Automated method of bronchus and artery dimension measurement in an adult bronchiectasis population

Angelina L.P. Pieters[1,2,13], Qianting Lv[1,2,13], Jennifer J. Meerburg[1,2], Tjeerd van der Veer[3], Eleni-Rosalina Andrinopoulou[4], Pierluigi Ciet[1,5], James D. Chalmers[6], Michael R. Loebinger[7,8], Charles S. Haworth[9,10], J. Stuart Elborn[11] and Harm A.W.M. Tiddens[1,2,12] on behalf of the iABC Study Group

[1]Erasmus MC, University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine, Rotterdam, The Netherlands. [2]Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Department of Pediatrics, division of Respiratory Medicine and Allergology, Rotterdam, The Netherlands. [3]Erasmus MC, University Medical Center Rotterdam, Department of Respiratory Medicine, Rotterdam, The Netherlands. [4]Erasmus MC, University Medical Center Rotterdam, Department of Biostatistics. Department of Epidemiology, Rotterdam, The Netherlands. [5]Department of Medical Sciences, University of Cagliari, Cagliari, Italy. [6]College of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [7]Host Defence Unit, Royal Brompton Hospital, London, UK. [8]NHLI, Imperial College London, London, UK. [9]Cambridge Centre for Lung Infection, Royal Papworth Hospital, Cambridge, UK. [10]University of Cambridge, Cambridge, UK. [11]School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK. [12]Thirona, Nijmegen, The Netherlands. [13]These authors contributed equally.

Corresponding author: Harm A.W.M. Tiddens (tiddens@erasmusmc.nl)

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The BA method can be used to quantify bronchial dimensions with great precision in bronchiectasis patients; this provides an objective assessment of a large number of bronchi to phenotype precision airway disease and to personalise treatment https://bit.ly/3YkzCWn

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Abstract

Aim Bronchiectasis (BE) is a disease defined by irreversible dilatation of the airway. Computed tomography (CT) plays an important role in the detection and quantification of BE. The aim of this study was three-fold: 1) to assess bronchus–artery (BA) dimensions using fully automated software in a cohort of BE disease patients; 2) to compare BA dimensions with semi-quantitative BEST-CT (Bronchiectasis Scoring Technique for CT) scores for BE and bronchial wall thickening; and 3) to explore the structure–function relationship between BA-method lumen dimensions and spirometry outcomes.

Methods Baseline CTs of BE patients who participated in a clinical trial were collected retrospectively. CTs were analysed manually with the BEST-CT scoring system and automatically using LungQ (v.2.1.0.1, Thirona, The Netherlands), which measures the following BA dimensions: diameters of bronchial outer wall (B_{out}), bronchial inner wall (B_{in}) and artery (A), and bronchial wall thickness (B_{wt}) and computes BA ratios (B_{out}/A and B_{in}/A) to assess bronchial widening. To assess bronchial wall thickness, we used the B_{wt}/A ratio and the ratio between the bronchus wall area (B_{wa}) and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}).

Results In total, 65 patients and 16 900 BA pairs were analysed by the automated BA method. The median (range) percentage of BA pairs defined as widened was 69 (55–84)% per CT using a cut-off value of 1.5 for B_{out}/A, and 53 (42–65)% of bronchial wall were thickened using a cut-off value of 0.14 for B_{wt}/A. BA dimensions were correlated with comparable outcomes for the BEST-CT scoring method with a correlation coefficient varying between 0.21 to 0.51. The major CT BA determinants of airflow obstruction were bronchial wall thickness (p=0.001) and a narrower bronchial inner diameter (p=0.003).

Conclusion The automated BA method, which is an accurate and sensitive tool, demonstrates a stronger correlation between visual and automated assessment and lung function when using a higher cut-off value to define bronchiectasis.

Introduction

Bronchiectasis in adults is a common complication of a wide array of respiratory diseases and is characterised by airway widening and clinical symptoms. Clinical symptoms can consist of cough, sputum

production, recurrent chest infections, malaise, chest discomfort and, in severe cases, haemoptysis and weight loss [1]. The presence of bronchiectasis can be suspected based on clinical symptoms, auscultatory abnormalities and on lung function impairment. Unfortunately, these indicators lack sensitivity and specificity. Patients diagnosed with bronchiectasis have airflow obstruction on spirometry in around 50% of cases, but restrictive or mixed obstructive patterns and preserved lung function are also frequently observed [2, 3]. For the objective and sensitive diagnosis of bronchiectasis chest computed tomography (CT) is considered the gold standard. The most widely accepted definition of bronchiectasis by radiologists as observed on chest CT is a dilatation of the airway that is larger compared with the adjacent artery, lack of tapering and visibility of an airway in the periphery of the lung [4–6]. However, these criteria are subjective, and it is unclear to what extent these criteria are correctly applied in clinical practice, clinical trials and research studies [4, 7]. In addition, chest CT image acquisition is poorly standardised, which can affect the diagnosis of bronchiectasis [5, 8, 9].

