Original Article: Cystic Fibrosis

Title manuscript

Quantitative assessment of airway dimensions in young children with cystic fibrosis lung disease using chest computed tomography¹.

Authors

Wieying Kuo 0000-0001-8846-3517 0000-0001-8846-3517, M.Sc.^{1, 2}, Thomas Soffers¹, Eleni-Rosalina Andrinopoulou, Ph.D.³, Tim Rosenow 0000-0003-3727-5131, B.Sc.⁴, Sarath Ranganathan, M.D., Ph.D.^{5, 6, 7}, Lidija Turkovic, Ph.D.⁴, Stephen M. Stick, M.D., Ph.D.^{4, 8, 9}, Harm A.W.M. Tiddens, M.D., Ph.D.^{1, 2}, on behalf of AREST CF

Author Affiliations

1. Department of Pediatric Pulmonology and Allergology, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands
2. Department of Radiology, Erasmus MC, Rotterdam, the Netherlands
3. Department of Biostatistics, Erasmus MC, Rotterdam, the Netherlands

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4. Telethon Kids Institute, The University of
Western Australia, Perth, Australia
5. Infection and Immunity Theme, Murdoch
Children's Research Institute, Melbourne, Australia
6. Department of Paediatrics, University of
Melbourne, Australia
7. Department of Respiratory Medicine, Royal
Children's Hospital, Melbourne, Australia
8. Princess Margaret Hospital for Children,
Perth, WA, Australia
9. School of Paediatrics and Child Health,
University of Western Australia, Perth, WA, Australia

Corresponding author

Author Harm A.W.M Tiddens, MD, PhD

Institution Erasmus MC

Adress 's-Gravendijkwal 230

3015 CE Rotterdam

The Netherlands

Phone +31 10 7040704

Fax

E-mail h.tiddens@erasmusmc.nl

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Running head

Airway and artery dimension in young children

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Abstract

Objective: To evaluate lung disease progression using airway and artery (AA) dimensions on chest CT over 2-year interval in young CF patients longitudinally and compare to disease controls cross-sectionally.

Methods: Retrospective analysis of pressure controlled end-inspiratory CTs: 12 routine baseline (CT₁) and follow up (CT₂) from AREST CF cohort; 12 disease controls with normal CT. All visible AA-pairs were measured perpendicular to the airway axis. Inner and outer airway diameters and wall (outer - inner radius) thickness were divided by adjacent arteries to compute $A_{in}A$ -, $A_{out}A$ -, and $A_{WT}A$ -ratios, respectively. Differences between CF and control data were assessed using mixed effects models predicting AA-ratios per segmental generation (SG). Power calculations were performed with 80% power and $\alpha=0.05$.

Results: CF: median age CT₁ 2 years; CT₂ 3.9 years, 5 males. Controls: median age 2.9 years, 10 males. Total of 4798 AA-pairs measured. Cross-sectionally: $A_{in}A$ -ratio showed no difference between controls and CF CT₁ or CT₂. $A_{out}A$ -ratio was significantly higher in CF CT₁ (SG 2-4) and CT₂ (SG 2-5) compared to controls. $A_{WT}A$ -ratio was increased for CF CT₁ (SG 1-5) and CT₂ (SG 2-6) compared to controls. CF longitudinally: $A_{in}A$ -ratio was significantly higher at CT₂ compared to CT₁. Increase in $A_{out}A$ -ratio at CT₂ compared to CT₁ was visible in $SG \geq 4$. Sample sizes of 21 and 58 would be necessary for 50 and 30% $A_{out}A$ -ratio reductions, respectively, between CF CT₂ and controls.

Conclusion: AA-ratio differences were present in young CF patients relative to disease controls. A_{out} A-ratio as an objective parameter for bronchiectasis could reduce sample sizes for clinical trials.

Introduction

Most patients with cystic fibrosis (CF), develop progressive structural lung disease (SLD) early in life ¹. SLD on chest computed tomography (CT) has been observed as early as 3 months of age, and in young asymptomatic patients with CF ^{2,3}. Early detection of SLD is considered important for clinical studies and for treatment guidance to prevent irreversible SLD or progression ⁴⁻⁶. Therefore, sensitive outcome measures are needed to monitor lung disease in young and non-cooperative patients with CF ⁷.

