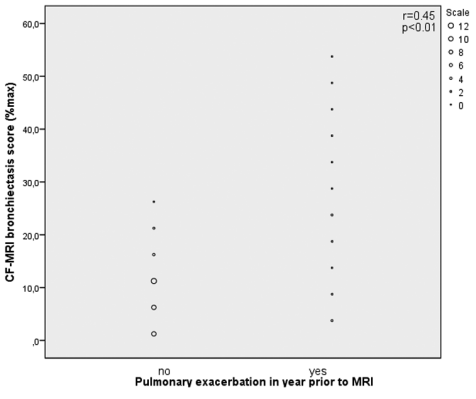


e-Figure 2.3 The significant association between CF-MRI trapped air scores and Pseudomonas aeruginosa.

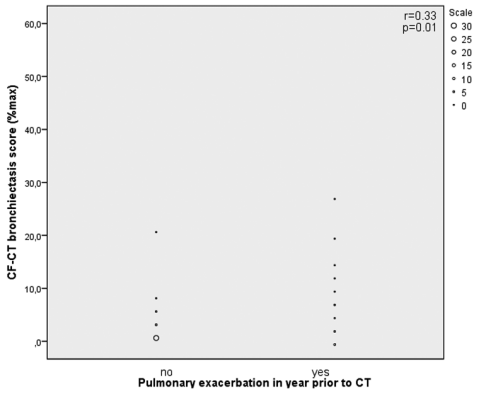


e-Figure 2.4 The association between CF-CT trapped air scores and Pseudomonas aeruginosa.

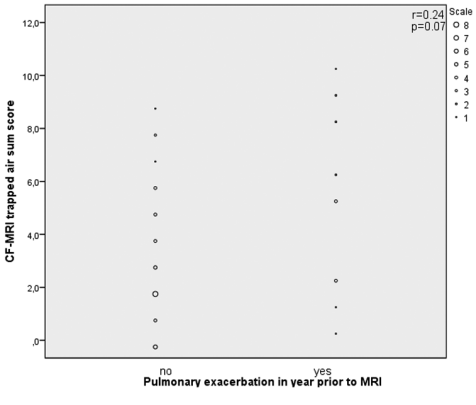
There was a significant association between CF-MRI bronchiectasis (Figure 4.1), CF-CT bronchiectasis (Figure 4.2) and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised. No associations were found for CF-MRI trapped air (Figure 4.3), CF-CT trapped air (Figure 4.4) and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised.



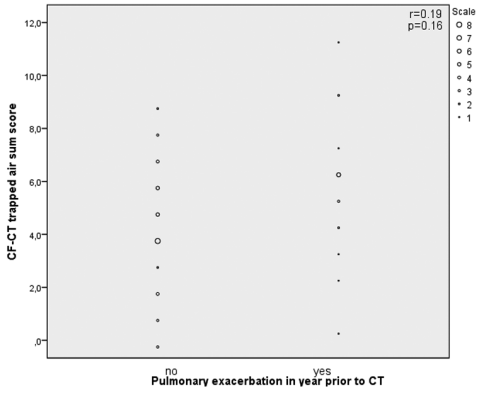
e-Figure 3.1 The significant association between CF-MRI bronchiectasis and pulmonary exacerbations in the year prior to MRI.



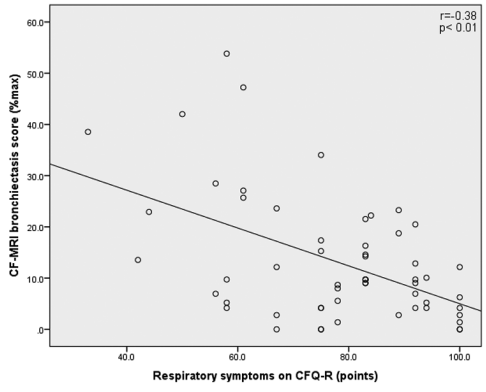
e-Figure 3.2 The significant association between CF-CT bronchiectasis and pulmonary exacerbations in the year prior to CT.



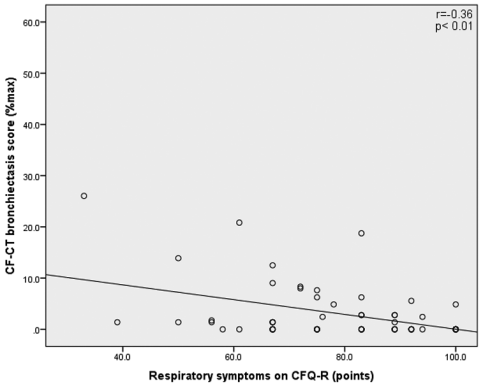
e-Figure 3.3 The association between CF-MRI trapped air scores and pulmonary exacerbations in the year prior to MRI.



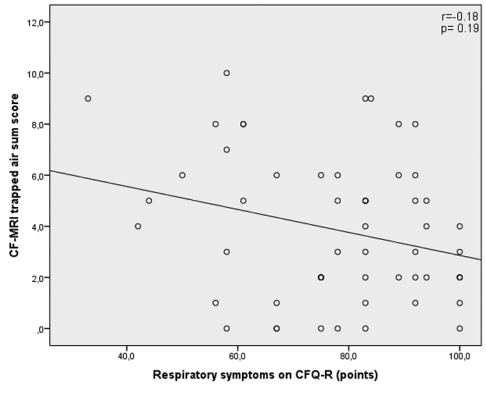
e-Figure 3.4 The association between CF-CT trapped air scores and pulmonary exacerbations in the year prior to CT.



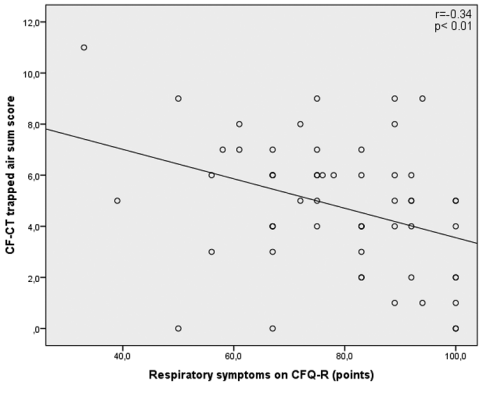
e-Figure 4.1 The significant association between CF-MRI bronchiectasis and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised (CFQ-R).



e-Figure 4.2 The significant association between CF-CT bronchiectasis and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised (CFQ-R).



e-Figure 4.3 The association between CF-MRI trapped air scores and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised (CFQ-R).



e-Figure 4.4 The associations between CF-CT trapped air scores and patient-reported respiratory symptoms measured with the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Chapter 7

Discussion

In this thesis, we aimed to further validate chest CT, chest MRI and the CFQ-R as outcome measures for clinical management and clinical trials in CF lung disease. In this chapter we discuss the main findings of our studies in the context of current literature, their implications and directions for further research.