For bronchiectasis disease, there is great need for an automated reproducible quantitative image analysis method to assess the presence and extent of bronchiectasis [4]. Over the past decade, several quantitative artificial intelligence-based image analysis systems were successfully developed to assess bronchiectasis in diseases such as COPD, cystic fibrosis and severe asthma [10–17]. However, to date, these systems have not been applied in bronchiectasis disease. Important for the validation of such an automated system for bronchiectasis disease is that it should be tested against the manual assessment. For the manual assessment the Bronchiectasis Scoring Technique for CT (BEST-CT) was developed based upon a validated morphometry-based scoring method to quantify structural lung damage in patients with cystic fibrosis (PRAGMA-CF) [18]. BEST-CT was shown to be a reproducible quantitative scoring system to phenotype and measure the severity and extent of structural lung abnormalities in bronchiectasis patients [19]. Disadvantages of the BEST-CT system are that it requires training of the observer of 1–2 weeks and is time consuming, taking up to 45 min to score one CT scan. Furthermore, the scoring is still based on eyeballing by the observer to estimate airway, artery and airway wall dimensions and ratios for the diagnosis of bronchiectasis and airway wall thickening.

Recently, a fully automated image analysis system was developed using artificial intelligence (AI) strategies, which allows the measurement of the dimensions of a large number of bronchus–artery (BA) pairs on a chest CT scan with great accuracy and precision. To date, this automated BA method has been used to assess BA dimensions in various cystic fibrosis cohorts, in a severe asthma cohort and in a large set of normal chest CTs [11, 12, 14, 20]. However, to date, this BA method has not been validated in bronchiectasis disease.

The aim of the current study was three-fold: 1) to assess BA dimensions using the fully automated BA method in a cohort of bronchiectasis patients that participated in a phase II clinical trial [19]; 2) to compare BA outcome dimensions with semi-quantitative BEST-CT scores for bronchial widening and bronchial wall thickening; 3) to explore the structure–function relationship between BA-method bronchial wall and lumen dimensions and spirometry outcomes.

We hypothesised that the automated BA method is an accurate and sensitive tool to assess airways disease in bronchiectasis patients and that its output correlates with the BEST-CT scoring system and spirometry outcomes.

Materials and methods

Study population

The CT scans for the study were retrospectively collected from bronchiectasis patients who participated in the iBEST study [21]. The iBEST study was a randomised placebo-controlled trial designed to evaluate the efficacy, safety and tolerability of tobramycin inhalation powder in bronchiectasis patients. The inclusion criteria for the study were patients (aged $\geqslant$18 years) with a proven diagnosis of bronchiectasis confirmed on a CT scan by the local radiologists and a history of $\geqslant$2 exacerbations treated with oral antibiotics or $\geqslant$1 exacerbation treated with parenteral antibiotic treatment as well as a respiratory sputum sample positive for *Pseudomonas aeruginosa*. The main exclusion criteria were diagnosis of cystic fibrosis, primary diagnosis of bronchial asthma and smoking-associated COPD. Other inclusion and exclusion criteria are detailed in the study design manuscript [22].

All CTs, which were baseline scans made prior to the trial, were previously analysed using the BEST-CT scoring system before treatment [23]. The inclusion criteria for the automated BA method were the availability of an inspiratory CT scan with a reconstructed slice thickness of axial images of $\leqslant$1.5 mm, no missing lung and no gaps between slices.

For all patients included in this sub-study the following spirometry outcomes were available and expressed as % predicted (% pred) using the Global Lung Initiative prediction equations [24]: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and forced expiratory flow (FEF) between 25 and 75% of vital capacity ($FEF_{25–75\%}$).

BEST-CT scoring

BEST-CT is a morphometric scoring system that uses a grid placed on 10 equally spaced axial chest CT slices between the lung apex and base. Each grid box is annotated by an observer for the presence or absence of structural lung abnormalities [19]. Each grid cell that contains at least 50% coverage of the lung is scored. The structures in the grid cell are scored with the following hierarchical system (highest to lowest priority): 1) atelectasis/consolidation (ATCON); 2) bronchiectasis with mucous plugging (BEMP); 3) bronchiectasis without mucous plugging (BEwMP); 4) airway wall thickening (AWT); 5) mucous plugging without bronchiectasis (MP); 6) ground-glass opacities (GGOs); 7) emphysema and/or bullae (EMPBUL); 8) healthy airways; and 9) healthy parenchyma. Bronchiectasis was considered by the observer when the outer wall of an airway was estimated to be wider than the adjacent artery and airway wall thickening when the internal diameter of the bronchus was <80% of the external diameter.

The total percentages of the lung volume occupied by bronchiectasis and airway wall thickening for BEST-CT are calculated in the following composite score, which is used for comparison with similar automated BA-method outcomes: %BE_BESTCT=%BEMP+%BEwMP and %AWT_BESTCT=%AWT.