Chest CT is currently the most sensitive imaging modality to assess SLD. The most important structural change related to CF is bronchiectasis, usually defined as an airway artery (AA)-ratio greater than one. Another important change is airway wall thickening ⁸⁻¹⁰. Both components have been objectively quantified on chest CT by measuring airway and adjacent artery dimensions perpendicular to the airway axis ¹¹ and showed good correlations with CF-CT and PRAGMA-CF scoring systems ¹². Using this AA-method in children with CF aged 6 years and older, major differences in AA-ratio and airway wall thickness were observed in our previous study¹¹, particularly in the small airways. In addition, to diagnose bronchiectasis the outer airway diameter was more reliable than the inner airway diameter¹¹ and the sensitivity of inspiratory scans to diagnose bronchiectasis was better compared to expiratory CTs¹¹. Airway wall thickness,

however, could be detected on both inspiratory and expiratory CTs. Lastly, the number of AA-pairs was shown to be more than doubled in patients with CF relative to controls¹¹. Hence, the AA-method seems to be a promising, sensitive quantitative method to detect structural airways changes that could be used as an outcome measure in clinical intervention trials. A sensitive method to detect changes is required in particular, for children below 6 years old in whom CT changes can be subtle and for whom interventions to prevent development and/or progression of disease are highly desirable. To gain further insight regarding this approach, AA-ratios on CTs were measured in a small group of pre-school children with CF and control subjects showing promising results^{3,13}. Limitations of previous studies were that measurements were executed on limited number of axial slices introducing a projection error, and only a small number of detectable AA-pairs was analyzed.

The aims of this study were to objectively assess early airway changes on chest CTs of young CF patients using the same AA-method as used for children above 6 years old^{11,12}, and to estimate the sensitivity of the AA- method which could be used as a sensitive outcome measure to detect structural airway changes in CF, relative to disease controls. We hypothesized that the AA-method is sensitive to detect changes in airway dimensions of small airways and that the AA-ratio is greater in young children with CF compared to disease controls.

Methods

Study population

Chest CTs of 12 randomly selected patients with CF from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) cohort with two CTs 2 years apart were analyzed retrospectively. Additionally chest CTs of 12 disease control patients were included for cross-sectional comparisons to CF. All patients were treated at the Princess Margaret Hospital, Perth, Australia.

CF subjects: Patients with CF diagnosed through newborn screening were monitored routinely with annual chest CT according to AREST CF protocol ¹⁴. Inclusion criteria were: diagnosis of CF; availability of two longitudinal pressure controlled inspiratory chest CTs; ages between 0 and 6 years old; absence of exacerbation requiring a course of intravenous antibiotics, meaning that all children were free of acute symptoms at the time of the CT scan and in the month prior to scanning. A course or maintenance with oral antibiotics for milder pulmonary symptoms were not considered an exclusion criteria for executing routine chest CT scans. In this cohort, children less than 2 years old were routinely prescribed prophylactic oral antibiotics. .

Disease control subjects: Control CTs were selected when meeting the following criteria; pressure controlled inspiratory chest CT scan; age between 0 and 6 years old; clinical indication for chest CT other than CF; CT acquired for a variety of clinical indications (Table 1) but assessed as normal with no lung abnormalities by experienced pediatric radiologist (CM, 15 years of experience). Single scans from the cross-sectional

control population matched the paired CF scans with regard to average age during acquisition.

CT scanning

All CTs for CF and disease controls were made supine, with pressure control under general anesthesia. To reduce atelectasis, alveolar recruitment maneuvers were performed consisting of 10 consecutive slow breath with inspirations pressure of 40 cm H₂O followed by a breath hold with end-inspiration pressure of 25 cm H₂O. Volumetric end-inspiratory acquisitions were obtained using a Philips Brilliance 64 scanner prior to 2012 and Siemens Definition Flash scanner from 2012 (for additional scanner information see **E-table 1**).