The first important finding in the validation of chest CT is that more severe bronchiectasis was significantly associated with worsening of respiratory symptoms as measured by the Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale (CFQ-R RSS). In the studies described in chapter 2 and 3, we showed that in a cohort of children with CF, more severe bronchiectasis and trapped air are associated with worse quality of life scores, as measured by the CFQ-R RSS. Although, the importance of bronchiectasis in CF lung disease has been well established (1-7), the impact of bronchiectasis on patient-reported outcome measures in CF had not been examined (8). Our finding that bronchiectasis and CFQ-R RSS are negatively associated further supports the validity of bronchiectasis as a clinically relevant outcome measure.

Trapped air has been less well validated as an outcome measure. We found a significant correlation between trapped air and CFQ-R RSS, independent of the presence of bronchiectasis. Although the association between CF-CT trapped air scores and CFQ-R RSS was significant, it was not as strong as the associations with bronchiectasis. This suggests that trapped air has less impact on patient functioning than bronchiectasis. This can be explained by previous studies showing that trapped air in contrast to bronchiectasis is reversible to some extent (4,5,9). Furthermore, a recent study showed that the patients with severe advanced lung disease and a high volume fraction of bronchiectasis, had a higher mortality risk compared to patients who predominantly had a high volume fraction of trapped air (5). Our results add further support to the importance of trapped air as a clinical relevant outcome measure for CF lung disease.

The second important group of findings of this thesis is the significant associations between CF-CT airway wall thickening, mucus plugging, opacities and the CFQ-R RSS in children and adolescents. Airway wall thickening and mucus plugging are considered to be early indicators of progressive CF lung disease, which are thought to lead to the development of bronchiectasis (4,5). These early indicators were also significantly associated with the CFQ-R RSS in the younger age group. These findings further validate both CT and the CFQ-R RSS as sensitive measures of structural lung damage in the early stages of CF lung disease. Additionally, this supports the view that airway wall thickening and mucus plugging could be used as outcome measure in clinical trials focused on the treatment of CF lung disease.

The third important group of findings presented in chapter 6 are the observed significant cross sectional correlations between bronchiectasis and trapped air scores detected by chest MRI and clinical parameters, FEV_1 % predicted, *Pseudomonas aeruginosa* infection, pulmonary exacerbations and patient reported outcomes. Some of these correlations for

MRI are even stronger than for CT, which is considered the gold standard for monitoring bronchiectasis and trapped air (10). This is the first study assessing these correlations and therefor contributes importantly to the validation of chest MRI related outcome measures as an imaging modality to detect and monitor CF lung disease in children and adolescents with CF. MRI and CT assess bronchiectasis and trapped air in a different way (11), as shown by the poor correlations and interclass correlation coefficients between the two, suggesting that MRI detects other aspects of CF lung disease than CT. These findings support our current clinical practice of alternating biennial MRI and CT in monitoring our CF patients. In addition it supports the importance of further validating MRI as a radiation free alternative in monitoring CF lung disease.

The fourth important finding was that a low quality of life as indicated by a low CFQ-R RSS score is associated with a higher risk for future pulmonary exacerbations, irrespective of other predictors. This novel finding shown in chapter 2, is in-line with what we would expect based on the results of the study performed by *Britto et al.* (12). They concluded that pulmonary exacerbations have a profound, negative impact on health-related quality of life in CF-children, using a generic instrument (Child Health Questionnaire). Furthermore, our data suggested that the CFQ-R RSS is sensitive to detect early, minor respiratory symptoms that are preceding pulmonary exacerbations. This stresses the importance of the CFQ-R RSS as a tool to systematically evaluate symptoms.

The fifth important finding was that two thirds of bronchiectases on CT did not reveal early structural changes in the CT made two years prior to the first occurance. In chapter 5, we describe the first longitudinal study to identify pre-stages of bronchiectasis in children with CF. In 17.7% of the newly developed bronchiectasis we identified mucous plugging as a pre-stage of bronchiectasis. This suggest that the presence of mucus plugging should be taken seriously as it could lead to irreversible bronchiectasis. Due to radiation exposure, it is not advisable to repeat CT-scanning within short time intervals. Therefore we have to identify other sensitive non-invasive outcome measures to detect mucus plugging. Furthermore our study confirmed that in the majority of cases, CT diagnosed bronchiectasis was persistent and therefore irreversible, which is consistent with the results of a study performed in young children up to the age of 6.5 years (4). This study together with our study highlights the importance to prevent the development of bronchiectasis.

The sixth important finding was that the strongest predictor for bronchiectasis in teenage years was the presence of bronchiectasis at a CT made 6 year earlier (CT_1). Predictors of bronchiectasis at that first CT were FEV_1, a pulmonary exacerbation in the year prior to the CT and *Pseudomonas aeruginosa* infection ever. CF-CT bronchiectasis score at CT_1 could predict only 0.03% of the increase in bronchiectasis during the 6-year follow-up, and none of the other tested variables could add any predictive value in the multivariate model. Another striking observation from this study was that in contrast to a previous cohort study performed by our group, the annual increase in the CF-CT bronchiectasis score decreased

from 1.7% to only 0.4% in our current cohort (13). The real difference might even be bigger since we used in our recent study a more sensitive CT protocol than used in the previous study. Many improvements in the monitoring strategy and treatment of CF lung disease can have contributed to this result, with routine biennials use of chest CT to direct therapy being one of them.

In addition to bronchiectasis we also investigated risk factors for the development of trapped air. The most important risk factors that were identified were bronchiectasis and trapped air. Using backward stepwise multivariate analyse, the female gender remained the strongest predictor of trapped air severity 6 years later. Previous studies have also reported a gender difference in clinical outcomes (14,15), which may be explained by the role of sex hormones (15). It is an interesting finding that requires further investigation in a larger cohort.