Bronchus–artery analysis

The automated BA method was performed using LungQ v.2.1.0.1 (Thirona, Nijmegen, The Netherlands; https://www.thirona.eu). The term “bronchus” and its abbreviation (B) was selected over “airway” and its abbreviation (A) to avoid confusion with the abbreviation of “artery” (A).

The automated BA method starts by automatically detecting and segmenting the bronchial tree on an inspiratory CT scan. Next, for each bronchus starting at the segmental bronchus (G_0) and for higher generations ($G_{1–14}$) the adjacent artery is identified using an AI-based BA-matching algorithm. Next, for each identified BA pair and segmental bronchus generation, the following dimensions are computed perpendicular to the longitudinal bronchus or artery axis (figure 1): Bronchial inner diameter (B_{in}); bronchial outer diameter (B_{out}); bronchial wall thickness (B_{wt} (=(B_{out}–B_{in})/2)), bronchial wall area (B_{wa}), bronchial outer area (B_{oa}) and artery diameter (A). 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. For each bronchial generation of G_0 and higher, the BA dimensions of each individual bronchial branch are computed as the average of all measurements within that branch. This detailed analysis, which measures the average for the entire lung but can generate lobar or even segmental outputs when needed, ensures that even subtle bronchial widening, which may be easily overlooked in visual assessments, is accurately identified.

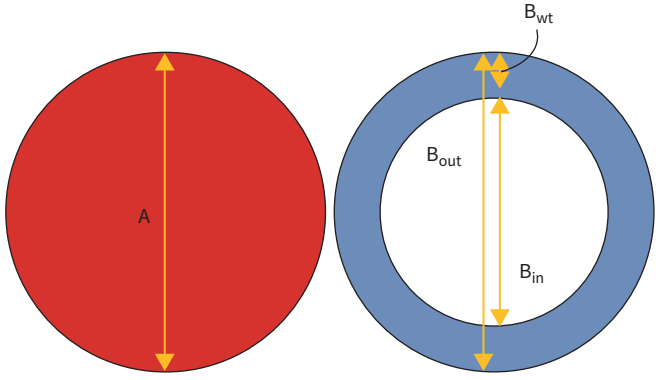

FIGURE 1 Bronchial artery (BA) ratio. An example of the dimensions measured on a chest computed tomography for each BA pair, as measured by the automated BA method software (LungQ, Thirona, The Netherlands). B_{out}: bronchial outer diameter; B_{in}: bronchial inner diameter; B_{wt}: bronchial wall thickness; A: adjacent artery diameter.

The following ratios for each BA pair are calculated by LungQ:

- B_{out}/A: the ratio between bronchial outer diameter and adjacent artery diameter;
- B_{in}/A: the ratio between bronchial inner diameter and adjacent artery diameter;
- B_{wt}/A: the ratio between bronchial wall thickness and adjacent artery diameter;
- B_{wa}/B_{oa} : the ratio between bronchial wall area and bronchial outer area.

In addition, we computed the P_{i10}, which is the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm [25, 26]. The P_{i10} has been used as an indicator for bronchial wall thickness in adult smokers, but it does not take body size nor generation into account and it can be influenced by a reduced internal diameter in relation to mucus. For this reason, we also used B_{wt}/A and the ratio between the wall area (B_{wa}) and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}) to assess bronchial wall thickness.

For each patient, bronchial dimensions and ratios are computed and plotted against segmental generation (G_1 and higher), as airways of the same generation have similar sizes and characteristics.

The cut-off values to determine bronchial widening and bronchial wall thickening are based on the automated BA method of a previous manually annotated dataset of chest CTs from patients with cystic fibrosis and from normal CTs of age-matched control subjects [27]. As there is no universally accepted definition for bronchial widening [5], we used a cut-off value for B_{out}/A of $\geqslant$1.1 based the automated BA method of a previous dataset [20] and a more conservative cut-off value of $\geqslant$1.5 [7] as suggested in a consensus publication based on a Delphi process by an international taskforce of experts to develop recommendations and definitions for bronchiectasis. Furthermore, we used cut-off values for B_{in}/A for bronchial widening of $\geqslant$0.8 and $\geqslant$1.5. Bronchial wall thickening was defined as B_{wt}/A $\geqslant$0.14 and assessed using the median of B_{wa}/B_{oa}. Total lung volume was assessed using LungQ.

Statistical analysis

BA dimension results are presented from the sub-segmental level onward ($G_{1–14}$), where G_1 represents the sub-segmental bronchi, G_2 the sub-sub-segmental bronchi and so on. For statistical analysis, we use the median values of BA dimensions and ratios of $G_{1–6}$ as these generations include the highest number of BA measurements in most patients and are less affected by body size and by higher visibility of the small airways in relation to airways disease. To investigate whether the differences between BEST-CT outcomes and the automated BA method and their relationship with clinical parameters depended on our selected segmental generations ($G_{1–6}$), we carried out a sensitivity analysis to determine the optimal number of segmental generations to be included ($G_{1–6}$ or $G_{1–14}$) in our analysis.

