Article title:

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

Running head: Chest CT and quality of life in CF

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ABBREVIATIONS

CF	Cystic fibrosis
CF-CT score	Cystic Fibrosis Computed Tomography score
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RSS	Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms scale
CT	Computed Tomography
EMA	European Medicines Agency
FDA	Food and drug administration
FEF_{75}	Forced expiratory flow at 75%
FEV_1	Forced expiratory volume in 1 sec
FVC	Forced vital capacity
ICC	Intraclass correlation coefficient

PFT   Pulmonary function test

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.

Aims: 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). The CFQ-R Physical Functioning scale, CFQ-R Vitality scale, CFQ-R Health Perceptions and CFQ-R Respiratory Symptoms scale (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 ® intrasense France*, and scored in random order by an observer blinded to clinical background (7). 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).

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: $\geq$ 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 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=-0.46, p<0.0001), 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=-0.37, p=0.002) (Figure 2).

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.

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, 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 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.

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TABLES AND FIGURES

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*.

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).

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

|	Children (6-13 years)						Adolescents (≥14 years)				Chil...
	CFQ-R Child Version (n=40)		CFQ-R Parent Version (n=37)				CFQ-R Teen/Adult Version (n=32)				T...
	Respiratory Symtoms	Physical Functioning	Respiratory Symptoms	Physical Functioning	Vitality	Health Perceptions	Respiratory Symptoms	Physical Functioning	Vitality	Health Perceptions	Respir Sympt
	-0.22	0.09	-0.35*	-0.26	0.01	-0.02	-0.46**	-0.50**	-0.23	-0.28	-0.38**
ng score	-0.51**	-0.13	-0.42*	-0.41*	-0.19	-0.18	-0.49**	-0.53**	-0.22	-0.37*	-0.51**
e	-0.63**	-0.15	-0.43**	-0.14	-0.09	-0.03	-0.49**	-0.49**	-0.25	-0.36*	-0.56**
	-0.42**	0.17	-0.31	0.14	0.07	0.20	-0.50**	-0.42*	-0.28	-0.30	-0.47**
	-0.26	0.08	-0.14	0.03	0.03	0.09	-0.40*	-0.37*	-0.26	-0.18	-0.35**

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).

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-va...
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	<0.0...
Positive culture *Pseudomonas aeruginosa* ‡	1.98	1.22-3.23	0.006	1.72	1.10-2.69	0.0...
Age (years)	1.21	1.02-1.44	0.030	1.52	1.00-2.30	0.0...
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.