Clinical implications

The results of our studies presented in this thesis, in addition to previous studies confirm the role that CT, MRI and CFQ-R all can play in the follow up of CF lung disease, but they all have different advantages, provide different information and have different recall windows. To monitor CF lung disease and to assess the effect on a patient's daily life multiple modalities are needed. Our studies showed that the variability in bronchiectasis and trapped air on chest CT was lower than the variability in CFQ-R RS, implying that CT was more sensitive than CFQ-R RSS at detecting a change in structural lung disease. However, the CFQ-R supplies us with insight into how CF lung disease impacts the lives of CF patients

We added a validation study to the portfolio of chest MRI as a radiation free monitoring modality for CF lung disease. Relative to chest CT many more studies are needed to further establish the role of chest MRI to monitor CF lung disease. MRI using today's technology is less sensitive to monitor bronchiectasis and trapped air especially in early disease. However, MRI can potentially be used in the future to evaluate the dynamic consequences of CF lung disease and to study lung perfusion in more detail. Our findings support our current strategy of alternating MRI and CT in following our CF patients to guide our therapy.

Although we showed that the annual increase in the CF-CT bronchiectasis score decreased from 1.7% to only 0.4%, we unfortunately have not succeeded yet in preventing the development of bronchiectasis. Importantly, studies in young CF patients are ongoing to prevent the development of bronchiectasis.

Future directions

General

The studies in this thesis added important information further validating chest imaging as an outcome measure for CF lung disease. Clinical studies have been initiated using chest CT as a primary outcome measure to monitor and assess the efficacy of various treatments. The use of chest CT as a more sensitive outcome measure for CF lung disease compared to the previously used functional outcome measures has important advantages. Such studies will require a smaller sample size to establish the effect of medications for CF lung disease. Chest CT could especially add important information for clinical studies evaluating the efficacy of recently developed expensive CFTR correctors and potentiators.

Image quality control and radiation

To allow clinical multi centre studies that include chest CT great effort should be put into worldwide standardization of CT protocols. Care should be taken to optimize image quality at the lowest possible radiation dose.

To further optimize image quality it is important to optimize volume control. This is of key importance for the assessment of bronchiectasis and trapped air (16,17). In addition, great effort should be directed to standardize and improve sensitivity of CT image analysis. Automated image analysis systems to quantify bronchiectasis and trapped air have great potential to replace time consuming scoring systems.

In order to reduce radiation exposure stratified personalized monitoring should be developed. Currently, monitoring protocols do not distinguish between high and low risk patients.

MRI and multimodality monitoring

Clearly, the use of MRI for monitoring CF lung disease is interesting. However, to introduce chest MRI on a wider scale standardization of protocols and validation of MRI related outcome measures is needed. Efforts should be directed towards further optimization of imaging quality of chest MRI. It is questionable whether morphological chest MRI protocols will ever be of sufficient quality to compete with the chest CT. More promising is the ability of chest MRI to study the consequences of CF lung disease on lung perfusion and ventilation. However, any newly developed MRI functional outcome measure will require an adequate validation program comparable to what has been done for chest related outcome measures.

Finally, our studies evaluated various modalities for monitoring CF lung disease each with their unique advantages and disadvantages. Therefore, future research should also focus on strategies for multi-modality monitoring.

REFERENCES

1 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

2 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

3 Pillarisetti N, Linnane B, Ranganathan S, AREST CF. Early bronchiectasis in cystic fibrosis detected by surveillance CT. Respirology 2010 Aug;15(6):1009-1011.

4 Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 2012 Jun;67(6):509-516.

5 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

6 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

7 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

8 Quittner AL, Alpern AN, Kimberg CI. Integrating Patient-Reported Outcomes into Research and Clinical Practice. Kending & Chernick's Disorders of the respiratory tract in children. 8th edic-tion:251-60.

9 Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. PLoS One 2011;6(8):e23932.

10 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

11 Eichinger M, Heussel CP, Kauczor HU, Tiddens H, Puderbach M. Computed tomography and magnetic resonance imaging in cystic fibrosis lung disease. J Magn Reson Imaging 2010 Dec;32(6):1370-1378.

12 Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002 Jan;121(1):64-72.

13 Tiddens HA, de Jong PA. Imaging and clinical trials in cystic fibrosis. Proc Am Thorac Soc 2007 Aug 1;4(4):343-346.

14 Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. Am J Epidemiol 1997 May 1;145(9):794-803.

15 Sutton S, Rosenbluth D, Raghavan D, Zheng J, Jain R. Effects of puberty on cystic fibrosis related pulmonary exacerbations in women versus men. Pediatr Pulmonol 2013 Mar 4.

16 Mott LS, Graniel KG, Park J, de Klerk NH, Sly PD, Murray CP, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. Chest 2013 Oct;144(4):1193-1198.

17 Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, et al. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009 Oct;253(1):223-229.

Chapter 8

Summary

Chapter 1 contains a general introduction to cystic fibrosis (CF) and formulates the aims of the studies presented in this thesis.

In the first part of this thesis we present the studies that aimed to assess the impact of CF on health related quality of life. The impact of CF lung disease is primarily determined by the development of bronchiectasis and trapped air (1). Studies showed that bronchiectasis are associated with pulmonary exacerbations (2,3), are an indicator of end-stage lung disease (1), and are associated with mortality (1). Compared to bronchiectasis, trapped air has been less well investigated. To date, trapped air has not yet been associated with clinical markers of disease severity, such as pulmonary exacerbations and patient-reported respiratory symptoms on a health-related quality of life measure. A well-validated health-related quality of life measure is the Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale (CFQ-R RSS) (4-12). Although a minimal important difference has been established for the CFQ-R RSS, it is not clear what change in respiratory symptoms reflects the extent of bronchiectasis and trapped air (13). The extent of bronchiectasis and trapped air can be assessed by chest CT (1,14-18). Therefore we investigated in **Chapter 2** whether CT scores for bronchiectasis and trapped air were correlated with quality of life scores (CFQ-R RSS) and what their predictive value for pulmonary exacerbations in the following year was. We included 40 children and 32 adolescents. Our most important finding was that bronchiectasis; trapped air and CFQ-R RSS were all significantly associated with each other and with pulmonary exacerbations in the following year. However, the CFQ-R RSS was the only independent predictor for pulmonary exacerbations in the following year. These results suggest that especially pulmonary exacerbations have a profound, negative impact on health-related quality of life in CF-children.