Data are shown as median and interquartile range (IQR) (25th to 75th percentile) or as mean±SD depending on the data distribution.

BEST-CT versus BA dimensions

For the comparison between BEST-CT results (%BE_BESTCT and %BWT_BESTCT) and comparable BA dimensions (B_{out}/A, B_{in}/A and B_{wt}/A) we used Spearman correlation coefficients because of the skewed data distribution. A correlation coefficient <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 0.8–1.0 as excellent [28].

Spirometry versus the automated BA method

For the comparison between BA dimensions related to airway obstruction we used ($B_{in,}$ B_{wt}, B_{out}/A, B_{in}/A, B_{wa}/B_{oa} and P_{i10} for $G_{1–6}$) and spirometry outcomes sensitive to airway obstruction (FEV_1 % pred, FEV_1/FVC % pred and log $FEF_{25–75\%}$ % pred) we used linear regression analysis. For the BA method, B_{in} was selected as the most relevant outcome measure, as the internal diameter of the airways is the most likely outcome measure determining maximal flows for a spirometry manoeuvre. For the spirometry outcomes FEV_1 % pred, FEV_1/FVC % pred and log $FEF_{25–75\%}$ % pred were selected, as these outcomes are considered dependent on bronchial lumen dimensions. Correlations between $B_{in,}$ B_{wt}, B_{out}/A, B_{in}/A B_{wa}/B_{oa} and P_{i10} and FEV_1, FEV_1/FVC and $FEF_{25–75\%}$ were assessed by Spearman (or Pearson) correlation coefficients, depending on whether the data had skewed distribution. We used a logarithmic scale for $FEF_{25–75\%}$ as the data distribution is skewed.

Adjusted p-values were used for multiple testing in relation to comparisons between the BA dimensions and spirometry outcomes.

All statistical analysis was carried out using R tooling, v.4.0.5 (R Foundation for Statistical Computing. Vienna, 2005). Statistically significant results were defined as $p<0.05$.

Results

CT collection and study population

84 inspiratory scans were analysed using the BEST-CT method and of these, 69 were eligible for the automated BA method using LungQ software. 15 scans could not be included in the analyses due to a slice thickness >1.5 mm and/or inconsistency in slice spacing. Patient characteristics are presented in table 1.

Automated analysis

A total number of 24 190 bronchi and 16 900 BA pairs were analysed by the automated BA method, ranging from segmental generations G_0 up to G_{14}. The median (IQR) of airway count per CT was 319 (228–441) and the median (IQR) of BA pair count per CT was 235 (165–344). The median percentage per CT of BA pairs defined as bronchial widening was 69% and 35% using B_{out}/A cut-off values of ⩾1.1 and ⩾1.5, respectively (table 1) (supplementary material, figure 1 and figure 2). Figure 3 shows an example of the output for the B_{out}/A analysis for $G_{1–6}$ of a patient with mild bronchiectasis disease and a patient with severe disease. The median percentage per CT of BA pairs defined as bronchial widening was 75% and 8% using B_{in}/A cut-off values of ⩾0.8 and ⩾1.5, respectively (table 1). An example of B_{out}/A is shown in supplementary material, figure 1 and figure 2). The median percentage per CT of BA pairs showing bronchial wall thickening was 53% for a B_{wt}/A cut-off of ⩾0.14 (table 1) (supplementary material, figure 1 and figure 2).

For the sensitivity analysis comparing $G_{1–6}$ with $G_{1–14}$, we did not find any significant differences in outcomes for BA dimensions *versus* BEST-CT analysis nor for the associations between BA dimensions and spirometry (supplementary tables 1–5).

Automated BA method versus *BEST-CT analysis*

We observed weak to moderate correlations between the automated BA method and BEST-CT outcomes (table 2). The correlations for the low cut-off values for bronchial widening (B_{out}/A cut-off of ⩾1.1 and B_{in}/A cut-off of ⩾0.8) were poor, whereas for the more conservative cut-off for bronchial widening (B_{out}/A cut-off and B_{in}/A cut-off of ⩾1.5), these were moderate. For bronchial wall thickness, there was a poor positive correlation between B_{wt}/A and %BWT_BEST-CT (table 2).

TABLE 1 Patient characteristics and results of computed tomography (CT) analysis by the automated bronchus–artery (BA) method

Age, years, median (IQR)	65 (58–74)
Gender (male/female), n (%)	24 (34.5)/45 (65.5)
Spirometry, median (IQR)	
FEV_1 % pred	58.1 (45.9–71.0)
FVC % pred	72.3 (64.4–89.4)
FEV_1/FVC % pred	72.3 (64.4–89.4)
$FEF_{25–75\%}$ % pred	30.3 (21.0–42.4)
Analysed CT scans, n	69
Total number of bronchi, n	24 190
Bronchi count per CT, median (IQR)	319 (228–441)
Total number of BA pairs, n	16 900
BA pair count per CT, mean±SD	235 (165–344)
Percentage of abnormal BA pairs, median (IQR)	
B_{out}/A cut-off ⩾1.1	68.5 (54.9–84.3)
B_{out}/A cut-off ⩾1.5	34.8 (23.0–43.6)
B_{in}/A cut-off ⩾0.8	74.9 (57.3–86.2)
B_{in}/A cut-off ⩾1.5	7.6 (3.3–15.9)
B_{wt}/A cut-off ⩾0.14	53.4 (42.0–65.4)