Quantitative analysis of airways and arteries

AA dimensions were measured with image analysis platform Myrian®, v1.18.1 (Lung XP module, Intrasure, Montpellier, France) as described previously ¹¹. In short, the bronchial tree was segmented automatically in 3D and remaining visible airways were added manually. Next, AA dimensions of all AA-pairs were measured perpendicular to the airway centerline. Measurements were made using an ellipse tool surrounding the inner and outer airway and adjacent artery boundaries in a window width of 1500 HU and window level of -200 HU (see **E-Figure 1**). Short and long axis diameters of the inner-, outer airway and adjacent artery were measured preferably in the middle of each reconstructed airway branch. The mean of short and long axis of the airway and artery was used to compute airway and artery diameters, respectively. Inner and outer airway

diameters were divided by artery diameter to compute $A_{in}A_{-}$, $A_{out}A_{-}$ -ratio respectively.

Wall thickness (= [outer airway - inner airway diameter] / 2) was divided by artery diameter to compute $A_{WT}A_{-}$ -ratio.

Airway generation and segmental bronchi were registered for every AA pair. Segmental bronchi were numbered according to Netter nomenclature¹⁵. As previously described¹¹, segmental generation (SG) was computed to allow all segmental bronchi to start at SG 1, correcting for generation discrepancy in each segmental bronchi (see **E-Figure 2**).

Observer reliability

All AA measurements were conducted by one observer (TS, medical student after one month training) blinded to disease status and time of scans. Three months after completion, 10 measurements were repeated in randomly selected segmental branch in each of the 36 CTs to establish intra-observer variability. In case less than 10 AA-pairs were visible and measured in the original random selected segmental branch, the following segmental branch was executed until 10 AA pairs were measured per CT.

Statistical Analysis

Patients' characteristics were summarized using median (range). Difference in number of AA-pairs was assessed using Wilcoxon signed-rank test and relationship between age and number of AA-pairs using linear regression. Differences in AA-ratios per SG for cross-sectional data (CF CT₁ and CT₂ versus disease controls) and longitudinal data (CF CT₁ vs CT₂) were examined with mixed effects models, accounting for correlation

within patients and lobes by including random effects. Influence of gender and age on AA-ratios was assessed by including them as potential confounding variables in the original models. Bonferroni correction was applied per outcome for 16 mixed effects models to predict AA-ratios per SG, with $p \leq 0.003$ considered to be significant.

Receiver operating characteristics (ROC) curves with corresponding area under curves (AUCs) were plotted to find AA-ratios with highest combined sensitivity and specificity differentiating between CF and disease controls.

Power calculations were performed assuming clustering of AA-pairs within individual patients and presented for AA-ratios based on a range of effect sizes, estimated as relative difference between CF and disease control group with 80% power and $\alpha = 0.05$

¹⁶.

Intraclass correlation coefficient (ICC) using a mixed effects model was calculated to determine intra-observer agreement with structure taken into account. The structure specifically included segmental branches within generation within patients. All analysis were conducted using R v3.1.0 ¹⁷.

IRB approved prospective collection of CTs according to AREST CF study and written informed consent was obtained for each procedure.

Results

Study population

Description of group characteristics is shown in Table 2.

Quantitative analysis of airways and arteries

A total of 4798 AA-pairs were identified in perpendicular view of the 3D airway segmentations. 37 Outliers by manual errors and 14 AA-pairs before beginning of the segmental branch were omitted (for more detail see **E-text**), leaving 4747 AA-pairs for analysis. In the CF group, a mean (range) of 127 (91-185) AA-pairs were measured at CT₁ and 148 (115-277) AA-pairs at CT₂. In controls a mean (range) of 121 (47-198) AA-pairs were measured. There were no significant differences cross-sectionally in number of AA-pairs between controls and CF at CT₁ ($p=0.83$) or CT₂ ($p=0.31$) and longitudinally between CF CT₁ and CF CT₂ ($p=0.09$). Figure 1 shows the number of AA-pairs by SG. As demonstrated in Figure 2 the number of AA-pairs is correlated with age (adjusted $r^2=0.28$, $p<0.001$) for CF and control patients combined.