Additionally we describe in **Chapter 3** the longitudinal associations between changes in bronchiectasis, trapped air, and patient-reported respiratory symptoms over a two years time period. In total 40 patients were included with a median age at T_1 of 12.6 years (range 6-17 years), and at T_2 14.5 years (range 8-19 years). Over two years, there was a significant progression in bronchiectasis (p=0.03) and trapped air (p=0.03). However, the progression of bronchiectasis and trapped air over two year did not correlate to changes in quality of life.

In part two of this thesis we describe two studies further contributing to the validation process of chest CT as an outcome measure. **Chapter 4** describes the first longitudinal study to identify predictors of subsequent bronchiectasis and trapped air severity in a cohort of children over 6 years of age. Twenty-three children with a median age of 9.4 years (range 7-13 years) with a follow up of 6 years were included. We showed that the bronchiectasis score at CT_1, FEV_1 % predicted at CT_1 and *Pseudomonas aeruginosa* infections before CT_1 were predictive of bronchiectasis severity at CT_2. However, the effect of the latter two appeared to be mediated through bronchiectasis at CT_1, which was the only independent predictor for bronchiectasis severity 6 years later in a multivariate model. The identified

predictors for trapped air severity at CT_2 were the bronchiectasis score at CT_1, a pulmonary exacerbation in the year prior to CT_1, and female gender. However, in backward stepwise multivariate analyses only the female gender remained as the strongest predictor of trapped air severity 6 years later.

An important step in the validation process of chest CT was to identify pre-stages of bronchiectasis in CF on chest CT and to determine which patients are at risk for a rapid progression of bronchiectasis. Our observations described in **Chapter 5** provide unique insight into the radiologic course of developing bronchiectasis. Our most important findings were that bronchiectasis appeared mostly within the 2-year timeframe between successive scans. Of the pre-stages that could be identified, mucus plugging was the most common predecessor of bronchiectasis. Development of bronchiectasis without clearly identifiable pre-stages of bronchiectasis was commonly seen in this study, suggesting that the development of most bronchiectasis is an acute process are not caused by a slow continuous progressive process visible on chest CT. This study illustrates the treacherous nature of CF lung disease and highlights the importance of more accurate and sensitive monitoring options in order to prevent the development of structural lung damage.

In part three of this thesis we describe the study that contributed to the validation of chest MRI as an outcome measure. However, for chest MRI, in contrast to chest CT, the validation process is at an early stage. Only few studies have validated MRI derived outcome measures for CF lung disease (19-21). In **Chapter 6** we describe the first study that validated MRI against established outcome measures of CF lung disease such as FEV_1, *Pseudomonas aeruginosa* infection, pulmonary exacerbations and quality of life, measured with the CFQ-R. We included fifty-seven patients (5.6-17.4 years). Our most important findings were the observed significant correlations between CF-MRI bronchiectasis scores and all investigated clinical parameters. Furthermore CF-MRI trapped air scores correlated with FEV_1 and *Pseudomonas aeruginosa* infection. The associations between CF-MRI scores and clinical parameters contribute to the validation of chest MRI in CF. When comparing the correlations of this MRI study with those of CT studies, less strong correlations are observed, suggesting that MRI provides different information than CT. The MRI could play an additional role in monitoring progression of CF lung disease.

Finally, **Chapter 7** provides the discussion of the main findings of the studies presented in this thesis, the clinical implications and suggestions for future research.

REFERENCES

1 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

2 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

3 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

4 Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest 2009 May;135(5):1223-1232.

5 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011 Nov 3;365(18):1663-1672.

6 Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011 Jan;46(1):36-44.

7 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol 2002 Apr;33(4):269-276.

8 Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. Pharmacotherapy 2000 Oct;20(10):1167-1174.

9 Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006 Jan 19;354(3):241-250.

10 Quittner AL. Measurement of quality of life in cystic fibrosis. Curr Opin Pulm Med 1998 Nov;4(6):326-331.

11 Quittner AL, Alpern AN, Kimberg CI. Integrating Patient-Reported Outcomes into Research and Clinical Practice. Kending & Chernick's Disorders of the respiratory tract in children. 8th edic-tion:251-60.

12 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005 Oct;128(4):2347-2354.

13 Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest 2009 Jun;135(6):1610-1618.

14 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

15 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

16 Pillarisetti N, Linnane B, Ranganathan S, AREST CF. Early bronchiectasis in cystic fibrosis detected by surveillance CT. Respirology 2010 Aug;15(6):1009-1011.

17 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

18 Tiddens HA, Brody AS. Monitoring cystic fibrosis lung disease in clinical trials: is it time for a change? Proc Am Thorac Soc 2007 Aug 1;4(4):297-298.

19 Eichinger M, Heussel CP, Kauczor HU, Tiddens H, Puderbach M. Computed tomography and magnetic resonance imaging in cystic fibrosis lung disease. J Magn Reson Imaging 2010 Dec;32(6):1370-1378.

20 Puderbach M, Eichinger M. The role of advanced imaging techniques in cystic fibrosis follow-up: is there a place for MRI? Pediatr Radiol 2010 Jun;40(6):844-849.

21 Puderbach M, Eichinger M, Haeselbarth J, Ley S, Kopp-Schneider A, Tuengerthal S, et al. Assessment of morphological MRI for pulmonary changes in cystic fibrosis (CF) patients: comparison to thin-section CT and chest x-ray. Invest Radiol 2007 Oct;42(10):715-725.

Chapter 9

Samenvatting

Hoofdstuk 1 is een introductie met achtergrond informatie over de ziekte cystic fibrosis (CF), de opbouw van dit proefschrift en beschrijft de doelstellingen van de studies die in dit proefschrift worden besproken.

