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Original Article

Automatic bronchus and artery analysis on chest computed tomography to evaluate the effect of inhaled hypertonic saline in children aged 3-6 years with cystic fibrosis in a randomized clinical trial

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ABSTRACT

Background: SHIP-CT showed that 48-week treatment with inhaled 7% hypertonic saline (HS) reduced airway abnormalities on chest CT using the manual PRAGMA-CF method relative to isotonic saline (IS) in children aged 3-6 years with cystic fibrosis (CF). An algorithm was developed and validated to automatically measure bronchus and artery (BA) dimensions of BA-pairs on chest CT. Aim of the study was to assess the effect of HS on bronchial wall thickening and bronchial widening using the BA-analysis.
Methods: The BA-analysis (LungQ, version 2.1.0.1, Thirona, Netherlands) automatically segments the bronchial tree and identifies the segmental bronchi (G_0) and distal generations (G_1-G_{10}). Dimensions of each BA-pair are measured: diameters of bronchial outer wall (B_{out}), bronchial inner wall (B_{in}), bronchial wall thickness (B_{wt}), and artery (A). BA-ratios are computed: B_{out}/A and B_{in}/A to detect bronchial widening and B_{wt}/A and B_{wa}/B_{oa} (=bronchial wall area/bronchial outer area) to detect bronchial wall thickening.
Results: 113 baseline and 102 48-week scans of 115 SHIP-CT participants were analysed. LungQ measured at baseline and 48-weeks respectively 6,073 and 7,407 BA-pairs in the IS-group and 6,363 and 6,840 BA-pairs in the HS-group. At 48 weeks, B_{wt}/A (mean difference 0.011; 95%CI, 0.0017 to 0.020) and B_{wa}/B_{oa} (mean difference 0.030; 95% 0.009 to 0.052) was significantly higher (worse) in the IS-group compared to the HS-group representing more severe bronchial wall thickening in the IS-group (p=0.025 and p=0.019

Abbreviations: CF, cystic fibrosis; CT, computed tomography; SHIP, the Saline Hypertonic in Preschoolers study; SHIP-CT, the Saline Hypertonic in Preschoolers + CT study; $LCI_{2.5}$, lung clearance index; PRAGMA-CF, Perth-Rotterdam Annotated Grid Morphometric Analysis for CF; BA, bronchus and artery; AI, artificial intelligence; TLC, total lung capacity; FRC, functional residual capacity; B_{in}, bronchial inner diameter; B_{out}, bronchial outer diameter; B_{wt}, bronchial wall thickness; A, artery diameter; B_{out}/A, bronchial outer diameter divided by adjacent artery diameter; B_{in}/A, bronchial inner diameter divided by adjacent artery diameter; B_{wt}/A, bronchial wall thickness divided by adjacent artery diameter; B_{wa}/B_{oa}, bronchial wall area divided by bronchial outer area; TLC-CT, total lung capacity measured on inspiratory chest CT scan; TLC-CT%, total lung capacity measured on inspiratory chest CT scan as a percentage of the predicted value; G, segmental generation; MBW, multiple breath washout; CFTR, cystic fibrosis transmembrane regulator.

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respectively). B_{wt}/A and B_{wa}/B_{oa} decreased and B_{in}/A remained stable from baseline to 48 weeks in the HS while it declined in the IS-group (all $p<0.001$). There was no difference in progression of B_{out}/A between two treatment groups.

Conclusion: The automatic BA-analysis showed a positive impact of inhaled HS on bronchial lumen and wall thickness, but no treatment effect on progression of bronchial widening over 48 weeks.

1. Introduction

Cystic fibrosis (CF) lung disease is characterized by impaired mucociliary clearance which contributes to a vicious cycle of airway inflammation and infection resulting in structural lung damage [1,2]. This damage can be observed on chest computed tomography (CT) early in life [3–10], and is associated with later decline in lung function [3,5-7,10], more frequent exacerbations [5,8], and poorer quality of life [7,9]. Thus, effective therapies should be started in early childhood to delay the onset and progression of lung damage and improve the long-term trajectory of lung disease for individuals with CF [7,11].

For the treatment of CF lung disease, inhaled hypertonic saline is used as an osmotic therapeutic agent to maintain mucus hydration, facilitating effective mucociliary clearance in CF. The efficacy of inhaled hypertonic saline in children aged 3-6 years was evaluated in two randomized controlled trials: the Saline Hypertonic in Preschoolers (SHIP) study [12] and the Saline Hypertonic in Preschoolers + CT (SHIP-CT) study [3]. Both studies showed a positive effect of hypertonic saline after 48-week treatment on the lung clearance index ($LCI_{2.5}$). Moreover, in the SHIP-CT study, a positive effect of hypertonic saline compared to isotonic saline was demonstrated on lung structure as assessed by chest CT. For the SHIP-CT study, chest CTs were scored by a certified observer using the manual Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF) method. PRAGMA-CF [4] is a morphometric scoring system that computes the volume fraction of structural lung components using a grid overlaying ten equally spaced axial CT slices. The primary outcome for SHIP-CT was PRAGMA-CF %Disease which is the percentage of total lung volume occupied by airways that show bronchiectasis, mucus plugging, and/or airway wall thickening. SHIP-CT showed that patients treated with hypertonic saline had lower %Disease compared to the group who were treated with isotonic saline. In addition, the hypertonic saline group also showed significantly less bronchiectasis which was a secondary outcome measure. One limitation of the PRAGMA-CF method is the use of a hierarchical system to annotate the airway abnormalities, therefore, specific contributions to total lung disease ranked following bronchiectasis such as mucus plugging and bronchial wall thickening can be under-estimated due to the hierarchical approach. Furthermore, the diagnoses of bronchial widening and bronchial wall thickening are not made based on precise measurements, but through eyeballing by the observer. The accurate differentiation between mild bronchial widening and bronchial wall thickening using PRAGMA-CF is difficult, which may affect the accuracy and sensitivity to measure bronchial changes over time. Finally, a set of only ten equally spaced slices are annotated to achieve PRAGMA-CF scores which may limit its' sensitivity for monitoring progression.