Overall mean (range) of the inner, outer, vessel diameter and wall thickness in all measurements in the CF and control group were 1.6 (0.3-4.4), 2.8 (1.3-6.6), 2.7 (1.1-6.8) and 0.3 (0.1-0.7) mm respectively. A_{inA-} , A_{outA-} , and $A_{WT A-ratio}$ did not increase significantly with age in the CF or control group (**E-figure 3**). Gender and age were found not to be significant in a mixed effects model with A_{inA-} , A_{outA-} , or $A_{WT A-ratio}$.

In the cross-sectional analyses, $A_{inA-ratio}$ did not show significant differences between control and CF CT₁ or CT₂ in any SG (Figure 3, Table 3). Difference in $A_{outA-ratio}$ between CF and control (Figure 4, Table 3) was significant from SG 2-4 for CT₁

($p \leq 0.002$) and SG 2-5 for CT₂ ($p \leq 0.001$). Difference in A_{WT}A-ratio between CF and control (Figure 5, Table 3) was significant from SG 1-5 for CT₁ ($p < 0.001$) and SG 2-6 in CT₂ ($p < 0.001$). Difference in A_{out}A-, and A_{WT}A-ratio between patients with CF CT₂ and disease controls became larger with each next segmental generation.

In the CF longitudinal analyses, A_{in}A-ratio showed small but significant differences between CT₁ and CT₂ along most SG (Figure 3, Table 3). A_{out}A-ratio showed an increasing difference between CT₁ and CT₂ as a function of SG, only significant in SG 6 ($p < 0.001$) (Figure 4, Table 3). A significant difference in A_{WT}A-ratio was observed between CF CT₁ and CT₂ in SG 1 and SG 3 respectively (Figure 5, Table 3).

The optimal threshold for A_{in}A-ratio was 0.7 (AUC= 0.49; sensitivity=0.14; specificity=0.91) and for A_{out}A-ratio was determined to be 1.06 (AUC=0.69; sensitivity=0.58; specificity= 0.69). The optimal threshold for A_{WT}A-ratio was 0.44 (AUC= 0.75; sensitivity=0.75; specificity=0.64). ROC curves based on A_{out}A- and A_{WT}A-ratio between the CF and control group are shown in **E-Figure 4**.

Reproducibility of airway measurements

388 AA-pairs were re-measured in total. ICC and 95% confidence interval for intra-observer variability was 0.62 (0.60-0.64) for inner airway diameter; 0.63 (0.63-0.65) for outer airway diameter; 0.55 (0.53-0.56) for artery diameter.

Sample size estimates

Mean (SD) A_{out}A-ratio for SG 3, 4 and 5 combined was 1.12 (0.18) in CF at CT₂ and 1.00 (0.14) in controls. Sample sizes of 21, 33, 58 and 131 per treatment arm were

calculated based on 50, 40, 30 and 20% reduction in $A_{out}A$ -ratio respectively in difference between CF CT₂ and controls. Mean (SD) $A_{WT}A$ -ratio for SG 3, 4 and 5 combined was 0.47 (0.08) in CF at CT₂ and 0.42 (0.07) in controls. Sample sizes of 53, 83, 148 and 331 per treatment arm were calculated based on 50, 40, 30 and 20% reduction in $A_{WT}A$ -ratio respectively in difference between CF CT₂ and controls. Mean number of AA-pairs with $A_{out}A$ -ratio > 1.1 for SG 3, 4 and 5 combined was 0.51 in CF at CT₂ and 0.22 in controls. Sample sizes of 30, 46, 82 and 184 per treatment arm were calculated based on 50, 40, 30 and 20% reduction in number of AA-pairs with $A_{out}A$ -ratio > 1.1 respectively in difference between CF CT₂ and controls.

Discussion

This study presents a unique dataset with all visible AA-pairs detected in 3D bronchial trees reconstructed from CT scans of young patients with CF. We compared AA-ratios between CF patients and disease controls and assessed progressive changes with time in children with CF.