Inspiratory scans were analysed by the automated BA method. Bronchial widening was defined as a bronchial outer diameter divided by adjacent artery diameter (B_{out}/A) cut-off of ⩾1.1 and ⩾1.5 and a bronchial inner diameter divided by adjacent artery diameter (B_{in}/A) cut-off of ⩾0.8 and ⩾1.5. Bronchial wall thickening was defined as a bronchial wall thickness divided by adjacent artery diameter (B_{wt}/A) cut-off of ⩾0.14. BEST-CT: Bronchiectasis Scoring Technique; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow between 25 and 75% of vital capacity; IQR: interquartile range.

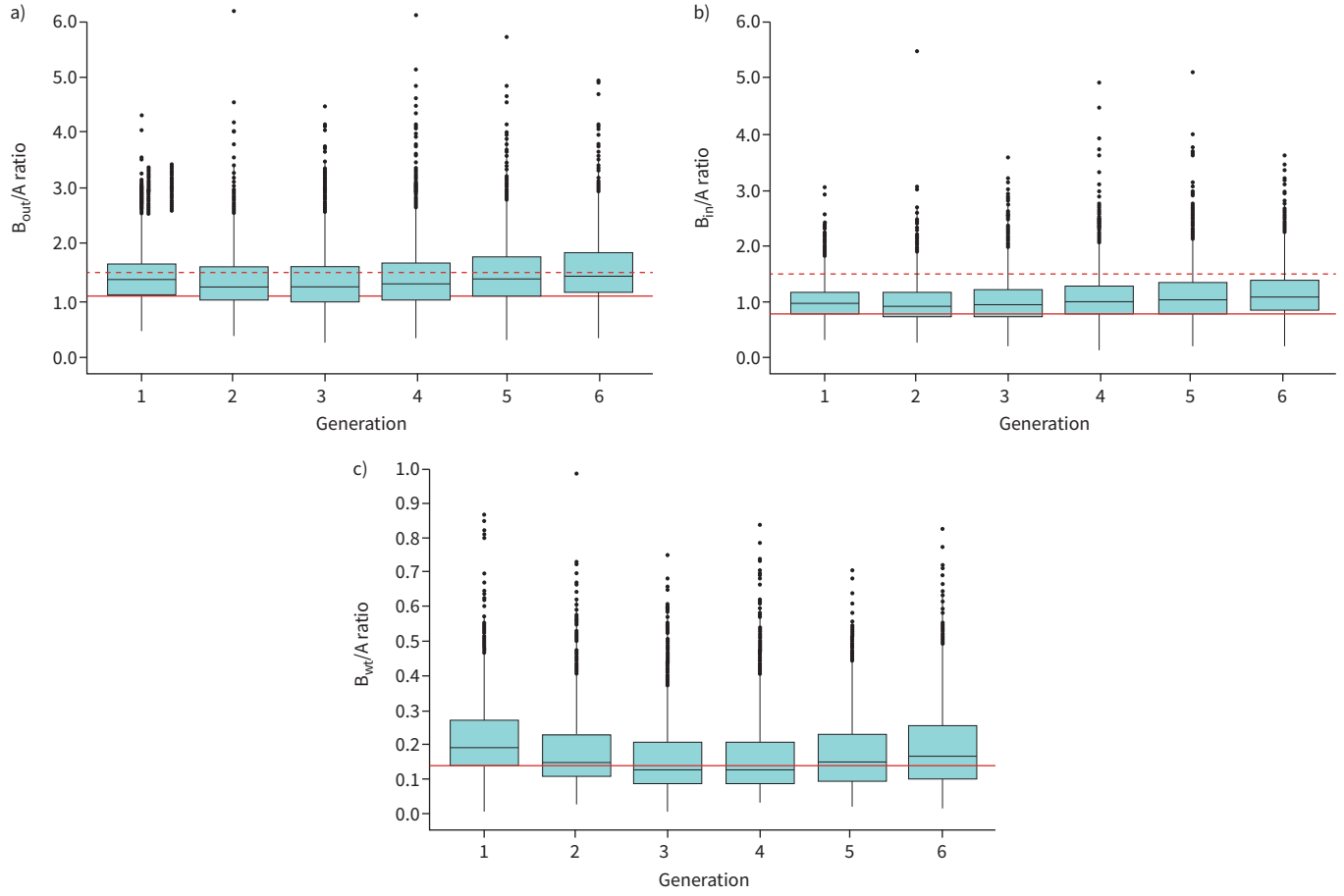

FIGURE 2 Bronchial artery ratios. The figure shows the bronchial outer diameter (B_{out})/adjacent artery diameter (A), bronchial inner diameter (B_{in})/A and bronchial wall thickness (B_{wt})/A ratios starting at the segmental level (generation 0) for generation 1–6. The dots indicate individual bronchus–artery ratios. The boxes indicate the median and interquartile range (25th to 75th percentile). a) B_{out}/A ratio. The solid red line indicates the B_{out}/A cut-off of ⩾1.1 and the dotted red line the cut-off of ⩾1.5 for bronchial widening. b) B_{in}/A ratio. The solid red line indicates the B_{in}/A ratio cut-off of ⩾0.8 and the dotted red line the cut-off of ⩾1.5. c) B_{wt}/A ratio. The solid red line indicates the B_{wt}/A cut-off of 0.14.

Associations between automated BA method and spirometry

We observed positive weak correlations between spirometry parameters (FEV_1 % pred, FEV_1/FVC % pred and $FEF_{25–75\%}$ % pred) and the median of B_{in} ($G_{1–6}$) (table 3). Regression analysis showed that spirometry parameters correlated significantly to B_{in} ($G_{1–6}$) (table 4).

We found significant correlations between spirometry parameters (FEV_1 % pred, FEV_1/FVC % pred and $FEF_{25–75\%}$ % pred) and the median of B_{wt} ($G_{1–6}$) (table 5). Similar p-values were observed for the P_{i10} and B_{wa}/B_{oa} as a measure for bronchial wall thickening (table 5). Higher B_{wt} ($G_{1–6}$), higher P_{i10} and higher B_{wa}/B_{oa} were associated with a lower FEV_1 % pred, FEV_1/FVC % pred and $FEF_{25–75\%}$ % pred. However, we did not find any significant correlations between spirometry parameters and BA ratios (B_{in}/A, B_{out}/A and B_{wt}/A) (supplementary tables 1–5).

Discussion