A more objective method to diagnose bronchial wall thickening and bronchial widening is to measure bronchus and artery (BA) dimensions using a three-dimensional image of the lung reconstructed from a chest CT. This was previously done manually in a proof of concept study in a limited number of school-aged children [13] and preschool children [14] with CF and in matched controls with normal chest CTs. The manual analysis was shown to be sensitive to detect bronchial wall thickening and bronchial widening even in young children [14]. Furthermore, the manual analysis showed more severe structural airway changes in the small airways relative to the more central larger airways [13,14]. A major disadvantage of the manual analysis is that it is extremely time-consuming, as it can take anywhere between 1 and 5 days to analyse a single CT, depending on the size of the subject. For this reason, an automatic artificial intelligence (AI) BA-analysis algorithm was developed and validated [15–17]. This automatic BA-analysis can detect a large number of BA-pairs in children older than 6 years with CF from segmental bronchi as segmental generation 0 up to the 12^{th} segmental generation [16,17]. Substantial differences in BA-dimensions between 11 CFs and 12 controls aged 6- 14 years were detected (data on file) and cut-off values to define bronchial wall thickening and bronchial widening were established [17]. Furthermore, the automatic BA-analysis outcomes for bronchial widening demonstrated a moderate to good correlation with corresponding PRAGMA-CF scores in children older than 6 years with CF [16]. Finally, using the automatic BA-analysis, progression of bronchial widening could be detected in two external CF cohorts [15,17]. In the original SHIP-CT analysis plan, BA-analysis outcomes were secondary outcomes. However, at the time of completion of SHIP-CT, the algorithm was still in its' validation stage and therefore was not included in the primary analysis. As the automatic BA-analysis has now been validated and certified for use in adults but not yet in children, we aimed to analyse all CTs to evaluate the effect of hypertonic saline inhalation on BA-dimensions.

We hypothesized that the automatic BA-analysis would be a sensitive and accurate tool to detect changes over time in bronchial wall thickening and bronchial widening and that BA-outcomes would correlate with functional measures of airway disease such as $LCI_{2.5}$ among participants in the SHIP-CT study.

2. Methods

2.1. Study population

The SHIP-CT study was a multicentre, randomized, double-blinded, controlled, parallel group trial conducted between May 2016 and December 2019 at 23 centres in Europe, North America, and Australia [3]. The details of the study have been reported previously [3]. Key inclusion criteria were a diagnosis of CF; age 36-72 months; ability to cooperate with chest CT imaging except for participants in Australia who underwent chest CT under general anaesthesia; and ability to comply with twice daily hypertonic or isotonic saline inhalations. Eligible participants were randomized 1:1 to inhale twice daily 7% hypertonic saline (treatment arm) or 0.9% isotonic saline (control arm) for 48 weeks.

The trial was registered (ClinicalTrials.gov identifier NCT02950883) and approved by the Institutional Review Boards and Human Research Ethics committee at each participating centre and written informed consent was obtained.

2.2. Chest CT scanning

Chest CT scans were performed at baseline and at 48 weeks according to a specific scan protocol for each centre, which was developed by the Erasmus Medical Centre Lung Analysis Core Laboratory (Rotterdam, the Netherlands) with the aim of standardizing image quality and lung volume. Participants in centres in Australia had their CTs obtained under general anaesthesia as per their routine clinical protocol. All other centres followed a technician or spirometry guided breath hold protocol without sedation. Participants were trained in the chest CT-related breath hold manoeuvres at each visit with the aim to optimize the lung volume and breath hold manoeuvre for the chest CT acquisition. The aim for the inspiratory CT scan was to obtain a volume level as close as possible to total lung capacity (TLC). If the participant had difficulties in following the volume specific manoeuvre, only an inspiratory chest CT was conducted at the best obtainable lung volume between functional residual capacity (FRC) and TLC.

2.3. Bronchus and artery analysis

The automatic BA-analysis was performed using LungQ (version 2.1.0.1, Thirona, Nijmegen, The Netherlands). LungQ is an AI-based medical image analysis platform that automatically identifies patient-specific anatomical features, structural abnormalities, and diseases from chest CT scans. The AI-based algorithms of LungQ are trained with a large variety of datasets to ensure robust performance against variation in patient characteristics (age, gender, BMI), variation in disease populations (chronic obstructive pulmonary disease, asthma, CF, interstitial lung disease, chronic bronchitis, bronchiectasis, COVID-19), and variation in image characteristics (manufacturer, dose, convolutional kernel, voxel spacing). To ensure a robust performance in patients with CF, additional training was performed on around 1.5 million training samples (including data augmentation techniques) from bronchus-artery matches in CT scans of CF patients.

The BA-analysis utilize two AI-based algorithms on the inspiratory CT scan: 1) to segment the bronchial tree from CT for bronchi with a visible lumen, and 2) to match each centreline point within the identified bronchial tree to the adjacent artery. For each matched (paired) centreline points, the bronchial inner diameter (B_{in}), bronchial outer diameter (B_{out}), bronchial wall thickness (B_{wt}), and artery diameter (A) are computed perpendicular to the longitudinal bronchus or artery axis. The bronchi quantification utilises a proprietary intensity profile quantification algorithm that allows for sub-resolution quantification for bronchial wall thickness. The algorithm quantifies each individual bronchus cross-section perpendicular to the local bronchial direction by calculating the bronchial dimensions in a multitude of radial intensity profiles with a sampling distance of higher resolution than the resolution of the scan. These measurements are used to compute the following BA-ratios: B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} (=bronchial wall area/bronchial outer area). The BA-dimensions of each individual bronchial branch is computed as the average of all measurements within that branch. Separate from the quantification analysis, anatomical branches are identified to determine the segmental generations within the bronchial branch. This information is combined with the quantifications of each branch to provide bronchial quantifications per generation. Furthermore, information of segmental generation, segmental parent, and lobe is registered for each BA-pair.

The cut-off values to determine bronchial wall thickening and bronchial widening are based on the automatic BA-analysis of a previously manual annotated dataset of chest CTs from 11 patients with CF and from 12 normal CTs of age-matched control subjects (mean [range] age is 11.8 [6-14] years) [14]. Based on this analysis, the cut-off value for bronchial wall thickening (B_{wt}/A) was set as 0.14 and for bronchial widening (B_{out}/A) was set at 1.1 (data on file).

2.4. PRAGMA-CF

All chest CT scans for the SHIP-CT study were previously analysed by PRAGMA-CF, which is a manual morphometric method using a grid projected over ten equally spaced axial CT slices. PRAGMA-CF computes a volume fraction of the following structural lung components hierarchically on the inspiratory CT scans: %Bronchiectasis, %Mucus plugging, %Airway wall thickening, %Atelectasis, and %Healthy. The composite score %Disease reflects all airway associated abnormalities and is defined as the sum of %Bronchiectasis, %Mucus plugging and %Airway wall thickening. More details can be found in the SHIP-CT study publication [3].