This study confirms our previous study in older CF patients that the outer airway diameter should be used for comparison with the adjacent artery rather than the inner airway in order to separate diseased CF airways from non-diseased CF airways, diameter¹¹. $A_{in}A$ -ratio did not show a significant difference between the disease control and CF group at CT₁ or CT₂. Relative to disease controls the $A_{out}A$ -ratio in CF patients was significantly higher in segmental generation two to four at CT₁ and higher in

segmental generation two to five for CT₂. A_{out}A-ratio > 1.06 was the best threshold to detect bronchiectasis in young children when using outer airway diameter for comparison to the artery diameter. This contrasts with previous studies that have suggested a smaller AA-ratio to define bronchiectasis ^{3,18}. This difference could be explained as these studies used the inner airway diameter to determine the AA-ratio. An additional finding of this study is that wall thickening was detected in our young CF population compared to disease controls. A_{WT}A-ratio was significantly higher in CF at segmental generation one to five for CT₁, and in segmental generation two to six for CT₂. Similar but more apparent changes have been demonstrated in the A_{out}A,- and A_{WT}A-ratios of older children with CF compared to controls ¹¹. Furthermore, AA-, and A_{WT}A-ratios of disease controls in this study were independent of age and gender, which is in concordance to previous control studies ^{11,18,19}.

Another important finding of this study is that in the longitudinal analysis of children with CF, a progressive increase in A_{out}A-ratio on CT₂ relative to CT₁ was seen in the peripheral airways after a two-year interval (segmental generation ≥ 4), with a significant increase in segmental generation six. For the A_{in}A-ratio, small but significant changes over the two-year interval were detected for segmental generation one to four and six. This could be interpreted as the outer diameter reflecting irreversible airway dilation i.e., bronchiectasis and this diameter is, in contrast to the inner diameter, less influenced by lung volume and/or mucus impaction ²⁰. The systematic increase in A_{out}A-ratio by segmental generation after an interval of two years suggests that there is progressive

bronchiectasis in the peripheral airways of young children with CF, although not statistically significant due to the small number of patients observed in this study. Based on our observations, larger studies that separately compare outer wall and inner wall to artery ratios could help to determine whether mucous impaction precedes the development of irreversible bronchial dilatation. For these studies automated analyses would be particularly useful ²¹. Structural lung changes has been reported in young children with CF previously ^{1,22–25}, and this study supports previous observations that the small airways play an important role in early CF lung disease ^{11,26,27}. In the longitudinal analysis of $A_{WT}A$ -ratio, no changes in airway wall thickness were detected after two years, except for a very small but significant reduction observed in segmental generation three. Similarly, airway wall thickness did not increase significantly over a two years interval in older CF patient using visual CF-CT scoring ²². These observations differ to those by de Jong et al. who demonstrated progression of airway wall thickening over two years in older children and adolescents with CF using quantitative measures ¹³. This discrepancy between our study and that of de Jong et al. is likely to be explained by differences in the study populations. The study by de Jong et al investigated a cohort of patients between 4 and 18 years of age. Disease progression at that time was likely to be more severe relative to our patient population diagnosed through newborn screening and evaluated between 0 and 6 years old. Furthermore, $A_{WT}A$ -ratio in early CF lung disease is relatively stable and progression too small to be detected in the small group of patients in our study, even with very sensitive quantitative assessment in a large number of airways.

Previous studies suggested that the number of visible AA-pairs could be used as a novel CT outcome measure to establish CF lung disease severity ^{11,12,28,29}. In our cross-sectional analysis we did not observe a significant difference in number of AA-pairs between CF and disease controls, nor did the longitudinal analysis between the two time points in CF patients demonstrate significant differences in number of AA-pairs. Age was found to be positively correlated to the number of AA-pairs in these young CF and disease controls. Number of airways that can be detected is highly dependent on lung volume during CT acquisition and on image resolution of the CT ^{30,31}. All CF and control patients in this study had identical volume control protocol during CT acquisition. Hence, this did not likely influence our results. It was possible that due to the resolution limitations of even modern CT scanners we were not able to pick up sufficient number of high generations small airways in these young patients, as airways with a diameter less than 1 mm were mostly not measureable on CT. Hence, based on our findings we do not recommend to use number of visible airways as an outcome measure in patients below the age of 6. Number of airways as outcome measure in studies of these young children could be confounded by age and resolution of chest CT ³². Nonetheless, in a cross-sectional study in children 6 years and older a sufficient amount of (small) airways can be sampled in CF and a control population to detect significant differences between those two groups ¹¹. We believe that in older children the growth of airways, and therefore the detection of number of AA-pairs is to a lesser extent confounded by age or CT resolution.