In het eerste deel van dit proefschrift beschrijf ik de impact van CF op de kwaliteit van leven. De ernst van CF wordt voornamelijk bepaald door de ernst van de longziekte. CF longziekte wordt gekenmerkt door onherstelbare afwijkingen van de kleine luchtwegen, genaamd trapped air en in de grote luchtwegen, genaamd bronchiectasiën. Met longscans (CT) kan deze longschade aan kleine en grote luchtwegen worden opgespoord en worden vervolgd

Verschillende onderzoeken in CF hebben aangetoond dat er een relatie bestaat tussen bronchiectasiën en een plotselinge verergering van de longklachten (pulmonale exacerbaties) (2,3), dat bronchiectasiën een belangrijke onderdeel zijn van eindstadium longziekte (1) en dat er een relatie bestaat tussen bronchiectasiën en de kans op vroegtijdig overlijden (1). In vergelijking met bronchiectasiën zijn er minder studies gedaan naar de klinische betekenis van trapped air. Zo waren er geen onderzoeken gedaan naar de samenhang tussen trapped air en relevante patiëntkenmerken zoals een plotselinge verergering van de longklachten (pulmonale exacerbaties) en kwaliteit van leven. Kwaliteit van leven is te meten met een gevalideerde vragenlijst, genaamd de Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale (CFQ-R RSS) (4-12). Van deze vragenlijst is bekend welke vermindering in score een verslechtering van kwaliteit van leven betekend. Nog niet bekend is of het ontstaan van bronchiectasiën en trapped air een vermindering in score tot gevolg heeft (13). De ernst van bronchiectasiën en trapped air kan met behulp van scoringsmethodes op een longscan worden gemeten (1,14-18). In **hoofdstuk 2** onderzoeken we in hoeverre er een samenhang is tussen deze van de longscan afgeleide scores voor bronchiectasiën en trapped air en kwaliteit van leven zoals gemeten met de CFQ-R RSS vragenlijst. Ook wordt onderzocht of en in hoeverre deze scores een plotselinge verslechtering van de longklachten in het jaar na de longscan (CT) kunnen voorspellen. Aan dit onderzoek deden 72 kinderen mee. Ons belangrijkste resultaat was dat er een samenhang bestaat tussen: het aantal bronchiectasiën, de hoeveelheid trapped air en kwaliteit van leven scores gemeten met de CFQ-R RSS vragenlijst en het voorkomen van een plotselinge verergering van de longklachten (pulmonale exacerbaties). De kwaliteit van leven scores gemeten met de CFQ-R RSS vragenlijst konden de kans dat er een jaar later een plotselinge verergering van de longklachten optreedt voorspellen.

In **hoofdstuk 3** beschrijven we de samenhang tussen een toename van bronchiectasiën en trapped air over een periode van 2 jaar en de kwaliteit van leven vragenlijst scores (CFQ-R RSS). We hebben in 40 patiënten met een gemiddelde leeftijd op het moment van de eerste longscan (T_1) van 12.6 jaar en bij de tweede longscan (T_2) van 14.5 jaar gekeken of er een toename was van het aantal bronchiectasiën en de hoeveelheid trapped air over een periode van 2 jaar en wat daarbij de kwaliteit van leven vragenlijst scores waren. Gedu-

rende de studieperiode van 2 jaar zagen we een duidelijke toename in bronchiectasiën en van trapped air. Deze toename van bronchiectasiën en trapped air hing echter niet samen met een verslechtering in de kwaliteit van leven scores.

Toename in bronchiectasiën en trapped air resulteert uiteindelijk bij 90% van de CF patiënten in vroegtijdig overlijden. Daarom is het voorkomen bronchiectasiën en trapped air een belangrijk behandelingsdoel. Om dit te voorkomen is het belangrijk dat vroege voorspellers voor bronchiectasiën en trapped air worden ontdekt zodat er tijdig behandeling kan worden ingesteld en onomkeerbare longschade kan worden voorkomen. Hoewel er veel onderzoek is verricht met longscans (CT), was er nog geen onderzoek gedaan naar voorspellers voor het optreden van longschade als bronchiectasiën en trapped air in kinderen ouder dan 6 jaar en naar het identificeren van vroege stadia of voorstadia van bronchiectasiën op CT. Deel 2 van dit proefschrift beschrijft een tweetal studies waar we dit onderzocht hebben. **Hoofdstuk 4** is de eerste studie in kinderen ouder dan 6 jaar waarin voorspellers voor de ernst van bronchiectasiën en trapped air worden geïdentificeerd. Voor deze studie werden 23 kinderen met een gemiddelde leeftijd van 9.4 jaar en met een follow-up van 6 jaar bestudeerd. Op de eerste CT (CT1) die gemaakt werd rond de leeftijd van 7-13 jaar werd gekeken wat de hoeveelheid bronchiectasiën was. Daarbij werd gekeken wat de longfunctie ten tijde van die longscan was, of de kinderen een plotselinge toename van de longklachten hebben gehad, of dat de kinderen een ernstige longinfectie met de *Pseudomonas aeruginosa* bacterie doorgemaakt hadden en of er geslachtsverschillen waren in het krijgen van bronchiectasiën en trapped air. Vervolgens werd gekeken of deze factoren de ernst van bronchiectasiën en trapped air 6 jaar later konden voorspellen. Bronchiectasiën op CT_1 bleek de belangrijkste onafhankelijke voorspeller te zijn voor de mate van bronchiectasiën 6 jaar later. De score voor bronchiectasiën op de eerste longscan, het hebben doorgemaakt van een ernstige longinfectie in het jaar voorafgaand aan de eerste longscan en het vrouwelijke geslacht konden de uitgebreidheid van trapped air op de longscan die 6 jaar gemaakt was voorspellen.

Hoofdstuk 5 beschrijft een studie die een uniek inzicht in de ontwikkeling van bronchiectasiën op een longscan geeft. Het beschrijft de studie waarin we voorstadia van bronchiectasiën op een longscan hebben bestudeerd. Tevens hebben we geprobeerd te bepalen welke patiënten een snelle toename van bronchiectasiën lieten zien. Onze belangrijkste bevinding was dat de meeste bronchiectasiën zich binnen een periode van 2 jaar ontwikkelden. Het enige voorstadium dat kon worden geïdentificeerd waren slijmpluggen. Voor de meeste bronchiectasiën kon met CT geen voorstadium worden geïdentificeerd. Dit kan betekenen dat de ontwikkeling van bronchiectasiën een snel optredend proces is of dat er nieuwe en meer gevoelige scans nodig zijn om meer subtiele voorstadia van bronchiectasiën tijdig op te sporen.