2.5. Lung volume

We also used LungQ (version 2.1.0.1, Thirona, Nijmegen, the Netherlands) to compute lung volumes as lung volume is an important determinant of the BA-ratios [18,19]. LungQ segments the left and right lung separately from which TLC-CT could be computed. TLC-CT measurements are expressed in millilitres and as a percentage of the predicted value for TLC-CT% using the Global Lung Function Initiative correcting for age (>5 years old), sex, and height of the study subject (online calculator http://gli-calculator.ersnet.org/index.html) [20]. For children younger than 5 years old, we inputted the age as 5 years in the predicted lung volume calculation as the proportion of children <5 years did not differ between treatment groups.

2.6. Lung clearance index

The nitrogen multiple breath washout (MBW) testing was performed on the same day as chest CT scanning at baseline, 24, and 48 weeks using an open-circuit, bias-flow system (Exhalyzer D, EcoMedics, Duernten, Switzerland) and associated software (Spiroware) according to a standardized protocol defined by the MBW Resource Centre at the Hospital for Sick Children (Toronto, Canada). From the MBW test, the corrected values of $LCI_{2.5}$ is derived. For this study, we aimed to compare the changes in BA-dimensions to the changes in $LCI_{2.5}$. For this comparison, we compared the difference in BA-dimensions between baseline and 48 weeks with the changes in $LCI_{2.5}$. Additional $LCI_{2.5}$ results have been reported in the SHIP-CT study publication(3).

2.7. Outcomes

In the SHIP-CT study, the primary outcome was the difference in PRAGMA-CF %Disease at 48 weeks between treatment groups, adjusted for baseline PRAGMA-CF %Disease and baseline age. Secondary outcomes included differences in PRAGMA-CF sub-scores (%Bronchiectasis, %Mucus plugging, %Airway wall thickening, %Atelectasis and %Trapped air) at 48 weeks and changes in PRAGMA-CF %Disease and its sub-scores, and $LCI_{2.5}$ from baseline to 48 weeks [3].

Secondary outcomes of the SHIP-CT study included the difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks between treatment groups. These outcomes were not reported in the SHIP-CT publication as the automatic BA-analysis was not validated at the time of the completion of the SHIP-CT study. For this study, the key outcome was difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks, adjusted for baseline PRAGMA-CF %Disease (to correct for

baseline differences in disease severity between treatment groups) and time-dependent TLC-CT.

2.8. Statistical analysis

Data are summarized as mean (standard deviation, SD) or median (interquartile range, IQR). The difference in BA-ratios at 48 weeks and change in BA-ratios from baseline to 48 weeks between treatment groups were assessed by a linear mixed-effects model. The model assumed time, treatment group, baseline age, sex, genotype, baseline height, baseline weight, TLC-CT (time-dependent), baseline PRAGMA-CF %Disease, and the interaction between time and treatment as fixed effects and accounted for the correlation between measurements that are taken from the same individual, measurements that are taken from the same segmental generation, and measurements that are taken from the same lobes as random effects. This interaction between time and treatment allows the effect of treatment on the outcomes to be different from baseline to 48 weeks. Sensitivity analysis was done by assuming the same model using different subsets of centrally segmental generations (G_1-G_6, G_1-G_{10}, or each segmental generation separately). Due to large variability in deeper generations, we investigated whether the differences between treatment groups were changed. Logarithmic transformation was used for BA-ratios expect for B_{wa}/B_{oa} since the normality (of the residuals) and homoscedasticity assumptions were not met. To facilitate the interpretation of the results, we generated effect plots to present predicted BA-ratios, which are the estimated outcomes when assuming specific values (mean) for the above mentioned variables.

Comparison between BA-ratios and $LCI_{2.5}$ were assessed by Spearman correlation analysis. Multiple measurements of BA-ratios per scan are first summarized as a median, and Spearman correlation coefficients were obtained. A correlation coefficient lower than 0.2 was rated as very weak, 0.2-0.4 as weak, 0.4-0.6 as moderate, 0.6-0.8 as strong, and 0.8-1 as excellent.

Statistical significance was accepted for p-values less than 0.05. No correction for multiple testing was performed [21]. Statistical analyses were done with R (version 4.0.5, packages: nlme, effects).

3. Results

3.1. Study population

A total of 220 scans of 116 participants were collected from SHIP-CT dataset. Five CT scans had to be excluded because of inconsistent slice spacing (n=4) and poor image quality (n=1). A total of 113 baseline and 102 48-week CT scans of 115 participants were included this study, 60 participants were in the isotonic saline group and 55 participants were in the hypertonic saline group. 100 participants have paired baseline and 48-week scans. Two participants have only 48-week scans because their baseline scans had poor image quality (n=1) and inconsistent slice spacing (n=1). Thirteen participants have only baseline scans because of lost to follow-up (n=11) and inconsistent slice spacing (n=2). Seven CTs from five participants from Australia were made under general anaesthesia. Thirteen CTs from eleven participants were made between FRC and TLC as participants had difficulties in following the volume specific manoeuvre. Median age at enrolment was 55 months. Clinical characteristics of the treatment groups are summarized in Table 1. Imaging characteristics per treatment group are shown in Table 2.

3.2. Bronchus and artery analysis

The automatic BA-analysis detected and quantified 6,073 BA-pairs (n=58) at baseline and 7,407 BA-pairs (n=54) at 48 weeks from segmental generation G_0 up to G_{10} in the isotonic saline group and 6,363 BA-pairs (n=55) at baseline and 6,840 BA-pairs (n=48) at 48 weeks from G_0 up to G_9 in the hypertonic saline group. In the isotonic saline group, a mean of 105 (SD, 54) BA-pairs per CT at baseline and 137 (SD, 61) BA-pairs per CT at 48 weeks were detected. In the hypertonic saline group, a mean of 116 (SD, 65) BA-pairs per CT at baseline and 142 (SD, 70) BA-pairs per CT at 48 weeks were detected. Participants in both treatment groups had the highest number of BA-pairs detected in segmental generation G_2 (Fig. 1). As 99% of BA-pairs were detected in segmental generations G_1-G_6, only BA-ratios in segmental generations G_1-G_6 were used for further analysis.