Lastly, this study suggests that with objectively quantified airway and artery ratios small sample sizes are needed to test effects of interventions or disease progression. A sample size of 21 per treatment arm was estimated based on 50% reduction in A_{out}/A_{in} ratio at age 6. In comparison, the semi-quantitative scoring technique PRAGMA-CF estimated a sample size of 100 per treatment arm based on 50% reduction in total airway disease at age 3²⁵. However, it must be noted that the smaller sample size required with objective airway and artery ratios could have been caused by the older age of the patients studied. Additionally, the sample size estimation is likely an underestimation of the true sample size needed due to the comparison between CF and non-CF airways as baseline. Nonetheless, the AA method appears to be sensitive for detecting abnormal airway dimensions on chest CT compared to controls, supporting the potential for AA-ratio determination as an outcome measure in clinical trials in young patients.

We acknowledge a number of limitations with the study. First, we have only studied a relative small population, due to the time consuming task to quantify AA dimensions manually. However, with 3,297 AA-pairs in CF and 1,450 in controls we had sufficient power to demonstrate differences in AA dimensions between CF and disease controls. For the longitudinal analysis a larger number of patients are needed to determine whether progressive increase in AA-ratios and in the number of AA-pairs can be detected. Second, our control group cannot be considered healthy, as they were patients referred by the pediatric pulmonologist for respiratory complaints. However,

their chest CTs were considered to be normal as evaluated by an experienced pediatric radiologist. The constant AA ratios in disease controls over successive generations observed in this study and in relation to age, is consistent with reported measures in controls ^{3,11,13}. In addition, it is likely that the use of disease controls underestimates differences between CF and controls. Third, the measurements made in the smaller airways are near the resolution limits of the CT scanner. However, with edge-enhancing reconstruction kernel and high image contrast between airway wall tissue and surrounding air or soft tissue, measurements of sub-millimeter structures were feasible. In addition, the accuracy of the measurements were improved by fixing the window width and level settings.

Unfortunately, despite the low radiation dose of modern scanners there are still ethical barriers for studying healthy children with chest CT, due to the potential risks from ionizing radiation. For this reason we were only able to collect single control CTs over the same age range covering the age range of CF patients with each 2 CTs. Finally, the intra-observer analysis was difficult to standardize as the manual measurements at mid-airway positions could have been made at different anatomic locations leading to the ICC of 0.62. However, this is being compensated by the large number of airway-artery pairs that could be sampled per patient (on average 132 pairs) resulting in small confidence intervals. The variability between the airway measurements can be improved when using automated analysis. Algorithms to do so are feasible and currently under development ²¹.

Summary

Our study demonstrates that young children with early CF lung disease have more dilated airways and thicker walls than disease controls. In CF, progression in outer diameter AA-ratio was detected after two years, especially in the peripheral airways. Results of this study are in concordance with previous literature reporting structural airway changes early in life of patients with CF on chest CT ^{2,3}. AA-ratios are an objective tool for measuring CF related airway disease severity in early life, and a sensitive outcome measure for use in clinical trials aiming to prevent early SLD. A larger study population of CF patients is needed to accurately define the progression of SLD on chest CT in young children, which will be the next step using automatic analysis techniques ²¹.

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Figure legends

Figure 1. Average amount of AA pairs visible per generation per control (light gray) and CF patients, for CT₁ (gray) and after a two-year interval for CT₂ (black).

Figure 2. Amount of AA pairs visible per generation per control (open circles, gray line) and CF patients, divided at CT₁ (filled circles, dotted gray line) and CT₂ (filled diamonds, black striped line). The number of AA pairs increases significantly with age ($p < 0.001$).

Note that for CF we have a CT₁ and CT₂ while for controls we have only a CT at one time point

Figure 3. Boxplots of the A_{in}A-ratio in the control group (light gray) and in the CF group at CT₁ (gray) and CT₂ (black). Each box shows median (horizontal line), interquartile range (solid box), 1.5*interquartile range (whiskers) and outliers (points). Table 2 describes the mean differences and p-values for each generation as plotted in the A_{in}A-ratio graph.