Using the automated BA method, we were able to detect and quantify a large number of bronchi and BA pairs to obtain BA dimensions on chest CT scans in a cohort of bronchiectasis disease patients participating in a clinical trial. We showed that the BA dimensions for bronchial widening correlated with comparable outcomes for the BEST-CT scoring method and that airway wall thickness and a wider bronchial lumen diameter, as assessed by the BA method, correlated with spirometry outcomes related to airflow obstruction.

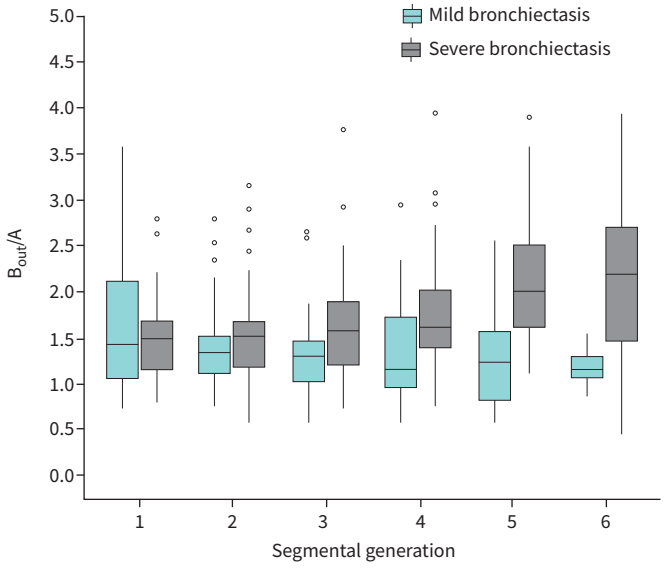

FIGURE 3 Example of bronchial outer diameter/adjacent artery diameter (B_{out}/A) analysis for patients with mild and severe bronchiectasis. The boxplot shows the B_{out}/A for a patient with mild bronchiectasis (% B_{out}/A >1.5=33.6% of bronchus–artery (BA) pairs) in blue and for a patient with severe bronchiectasis (% B_{out}/A >1.5=61.2% of BA pairs) in grey for subsegmental generation 1 to 6. Each box shows the median (horizontal line), interquartile range (solid box), 1.5 times the interquartile range (whiskers) and outliers (circles).

Quantitative image analysis

Using the automated BA method, we were able to quantify BA dimensions with great precision of a large number of airways and BA pairs. It is not feasible to execute such analysis manually as it is extremely time consuming [29].

We showed that BA dimensions for bronchial widening correlated with comparable outcomes for the BEST-CT scoring method, especially for the higher cut-off values. The most plausible reason for this difference is that it is difficult for even a trained observer to recognise subtle widening of especially smaller airways (*i.e.* B_{out}/A between 1 and 1.5 or B_{in}/A between 0.8 and 1.5) when visually scoring chest CT scans. This observation is in support of the consensus statement by Alberti *et al.* [7] to use a conservative cut-off value for inner or outer airway–artery diameter ratio of 1.5 for the diagnosis of bronchiectasis or more when assessing chest CTs by eyeballing to diagnose bronchiectasis. It is likely that we are overestimating the extent and severity of bronchiectasis to some extent as we did not consider possible progressive bronchial dilatation in relation to age, for which reference values are lacking [30, 31]. However, bronchial widening due to ageing is also not included in the clinical routine assessments of CTs.