Baseline imaging characteristics were balanced between treatment groups (Table 2). The mixed-effects model analyses (Table S1, main effect: treatment) showed that at 48 weeks, B_{wt}/A and B_{wa}/B_{oa} was significantly higher in the isotonic saline group compared to the hypertonic saline group (p=0.025 and p=0.019, respectively; Figure S4 and S5 for sensitivity analysis). As shown in Fig. 2, mean predicted B_{wt}/A in the in the isotonic saline group was 0.171 (95%CI, 0.164 to 0.178) and in the hypertonic saline group was 0.160 (95%CI, 0.154 to 0.167) with a mean difference of 0.011 (95% CI, 0.0017 to 0.020) adjusted for the mean of age, height, weight, lung volume, PRAGMA-CF %Disease or mode of sex, race, and genotype. Mean predicted B_{wa}/B_{oa} in the isotonic saline group was 0.585 (95%CI, 0.567 to 0.602) and in the hypertonic saline group was 0.554 (95%CI, 0.536 to 0.572) with a mean difference of 0.030 (95% CI, 0.009 to 0.052). There was no significant difference in B_{out}/A (p=0.94) and B_{in}/A (p=0.21) at 48 weeks between treatment groups (Fig. 2; Figure S2 and S3 for sensitivity analysis). Mean predicted B_{out}/A at 48 weeks was 0.983 (95%CI, 0.947 to 1.021) in the isotonic saline group and 0.986 (95%CI, 0.949 to 1.024) in the hypertonic saline group. Mean predicted B_{in}/A at 48 weeks was 0.614 (95%CI, 0.582 to 0.647) in the isotonic saline group and 0.644 (95%CI, 0.610 to 0.679) in the hypertonic saline group.

The mixed-effects model analyses (Table S1, main effect: interaction between time and treatment) showed that changes in B_{wt}/A, B_{in}/A, and B_{wa}/B_{oa} from baseline to 48 weeks were significantly different between treatment groups favouring the hypertonic saline group (all p<0.001; Figure S6 for sensitivity analysis). As shown in Fig. 3, mean predicted B_{wt}/A in segmental generations G_1-G_6 increased from 0.156 (95%CI, 0.150 to 0.163) at baseline to 0.171 (95%CI, 0.164 to 0.178) at 48 weeks in the isotonic saline group and from 0.152 (95%CI, 0.146 to 0.159) to 0.160 (95%CI, 0.154 to 0.167) in the hypertonic saline group. Mean predicted B_{wa}/B_{oa} in segmental generations G_1-G_6 increased from 0.551 (95%CI, 0.534 to 0.569) at baseline to 0.585 (95%CI, 0.567 to 0.602) at 48 weeks in the isotonic saline group and from 0.541 (95%CI, 0.523 to 0.559) to 0.554 (95%CI, 0.536 to 0.572) in the hypertonic saline group. Mean predicted B_{in}/A decreased from 0.633 (95%CI, 0.601 to 0.668) at baseline to 0.614 (95%CI, 0.582 to 0.647) at 48 weeks in the isotonic saline group and was stable at 0.642 (95%CI, 0.608 to 0.678) at baseline and 0.644 (95%CI, 0.610 to 0.679) at 48 weeks in the hypertonic saline group. Progressive B_{out}/A was found in both treatment groups (Table S1, main effect: time, p<0.001), but there was no significant difference between hypertonic saline and isotonic saline groups (p=0.39). Mean predicted B_{out}/A increased from 0.968 (95%CI, 0.932 to 1.005) to 0.983 (95%CI, 0.947 to 1.021) in the isotonic saline group and from 0.964 (95%CI, 0.928 to 1.002) at baseline to 0.986 (95%CI, 0.949 to 1.024) in the hypertonic saline group (Fig. 3).

Distribution of bronchial wall thickening as defined by $B_{wt}/A > 0.14$ and bronchial widening as defined by $B_{out}/A > 1.1$ of each lobe in both groups at baseline is shown in Fig. 4. Bronchial wall thickening was present between 64% and 75% and bronchial widening was present between 28% and 40% of total BA-pairs in different lobes. The right upper lobe was the most affected lobe.

Table 1
Demographic characteristics of SHIP-CT participants at baseline.

Characteristic	Isotonic saline group (n=60)	Hypertonic saline group (n= 55)
Age (months)	54.6 (43.6, 65.7)	55.1 (50.0, 63.7)
Sex		
Male	30 (50%)	28 (51%)
Female	30 (50%)	27 (49%)
CFTR genotype		
Homozygous ΔF508	21 (35%)	27 (49%)
Compound heterozygote ΔF508	30 (50%)	23 (42%)
Other	9 (15%)	5 (9%)
Race		
Caucasian	56 (93%)	53 (96%)
Asian	1 (2%)	0
Pacific	1 (2%)	0
Indian	1 (2%)	1 (2%)
Other	1 (2%)	1 (2%)
Ethnicity		
Hispanic or Latino	3 (5%)	2 (4%)
Non-Hispanic or Latino	57 (95%)	53 (96%)
Weight (kg)	18.0 ± 3.3	17.9 ± 2.9
Height (cm)	105.6 ± 7.7	106.7 ± 7.5

Data are median (IQR), n (%), or mean ± SD. CFTR= cystic fibrosis transmembrane conductance regulator.

Table 2
Chest CT-related characteristics at baseline and 48 weeks.

	Isotonic saline group (n=60)		Hypertonic saline group (n=55)	
	Baseline	48 weeks	Baseline	48 weeks
BA-outcomes*				
BA-pair count	105±54	137±61	116±65	142±70
B_{out}/A	0.983 (0.824, 1.170)	0.990 (0.834, 1.175)	0.989 (0.820, 1.189)	1.002 (0.834, 1.210)
B_{in}/A	0.619 (0.494, 0.768)	0.642 (0.526, 0.784)	0.629 (0.513, 0.771)	0.673 (0.537, 0.827)
B_{wt}/A	0.173 (0.134, 0.224)	0.165 (0.126, 0.212)	0.170 (0.131, 0.223)	0.160 (0.122, 0.210)
B_{wa}/B_{oa}	0.588 (0.497, 0.672)	0.562 (0.467, 0.646)	0.573 (0.498, 0.661)	0.544 (0.459, 0.625)
Lung Volume				
TLC-CT (ml)	1208 (924, 1498)	1477 (1158, 1854)	1191 (956, 1526)	1549 (1036, 1762)
TLC-CT%	87 (75, 105)	96 (84, 105)	88 (68, 103)	93 (74, 109)
PRAGMA-CF				
%Disease	1.03 (0.40, 1.93)	1.45 (0.63, 4.31)	0.91 (0.44, 2.03)	1.16 (0.37, 2.37)
%Bronchiectasis	0.62 (0.20, 1.56)	1.19 (0.51, 3.08)	0.70 (0.24, 1.86)	0.95 (0.22, 2.18)
%Airway wall thickening	0.03 (0.00, 0.30)	0.03 (0.00, 0.27)	0.00 (0.00, 0.19)	0.00 (0.00, 0.12)

Data are mead ± SD or median (IQR). BA = bronchus and artery. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner diameter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa}= bronchial wall area divided by bronchial outer area. TLC-CT = total lung capacity measured on inspiratory chest CT scan. TLC-CT% = total lung capacity measured on inspiratory chest CT scan as a percentage of the predicted value. PRAGMA-CF = Perth-Rotterdam Annotated Grid Morphometric Analysis for cystic fibrosis. %Disease = total volume of abnormal airways expressed as a percentage of total lung volume. %Bronchiectasis = total volume of bronchiectasis expressed as a percentage of the total lung volume. %Airway wall thickening = total volume of airway wall thickening expressed as a percentage of total lung volume. *BA-outcomes included all segmental generations (G_0- G_{10}). Baseline BA-outcomes were assessed from 58 participants in the isotonic saline group and 55 participants in the hypertonic saline group. 48-week BA-outcomes were assessed from 54 participants in the isotonic saline group and 48 participants in the hypertonic saline group.