Figure 4. Boxplots of the A_{out}A-ratio in the control group (light gray) and in the CF group at CT₁ (gray) and CT₂ (black). Each box shows median (horizontal line), interquartile range (solid box), 1.5*interquartile range (whiskers) and outliers (points). Table 2 describes the mean differences and p-values for each generation as plotted in the A_{out}A-ratio graph. Note that the A_{out}A-ratio increases in the CF CT₂ group by segmental

generation compared to controls. The number of AA pairs observed decreases in the higher segmental generation for all 3 groups as shown in figure 1 and table 2.

Figure 5. Boxplots of the A_{WTA} -ratio in the control group (light gray) and in the CF group at CT₁ (gray) and CT₂ (black). Each box shows median (horizontal line), interquartile range (solid box), 1.5*interquartile range (whiskers) and outliers (points). Table 2 describes the mean difference and p-value for each generation as plotted in the A_{WTA} -ratio graph. Note that the A_{WTA} -ratio is higher in the CF groups at CT₁ and CT₂ compared to controls. The number of AA pairs observed decreases in the higher segmental generation for all 3 groups as shown in figure 1 and table 2.

Tables

Controls		
Clinical diagnosis	Reason for CT	No of subjects
Recurrent respiratory infections/ chronic cough/ persistent tachypnoea	Bronchiectasis? Tracheobronchomalacie?	10
Developmental delay	Aspiration?	2

Table 1. clinical diagnosis and indications for chest CT of the disease control group.

	Patients with CF			Disease controls
	CT ₁	CT ₂	CT ₁ +CT ₂	
N			12	12
Gender (% male)			42% (5)	83% (10)
Age (in years)	2 (0.6-3.2)	3.9 (2.6-5.2)	2.9 (0.6-5.2)	2.9 (1-5.2)
Homozygote DeltaF508			50% (6)	
Heterozygote DeltaF508			50% (6)	
Pancreatic sufficiency			25% (3)	

Pseudomonas aeruginosa infection (%)	0% (0)	8% (1)		
Pseudomonas aeruginosa infection ever (%)			25% (3)	
Inner airway diameter (in mm)	1.46 ± 0.49	1.59 ± 0.55		1.63 ± 0.53
Outer airway diameter (in mm)	2.77 ± 0.70	2.91 ± 0.76		2.78 ± 0.80
Vessel diameter (in mm)	2.58 ± 0.72	2.67 ± 0.81		2.82 ± 0.85
A _{in} A-ratio	0.57 ± 0.10	0.60 ± 0.13		0.58 ± 0.09
A _{out} A-ratio	1.09 ± 0.14	1.12 ± 0.18		1.00 ± 0.14
A _{WT} A-ratio	0.52 ± 0.11	0.52 ± 0.13		0.42 ± 0.10

Table 2. Demographics of the CF and control cohort. Data is represented as mean ± standard deviation or percentage (absolute numbers) as appropriate, with the exception of age which is described as median (range).