In het derde deel van dit proefschrift beschrijven we een studie waarin we onderzoeken of MRI een goede methode is om bronchiectasiën en trapped air op te sporen. Dit wordt va-

lidatie genoemd. Het validatieproces van de MRI als uitkomstmaat bevindt zich nog in een vroege fase (19-21). In **hoofdstuk 6** presenteren we de eerste studie die de samenhang onderzoekt tussen MRI scores voor bronchiectasiën en trapped air en longfunctie, het hebben doorgemaakt van een *Pseudomonas aeruginosa* infectie, een pulmonale exacerbatie en kwaliteit van leven. Voor dit onderzoek werden 57 patiënten onderzocht. Onze belangrijkste bevinding was de samenhang tussen bronchiectasiën en alle onderzochte markers. De ernst van trapped air hing samen met de longfunctie en het hebben doorgemaakt van een *Pseudomonas aeruginosa* infectie. Als we deze MRI resultaten vergelijken met soortgelijke studies voor CT dan zien we dat de samenhang voor MRI minder overtuigend is dan CT. Dit suggereert dat MRI een minder gevoelige techniek is om een toename van bronchiectasiën en trapped air te meten. Verder suggereert dit resultaat dat de MRI andere informatie weergeeft dan de CT. Het blijft dus mogelijk dat de MRI van aanvullende waarde kan hebben voor het monitoren van CF longziekte.

Tot slot bevat **hoofdstuk 7** een discussie van de belangrijkste bevindingen van de studies die gepresenteerd worden in dit proefschrift, de klinische consequenties van de resultaten en suggesties voor verder onderzoek.

REFERENCES

1 Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009 Oct;64(10):876-882.

2 Loeve M, Gerbrandts K, Tiddens HA, Hartmann I, Hop WC. Bronchiectasis and pulmonary exacerbations in children and young adults with Cystic Fibrosis. Chest 2011;140(1):178-185.

3 Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005 Nov 1;172(9):1128-1132.

4 Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest 2009 May;135(5):1223-1232.

5 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011 Nov 3;365(18):1663-1672.

6 Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011 Jan;46(1):36-44.

7 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol 2002 Apr;33(4):269-276.

8 Johnson JA, Connolly M, Zuberbuhler P, Brown NE. Health-related quality of life for adults with cystic fibrosis: a regression approach to assessing the impact of recombinant human DNase. Pharmacotherapy 2000 Oct;20(10):1167-1174.

9 Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006 Jan 19;354(3):241-250.

10 Quittner AL. Measurement of quality of life in cystic fibrosis. Curr Opin Pulm Med 1998 Nov;4(6):326-331.

11 Quittner AL, Alpern AN, Kimberg CI. Integrating Patient-Reported Outcomes into Research and Clinical Practice. Kending & Chernick's Disorders of the respiratory tract in children. 8th edic-tion:251-60.

12 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005 Oct;128(4):2347-2354.

13 Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. Chest 2009 Jun;135(6):1610-1618.

14 Stick SM, Brennan S, Murray C, Douglas T, von Ungern-Sternberg BS, Garratt LW, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009 Nov;155(5):623-8.e1.

15 Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009 Jul 15;180(2):146-152.

16 Pillarisetti N, Linnane B, Ranganathan S, AREST CF. Early bronchiectasis in cystic fibrosis detected by surveillance CT. Respirology 2010 Aug;15(6):1009-1011.

17 Tiddens HA. Chest computed tomography scans should be considered as a routine investigation in cystic fibrosis. Paediatr Respir Rev 2006 Sep;7(3):202-208.

18 Tiddens HA, Brody AS. Monitoring cystic fibrosis lung disease in clinical trials: is it time for a change? Proc Am Thorac Soc 2007 Aug 1;4(4):297-298.

19 Eichinger M, Heussel CP, Kauczor HU, Tiddens H, Puderbach M. Computed tomography and magnetic resonance imaging in cystic fibrosis lung disease. J Magn Reson Imaging 2010 Dec;32(6):1370-1378.

20 Puderbach M, Eichinger M. The role of advanced imaging techniques in cystic fibrosis follow-up: is there a place for MRI? Pediatr Radiol 2010 Jun;40(6):844-849.

21 Puderbach M, Eichinger M, Haeselbarth J, Ley S, Kopp-Schneider A, Tuengerthal S, et al. Assessment of morphological MRI for pulmonary changes in cystic fibrosis (CF) patients: comparison to thin-section CT and chest x-ray. Invest Radiol 2007 Oct;42(10):715-725.

Chapter 10

Acknowledgments

In de afgelopen 4 jaren heb ik met een heleboel mensen samengewerkt en mede dankzij hen is dit proefschrift tot stand gekomen. Graag wil ik iedereen bedanken die mij in de afgelopen jaren heeft geholpen en een paar mensen in het bijzonder.

Allereerst mijn promotor, Prof. Dr. H.A.W.M. Tiddens, beste Harm. Jij hebt mij de kans geboden om promotieonderzoek te doen. Ik wil je in het bijzonder bedanken voor je enthousiasme en positieve energie waarmee je me hebt weten te inspireren. Toen ik in 2010 aan dit traject begon was er voor 1 jaar financiering. Hierdoor heb je me de kans geboden om ervaring op te doen met het aanvragen van subsidies. Daarnaast gaf je me de vrijheid om de studies zelfstandig te organiseren en was er ruimte om me bezig te houden met andere bestuurlijke en organisatorische taken. De mogelijkheden die je me bood om mijn blik te verruimen, zoals het bezoeken van diverse congressen en de workshops en cursussen die ik heb kunnen volgen, waardeer ik enorm. Dit alles heeft geleid tot een zeer divers promotietraject waarbij je me hebt geïnspireerd en me volop de kans hebt gegeven om me persoonlijk te ontwikkelen. Bij deze wil ik je daarvoor hartelijk bedanken.

Mijn tweede promotor, Prof. Dr. G.P. Krestin, beste Professor Krestin. Bedankt voor uw ondersteuning tijdens dit promotietraject. Uw passie en enthousiasme voor uw vak is erg inspirerend. Ik denk met plezier terug aan de jaarlijkse PhD diners, waarbij uw toespraken zeer motiverend waren.

Mijn co-promotor, Ass. Prof. Dr. Marleen de Bruijne, beste Marleen. De samenwerking met jou heb ik als zeer plezierig ervaren. Je input, kritische blik, enthousiasme en expertise in beeldanalyse hebben mij erg geïnspireerd. Bij deze wil ik je dan ook hartelijk bedanken.

Mijn co-promotor, Ass. Prof. Dr. Lisbeth Utens, beste Lisbeth. Jouw ervaring in het doen van onderzoek en enthousiasme voor de psychologie waren zeer waardevol voor de kwaliteit van leven artikelen. Ik wil je bij deze bedankten voor de prettige en dynamische samenwerking.

De leden van de commissie, Prof. Dr. I.K.M. Reiss, secretaris van de kleine commissie, hartelijk dank voor uw deelname aan de kleine commissie en het grondig doorlezen en beoordelen van dit proefschrift. Prof. Dr. C. De Boeck en Prof. Dr. E. Steyerberg, wil ik bij deze hartelijk bedanken voor uw bereidheid om zitting te nemen in de grote commissie.