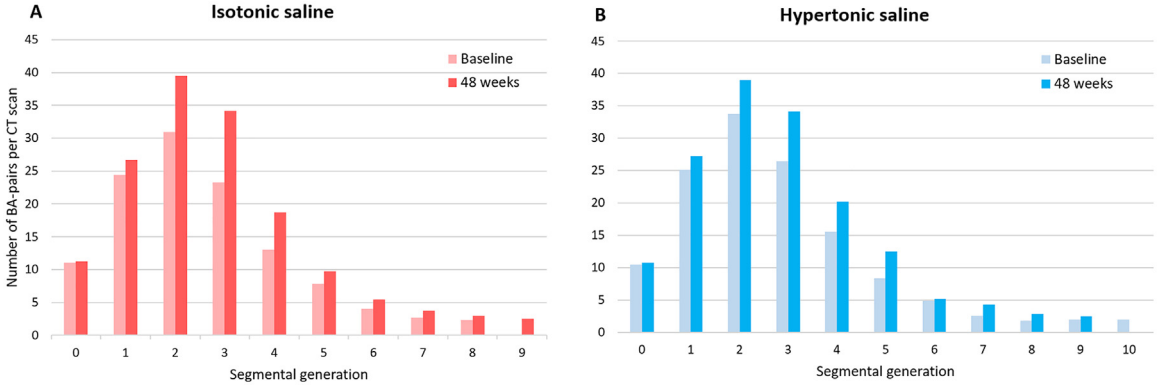

Fig. 1. Average number of BA-pairs per segmental generation at baseline and 48 weeks between treatment groups. The figure shows (A) the average number of BA-pairs per segmental generation in isotonic saline group at baseline (light red) and 48 weeks (dark red). (B) The average number of BA-pairs per segmental generation in hypertonic saline group at baseline (light blue) and 48 weeks (dark blue). BA = bronchus and artery. Note that the highest number of BA-pairs in both treatment groups could be detected in segmental generation G_2 and more BA-pairs could be detected at 48 weeks compared to baseline which can be the result of growth and/or disease progression [14].

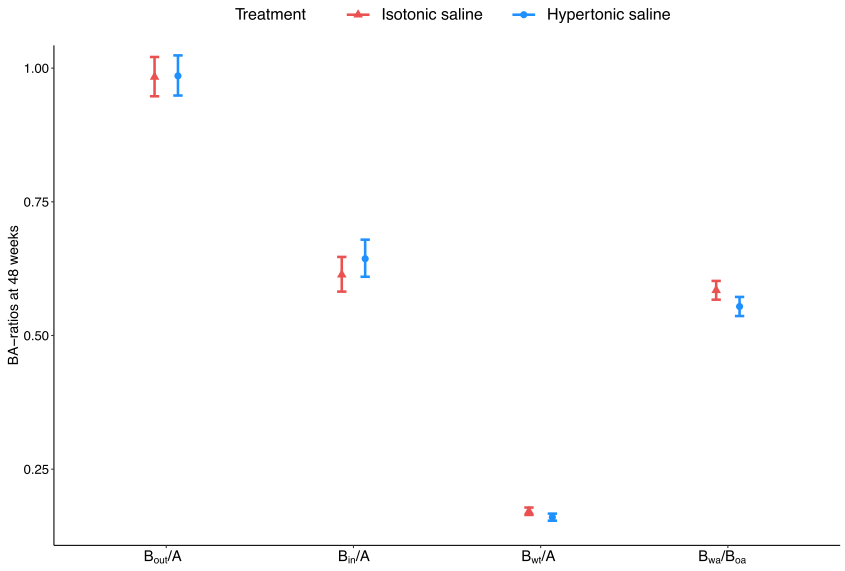

Fig. 2. Comparison of predicted B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1-G_6 at 48 weeks between treatment groups. Mean predicted (95%CI) values of B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1-G_6 at 48 weeks were estimated from mixed-effects model. Significant differences at 48 weeks between treatment groups were found in B_{wt}/A (p=0.025) and B_{wa}/B_{oa} (p=0.019) but not in B_{out}/A (p=0.94) and B_{in}/A (p=0.21). Predicted BA-ratios are the estimated outcomes when assuming specific values (mean) for other variables. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner diameter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa} = bronchial wall area divided by bronchial outer area. G=segmental generation. Error bars indicate 95%CI.