TABLE 2 Correlation between the Bronchiectasis Scoring Technique (BEST-CT) and automated bronchus–artery (BA) method

	Automated BA method for bronchial widening			
	B_{out}/A ⩾1.1	**B_{out}/A ⩾1.5**	**B_{in}/A ⩾0.8**	**B_{in}/A ⩾1.5**
%BE_BEST-CT	R=0.30 (0.05–0.53)	R=0.51 (0.29–0.69)	R=0.21 (-0.05–0.44)	R=0.46 (0.24–0.64)
	Automated BA method for bronchial wall thickening			
	B_{wt}/A ⩾0.14			
%BWT_BEST-CT	R=0.26 (0.034–0.47)			

Correlation between Bronchiectasis Scoring Technique (BEST-CT) outcomes (%BE, %BWT) and automated BA method ratios by the automated BA method (bronchial outer dimeter divided by adjacent artery diameter (B_{out}/A), bronchial inner dimeter divided by adjacent artery diameter (B_{in}/A) and bronchial wall thickness divided by adjacent artery diameter (B_{wt}/A)) in generations ($G_{1–6}$). Bronchial widening was defined as a B_{out}/A ⩾ cut-off of 1.1 and a ⩾1.5 and a B_{in}/A ⩾ cut-off of 0.8 and 1.5. Bronchial wall thickening was defined as a B_{wt}/A ⩾ cut-off of 0.14. Pearson correlation coefficients (R) and 95% CIs are presented.

TABLE 3 Correlation between spirometry parameters and bronchial inner diameter ($B_{in,}$) derived from automated bronchus–artery (BA) method

Spirometry	Median of B_{in}
FEV_1 % pred	R=0.27 (0.04–0.48)
FEV_1/FVC % pred	R=0.27 (0.03–0.48)
$FEF_{25–75\%}$ % pred	R=0.23 (−0.01–0.45)

Spirometry outcomes and the median of B_{in} were derived from the automated BA method in limited generations ($G_{1–6}$). Data are shown as Spearman (or Pearson) correlation coefficient (R) and 95% CIs. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow between 25 and 75% of vital capacity.

TABLE 4 Results of linear regression analysis: investigating the association between spirometry parameters and bronchial inner diameter (B_{in}) derived from the automated bronchus–artery (BA) method

Spirometry	Median of B_{in}	
	Estimates (SE)	p-value
FEV_1 % pred	18.84 (7.62)	0.02*
FEV_1/FVC % pred	14.34 (4.66)	<0.01*
log ($FEF_{25–75\%}$ % pred)	17.01 (9.03)	0.07

Regression analysis for spirometry (forced expiratory volume in 1 s (FEV_1) % predicted, forced vital capacity (FVC) % pred, FEV_1/FVC and log forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25–75\%}$) % pred) *versus* the median of B_{in}. *: significant p-value.

TABLE 5 Results of linear regression analysis: investigating the association between spirometry parameters and bronchial wall thickening by the automated bronchus–artery (BA) method

Spirometry	Automated BA method					
	Median of B_{wt}/A		P_{i10}		Median of B_{wa}/B_{oa}	
	Estimates (SE)	p-value	Estimates (SE)	p-value	Estimates (SE)	p-value
FEV_1 % pred	−67.12 (27.83)	0.08	−22.65 (5.71)	<0.01*	−103.15 (28.64)	<0.01*
FEV_1/FVC % pred	−64.54 (16.22)	<0.01*	−14.55 (3.57)	<0.01*	−71.26 (17.58)	<0.01*
log ($FEF_{25–75\%}$ % pred)	−1.97 (0.77)	0.08	−0.50 (0.17)	0.03*	−2.33 (0.84)	0.05*

Data show the regression analysis for spirometry (forced expiratory volume in 1 s (FEV_1) % predicted, forced vital capacity (FVC) % pred, FEV_1/FVC and log forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25–75\%}$) % pred) *versus* the median of bronchial wall thickening described as bronchial wall thickness divided by adjacent artery diameter (B_{wt}/A), square root of wall area for a hypothetical airway with an internal perimeter of 10 mm (P_{i10}) and ratio between the bronchus wall area (B_{wa}) and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}). *: significant p-value.

For bronchial wall thickening there was a weak positive correlation between BA dimensions and the BEST-CT scoring method. It is well known that visual scoring of airway wall thickening is difficult, as illustrated by low reproducibility scores [20, 32]. It is often not possible for an observer to determine by eyeballing for each BA pair whether the thickness of the bronchial wall is above or below the cut-off value of 0.14 compared with the diameter of the adjacent artery. A great advantage of the automated BA method is that for each segmental bronchus generation a large number of measurements can be executed to compute the mean bronchial wall thickness for that segment. In the future, the objective assessment of bronchial wall thickness is likely to add relevant objective information that can be used for clinical care [7, 33].