De rechterhanden van Harm: Irma Stok-Beckers en Els van der Wiel.

Beste Irma, als rechterhand van Harm hebben we vaak met elkaar te maken gehad. Als ik ergens tegenaan liep, kwam jij altijd weer met een praktische oplossing. Ook wist je altijd weer een plekje voor mij vrij te roosteren in de drukke agenda van Harm. Daarbij ben je de beste proof-reader die een PhD zich kan wensen en was het altijd gezellig om even bij je 'te buurten'.

Beste Els, hartelijk dank voor alle hulp in de afgelopen jaren en de fijne samenwerking. Ondanks je drukke agenda maakte je altijd tijd om te brainstormen over projecten, voor adviezen of een luisterend oor. Ik denk met een grijns terug aan New York en de mooie congreservaringen. We hebben veel gedeeld en ontzettend veel gelachen.

Prof. Dr. A.L. Quittner, dear Alexandra, You are an inspirator! Working with you was a great pleasure. Your enthousiasm, passion for quality of life and knowlege works encouraging. Thank you so much for your valuable feedback on the quality of life papers. We had a great time when you were here in Holland for your sabbatical. Your writing course surely helped me a lot to complete this thesis. Thank you so much for all the teaching moments and I am still using your 'things I wish I had known earlier in my carreer' list.

Graag wil ik in het bijzonder mijn directe college-promovendi bedanken.

My radiology colleagues: Karla Gonzalez-Graniel, Pierluigi Ciet, Goffredo Serra. Your radiology skills were very valuable for my research. You all taught me how to interpret CT images, which was not only valuable for my PhD but also in clinical practice. It was a pleasure to work with you and this resulted in a nice friendship.

The ozzies: Elisabeth Salamon, Karla Logie and Tim Rosenow. It was great working with you. Your research mind, critical review and linguistic skills were of great value for this thesis. I am happy you took the opportunity to come to Holland, resulting in a nice collaboration and friendship. Thank you all!

De overige promovendi van Harm: Marije van den Beukel, Martine Loeve, Aukje Bos, Wieying Kuo. Jullie waren ten alle tijde bereid om te brainstormen over een studie opzet, praktische problemen, interpretatie van resultaten of voor gezelligheid buiten werktijd. Dank jullie wel voor de fijne momenten!

De overige promovendi binnen de afdeling Kinderlongziekten: Agnes Sonnenschein, Sandra Voorend-van Bergen, Esther van Mastrigt, Jeroen Tibboel, Ralf van der Valk. Dank jullie wel voor jullie kritische blik en input die jullie door de jaren heen hebben gegeven.

Ook alle leden van de afdeling Kinderlongziekten wil ik hartelijk bedanken voor de input die jullie hebben gegeven op de researchmeetings. Voor alles kon ik bij jullie terecht: een praktische vraag, een statistische vraag of het kritisch beoordelen van presentaties die elders gegeven moesten worden, jullie waren altijd bereid om mee te denken. Hartelijk dank voor de fijne tijd die ik bij jullie heb gehad.

Ook de CF verpleegkundigen: Annelies Kok en Inge Heeres wil ik bedanken. Jullie hebben ervoor gezorgd dat de CFQ-R structureel bij alle CF kinderen werd afgenomen tijdens het groot onderzoek. Dankzij jullie heb ik die data kunnen gebruiken voor de artikelen die in dit

proefschrift beschreven staan. Verder wil ik jullie bedanken voor de prettige samenwerking aan het transitie project: 'op eigen benen vooruit'. Ook denk ik met plezier terug aan de goede tijd die we samen hebben gehad tijdens de congresbezoeken in het buitenland.

Daarnaast wil ik graag alle longfunctie assistenten en collegae van de longpoli bedanken voor de fijne samenwerking en hun ondersteuning.

Ten aanzien van de statistische input voor de onderzoeken beschreven in dit proefschrift wil ik in het bijzonder Daan Caudri en Hugo Duivenvoorden bedanken. Jullie statistische input en interpretatie van resultaten waren zeer waardevol. Hartelijk dank hiervoor.

De ondersteuning vanuit de Radiologie was zeer waardevol: Linda Everse, Fania Jarmohamed en radiologie-medewerkers: Roland, Margreet, Edith, hartelijk dank voor jullie hulp. In het bijzonder wil ik Ton Everaers bedanken voor alle grafische ontwerpen waaronder de lay-out van dit proefschrift en vele poster ontwerpen die hij in de afgelopen 4 jaar heeft gemaakt. Daarbij was het altijd gezellig om even te komen buurten om een poster op te halen en dan over onze gezamenlijke passie het surfen te praten.

Ook de leden van de Erasmus MC Lung Imaging group zou ik bij deze graag willen bedanken voor hun input in dit proefschrift. Jullie wisten de onderzoeken en resultaten van een andere uitgangspositie te belichten, hetgeen erg waardevol was.

Daarbij wil ik alle Sophia onderzoekers bedanken voor de goede tijd die ik tijdens mijn promotietraject heb gehad! De gezamenlijke lunchtijd, en de jaarlijks terugkomende sociale events als de Nieuwjaars-diners, picnic in the parc en de ski-reis waren super!

Dit proefschrift is tot stand gekomen dankzij de financiële support van Steun door zeevaart - SSWO en Gilead sciences Inc. Daarbij heeft Intrasense het mogelijk gemaakt dat ik de juiste software tot mijn beschikking kreeg om de analyses mogelijk te maken. Thank you so much for the support you gave me during those four years!

Tot slot wil ik nog een paar mensen bedanken die me erg dierbaar zijn.

Mijn paranimfen Esther van Mastrigt en Margriet van der Wal: Lieve Esther en Margriet, hartelijk dank voor alle steun die jullie mij de afgelopen jaren hebben gegeven. Met van alles kan ik bij jullie terecht! Ik kan me geen betere paranimfen wensen. Jullie zijn toppers en onze vriendschap is me zeer waardevol.

Mijn familie: Lieve Pap, Mam, Marianne en Jeroen, hartelijk bedankt voor jullie onvoorwaardelijke steun en support. Jullie hebben me altijd gestimuleerd om datgene te doen wat ik graag wil. Jullie nuchtere blik, positiviteit en vertrouwen heeft me zover gebracht en het is fijn dat ik altijd bij jullie terecht kan!