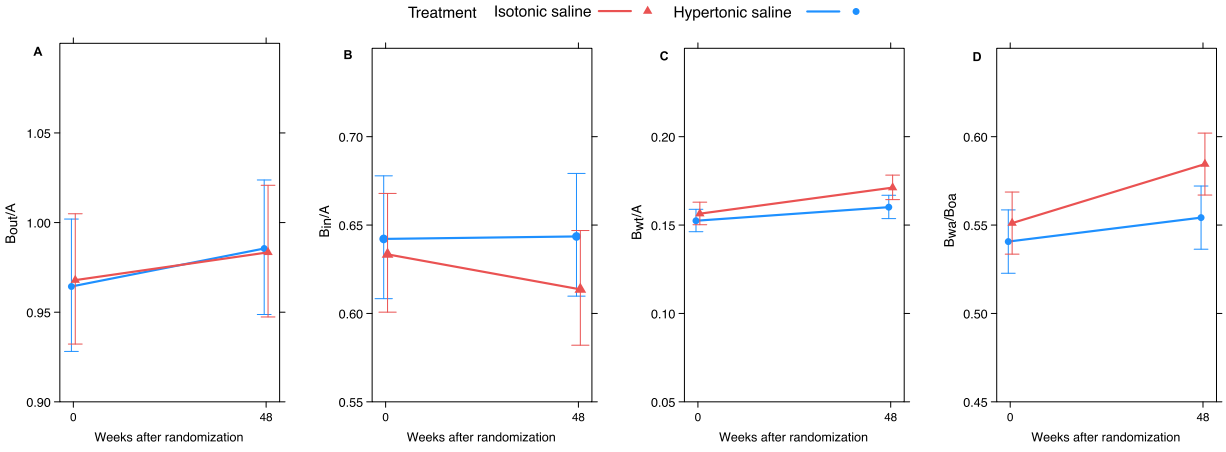

Fig. 3. Change in B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} in segmental generations G_1- G_6 from baseline to 48 weeks between treatment groups. Change in B_{out}/A (A), B_{in}/A (B), B_{wt}/A (C), and B_{wa}/B_{oa} (D) in segmental generations G_1-G_6 from baseline to 48 weeks between treatment groups were estimated with mixed-effect models for repeated measures. Significant differences in change from baseline to 48 weeks between treatment groups were found in B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} (all $p<0.001$), but not in B_{out}/A (p=0.39). Predicted B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} are the estimated outcomes when assuming specific values (mean) for other variables. B_{out}/A = bronchial outer diameter divided by adjacent artery diameter. B_{in}/A = bronchial inner dimeter divided by adjacent artery diameter. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa} = bronchial wall area divided by bronchial outer area. G = segmental generation. Error bars indicate 95%CI.

3.3. Lung volume

At baseline, median TLC-CT was 1,191mL (IQR, 926, 1,526) and median TLC-CT% was 88% (IQR, 71, 105). At 48 weeks, the median TLC-CT was 1,527mL (IQR, 1,155, 1,820) and the median TLC-CT% was 95% (IQR, 81, 108). There was a considerable variability in the trajectories of TLC-CT% from baseline to 48 weeks in both treatment groups (Figure S1).

3.4. Comparison between BA-ratios and $LCI_{2.5}$ outcomes

The correlation coefficients between BA-ratios and $LCI_{2.5}$ are shown in Table S2 (Appendix). B_{wt}/A correlated weakly with $LCI_{2.5}$ at both baseline and 48 weeks but correlated very weakly when analysing changes over time. For the comparison between B_{wt}/A and $LCI_{2.5}$, there were 104 participants who had paired B_{wt}/A-$LCI_{2.5}$ data at baseline and 85 participants at 48 weeks. To evaluate the changes over time, there were 85 participants who had paired baseline and 48-week $LCI_{2.5}$ and paired B_{wt}/A data. In 16/40 (40%) participants in the hypertonic saline group and 23/45 (51%) participants in the isotonic saline group, change in $LCI_{2.5}$ from baseline to 48 weeks was discordant with the change in B_{wt}/A (Fig. 5). As shown in Figure S7, there was a variability in the trajectories of $LCI_{2.5}$ and B_{wt}/A per participant from baseline to 48 weeks in both treatment groups.

4. Discussion

Using an automatic analysis to measure dimensions of visible BA-pairs, the automatic BA-analysis was able to detect and quan-

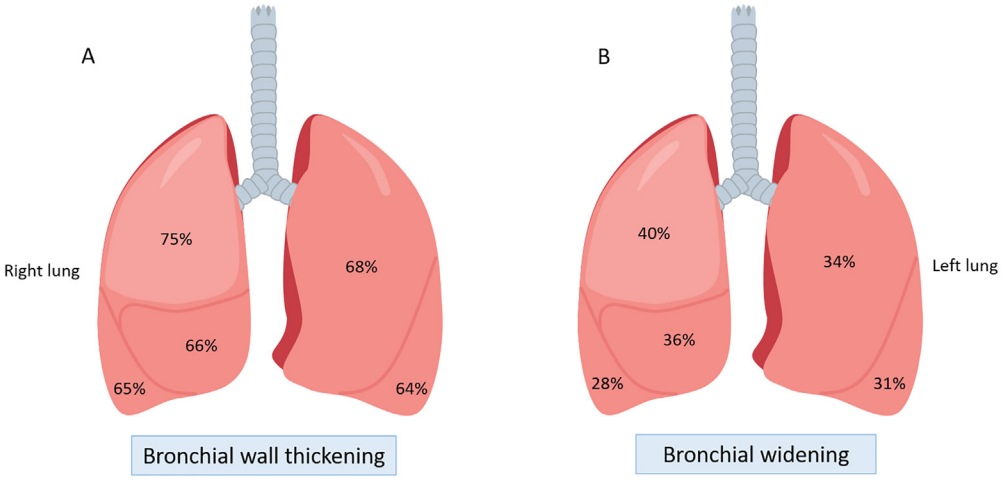

Fig. 4. Radiological distribution of bronchial wall thickening and bronchial widening of each lobe at baseline in both groups. The figure shows the percentages of bronchus-artery pairs for each lobe showing bronchial wall thickening (A) and bronchial widening (B) at baseline in both groups. Bronchial wall thickening is defined by a ratio between bronchial wall thickness and artery (B_{wt}/A) >0.14. Bronchial widening is defined by a ratio between bronchial outer diameter and artery (B_{out}/A) >1.1. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. B_{out}/A = bronchial outer dimeter divided by adjacent artery diameter.