1. Number of AA pairs	Segmental generation							
	1	2	3	4	5	6	7	8
Controls	151	364	456	333	102	29	11	4
CF CT ₁	158	368	493	338	121	38	3	0
CF CT ₂	155	391	526	406	193	78	21	6
2. A _{in} A-ratio	Segmental generation							
	1	2	3	4	5	6	7	8
Control vs CT ₁	0.00, -0.05-0.05 (p=0.91)	-0.01, -0.06-0.03 (p=0.65)	-0.01, -0.06-0.03 (p=0.56)	-0.02, -0.06-0.02 (p=0.36)	-0.03, -0.09-0.02 (p=0.23)	-0.08, -0.16-0.00 (p=0.06)	-0.08, -0.27-0.11 (p=0.35)	
Control vs CT ₂	0.03, -0.02-0.08 (p=0.22)	0.02, -0.02-0.07 (p=0.37)	0.01, -0.03-0.06 (p=0.55)	0.01, -0.03-0.01 (p=0.59)	-0.01, -0.06-0.05 (p=0.84)	-0.01, -0.09-0.07 (p=0.78)	0.11, -0.01-0.24 (p=0.08)	0.16, -0.25-0.58 (p=0.24)
CT ₁ -CT ₂	0.03, 0.01-0.05 (p=0.002)*	0.03, 0.02-0.04 (p<0.001)*	0.03, 0.01-0.04 (p<0.001)*	0.03, 0.02-0.05 (p<0.001)*	0.03, 0.01-0.05 (p=0.017)	0.07, 0.03-0.11 (p<0.001)*	0.19, 0.01-0.38 (p=0.046)	
3. A _{out} A-ratio	Segmental generation							
	1	2	3	4	5	6	7	8
Control vs CT ₁	0.07, 0.02-0.11 (p=0.009)	0.08, 0.03-0.13 (p=0.002)*	0.10, 0.05-0.14 (p<0.001)*	0.08, 0.03-0.13 (p<0.001)*	0.09, 0.02-0.16 (p=0.012)	0.00, -0.11-0.11 (p=0.99)	0.08, -0.16-0.33 (p=0.53)	
Control vs CT ₂	0.06, 0.01-0.11 (p=0.016)	0.10, 0.05-0.15 (p<0.001)*	0.10, 0.05-0.14 (p<0.001)*	0.11, 0.07-0.16 (p<0.001)*	0.12, 0.05-0.18 (p<0.001)*	0.12, 0.02-0.23 (p=0.019)	0.26, 0.12-0.40 (p=0.006)	0.21, -0.34-0.75 (p=0.24)
CT ₁ -CT ₂	-0.01, -0.03-0.02, (p=0.65)	0.02, 0.00-0.04 (p=0.04)	0.00, -0.02-0.02 (p=0.83)	0.03, 0.01-0.05 (p=0.006)	0.03, -0.01-0.07 (p=0.10)	0.12, 0.07-0.18 (p<0.001)*	0.18, -0.05-0.41 (p=0.16)	
4. A _{WT} A-	Segmental generation							

ratio	1	2	3	4	5	6	7	8
Control vs CT ₁	0.07, 0.03-0.10 (<i>p</i> <0.001)*	0.09, 0.05-0.12 (<i>p</i> <0.001)*	0.11, 0.07-0.15 (<i>p</i> <0.001)*	0.10, 0.06-0.14 (<i>p</i> <0.001)*	0.12, 0.08-0.17 (<i>p</i> <0.001)*	0.08, 0.01-0.16 (<i>p</i> =0.026)	0.17, -0.04-0.37 (<i>p</i> =0.10)	
Control vs CT ₂	0.03, 0.00-0.07 (<i>p</i> =0.08)	0.08, 0.04-0.11 (<i>p</i> <0.001)*	0.09, 0.05-0.13 (<i>p</i> <0.001)*	0.10, 0.06-0.14 (<i>p</i> <0.001)*	0.13, 0.08-0.17 (<i>p</i> <0.001)*	0.13, 0.06-0.20 (<i>p</i> <0.001)*	0.13, 0.02-0.25 (<i>p</i> =0.029)	0.04, -0.21-0.29 (<i>p</i> =0.57)
CT ₁ -CT ₂	-0.04, -0.05--0.02 (<i>p</i> <0.001)*	-0.01, -0.02-0.00 (<i>p</i> =0.18)	-0.02, -0.04--0.01 (<i>p</i> <0.001)*	0.00, -0.02-0.01 (<i>p</i> =0.78)	0.00, -0.02-0.03 (<i>p</i> =0.86)	0.05, 0.01-0.10 (<i>p</i> =0.022)	-0.03, -0.22-0.16 (<i>p</i> =0.72)	

Table 3. This table shows the number of AA pairs (1), differences in A_{in}A-ratio (2) , differences in A_{out}A-ratio (3) and differences in A_{WT}A-ratio (4) for each segmental generation. Differences in A_{in}A-ratio, A_{out}A-ratio and A_{WT}A-ratio were analyzed for control vs CF CT₁; control vs CF CT₂; and progression of CF in CT₁ vs CT₂. Differences were assessed with the mixed effects model for each generation demonstrating the mean difference, 95% confidence interval and p-values (an * indicates significant difference).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

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Author/s:

Kuo, W;Soffers, T;Andrinopoulou, E-R;Rosenow, T;Ranganathan, S;Turkovic, L;Stick, SM;Tiddens, HAWM

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