Figure 1. Correlation between CFQ-R RSS and CF-CT bronchiectasis score across ages (n=72) ** p < 0.01.
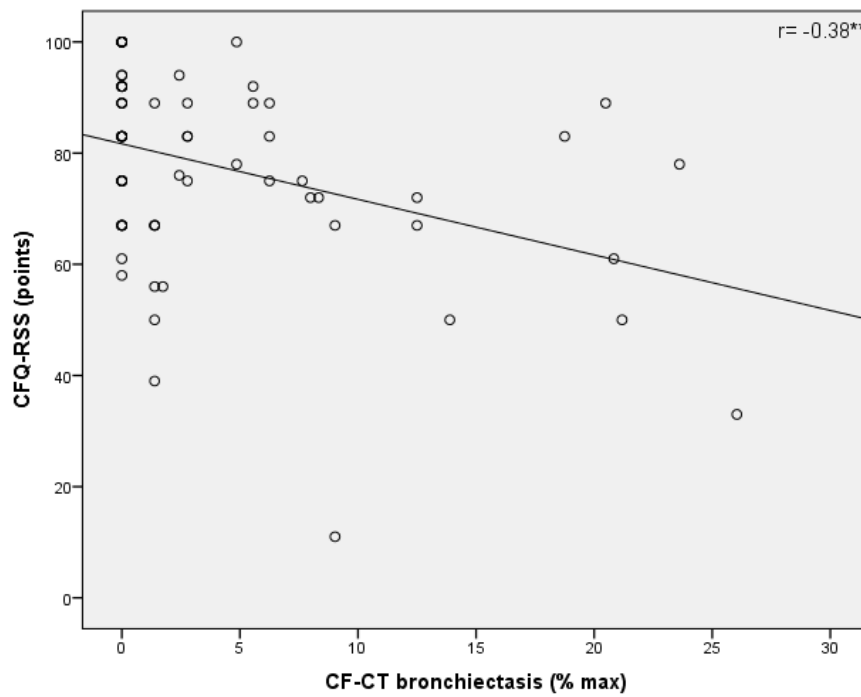
Figure 2. Correlation between CFQ-R RSS and CF-CT trapped air score across ages (n=72) ** p < 0.01.
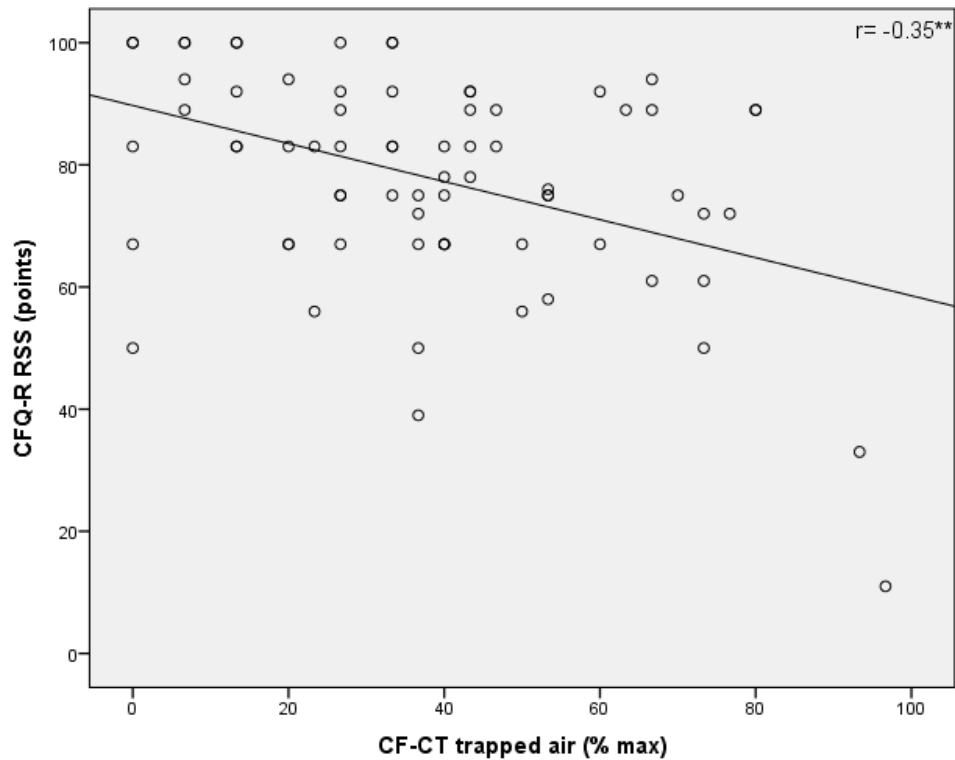
CONTRIBUTIONS OF AUTHORS

Leonie Tepper is the primary investigator of this study. She made substantial contributions to conception and design, acquisition of data, analysis and interpreting data, has drafted and revised the submitted article critically, and has provided final approval of the version to be published.

Dr. Elisabeth Utens has made substantial contributions to concept and design and interpretation of the data. She revised the submitted article critically and has provided final approval of the version to be published.

Dr. Daan Caudri has made substantial contributions to analysis and interpreting data. He has drafted and revised the submitted article critically and has provided final approval of the version to be published.

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Prof. Harm Tiddens is the senior investigator for the study. He made substantial contributions to conception and design, analysis and interpreting data, has revised the submitted article critically, and has provided final approval of the version to be published. He's identified as the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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