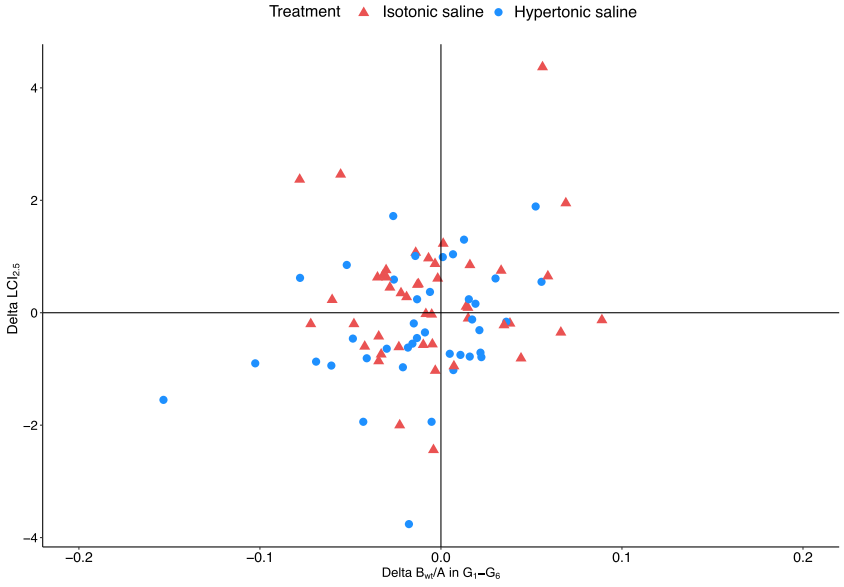

Fig. 5. Scatter plot of the change in $LCI_{2.5}$ and change in median B_{wt}/A in segmental generations G_1-G_6 from baseline to 48 weeks between treatment groups. Change in $LCI_{2.5}$ and change in B_{wt}/A in segmental generations G_1-G_6 between baseline and 48 weeks were assessed from 47 participants in the isotonic saline group and 41 participants in the hypertonic saline group. $LCI_{2.5}$ = lung clearance index. B_{wt}/A = bronchial wall thickness divided by adjacent artery diameter. Delta $LCI_{2.5}$ = the difference in $LCI_{2.5}$ between baseline and 48 weeks. Delta B_{wt}/A in G_1-G_6 = the difference in median B_{wt}/A in segmental generations G_1-G_6 between baseline and 48 weeks. G = segmental generation. Note that in 16/40 (40%) participants in the hypertonic saline group and 23/45 (51%) participants in the isotonic saline group, delta $LCI_{2.5}$ from baseline to 48 weeks was discordant with delta median B_{wt}/A in segmental generations G_1- G_6.

tify a large number of BA-pairs on chest CT scans in children aged 3-6 years with CF. We showed that CTs of children randomized to the hypertonic saline group had significantly thinner bronchial walls and larger bronchial lumens over 48 weeks relative to the isotonic saline group. There was no difference in progression of bronchial widening between treatment groups.

The bronchial wall observed on chest CT scans became significantly thinner with the treatment of hypertonic saline over 48 weeks. The mean difference between treatment groups in B_{wt}/A at 48 weeks was 0.011 (95%CI, 0.0017 to 0.020) which might seem small. To put this difference into perspective, we can express this difference as a percentage of the ratio as observed in a control population of children aged 3-6 years with normal chest CTs where BA-pairs can be detected up to the 5th segmental generation. The median B_{wt}/A for segmental generations G_1-G_5 was 0.18 (data on file). The mean difference between treatment groups in the SHIP-CT study thus corresponds to an increase of 0.011/0.18=6% in the B_{wt}/A ratio. This means children aged 3-6 years with CF who were treated with hypertonic saline had a 6% thinner bronchial wall over 48 weeks relative to the isotonic saline group. Similarly, B_{wa}/B_{oa}, which is the ratio between the bronchial wall area and the bronchial outer area, provides information on the degree of bronchial wall thickening independent of artery diameter changes. A significant smaller progression in B_{wa}/B_{oa} was observed in the hypertonic saline group relative to isotonic saline group. A reduction in bronchial wall thickening can reflect both more effective clearance of mucus and/or reduction of inflammatory thickening.

We speculate that the reduced bronchial wall thickness from baseline to 48 weeks in the hypertonic saline group compared to the isotonic saline group can be explained by two possible mechanisms. Firstly, hypertonic saline is likely to reduce bronchial wall

thickness due to improved mucus clearance. Hypertonic saline allows water to move from the submucosa to the bronchial lumen facilitating mucociliary clearance [22–24]. As more mucus is cleared from the bronchi, the bronchial wall on CT may become thinner and the bronchial inner diameter becomes larger [25]. Secondly, improved mucociliary clearance is likely to facilitate the clearance of microorganisms, reduce inflammation and its' associated mucosal swelling [23,26–29]. Using chest CT, mucus cannot be differentiated from the bronchial wall when the bronchus is completely obstructed, however, this only accounts for a small fraction of the full set of observable bronchi. It could theoretically be that some (inflamed/obstructed) bronchi are missed in the analysis. Therefore, the true difference in bronchial wall thickness between treatment groups may have been to some extent underestimated. Despite this fact the algorithm was sensitive enough to measure bronchial wall thickness and even detect a significant difference between the two treatment groups. The impact of inflammation on bronchial dimensions is probably much smaller than that of mucus adherent to the mucosa [22]. The reduced bronchial wall thickness, lower volumes of low attenuation regions and lower $LCI_{2.5}$ as reported previously [3] all consistently point towards more efficient mucociliary clearance in the bronchial in the hypertonic saline group relative to the isotonic saline group.

Using the automatic BA-analysis, we found a significant but small progression in bronchial widening using B_{out}/A in both treatment groups over 48 weeks. B_{out}/A is the most accurate quantitative metric for the diagnosis of bronchial widening (or bronchiectasis) [13,30,31]. However, there was no significant difference in progression of B_{out}/A between hypertonic saline and isotonic saline groups. This result contrasts with our previous report which showed that the PRAGMA-CF %Bronchiectasis score, a secondary outcome measure for SHIP-CT, was significantly lower in the hypertonic saline group at 48 weeks compared to the isotonic saline group [3]. This discrepancy can be explained by differences in the methodology. PRAGMA-CF [4] is a scoring method where the observer annotates all grid cells on ten equally spaced axial slices using the following hierarchical order: 1) Bronchiectasis, 2) Mucus plugging, 3) Airway wall thickening. For the diagnosis of bronchiectasis, the observer compares the outer diameter of the bronchus to the diameter of an adjacent artery by visual assessment and not by actual measurements. In cases where the bronchial outer diameter is substantially greater than that of the adjacent artery in combination with a thickened bronchial wall, the observer will easily classify such a bronchus as bronchiectasis. However, it is likely that especially in early stages of disease, bronchi showing thickening but no widening are more readily misclassified by the observer as bronchiectasis. With the automatic BA-analysis, we now show that in the hypertonic saline group, less bronchi at 48 weeks had thickened bronchial walls. Bronchi with a normal thin wall are less likely to be misclassified as bronchiectasis using PRAGMA-CF. In addition, improved mucus clearance in the hypertonic saline group might also have resulted in a lower number of bronchi easily visible to the observer. The automatic BA-analysis quantifies BA-dimensions in cross section throughout the bronchial tree with high precision, differentiating with strict rules between normal size and widening. Thus, we consider the assessment of bronchial widening being a hallmark of bronchiectasis by the automatic BA-analysis as more precise and more reliable than that of PRAGMA-CF. However, the findings of our automatic BA-analysis are in line with that of SHIP-CT, which showed a positive response in the primary outcome measure, PRAGMA-CF %Disease, which includes all bronchi-related abnormalities [3]. Based on our automatic BA-analysis, we can conclude that the reduction in %Disease was primarily driven by clearance of mucus in the hypertonic saline group and not by a reduction in bronchial widening (bronchiectasis) [23].