Lieve Martin, altijd sta je voor me klaar! Hoewel al die uren die werden geïnvesteerd om tot dit eindresultaat te komen voor jou niet altijd makkelijk waren heb je me door dik en dun gesteund! Ik wil je bedanken voor je support en alle mooie momenten. Ik weet zeker dat we een fijne toekomst hebben samen.

Chapter 11

Curriculum Vitae

Leonie Tepper was born on April 7th 1981 in Groningen, and raised in Hoogezand-Sappemeer. She graduated in 2000 from secondary school at Aletta Jacobs College in Hoogezand. After a year of law school she started in 2001 her medical training at the University of Leiden.

During her studies she worked in several medical student teams at the Leids Universitair Medisch Centrum (LUMC) in Leiden. She also worked as a nurse and mentor in a home for disabled due to non-congenital brain injuries. She followed courses in recognizing anxiety in children and adolescents and recognizing child abuse at an early stage. In 2005 she was invited to perform research at the pediatric endocrinology ward in the Royal Hospital for Sick Children in Edinburgh, Schotland. This research project was her final thesis to obtain her master degree and was nominated for the student research award. Afterwards the clinical rotations started. Her final rotation was in pediatrics in the Juliana kinderziekenhuis in Den Haag. She obtained her medical degree in 2008 and started to work as a pediatric intern in the Sint Franciscus Gasthuis. In 2009 she started to work as a pediatric intern at the Erasmus MC Sophia Children's hospital. In 2010 she started as a PhD student on the department of pediatric Pulmonology and radiology in the Erasmus MC Sophia Children's hospital working on the studies described in this thesis. In January 2014 she started as a pediatric resident in the Beatrix kinderziekenhuis, Universitatir Medisch Centrum, Groningen.

Chapter 12

List of publications

- Impact of bronchiectasis and trapped air on quality of life and exacerbations in CF. **Tepper LA**, Utens EMWJ, Caudri D, Bos A, Gonzalez-Graniel K, Duivenvoorden H, van der Wiel E, Quittner AL, Tiddens HAWM. *Eur Respir J. 2013 Aug;42(2):371-9.*

- Tracking CF disease progression with CT and respiratory symptoms in a cohort of children aged 6-19 years. **Tepper LA**, Caudri D, Utens EMWJ, van der Wiel ECW, Quittner AL, Tiddens HAWM. Pediatr. Pulmonol. 2014 Feb 12. doi: 10.1002/ppul.22991. [Epub ahead of print]

- Early predictors of bronchiectasis and trapped air severity in cystic fibrosis. **Tepper LA**, Caudri D, Rosenfeld M, Tiddens HAWM. *Submitted to Journal of Cystic Fibrosis*

- The development of bronchiectasis on chest computed tomography in children with cystic fibrosis: Can pre-stages be identified? **Tepper LA**, Caudri D, Perez Rovira A, Tiddens HAWM, de Bruijne M. *Submitted to Radiology*

- Validating chest MRI to detect and monitor cystic fibrosis lung disease in a pediatric cohort. **Tepper LA**, Ciet P, Caudri D, Quittner AL, Utens EMWJ, Tiddens HAWM. *Submitted Ped. Pulmonol.*

- Bronchiectasis and trapped air in cystic fibrosis: a systematic review. Gongxeka H, **Tepper LA,** Oudraad M, Tiddens HAWM, Masekala R. *In progress.*

- Monitoring Small Airways Disease (SAD) in Cystic Fibrosis (CF). Groothuis I, Lever S, Gonzalez Graniel K, **Tepper LA**, Nieuwhof EM, Weijde vd J, Wiel vd EC, Tiddens HAWM. *In progress*.

Chapter 13

PhD Portfolio Summary

Name PhD student: Leonie Tepper
Erasmus MC Department:
1. Pediatric Pulmonology
2. Radiology

Research School: National Institute of Health Sciences in Rotterdam

PhD period: 01/01/2010-01/01/2014
Promotor(s): Prof. Dr. H.A.W.M. Tiddens
Prof. Dr. G.P. Krestin

1. PhD training

	Year	*Workload (Hours/ECTS)*
General courses		
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2010	0.5
- Biomedical English Writing and Communication	2010	4.0
Research skills		
- Statistics:		
- Biostatisctics for clinicians	2011	1.0
- Regression analysis for clinicians	2011	1.9
- Repeated measurements	2011	1.4
- Methodology		
- Mini course: Methodology of clinical research and grant applications	2010	0.2
- Course grant writing ZonMw	2011	0.2
- Course NIH grant writing, Erasmus MC	2012	2.0
In-dept courses		
- ERS School Course "CF basic course"	2010	0.9
Seminars and workshops		
- New insights into pulmonary infectious disease	2010	0.2
- Symposium Nederlands Cysitic Fibrosis stichting (posterpresentatie)	2011	0.3
- Symposium Nederlands Cysitic Fibrosis stichting (posterpresentatie)	2012	0.3
- CF centrale (oral presentation)	2011	0.2
- 5e Jonge onderzoekersdag NVK: Onderhandelen en presentatietechnieken	2011	0.3

(Inter)national conferences		
- 24th North American Cystic Fibrosis Conference, Baltimore, USA (poster presentation)	2010	1
- 25th North American Cystic Fibrosis Conference, Anaheim, UAS (poster presentation)	2011	1
- 21th European Respiratory Society Conference, Amsterdam (poster presentation)	2011	0.3
- 35th European Cystic Fibrosis Conference, Dublin, Ireland (poster presentation)	2012	0.3
- 26th North American Cystic Fibrosis Conference, Orlando, USA (oral presentation)	2012	1
- 27th North American Cystic Fibrosis Conference, Salt Lake City, USA (poster presentation)	2013	1
Didactic skills		
- Instructor CT scoring	2010-2014	1

2. Teaching

Supervising practicals and excursions, Tutoring		
- Asthma and inhalation medication (1th year medical students)	2011	0.3
Supervising Master's theses		
- A.C. Bos: "Effect of air trapping on quality of life in cystic fibrosis lung disease."	2011	0.3
Other		
- Outpatient clinic pediatric pulmonology	2010-2014	6
- Writing club	2012-2013	3
- Researchmeeting (every Friday)	2010-2014	3
- Quality of life PhD meeting (monthly)	2012-2014	1
- Peer review for articles for scientific journals	2011	1.5
Total		34.1