We observed that both bronchial wall thickness and the bronchial lumen diameter correlated weakly with spirometry indicators of airflow obstruction. Similar observations were done in COPD and asthma [10, 11].

Pathophysiologically, we expected that the internal diameter of the bronchus as assessed by the BA method would be the most important CT outcome measure determining the maximal flow for spirometry manoeuvres. Airway obstruction in bronchiectasis is often associated with more severe disease, more exacerbations and more hospital admissions [34, 35]. The internal diameter of bronchi can be reduced for a number of reasons, such as inflammation-associated mucosal swelling, folding of the mucosa, mucus impaction, loss of parenchymal attachments and smooth muscle contraction. From our analysis, we cannot tell which of the five components is most important for the studied patient population. However, it is likely that there will be substantial heterogeneity in the origin of the reduced bronchial lumen and in the contribution of the above-mentioned components to the reduced spirometry indicators of airway obstruction [36–38]. We feel that the most important reason for the weak correlations that we observed between spirometry indicators of airflow obstruction and BA dimensions can be explained in part by the fact that a chest CT is taken during a static breath hold, whereas spirometry outcomes include dynamic phenomena that can contribute to airways obstruction.

Limitations

This study has some limitations. First, CT scans were collected retrospectively and acquisition, image reconstruction and lung volume during scanning were not standardised. Lung volume for an inspiratory CT scan is an important determinant for the diagnosis of bronchiectasis, as bronchial diameters are more dependent on lung volume compared with the arterial diameter [19]. Moreover, different CT scanners and protocols (*i.e.* kernels) were used for different patients, which could lead to slightly different BA-method outcomes. This effect is thought to be small as the BA algorithm corrects for these differences. However, these limitations may have somewhat reduced the sensitivity of our analysis. For future studies and for clinical care, it is important to harmonise chest CT imaging protocols across centres and scanners and optimise lung volume during CT acquisition by adequate training and coaching the patient [5, 9].

For our automated BA method, we focused on the analysis of BA pairs and not on absolute dimensions. It should be kept in mind that airways for which no adjacent artery can be identified by the software are not included in the BA metrics. This might lead to some underestimation of the severity of airway changes, especially of the smaller airways. However, for the most recent versions of the LungQ software, the difference between the total number of airways and number of BA pairs is small. Moreover, pulmonary arterial diameters can be reduced in relation to hypoxic pulmonary vasoconstriction [5]. Therefore, there might be patients with early stages of pulmonary hypertension resulting in increased diameters of more central pulmonary arteries. For this reason, it is important to also investigate in the future, bronchus-related outcome measures independent of their ratio with the adjacent arteries. To do so, reference values obtained in healthy populations are needed. It is remarkable that to date there are no well-defined cut-off values to define bronchial (*e.g.* airway) widening and thickening for the diagnosis of bronchiectasis, especially as Reid [39] already described its importance in 1950. As radiation doses for chest CTs have come down substantially, and will go down further thanks to developments such as photon counting CT, inclusion of chest CTs in population studies to obtain reference values in addition to epidemiological questions might become feasible [40]. Such reference values are needed for the objective diagnosis of airway widening and airway wall thickening.

The BA method is able to assess the bronchial dimensions with greater precision than the BEST-CT scoring method and then in routine radiology reporting. However, in contrast with BEST-CT, the BA method does not include an assessment of mucus plugging, atelectasis and/or consolidations. For this reason, Thirona recently developed a fully automated algorithm to detect mucus plugs and to compute the total number of plugs and their volume, which can be used for further validation studies. For a more-complete, automated analysis of CTs of bronchiectasis patients, future versions of the software are needed that also quantify relevant parenchymal changes in patients. However, measurements of bronchial wall thickness can also be considered an estimate of mucus volume, as this is thought to contribute importantly to the bronchial wall thickness as seen on CT.

Additionally, future studies should incorporate spirometer-controlled CT scans to ensure consistent inspiration depth and improve the accuracy of quantitative CT metrics.

Clinical implications

Our study shows that the automated BA method can be used to quantify bronchial dimensions with great precision in bronchiectasis disease patients, potentially replacing the current subjective analysis in the near future for the diagnosis of airways disease and for monitoring of disease progression in daily practice [41].

In conclusion, we have shown that the automated BA method is an accurate tool for assessing bronchus and artery dimensions in a large number of BA pairs on retrospectively collected chest CTs of

bronchiectasis disease patients. Furthermore, we have observed a stronger correlation between visual assessment, BA software and lung function when utilising a cut-off value of 1.5. These BA-method outcomes have the potential to replace the scoring methods such as the semi-quantitative BEST-CT scoring method for clinical studies and reporting for clinical care for bronchiectasis patients.

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