The automatic BA-analysis allows us to address several issues related to the current challenges of defining bronchial widening (or bronchiectasis). Firstly, the automatic BA-analysis is capable of measuring a large number of visible BA-pairs, including small airways in the periphery of the lung. Secondly, it provides objective measurements of BA-ratios by automatically measuring BA-dimensions rather than relying on subjective human-observation. Thirdly, the automatic BA-analysis allows for the assessment of both bronchial wall thickening and bronchial widening independently. This analysis provides a more comprehensive evaluation of bronchial dimensions and morphology, allowing for a more accurate and detailed characterization of bronchial remodelling of lung disease. Finally, the output of the automatic BA-analysis also supplies information specified by segmental generation, segmental parent and lobe. This allows to locate bronchiectasis even in non-diffuse lung diseases.

We observed only weak correlations between changes in bronchial wall thickness as measured by the automatic BA-analysis and the changes in $LCI_{2.5}$ outcome. Similarly, in previous studies, poor correlations were observed between CT changes as measured by various scoring methods and functional outcomes as measured by spirometry and MBW [10,32,33]. The weak correlation between BA-outcomes and $LCI_{2.5}$ can be explained by the differences in the compartment measured by their techniques. $LCI_{2.5}$ is a measure of ventilation inhomogeneity which is thought to be especially sensitive to abnormalities of the small airways [34]. Small airways are defined as bronchi of 2 mm or less. In a 25-year old male without lung disease this corresponds to bronchi ranging from the 19^{th} generation to 25^{th} generation starting from the trachea as G_0 [27]. This would be equivalent to sub-segmental generation G_{15} and higher in our automatic BA-analysis. The automatic BA-analysis can measure bronchi down to a diameter of 2 mm as determined by the resolution of the CT scanner. Hence, for the SHIP-CT study, bronchi down to the 10^{th} segmental generation could still be detected. This means a large number of smaller bronchi in higher generations that are likely to contribute to the $LCI_{2.5}$ are not visible on CT in these young children. In our study, 39/85 participants were discordant when comparing changes in CT as measured by B_{wt}/A and $LCI_{2.5}$. This finding is similar to a previous study where 50% of children had discrepancy between changes in CT and $LCI_{2.5}$ outcomes over two years [35]. Therefore, both structural CT outcomes and functional $LCI_{2.5}$ outcomes should be considered as outcome measures to monitor CF lung disease in young children as they measure different aspects of the disease.

A limitation of measuring BA-dimensions and BA-ratios is that these outcomes may vary depending on the level of inspiration [18,19,30,36]. As can be seen on the lung volumes computed from the CT (Appendix Figure S1), there was quite some variability in lung volume both at baseline and at 48 weeks for these children aged 3-6 years. These differences in lung volume between baseline and 48 weeks is likely to have reduced the sensitivity of the method to detect differences between the two treatment groups. In older more cooperative children with lung volumes closer to TLC during CT acquisition, the sensitivity of the BA-analysis to track disease is likely to be better. Another limitation of the automatic BA-analysis for young children is related to the relatively poor spatial resolution as discussed above. However, it is important to note that geometrical changes in central airways are correlated with changes in more peripheral airways [37]. Furthermore, small airway disease can be reflected as low attenuation regions on expiratory scans [38,39]. The recently introduced photon-counting CT with superior resolution and lower radiation exposure is able to detect structures up to 0.2 mm in size [40]. This innovation in CT technology will therefore be of great importance for the sensitive detection and monitoring of small airways disease in children aged 3-6 years.

5. Conclusion

The automatic BA-analysis is able to detect and measure a large number of BA-pairs on chest CTs in children aged 3-6 years with CF who participated in the SHIP-CT study. We showed that twice daily hypertonic saline inhalation reduced bronchial wall thickness relative to the isotonic saline group. There was no difference in progression of bronchial widening between treatment groups. The automatic analysis of BA-dimensions allows for objective and sensitive detection of bronchial wall thickening and bronchial widening which is important not only for clinical studies but also for clinical care to monitor the effect of CF transmembrane regulator (CFTR) modulator therapy on structural airway changes. Future clinical care for patients across different age groups who respond positively to CFTR modulator therapy, which are currently being investigated in several real-life studies such as RECOVER (NCT04602468), MODUL-CF (NCT04301856), and ENRICH (Grant003138121).

Declaration of Competing Interest

HAWMT reports grants from the Cystic Fibrosis Foundation and Health Holland, has received in the last 5 years multiple grants from the following public and institutional grant institutions for lung structure and function research: NHMRC, NIH, CFF, ECFS, IMI, Sophia Foundation and unconditional grants for investigator-initiated research from Chiesi, Vectura, Novartis, and Insmed, has acted as consultant for Insmed, TBIO, Thirona, Neupharma and Boehringer, has a part time position as chief medical officer for Thirona, functions as vice chair and faculty for the Advance course sponsored by Vertex, and owns no shares. Erasmus MC and Telethon Kids Institute have licensed the use of PRAGMA-CF to Thirona and Resonance Health. LGE is a scientist working at Thirona. JPC is Co-founder and shareholder at Thirona. DC is director of the Erasmus MC- LungAnalysis laboratory. SDD reports grants from Cystic Fibrosis Foundation. MR reports grants from Cystic Fibrosis Foundation. FR serves as consultant for Vertex, Bayer, Roche, Genentech, and Proteostasis. RAK reports grants from Cystic Fibrosis Foundation. KDHS reports grants from Cystic Fibrosis Foundation. SMS reports grants from the Cystic Fibrosis Foundation and National Health and Medical Research Foundation and Erasmus MC and Telethon Kids Institute have licensed the use of PRAGMA-CF to Thirona and Resonance Health. All other authors declare no competing interests.

CRediT authorship contribution statement

Yuxin Chen: Data curation, Writing – original draft, Formal analysis, Investigation, Validation, Visualization. **Qianting Lv:** Data curation, Validation, Writing – review & editing. **Eleni-Rosalina Andrinopoulou:** Formal analysis. **Leticia Gallardo-Estrella:** Software, Data curation, Validation. **Jean-Paul Charbonnier:** Software, Data curation, Validation. **Daan Caudri:** Writing – review & editing. **Stephanie D. Davis:** Writing – review & editing. **Margaret Rosenfeld:** Writing – review & editing. **Felix Ratjen:** Writing – review & editing. **Richard A. Kronmal:** Writing – review & editing. **Karen D. Hinckley Stukovsky:** Writing – review & editing. **Stephen Stick:** Writing – review & editing. **Harm A.W.M. Tiddens:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Funding acquisition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.05.013.

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